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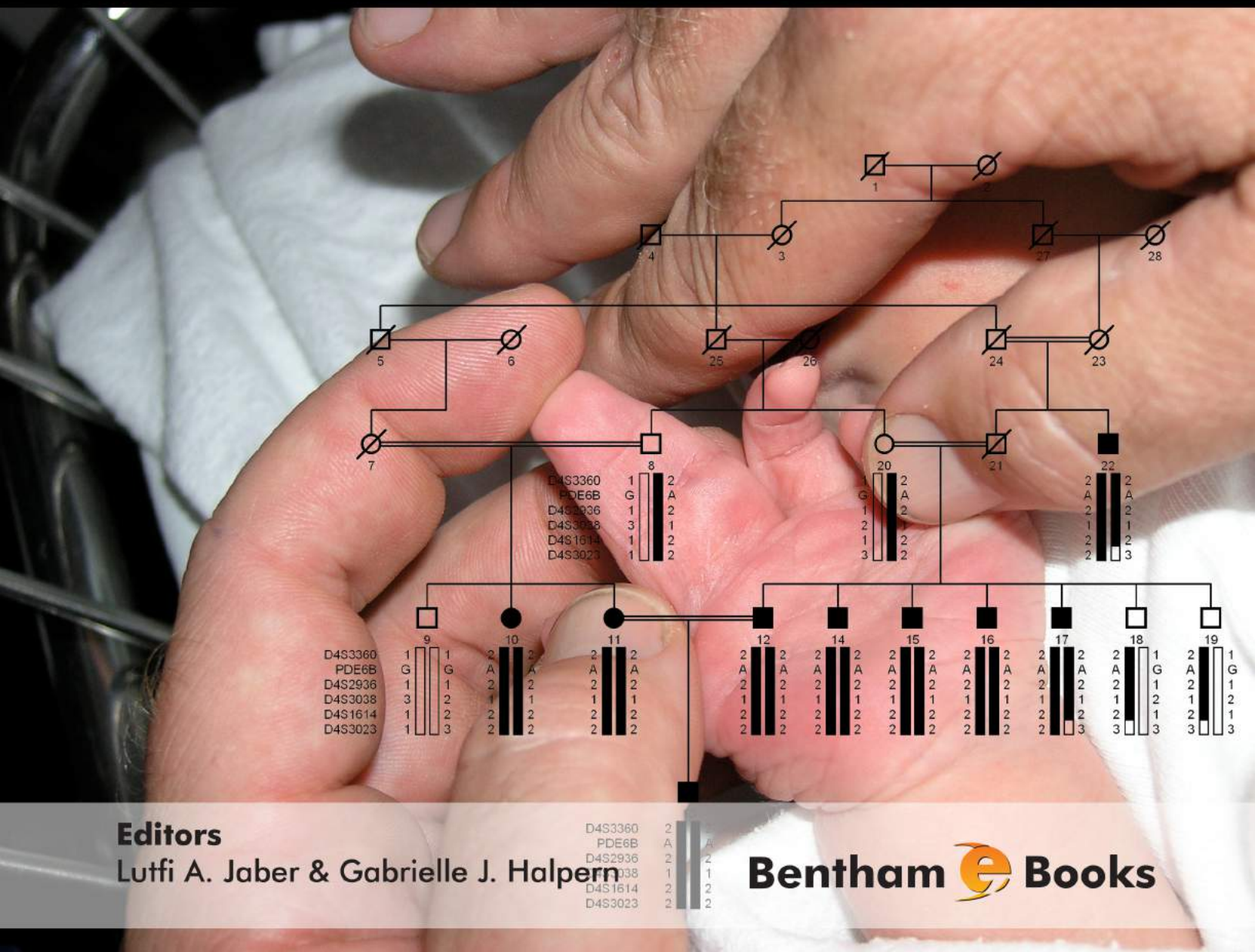
Consanguinity
Its Impact, Consequences and Management



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Consanguinity – Its Impact, Consequences and Management

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Editor's Biography

Professor Lutfi A. Jaber, M.D., is one of the foremost experts in the field of consanguinity and the problems associated with consanguineous marriages. This is still a major problem in many countries in the Middle East and Asia and Professor Jaber has studied it intensively and written many articles about the issue.

As a pediatrician who is Director of a busy pediatric clinic in a large Arab town in Israel and who also works in the Institute of Neurology at a large tertiary children's hospital, he sees first-hand every day the consequences of these marriages as the various illnesses among the children he treats. He is also a Professor in the Sackler Faculty of Medicine, Tel Aviv University, Israel. By teaming up with colleagues in the Department of Genetics at a local tertiary medical center, he also contributes to ongoing research into the genetic conditions that result from consanguineous marriages.

FOREWORD

Consanguineous marriages have been common throughout human history and remain, even nowadays, frequent in a large part of the world. While consanguineous marriages have become very rare in the industrialized world, immigration from developing countries has increased their frequency, and, as a result, in many of those countries a significant percentage of the children are born to consanguineous couples.

Over the centuries, the social advantages of consanguineous marriages were evident, while the medical consequences were known but not considered important. The concerns about the medical consequences of consanguinity became particularly relevant after the dramatic reduction in neonatal mortality mainly due to the successful treatment of infectious diseases. In the last decades, congenital malformations and genetic diseases have become major factors underlying neonatal mortality in many developing countries. The mounting awareness regarding prevention of congenital and genetic disorders is generating an increasing number of studies on their relation to consanguinity.

The book edited by Professor Lutfi A. Jaber and Dr. Gabrielle J. Halpern provides a broad overview of the various facets of consanguinity including social and religious aspects as well as various characteristics of its medical impact. The various chapters written by the editors as well as by additional experts in their respective fields not only allow the reader to understand better the wide range of medical problems linked with consanguinity, but also propose strategies to reduce the burden. The book should be useful to all those working in communities in which consanguineous marriages are frequent.

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PREFACE

Consanguinity means blood relationship by descent from the same ancestor, and not by marriage or affinity, and a consanguineous marriage is one contracted between biologically related individuals. In the main, the detrimental health effects associated with these marriages are caused by the expression of rare, recessive genes inherited from a common ancestor or ancestors. Many genetic diseases are recessive, meaning only people who inherit two abnormal genes for the same disease, one from each parent, will develop the disease. Since close relatives have more genes in common than unrelated individuals, there is an increased chance that parents who are closely related will carry the same disease genes and thus have an affected child. The rate of congenital malformations among the offspring of consanguineous marriages is approximately 2.5 times higher than that among the offspring of unrelated parents, and first cousin consanguinity has been shown to be significantly associated with an increased risk of various disorders.

People who share a recent common ancestor share more than 99.5% of their DNA; the closer the relatives are the more DNA they share. The amount of genetic material shared by first cousins is four times higher than that shared by second cousins. Once the relationship is between fourth cousins, the original amount of shared DNA reverts to the basic amount of 99.5%. Unions between individuals biologically related as second cousins or closer are categorized as consanguineous. Chapter 1 gives a general overview of consanguinity, including the background and history. There are also sections that discuss the legal, religious and biological (genetic) aspects.

The frequency of consanguineous marriages varies from one population to another. Consanguineous marriage is not restricted to specific religions or to population isolates, but is a long-standing practice in many regions of the world and it continues to be preferred by many populations, with more than 1,000 million people living in countries where between 20% and 50+% of marriages are consanguineous. The highest levels occur in the northern part of Africa, the Middle East and parts of Asia, whereas in what is described as the "Western

world" – *i.e.* the entire North American continent, the whole of Europe (with the exception of Spain), Australia and New Zealand – the frequency is less than 1%. Chapter 2 gives a detailed account of the prevalence in the different parts of the world.

Chapter 3 discusses general health topics associated with consanguinity, genetic disorders and congenital malformations, and also describes the benefits and advantages that can accrue as a result of consanguineous marriages. These include socioeconomic advantages, the main ones of which are preservation of property, especially land, and the desire to keep this within the family, and the popular belief that in intrafamilial marriage, it is more likely that the bride will be compatible with her husband's family, and the bride herself finds it reassuring to marry into a known family background.

Although it is well known that offspring of consanguineous parents have an increased risk for monogenic autosomal recessive diseases, the contribution of parental consanguinity to the development of common multifactorial diseases is controversial. Most of the common diseases are multifactorial in etiology, *i.e.* the disease will manifest only after the risk factor level, both genetic and environmental, has exceeded a certain cut-off point. Chapter 4 explores the association between consanguinity and susceptibility to common diseases.

Chapter 5 investigates the contribution of consanguinity to reproductive issues and fertility. While it used to be generally believed that inbreeding resulted in detrimental effects on reproductive outcome, some studies have shown only a moderate to slight impact. The fertility of consanguineous couples has also been extensively studied and numerous reports have concluded that consanguinity is not associated with either a significant positive or negative effect. However, in general, higher total fertility rates have been reported in consanguineous marriages. Similarly, reports regarding the association of consanguinity and fetal wastage have been conflicting, with some reporting that the total prenatal losses were essentially the same for consanguineous and non-consanguineous couples.

Awareness of the issues and problems associated with consanguineous marriages is the subject of Chapter 6. In many traditional Arab societies, in which the

frequency of consanguineous marriages is very high, there is generally a low level of genetic literacy both among the public and most health care providers, and therefore the need for education is of vital importance in such communities in order to be able to establish programs aimed at reducing the rates of these marriages. The main factor in establishing such educational and counseling programs is to identify the target group(s) who would benefit most from such programs. Several studies carried out in different countries with high rates of consanguineous marriages are described; the purpose of these was to assess the levels of awareness among various groups, both general public and health care professionals, regarding the health problems associated with such marriages. The information gained from these surveys was used in each case to establish educational and counseling programs geared to that specific society. The results of various surveys that explored acceptance of prenatal diagnosis and termination of pregnancy among different populations and also attitudes to consanguinity are discussed.

Chapters 7 and 8 discuss future strategies for reducing both the frequency of consanguineous marriages and the number of affected children born to consanguineous parents. Chapter 7 continues the theme of Chapter 6 and details the requirements for the establishment of educational and counseling programs. Attempts in various countries to offer training, educational and counseling programs aimed at reducing the incidence of consanguineous marriages are described. The question as to whether religious intervention to discourage the practice of consanguineous marriage would be effective is also raised and an overview is given of the general trend of a decline in the worldwide rates of consanguineous marriages.

Chapter 8 concentrates on the genetic aspects, including genetic counseling and screening and a discussion of genetic testing and molecular analysis. The methods and techniques used for the identification of disease-related genes in consanguineous populations are described; once the causative gene for a specific disease has been identified, carrier screening in the specific community can be offered and prenatal diagnosis carried out in the case of carrier couples. Termination of pregnancy can then be offered in the case of an affected fetus. Preimplantation genetic diagnosis, which is a technique used to analyze embryos

genetically before their transfer into the uterus in order to enable only unaffected embryos to be transferred, is also discussed.

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CHAPTER 1

Definition, Background, History, and Legal, Religious and Biological Aspects

Lutfi Jaber[1,2,3,*] and Gabrielle J. Halpern[4]

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Abstract: The term "consanguinity" refers to relationship by descent from the same ancestor and means the amount of shared (identical) DNA. The term "consanguineous marriage" refers to unions between biologically related individuals. This chapter explores the historical, legal and religious aspects of consanguinity and discusses genetic aspects including population genetics and molecular genetics. The types of consanguineous unions allowed vary between different countries, and different religions have different traditions regarding which consanguineous unions are allowed. The main reasons for the continuation of consanguineous marriages are social and economic. People who share a recent common ancestor share more than 99.5% of their DNA; the closer the relatives are the more DNA they share. Once the relationship is between fourth cousins, the original amount of shared DNA reverts to the basic amount of 99.5%. Inbreeding is measured by the inbreeding coefficient, F, which is the probability that two genes at any locus in one individual have been inherited from a common ancestor. Many genetic diseases are recessive, meaning only people who inherit two abnormal genes for the same disease, one from each parent, will develop the disease. Since close relatives have more genes in common than unrelated individuals, there is an increased chance that parents who are closely related will carry the same disease genes and thus have an affected child.

Keywords: Autosomal recessive diseases, consanguineous marriages, cousins, DNA, forbidden marriages, genes, inbreeding, mutations, religion.

INTRODUCTION

The issue of consanguinity and consanguineous marriages is very important

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Lutfi A. Jaber and Gabrielle J. Halpern (Eds.)

because of the associated health problems. While such marriages used to be more or less confined to Middle Eastern and North African countries and parts of Asia – notably India – nowadays, with widespread migration of citizens of those countries to the "Western" world – *i.e.* Europe, North America and Australia in particular – the problems associated with these marriages have also been "exported". This means that health care workers in Western countries need to become acquainted with these issues in order to be able to offer optimum care to their clients.

According to the Online Etymology Dictionary, the term "consanguinity" dates from c.1400, from Middle French consanguinité, from Latin consanguinitatem (nominative consanguinitas), from consanguineus "consanguineous, of the same blood," – from com- "together" + sanguineus "of blood".

The term "consanguineous marriage" refers to a union between couples who are second cousins or more closely related. This includes double first cousins, first cousins, first cousins once removed, and second cousins. Consanguinity may also refer to unions of individuals with at least one common ancestor, such as those occurring within population isolates such as the Amish in Lancaster County, Pennsylvania; small towns, tribes, intra-community, or endogamous marriages, as is frequently the case among Arab Muslim communities.

Consanguinity is categorized as first, second and third degree, the first being the closest kinship. The first degree includes all relationships that are considered incestuous. The definition of incest according to the Merriam-Webster Dictionary is: "Sexual intercourse between persons so closely related that they are forbidden by law to marry; *also* the statutory crime of such a relationship". In the dictionary definition, and legally in general, incest means penetrative sexual intercourse between closely related lineal relatives. This means having relations with a parent, child, brother, sister, grandparent or grandchild. "Brother" and "sister", respectively, include half-brother and half-sister. The definitions of consanguinity also include the legal and genetic definitions.

HISTORICAL ASPECTS

The Bible

Right from the beginning of the **Old Testament**, there are descriptions of both incestuous and consanguineous unions. Both the surviving sons of Adam and Eve – Cain and Seth – had to marry their sisters since there were no other women for them. Of the Old Testament Patriarchs (Fig. **1**), Abraham married Sarah, who was his half-niece – daughter of his half-brother Haran – and their son Isaac married Rebecca, who was Isaac's first cousin once removed (daughter of Bethuel, who was the son of Abraham's brother Nachor, and granddaughter of Milcah and Nachor). Nachor married his half-niece Milcah, daughter of his half-brother Haran. Abraham's nephew Lot, son of his half-brother Haran and Milcah's and Sarah's brother, had two daughters. After the destruction of Sodom the daughters thought that they and their father were the only people left alive in the world, and both became pregnant by their father Lot in order to continue the human race, thus creating the Moabites and Ammonites.

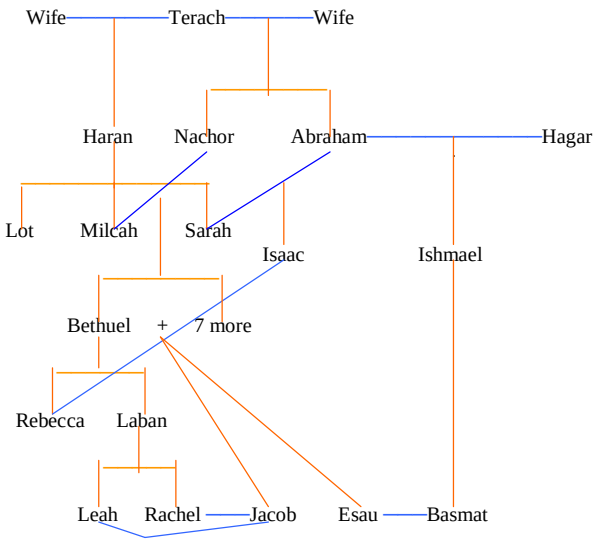


Figure 1: Family tree of the Old Testament Patriarchs.

Abraham's grandson Jacob (Isaac's son) married two of his first cousins, the sisters Leah and Rachel, who were the daughters of Laban, his (Jacob's) mother Rebecca's brother. The twelve sons and one daughter of Jacob, several of whom arose from third generation consanguineous marriages, were the ancestors of millions of people. Esau, Jacob's twin brother, had three wives, one of whom was Basmat, the daughter of Ishmael, Isaac's half-brother, and therefore his half-first cousin.

Amram married his aunt Jochebed and they were the parents of Miriam, Aaron and Moses. All of the marriages mentioned here are recounted in Genesis or the first part of Exodus, and therefore took place prior to the Book of Leviticus in which the laws against various types of marriages are detailed (see below). Cousin marriage, however, was not banned according to Leviticus.

Later, in the book of Numbers (chapter 36, especially verse 11), it is recorded that the five daughters of Zelophehad – Mahlah, Tirzah, Hoglah, Milcah and Noah – were married to their father's brother's sons – *i.e.* their first cousins. However, some commentators have suggested that some of the spouses were not actual biological first cousins, but merely other members of the same tribe. All these marriages were enacted principally in order for the daughters' inheritances to remain within their father's tribe, since if they had married outside their tribe, these would have passed to their husbands' tribes. This was very important in the case of Zelophehad since he had no sons. Also, the daughters of Eleazer married the sons of Eleazer's brother Kish in the time of David (1 Chronicles 23:22).

Regarding the **New Testament**, it is possible that Jesus's mother Mary was the first cousin of her husband Joseph, since it is thought that Mary was Joseph's father's brother's daughter. Joseph had been born as the result of a levirate marriage, which is a marriage in which a brother marries the widow of his deceased brother in order to produce children (levir is Latin for brother-in-law). However, normative Christian doctrine teaches that Jesus was born to Mary as the son of God following a virgin birth, and that therefore he did not have a biological father.

In **Islam**, it is well known that the Prophet Muhammad had 13 wives (Fig. **2**), of whom one, Zaynab bint Jahsh, was his first cousin, the daughter of Umaimah bint

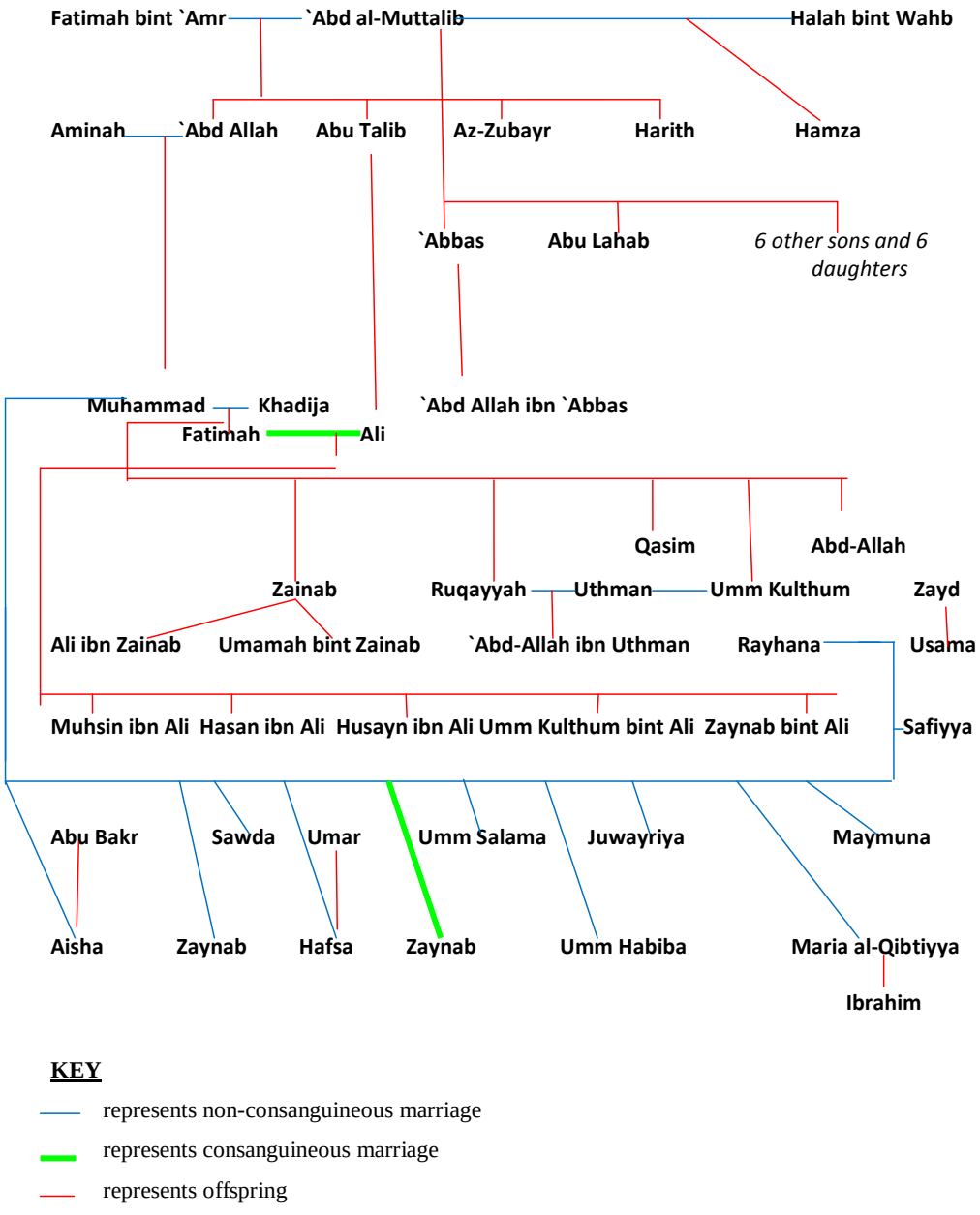


Figure 2: The few consanguineous marriages in the family of the Prophet Muhammad.

Abd al-Muttalib, one of his father's sisters. One of Muhammad's daughters, Fatimah, married her father's cousin – her first cousin once removed – Ali Ibn Abi Talib ibn Abdul-Muttalib, who later became the fourth Rightly-Guided Caliph of

Islam. The second Caliph, Umar ibn al-Khattab, also married his first cousin, Atikah bint Zayd ibn Amr ibn Nufayl. There are no other recorded instances of consanguineous marriages, and it has been suggested that the supposition that Islam favors marriage between close relatives other than the proscribed ones such as siblings, parent and child, uncle and niece or aunt and nephew, is, in fact, erroneous [1]. There are actually no passages in the Koran that can be interpreted as encouraging consanguineous marriages; indeed, the Islamic faith actually discourages such unions, and Muhammad, the prophet of Islam, in his Traditions in fact stated: "Alienate the sibling spousal" [2].

Considering the excessively high prevalence of consanguineous marriages among the Old Testament Patriarchs (Fig. **1**), as well as the other instances of consanguineous and incestuous unions recorded in the Old Testament (see above), and the discouragement of such unions in the Koran, it is very interesting that in the contemporary world, the opposite is the case. The rate of consanguineous marriages among Jews originating from the Western world and most Jews currently living in Israel regardless of origin is extremely low (it used to be higher among Jews originating from Eastern countries – see Chapter 2), whereas among many Muslims, the rate is extremely high, reaching over 50% in some countries (Chapter 2). Reasons for the high prevalence among Muslims are mainly associated with social and economic factors within traditional societies (described in more detail in Chapter 3).

A comprehensive account of inbreeding practices in earlier civilizations is given by Ludovici in a paper on eugenics and consanguineous marriages, read before the Eugenics Society in July 1933 [3]. It describes both incestuous and consanguineous marriages practiced by many peoples in ancient times, including Persians, Phoenicians, Assyrians, Scythians, Tartars, Egyptians, Jews, Greeks, Siamese aristocracy, Burmese, Cambodians, Mongols, and some Peruvian Sapa Incas.

In **ancient Greece**, Spartan King Leonidas I was married to his half-niece Gorgo, daughter of his half-brother Cleomenes I. Greek law allowed marriage between a half-brother and half-sister provided that they had different mothers. Some accounts say that Elpinice was for a time married to her half-brother Cimon.

Ancient Egypt

In **ancient Egypt** the practice of both incestuous and consanguineous unions can be traced back to the pre-Christian era. A fascinating glimpse into the consanguineous practices of ancient Egyptians is given in a paper published in 1919 by Ruffer [4]. This paper, although written before the advent of contemporary genetics, did, however, come after the re-discovery of Mendel's work, but even so, no reference whatsoever is made in the paper to Mendel's theories. The paper opens with the comments: "The question of the effect on the offspring of marriage between blood relations is still an open one. Whereas the view that the children of consanguineous marriages are likely to be weak and to be the bearers of some congenital defect is widely held, some students of heredity maintain that the facts on which this view is based are not convincing; and it must be admitted that, from the same data, divergent conclusions have been drawn". However, Ruffer does note that "As consanguineous unions were so common, the evil results should have been numerous and have attracted popular notice. Yet, as far as I know, no such observations are recorded in Egyptian literature". The paper gives historical accounts of incestuous and consanguineous marriages in various different cultures, and then describes in great detail the Egyptian practices. Among the **eighteenth Dynasty** kings, Queen Aahotep I's first husband was certainly her brother, while her second husband was a relative and possibly also a brother. Her son, Ahmose I, who was thus the son of an incestuous union, married his sister or half-sister, Nefertari. Amenhotep I, son of Ahmose I, married his sister, Aahotep II. One of his daughters, Aahmes, married her half-brother, Thutmose I. This marriage produced among others a daughter, Queen Hatshepsut I, who married her half-brother, Thutmose II. Thutmose III, Hatshepsut's nephew and step-son, married his half-sister, Meryt-Ra Hatshepsut, Queen Hatshepsut's daughter. This dynasty continued for several more years, and Ruffer commented that: "In these nine generations, issued from consanguineous marriages, there is no diminution of mental force", and also that: "There is no evidence to show that idiocy, deaf-mutism, or other diseases generally attributed to consanguineous marriage, ever occurred among the members of this dynasty, and as far as can be ascertained from mummified bodies, masks and statues, the features of both men and women were fine, distinguished and handsome" [4].

The kings and queens of the **nineteenth Dynasty** were probably lineal descendants of those of the eighteenth Dynasty [4]. Ramses II, the great historical figure of this dynasty, married two of his sisters, and is also said to have married two of his daughters, but the evidence on this point is not conclusive. Merenptah, the son of Ramses II by his first sister, married Ast-Nefert II, most probably his sister. In the **twenty-first Dynasty**, consanguineous marriages were common, but marriages between brother and sister very few. The **Ethiopian Dynasty** also engaged in close intermarriage; Queen Amenertas married her brother Piankhi II, and their daughter, Shepenapt III, married her half-brother, Taharka [4].

In ancient Egypt, royal women carried the bloodlines, and so it was an advantage for a pharaoh to marry either his sister or half-sister. A paper by Ager in 2005 details the extensive incestuous unions in the last **Ptolemaic dynasty** of ancient Egypt, whose rule lasted for 275 years from 305 BC to 30 BC [5]. The first sibling-marriage in the Ptolemaic dynasty was between Arsinoë II and her paternal half-brother Ptolemy Keraunos. Arsinoë II later married her full-brother Ptolemy II Philadelphos, but neither marriage produced any children; Ptolemy II's son Ptolemy III was from a previous marriage. Ptolemy III married his half-first cousin, Berenike II, daughter of Magas of Cyrene, and their son, Ptolemy IV, married his full-sister, Arsinoë III. This marriage produced a son, Ptolemy V, who was thus the first product of a Ptolemaic full-sibling marriage. Ptolemy V, an only child, married his third cousin, Cleopatra I, and this union produced two sons and one daughter. The older son, Ptolemy VI, married his full-sister, Cleopatra II, and they had three or four children, one of whom was Ptolemy VII. Ptolemy VI died young, following which his sister/widow Cleopatra II married her other brother, Ptolemy VIII. They had a son, Ptolemy Memphites. Subsequently Ptolemy VIII fathered a son with Cleopatra II's daughter by Ptolemy VI, Cleopatra III (Ptolemy VIII's niece twice over). He then married Cleopatra III and together they had several more children. The later Ptolemaic generations also engaged in incestuous marriages [5].

It is very interesting that in spite of the extensive occurrence of incestuous marriages in ancient Egypt, apparently none of the offspring, even those of full-brother/full-sister marriages, suffered from any demonstrable genetic diseases even though for full-brother/full-sister unions the coefficient of inbreeding is 0.25

and the number of shared genes is one half (50%). Ruffer alluded to this when he stated that: "In these nine generations (of the eighteenth Dynasty), issued from consanguineous marriages, there is no diminution of mental force", and also that: "There is no evidence to show that idiocy, deaf-mutism, or other diseases generally attributed to consanguineous marriage, ever occurred among the members of this dynasty" (see above), but he did not offer any explanations as to why this might be the case [4].

Two prospective studies reporting on the follow-up of children from incestuous unions found a very different situation. One described 13 offspring of incestuous unions, six father-daughter and seven brother-sister, of whom only five were reported as being normal [6]. Of the others, three had died, of cystic fibrosis, progressive cerebral degeneration with blindness and Fallot's tetralogy respectively, and five were mentally retarded, one severely. The other report described 18 offspring of incestuous unions, 6 father-daughter and 12 brother-sister [7]. Seven of the 18 were normal, but the remaining 11 had died or suffered from some degree of morbidity. Of these, one died from glycogen storage disease, one had a bilateral cleft lip, two were severely retarded with epilepsy and cerebral palsy, and three were less severely retarded. The remaining four all died in the first few months of life from serious diseases.

It is, of course, possible that the offspring of the incestuous marriages in ancient Egypt did actually suffer from certain genetic diseases, which obviously would not have been diagnosable then, but such diseases, if they were present at all, could not have been too severe or incapacitating since all the personages described appeared to be healthy and to function normally [4]. Alternatively, one might question the veracity of the reports of such extensive incestuous marriages, but so much evidence exists that they did take place that this is almost certainly not an explanation either. Another theory – that maybe they killed defective offspring – is also extremely unlikely, since in Egyptian households, at all social levels, children of both sexes were valued and there is no evidence of infanticide [8]. In fact, the religion of the ancient Egyptians forbade infanticide.

Famous People

Henri Marie Raymond de Toulouse-Lautrec-Monfa was the firstborn child of Comte Alphonse de Toulouse-Lautrec-Monfa and Adèle Tapié de Celeyran. The

Comte and Comtesse were first cousins (Henri's two grandmothers were sisters) and Henri suffered from congenital health conditions sometimes attributed to this consanguinity. In his teens Henri fractured both his femurs and the breaks did not heal properly. This has been attributed by modern physicians to an unknown genetic disorder, possibly pycnodysostosis, which is transmitted by autosomal recessive inheritance and is also sometimes known as Toulouse-Lautrec Syndrome, or another condition such as osteopetrosis, achondroplasia, or osteogenesis imperfecta, which are transmitted by autosomal dominant inheritance. Rickets associated with praecox virilism has also been suggested. His legs stopped growing, so that as an adult he was extremely short. He had an adult-sized torso, but child-sized legs.

There are very many examples in contemporary times of famous people who married relatives. Some of the better-known include Charles Darwin, who married his first cousin, Emma Wedgwood. In addition, their grandparents, Sarah Wedgwood and Josiah Wedgwood, were third cousins (see below). Other examples include Johann Sebastian Bach, who married his second cousin Maria Barbara Bach; Albert Einstein, whose second wife, Elsa Löwenthal née Einstein, was both his first cousin through his mother and second cousin through his father; Jerry Lee Lewis, rock and roll musician, who married his first cousin once removed, Myra Gale Brown, and H. G. Wells, author, whose first wife, Isabel Mary Wells, was his first cousin. A full list can be found in the Wikipedia website "List of coupled cousins", link: http://en.wikipedia.org/wiki/List_of_coupled_cousins.

Among royalty, the list is extremely long, since it has generally been deemed inappropriate for royals to marry commoners. The later generations of British royals have to a large extent broken this pattern, with Prince William's wife Kate Middleton being of totally non-royal heritage. Although William's parents, Prince Charles and Lady Diana Spencer, were related, the relationship is so far distant (7th cousins once removed through their mutual ancestor William Cavendish, 3rd Duke of Devonshire who died in 1755) that from a biological point of view it is not relevant. However, Charles's parents, Queen Elizabeth II and Prince Philip, are related – they are second cousins once removed through Christian IX of Denmark and third cousins through Queen Victoria. A full list of royal

consanguineous marriages can be found in the Wikipedia website "List of coupled cousins", link: http://en.wikipedia.org/wiki/List_of_coupled_cousins

One of the most famous examples of a genetic disorder associated with royal family intermarriage is the House of Habsburg, in which consanguineous marriages were particularly frequent. The condition in this family is a type of mandibular prognathism, known as the 'Habsburg jaw', 'Habsburg lip' or 'Austrian lip'. Many Habsburg relatives over a period of six centuries had this condition, which progressed through the generations to the point that the last of the Spanish Habsburgs, Charles II of Spain, was unable to chew his food properly.

In addition to the jaw deformity, Charles II also had a large number of other genetic physical, intellectual, sexual, and emotional problems. It is thought that the simultaneous occurrence in Charles II of two different genetic disorders – combined pituitary hormone deficiency and distal renal tubular acidosis – might explain most of the complex clinical problems of this king, including his impotence/infertility that led to the extinction of the dynasty.

Francis II, from the house of Habsburg-Lorraine, married his double first cousin Maria Theresa and several of their children had what were probably genetic health problems. Their daughter Marie Anne suffered from a hideous facial deformity and was also mentally deficient. Their son Ferdinand, who became an emperor, was also mentally deficient and in addition suffered from hydrocephalus, which resulted in an enlarged head and several seizures every day. Another five of the children of Francis II died in infancy or early childhood.

Another famous genetic disease among European royalty was hemophilia. However, this is an X-linked condition transmitted by a carrier mother, and therefore is not associated at all with consanguinity, although rare cases of hemophilia in girls (not including Queen Victoria) can occur from marriages between hemophiliac men and their cousins. In spite of this, because the progenitor, Queen Victoria, was in a first cousin marriage, it is often mistakenly believed that the consanguinity did play a part.

Charles Darwin (1809 – 1882) was an English naturalist who developed the theory of evolution and the concept of "natural selection". He proposed that

natural selection was the "basic mechanism of evolution", and his work established evolutionary descent with modification as the major scientific explanation of diversification in nature. According to Darwin, because many more individuals of each species are born than can possibly survive, there is a frequently recurring struggle for existence and therefore any individuals possessing traits that are advantageous relative to the general population of the species will have a better chance of surviving, and thus be naturally selected. These genetically advantaged individuals will then propagate their new and modified form. Darwin's book, "On the origin of species", in which he delineated his theory with compelling evidence for evolution, was published in 1859 [9].

Darwin married his first cousin, Emma Wedgwood, and they had 10 children. Of these, two died in infancy (one, the last-born, who may also have had Down's syndrome, from scarlet fever, and the other from an unknown cause), and one died aged 10 years from tuberculosis. Six of the surviving seven married, but three of those marriages bore no children, suggesting that his children suffered from infertility. Not only were Darwin and his wife first cousins, but his mother's parents were third cousins, and it has been calculated that for 6.3% of their genetic sequences, Darwin's children inherited the same DNA from their mother and father. This may well explain both the high rate of infertility among his adult children and the death from childhood infectious diseases in at least two of the three who died in childhood, since it has been shown that homozygosity is strongly associated with childhood mortality resulting from invasive bacterial diseases [10]. However, one son, George Darwin, went on to become an eminent astronomer and mathematician and he authored various papers on consanguineous marriages [11], while two of his brothers, Francis and Horace, became a botanist and a civil engineer respectively. All three were Fellows of the Royal Society.

Gregor Mendel (1822 – 1884) is known as the "father of modern genetics". Although his work was not connected in any way with consanguinity or the concept of "related unions" in plants, a short account is given here since it demonstrates the role of recessive genes, which, as described below, are responsible for many of the problems associated with consanguineous marriages among humans. Mendel carried out his original experiments on pea plants. Between 1856 and 1863 he cultivated and tested some 29,000 pea plants (*Pisum*

sativum), and discovered that one in four had purebred recessive alleles, two out of four were hybrid, and one out of four were purebred dominant. As a result of these experiments he made two generalizations: the Law of Segregation and the Law of Independent Assortment, which later became known as Mendel's Laws of Inheritance. Even though his paper, Versuche über Pflanzenhybriden (Experiments on Plant Hybridization) [12] was received favorably and generated reports in several local newspapers, his work was unfortunately largely ignored for around 35 years since it was seen to be essentially about hybridization rather than inheritance, and it was not until the early 20th century that the importance of his ideas was finally realized [12].

LEGAL ASPECTS

Legal Definition

"Consanguinity is the degree of relationship of family members who share at least one common ancestor. It is the blood-relationship (cognatio naturalis), or the natural bond between persons descended from the same stock. When persons are related by a direct line of descendancy from a common ancestor, it is called lineal consanguinity. When persons are related by descendancy from a common ancestor, but not in a direct line, it is called collateral consanguinity" (US Legal, Inc. http://uslegal.com/).

Consanguinity is an important legal concept in that many jurisdictions consider it not only as a factor in deciding whether two individuals may marry – for example, marriage between people in incestuous relationships is not allowed – but also whether a given person receives property when a deceased person has not left a will.

According to the law of some countries, the prohibition is limited to the defined incestuous relationships, while uncle/niece unions are permitted, whereas other countries prohibit all these relationships.

In the **United States of America**, thirty-one states still have laws forbidding first-cousin marriages; three of these, Kentucky, Maine and Texas, enacted the relevant law quite recently (in 1946, 1985 and 2005 respectively). One state, Colorado,

enacted this law during the 1860's but later repealed it, and 18 states have never had legislation banning first-cousin marriages [13].

No **European countries** have current laws banning first-cousin marriages, although such legislation did exist in certain countries in the past, such as Austria, Hungary, Sweden and Spain. Among indigenous Europeans the custom is generally not popular, although England maintained a small but stable proportion of cousin marriages for centuries [14]. The rates for Europe are on the whole extremely low.

Among **African countries**, in **Rwanda**, a Presidential Decree was enacted in 1992 whose principal provisions relate to civil marriage, but which also prohibits consanguineous marriages down to the seventh line of the family tree [15]. In **Ethiopia**, among the Christian community, traditionally the groom's parents search for a bride for their son, but before they make any contact with the would-be bride's parents they investigate to ensure that the families are not related by blood. In the past they checked back seven generations, but now five generations is acceptable (Ethiopian Treasures). In **Nigeria**, among the Ibos, Yorubas, Ijaws and Itsekiris, once a blood relationship can be traced between the parties, most systems of customary law prohibit their marriage. Sometimes, if the blood relationship is distant and not directly traceable, such a marriage may be allowed after the giving of sacrifices, which are regarded as severing the relationship and thereby leaving the parties free to intermarry (Online Nigeria – Community Portal of Nigeria).

Contrary to the situation in many Western counties, certain **Asian countries**, such as **Taiwan** and both **North** and **South Korea**, do prohibit first-cousin marriage [13]. The 1981 Marriage Law of the **People's Republic of China** prohibits marriage between couples related as first cousins or closer [16].

RELIGIOUS ASPECTS

Different religions have different traditions regarding consanguineous marriages. The **Muslim** religion permits marriages between first cousins, including double first cousins, but not those between uncle and niece or aunt and nephew. The

proscribed and permitted unions are described in the Koran, Sura 004, Al-Nisa, verse 023. This states: "Prohibited to you (for marriage) are: Your mothers, daughters, sisters, father's sisters, mother's sisters, brother's daughters, sister's daughters, foster-mothers (who gave you suck), foster-sisters, your wives' mothers, your step-daughters under your guardianship, born of your wives to whom ye have gone in – no prohibition if ye have not gone in; (those who have been) wives of your sons proceeding from your loins, and two sisters in wedlock at one and the same time, except for what is past; for Allah is Oft-forgiving, Most Merciful".

In **Judaism**, both first-cousin and uncle-niece marriages are allowed, but not those between aunt and nephew. The proscribed unions are based on Leviticus Chapter 18 verses 6 – 18. Verse 6 states "None of you shall approach to any that is near of kin to him, to uncover their nakedness" and verses 7 to 18 detail the exact nature of the relationships that are forbidden. These include: father; mother; half-sister (daughter of father or daughter of mother); son's daughter and daughter's daughter (*i.e.* granddaughter); father's sister, and mother's sister. There are also other forbidden unions, but these are not consanguineous. No special reference is made to sexual relations with a daughter or with a full sister; however, according to the Talmud, even though these relationships are not specifically mentioned, scholars have deduced from analysis of various other Biblical chapters that these unions are, in fact, prohibited.

In the **Roman Catholic Church**, unwittingly marrying a closely-consanguineous blood relative is grounds for an annulment. The Canon law of the Roman Catholic Church in fact annulled marriages between first cousins and banned marriages within the fourth degree of a consanguineous relationship from around 1215, and even though dispensations could be granted to get around legal barriers, they became harder to get the closer the couple were related.

The **Church of England** traditionally follows the rules set out in the Book of Common Prayer, which includes a "Table of Kindred and Affinity". This details which relationships are permitted and which are not. In brief, proscribed relationships for men comprise mother, daughter, grandmother (either maternal or paternal), son's daughter or daughter's daughter (*i.e.* granddaughter), sister,

father's sister, mother's sister, brother's daughter, sister's daughter. Other unions are also prohibited but these are not consanguineous [17].

Relationships forbidden to women comprise father, son, grandfather (either maternal or paternal), son's son or daughter's son (*i.e.* grandson), brother, father's brother, mother's brother, brother's son, sister's son. Other unions are prohibited also but these are not consanguineous. In all cases, the term "brother" includes half-brother, and the term "sister" includes half-sister.

Until the 20th century the **Russian Orthodox Church** explicitly prohibited marriage within seven degrees of kinship. Many Old Believer groups maintain the prohibition to this day. Nevertheless, sexual relations between in-laws were fairly common in Imperial Russia.

In the **Cypriot Orthodox Church**, marriages are not allowed between second cousins or closer and between second uncles/aunts and second nieces/nephews (between first cousins once removed) or closer. Additionally, marriages that produce children that are closer genetic relatives than legal are also not permitted.

Different groups of **Hindus** have different laws about consanguineous marriages. The **Aryan Hindus** of Northern India forbid marriage between biological kin for approximately seven generations on the male side and five generations on the female side, whereas **Dravidian Hindus** of South India strongly favor marriage between first cousins of the type mother's brother's daughter (MBD) [18, 19]. Also, particularly in the states of Andhra Pradesh, Karnataka and Tamil Nadu, uncle-niece marriages are widely contracted [19]. Cross-cousin marriage was recognized in the Hindu Marriage Act of 1955, although this Act banned uncle-niece marriages. However, the legality of uncle-niece unions was subsequently confirmed in the Hindu Code Bill of 1984 [16, 20, 21]. In southern Asia, **Buddhism** permits marriage between first cousins, whereas the **Sikh** religion forbids consanguineous marriage, although some minority Sikh groups appear to be somewhat flexible in their observance of this prohibition [19]. The **Zoroastrian**/**Parsi** tradition permits first-cousin marriage [16].

GENETIC ASPECTS

Genetic Definition

The GeneReviews Glossary (GeneReviews Website: http://www.ncbi.nlm.nih.gov/books/NBK1116/) gives the definition of consanguinity as "Genetic relatedness between individuals descended from at least one common ancestor".

Population Genetics

Another name for consanguinity is **inbreeding**, which is defined as reproduction from the mating of two genetically related parents. Inbreeding results in increased homozygosity, which can increase the chances of offspring being affected by recessive or deleterious traits. This generally leads to the decreased fitness of a population, which is called **inbreeding depression**. However, it has recently been suggested that inbreeding depression, which is defined as the deleterious effects that result from matings between related individuals, may be associated with epigenetic mechanisms rather than DNA sequence alterations [22]. Most studies have indicated that inbreeding depression in humans is moderate in effect and can conveniently be analyzed by studying the "genetic load", *i.e.*, the reduction in fitness due to deleterious genes maintained in the population by mutation in the face of elimination by natural selection [23].

The **inbreeding coefficient**, **F**, is the probability that two genes at any locus in one individual are identical by descent, *i.e.* have been inherited from a common ancestor. F is larger the more closely related the parents are (Table **1**). The mean population coefficient of inbreeding (α) is calculated according to the formula $\alpha = \Sigma p_i F_i$ where p_i is the proportion of couples in each consanguinity class F_i. The method of calculating F is Wright's Equation:

$$F_x = \sum \left[\left(\frac{1}{2} \right)^{n_1+n_2+1} (1 + F_A) \right] \quad [24]$$

In a large random-mating population, where the frequency of a harmful recessive gene (a) is q, the proportions of affected individuals and carriers can be estimated from the Hardy-Weinberg Law as follows:

Aa (carriers)	aa (affected)
$2q(1 - q)$	q^2

However, if any inbreeding has occurred, Wright's Equilibrium Law enables a further prediction to be made about the increased risk of inheriting any harmful conditions caused by homozygous recessive genes. The expected frequency following inbreeding rises to:

aa (affected)

$$q^2 + Fq(1 - q) \text{ [24]}$$

Endogamy is the practice of marrying within a specific ethnic group, class, or social group, rejecting others on such bases as being unsuitable for marriage or other close personal relationships. Jewish populations, and particularly the large Ashkenazi Jewish population, exhibit a high degree of endogamy. Today's Ashkenazi Jews are descended from a small group of founders, and for centuries, for political and religious reasons, Ashkenazi Jews were genetically isolated from the population at large. As a result of this, certain disorders tend to be more common among Ashkenazi Jews, due to the "founder effect" and "genetic drift" [25]. Marriage between cousins can be considered as endogamy on a small scale, with the common ancestor(s) providing the founder effect.

Founder Effect

The founder effect occurs when populations start off from a small number of individuals ("founders") of an original population. It is believed that most of today's Ashkenazi Jews are descended from a group of perhaps only a few thousand Ashkenazi Jews who lived 500 years ago in Eastern Europe. Today millions of people can probably trace their ancestry directly to these founders. Thus, even if just a few of the founders had a mutation, the gene defect would become amplified over time. The founder effect of Jewish genetic disorders refers to the chance presence of various defective genes among the founders of today's Ashkenazi Jewish population [25]. Another example is the situation regarding Israeli Arabs. Most live in villages where each village was founded by only a few

original families, and there is only a small proportion of inter-village mating. This results in an increased risk for a genetic founder effect [2].

Genetic Drift

Genetic drift refers to a mechanism of evolution whereby inheritance of a particular gene is enhanced merely by random chance rather than through natural selection. If natural selection were the only active mechanism of evolution, the likelihood is that only "good" genes would persist. However, in a circumscribed population like the Ashkenazi Jews, the random action of genetic inheritance has a somewhat higher probability, compared with that in a much larger population, of allowing certain mutations that do not confer any evolutionary advantage, like the ones causing specific "Ashkenazi" diseases, to become more prevalent. Genetic drift is a general theory that explains why at least some "bad" genes have persisted [25].

Another factor can come into play in those communities that are subdivided into subgroups. When a population is substructured into several cryptic subpopulations, for example caste, excess homozygosity greater than that expected according to Hardy-Weinberg can occur. This is the Wahlund effect, which can also potentially increase the incidence of recessive disorders [26, 27].

Certain population groups that practice endogamy can be broadly considered as one large family from a genetic point of view. Jewish populations, and particularly the large Ashkenazi Jewish population, exhibit a high degree of endogamy. Today's Ashkenazi Jews are descended from a small group of founders, and for centuries, for political and religious reasons, Ashkenazi Jews were genetically isolated from the population at large. As a result of this, certain autosomal recessive disorders tend to be more common among Ashkenazi Jews, due to the founder effect and genetic drift [25]. These disorders, described and listed by Charrow, include many with carrier rates of higher than 1 in 40, such as Gaucher disease (1:14), Tay-Sachs disease (1:30), familial dysautonomia (1:27) and Canavan disease (1:38) [25]. Cystic fibrosis and *DFNB1* congenital deafness have similarly high carrier rates in Ashkenazi Jews, but these are comparable to the rates in the general population.

The Amish community, which was established in Pennsylvania, Ohio and Indiana, form a distinct and biologically isolated community by virtue of their strong cultural and religious beliefs [28, 29]. They originated in Europe and traveled to America in the 18th century. There were only 200-400 original immigrants, but the population has since expanded to around 180,000. First cousin marriages are unusual in this community, but the pattern of many marriages between more distant cousins over 3-4 centuries has led to a high degree of consanguinity. As a result, there are several autosomal recessive diseases with high carrier rates in this community, including Ellis van Creveld syndrome, Mast syndrome, Troyer syndrome and glutaric aciduria type 1, which result from the combined factors of the founder effect and cultural isolation.

Another group, the Hutterian Brethren, or Hutterites, are a closed population with high levels of fertility and consanguinity [30]. They are Anabaptists who originated in the Tyrolean Alps in the 1500s and who immigrated to North America in the latter part of the 19th century. They settled originally mainly in the Dakotas, and as a result of rapid population growth, today there are more than 30,000 contemporary Hutterites living in about 300 colonies in the northern United States and western Canada. Virtually all are descendants of the founding population, who were themselves descendants of less than 90 independent genomes [31]. They are the most inbred population in North America, in which respect they exceed the Amish. Because of the relatively small numbers of immigrant ancestors, strict endogamy and the limited size of the subgroups, there is a high mean coefficient of consanguinity. Studies have shown that the average husband and wife are more closely related than second cousins but not as closely related as first-cousins-once-removed. As a result of the founder effect and cultural isolation, there are many diseases that are common in this population, including autosomal recessive limb-girdle muscular dystrophy.

All the people alive today can trace their ancestry back to about 10,000 people who lived around 175,000 years ago. Therefore, since each of us shares about 99.5% of our DNA with everyone else, in a way we are all related. However, people who share a recent common ancestor share more than 99.5% of their total DNA. The closer the relatives are the more DNA they share, and, conversely, the more distant relatives are the less DNA they share. Although the probability of the

common ancestor having a mutation in any one disease-associated gene is extremely low, such a risk exists for each of the over 20,000 genes in the human genome. Therefore, these offspring are at an increased risk for having homozygous mutations for disease-associated genes as compared with offspring of non-consanguineous parents. Once the relationship is between fourth cousins, the original amount of shared DNA reverts to the basic amount of 99.5%.

It is likely that 80% of all marriages in history have been between second cousins or closer. It is generally accepted that the founding population of *Homo sapiens* was small, anywhere from 700 to 10,000 individuals, and combined with the population dispersal caused by a hunter-gatherer existence, a certain amount of inbreeding would have been inevitable [32].

Individuals whose parents are consanguineous are expected to have an increased proportion of their genome that is homozygous. The more closely the parents are related, the greater this effect is expected to be [33]. The amount of genetic material shared by first cousins is four times higher than that shared by second cousins. First cousins once removed have half the amount of shared DNA as full first cousins, whereas half fourth cousins cannot be detected at the DNA level. Unions between individuals biologically related as second cousins or closer are categorized as consanguineous. Couples related to a lesser degree would usually be expected to differ only slightly from what is observed in the general population; however, in some populations, more distant biological relationships may be clinically significant and cause an increase in the frequency of autosomal recessive diseases due to founder effect, genetic drift and high levels of random inbreeding, such as in Finland [34]. The chance of there being a significant medical problem in the offspring of a consanguineous couple depends on two additive risks: the background population risk and the additional risk due to consanguinity. Within consanguineous populations, a specific recessively inherited disease is often transmitted as a result of just one founder mutation [35].

Generally the most common type of consanguineous union is between first cousins, in which the spouses inherit 1/8 (12.5%) of their genes from a common ancestor. The progeny of such a union are homozygous at 1/16 of all loci and are predicted to have inherited identical genes from each parent at 6.25% of all gene

loci, over the base line level of homozygosity in the general population [16]. The chance that these offspring will inherit an identical gene from each parent, if each parent carries one copy, is 1/4. Thus the risk the offspring will inherit two copies of the same allele is 1/8 × 1/4, or 1/32, about 3 percent. Woods *et al*. determined that theoretical calculations predict that, in a child whose parents are first cousins, 6% of the genome will be homozygous and that the average homozygous segment will be 20 cM in size [36]. They also found that in individuals with a recessive disease whose parents were first cousins, on average, 11% of their genomes were homozygous, and they concluded that this implies that prolonged parental inbreeding has led to a background level of homozygosity increased ~5% over and above that predicted by simple models of consanguinity [36]. The level of homozygosity is higher in unions between double first cousins and uncles-nieces (Table **1**, Fig. **3**) (Fig. **3**: Copyright (2001) Springer. Used with permission from Hamamy H. Consanguineous marriages: Preconception consultation in primary health care settings. J Community Genet 2012; 3: 185-92 [37]).

There are four different types of first-cousin marriages. Marriages between parallel cousins are marriages between children of two brothers or two sisters, whereas cross-cousin marriages are those between the children of one brother and one sister. These various combinations are: mother's sister's daughter (MSD), father's brother's daughter (FBD), mother's brother's daughter (MBD), and father's sister's daughter (FSD). Different types are more prevalent or less prevalent in different communities. It is important to note that, of course, the structure of consanguineous marriages does not affect the coefficient of inbreeding for autosomal genes, since the probability that any one of these genes passes from one to the following generation is independent of the sex of the individuals concerned [38].

Double first cousins arise when two siblings of one family reproduce with two siblings of another family. The resulting children are related to each other through both parents' families. Double first cousins share both sets of grandparents in common and therefore have double the degree of consanguinity as compared with ordinary first cousins. Genetically, they are related to the same degree as half-siblings. However, even though double first cousins have the same coefficient of coancestry as half-siblings, they do have a higher chance of sharing both alleles

and a lower chance of sharing one allele with each other than half-siblings (Table **1**, Fig. **3**) (Fig. **3**: Copyright (2001) Springer. Used with permission from Hamamy H. Consanguineous marriages: Preconception consultation in primary health care settings. J Community Genet 2012; 3: 185-92 [37]).

When identical twins marry siblings, the resulting children are more related than half-siblings but less related than full siblings. Half-siblings share only one parent, and one-and-a-half cousins may be produced when two full siblings have children with two half-siblings.

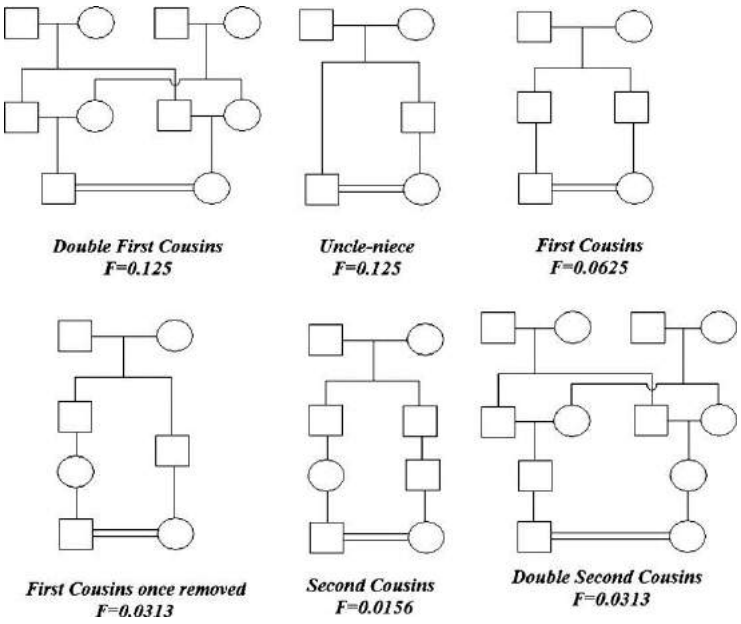


Figure 3: Categories of consanguineous marriages.

Molecular Genetics

Every person has a total of 46 **chromosomes**, arranged as 23 pairs. Of these, 22 pairs control most of the body characteristics and diseases and one pair is responsible for determining sex. The **genes** are situated on the chromosomes, and each chromosome of a pair contains one copy of each gene, so that everybody has two copies of each gene, one inherited from the father and the other from the mother. These corresponding genes are called **alleles**. Even though both alleles determine the same body characteristic or disease, they are not necessarily

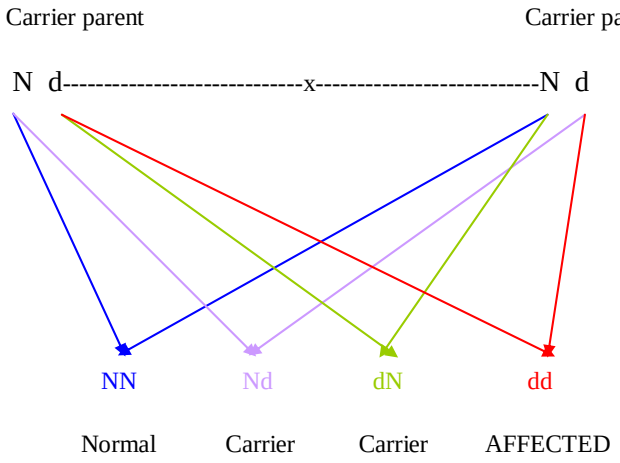
identical and may in fact differ from each other in certain ways. A change in a gene is known as a **mutation**. Mutations in genes may affect the normal function of the gene and the proteins that it encodes and this may cause problems in certain situations.

Table 1: Consanguineous marriage relationships

Biological Relationship	Genetic Relationship	Coefficient of Inbreeding (F)	Number (Percentage) Shared Genes
Father-daughter Mother-son Brother-sister	First degree	0.25	1/2 (50)
Half-siblings Uncle-niece Aunt-nephew Double first cousin	Second degree	0.125	1/4 (25)
First cousin	Third degree	0.0625	1/8 (12.5)
First cousin once removed Double second cousin	Fourth degree	0.03125	1/16 (6.25)
Second cousin	Fifth degree	0.015625	1/32 (3.13)
Second cousin once removed Double third cousin	Sixth degree	0.0078125	1/64 (1.56)
Third cousin	Seventh degree	0.0039	1/128 (0.78)

When a person is a **carrier** of one of the inherited diseases, he has one normal gene and one abnormal gene for the condition. In autosomal **recessive** diseases, the action of the healthy gene predominates over that of the abnormal gene, meaning that only people who inherit two copies of an abnormal gene, one from each parent, will develop the disease. Because of the increased chance that closely related individuals carry the same abnormal gene, the likelihood that their offspring will inherit an abnormal copy of the gene from each parent, and

therefore be affected by the disease, is higher. When both parents are known to be carriers of the same autosomal recessive disease, the risk that the child will be affected is 1:4 (25%) (Fig. **4**). Overall, the risk of having a child affected with a recessive disease as a result of a first cousin mating is approximately 3 percent, in addition to the background risk of 3 to 4 percent that all couples face (Fig. **5**).



KEY: **N** = Normal gene; **d** = abnormal (disease) gene

N N – this person is completely healthy and is not a carrier.

N d – this person is completely healthy but is a carrier.

d N – this person is completely healthy but is a carrier.

d d – this person is affected and suffers from the condition because he or she has received two abnormal genes, one from each parent, and therefore has no normal gene to protect him/her from the deleterious effects of the abnormal genes. These, therefore, are fully expressed.

Figure 4: The possible offspring of a couple when both spouses are carriers of the same autosomal recessive disease.

It used to be thought that new recessive mutations were rare. However, more recently it has been estimated that new mutations in general are, in fact, frequent, and that there have been more than 1.6 new deleterious mutations per diploid genome per generation in the human lineage [39]. While *de novo* mutations are

easily identified in dominant and X-linked recessive disorders, the presence of new autosomal recessive mutations is much more difficult to detect, giving the impression that recessive mutations are rare. However, the actual finding of many unique mutations among patients with autosomal recessive diseases in, for example, Arab populations, is an indirect demonstration that new recessive mutations are not rare [40].

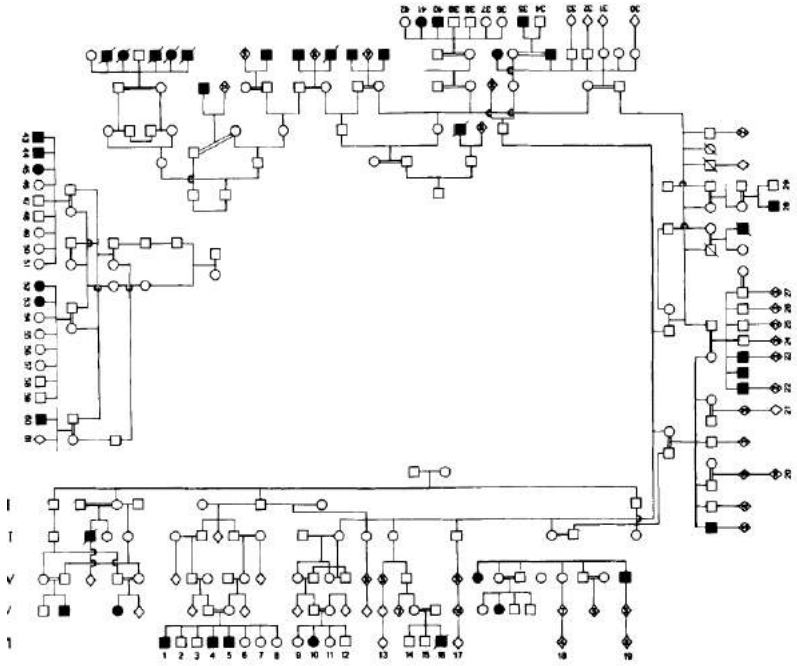


Fig. 1. Pedigree.

KEY: Double lines between spouses indicate consanguineous unions.

Black squares/circles indicate affected males/females.

Figure 5: Pedigree of an extended family with multiple consanguineous marriages in which many family members suffer from arthrogryposis multiplex congenita, an autosomal recessive disorder. (Copyright (1995) Wiley. Used with permission from Jaber L, Weitz R, Bu X, Fischel-Ghodsian N, Rotter JI, Shohat M. Arthrogryposis multiplex congenita in an Arab kindred: update. Am J Med Genet 1995; 55: 331-4 [41]).

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CONFLICT OF INTEREST

The authors confirm that this chapter contents have no conflict of interest.

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CHAPTER 2

Prevalence and Epidemiology

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Abstract: The frequency of consanguineous marriages varies from one population to another. Consanguineous marriage is not restricted to specific religions or to population isolates, but is a long-standing practice in many regions of the world and it continues to be preferred by many populations, with more than 1,000 million people living in countries where between 20% and 50+% of marriages are consanguineous. Levels above 5% occur in the northern part of Africa, the Middle East and parts of Asia, whereas in what is described as the "Western world" – *i.e.* the entire North American continent, the whole of Europe (with the exception of Spain), Australia and New Zealand – the frequency is less than 1%. In South America, parts of eastern and south-east Asia, Spain and various parts of Africa the rate is between 1 and 10%. In other parts of the world the frequencies are unknown.

Keywords: Africa, consanguineous marriages, frequency, Middle East, populations.

INTRODUCTION

The frequency of consanguineous marriages varies from one population to another. Consanguineous marriage is not restricted to specific religions or to population isolates, but is a long-standing practice in many regions of the world and it continues to be preferred by many populations. Currently more than 1,000 million people are living in countries where between 20% and 50+% of marriages are consanguineous [1]. Figures from 2009 indicate that some 10.4% of the 6.7 billion global population are related as second cousins or closer ($F \geq 0.0156$) [2]. According to the Population

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Reference Bureau, 2010 World Population Data Sheet, in 2010 there were 140,184,169 births worldwide (http://www.prb.org/pdf10/10wpds_eng.pdf), which leads to the conclusion that around 13.5 million of those children have consanguineous parents.

PREVALENCE

The prevalence varies from country to country. Reviewing a world map reveals that levels above 5% occur in the northern part of Africa, the Middle East and parts of Asia [3]. Denic and Nicholls (2007) show in their Table **2** the overall rates in several different countries as a percentage of the total population of the country [4].

A study by Bittles reports the global prevalence of consanguineous marriages in the year 2000 [5]. In almost the whole of what is described as the "Western world" – *i.e.* the entire North American continent, the whole of Europe (with the exception of Spain), Australia and New Zealand – the frequency is less than 1%. In South America, parts of eastern and south-east Asia, Spain and various parts of Africa the rate is between 1 and 10%, and in most of north Africa, the Middle East and southern India it is between 20 and 50+%. In other parts of the world, predominantly most of sub-Saharan Africa, Central America, Greenland and various islands of south-east Asia, the frequencies are unknown (Fig. **1**).

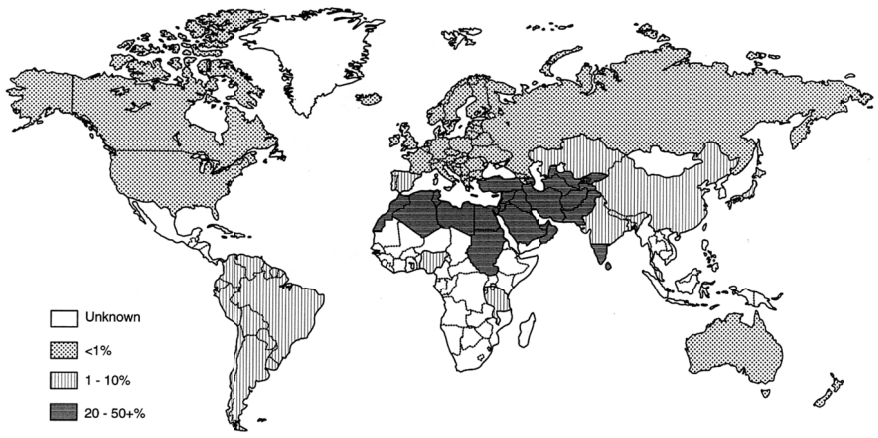

Figure 1: The current global prevalence of consanguineous marriage. (Copyright (2001) Wiley. Used with permission from Bittles AH. Consanguinity and its relevance to clinical genetics. Clin Genet 2001; 60: 89-98. [5]).

The rate is also high among groups of immigrants from Middle Eastern and Asian countries with high rates, and in certain such communities it can be even higher than among the communities in the original countries. Darr and Modell studied a group of British Pakistani mothers in the postnatal wards of two hospitals in West Yorkshire, England, in order to gather information on different marriage patterns [6]. The study was designed to determine whether the frequency of consanguineous marriage was changing with time. Out of a total of 100 women interviewed, 55 were married to first cousins, none of whom were double first cousins. Nine women were married to first cousins once removed, three to second cousins, and three to more distant relatives. Only 17 women definitely had completely unrelated husbands, but for the purpose of the study, 30 of the 100 couples could be considered as genetically unrelated.

An enquiry among 900 women in a hospital in Lahore, Pakistan, in 1983 found 36% first cousin marriages, 4% first cousin once removed, 8% second cousin, and 53% unrelated. These figures are almost identical with those reported by Darr and Modell for the grandparental generation, who married while in Pakistan. These figures support the conclusion that the frequency of close consanguineous marriage is increasing among British Pakistanis [6].

There are several reasons for this, chief among which is constraints imposed by migration. The parents prefer to select someone they know well, and in countries where Pakistanis comprise an ethnic minority group, such as England, there is limited availability of suitable persons in the restricted local community. Therefore, for groups with a tradition of consanguineous marriage, the choice of partner naturally falls progressively closer within the family circle [6].

The Americas and Canada

Even though the overall rate of consanguineous marriages in the **USA** is 0.1 – 0.2%, and in **Canada** 0.3 – 1.5%, the rate is considerably higher among certain isolated population groups such as the Amish. In this community, although first cousin marriages are unusual, the repeated marriages between more distant cousins over 3 – 4 centuries have lead to a high degree of consanguinity [7]. Another group, the Hutterian Brethren, or Hutterites, are a closed population with

high levels of fertility and consanguinity. They are the best defined inbred population in North America, in which respect they exceed the Old Order Amish. Because of the relatively small numbers of immigrant ancestors, strict endogamy and the limited size of the subgroups, there is a high mean coefficient of consanguinity. Studies have shown that the average husband and wife are more closely related than second cousins but not as closely related as first-cousins-once-removed [8].

High rates of consanguinity also occur in many of the Native American communities, such as the Cree Indians in northern Saskatchewan, Canada [9], the Lumbee Indians of North Carolina [10, 11], and Native American groups from Central and South America [12].

In the countries of **South America** the rates of consanguineous marriage are generally fairly low – the lowest are in Argentina (0.29%) and the highest in Venezuela (1.84%) [13]. First-cousin marriages account for slightly less than half of the total consanguineous marriages. However, the rate is high among several groups of Native Americans; for example, among the Karitiana group, who live in the western Amazon region of Brazil, preferential marriage is with cross-cousins [12].

Asia

In **Asian** countries the rate also varies widely – in the Philippines it is low, while in Kyrgyzstan it is 45.2% [14]. Table **1** shows the percentages of consanguineous marriages in countries with high frequencies in Asia and Africa.

Table 1: Percentages of consanguineous marriages in countries with high frequencies in Asia and Africa

Country	First Cousin and Closer (%)	More Distantly Related (%)	References
Afghanistan	34.7	11.5	[49]
Algeria	22 – 40.5		[27, 28]
Bahrain	21	18.4	[44]
Egypt (Cairo)	29		[31]
Egypt (Alexandria)	15.8	7	[32]

Table 1: contd…

India (south)*	13 – 46.3		[15]
India (north)	0.1 – 43.4		[19]
Iran	19		[48]
Iraq	25.3 – 57.9		[41, 42]
Israel SEE TABLE **3**			
Jordan	29.8 – 38	17.3	[33]
Kuwait	32.2	22.2	[38]
	37.8		[39]
Lebanon	31.6	6.2	[45]
Libya	30	18	[29]
Mauritania	30.5 – 74.5		[22]
Morocco	15.25		[25]
Nigeria	51		[23]
Oman	53		[50]
Pakistan	36	12	[6]
Palestinians SEE TABLE **2**			
Qatar	37.9	16.6	[47]
Saudi Arabia	33.6	22.4	[51]
Sudan	49.5	13.8	[20]
Syria	28.7	6.7	[35]
Tunisia	17.4	7.4	[28]
Turkey	16.8	5.2	[52]
UAE**	29.7	20.8	[34]
Yemen	32.0 – 33.9	6.0 – 12.7	[53, 54]

*Predominantly uncle-niece marriages ($F = 0.125$) **UAE = United Arab Emirates

In the **Indian subcontinent**, the rate of consanguineous marriages varies extremely widely according to region. Overall, the lowest rate is in northern India, where it ranges from 0.1 to 43.4%, and the highest is in southern India where it is between 13 and 46.3%. Marriages between biological kin are uncommon in the northern, eastern and northeastern states because of a general prohibition on consanguineous marriage in the majority Hindu population [15]. However, because of their traditional status, consanguineous unions are regarded as

customary for the peoples of southern India (those living south of the Narmada River). As a result of the legalization of certain types of consanguineous marriages, increases in prevalence in the states south of the Narmada have been reported, with the highest rates in Andhra Pradesh, Karnataka and Tamil Nadu. In southern India, uncle-niece marriages are very common [15]. However, a definite decline has been observed in the past three or four decades in Andhra Pradesh and Tamil Nadu, and due to recent changes in the demographic and social situation in these states, this decline in consanguinity appears likely to continue [16].

In Kerala the frequency of consanguineous marriages is very low, partly because of the strict avoidance of consanguineous marriage among members of the Christian Syrian Orthodox church and partly because of lower levels of consanguinity in a long-established local Muslim community. No comparable north-south division exists in the Muslim population of India, and consanguineous marriage is common in all Indian Muslim communities. While consanguineous unions have been reported in all religions, nationally the highest rates are observed in the Muslim and Buddhist communities and the lowest among Sikhs and Jains [15].

In **Pakistan** there has always been a very high rate of consanguineous marriages. A study by Hussain and Bittles in 1998 described the nature and extent of consanguineous marriages in an urban slum in Karachi and compared the findings to those from a Demographic and Health Survey (DHS) carried out in the years 1990 – 1991 [17]. Consanguinity was 58.7% in the Karachi survey and 62.7% in the DHS; 83.6% of consanguineous marriages in the Karachi survey, and 80.4% in the DHS, were between first cousins. The mean coefficient of inbreeding in the children of the generation studied was 0.0316 in the Karachi study and 0.0331 in the DHS, although the actual levels were probably much higher. A total of 69.9% of consanguineous women in the Karachi study, and 79.2% in the DHS study, were women with no formal schooling. Consanguinity was practiced by all three of the religious groups – Muslim, Christian and Hindu – and in both urban and rural areas [17].

Africa

In **Africa**, the prevalence of consanguineous marriages varies according to geography (Table **1**, Fig. **1**). Most of the studies were carried out several years ago

and unfortunately there is a dearth of up-to-date information on the frequency in the various countries. For sub-Saharan Africa, there is scant information. A few examples where studies have been carried out are described below.

Among the **Fulani**, a broad ethnic category of nomadic and seminomadic pastoralists and agropastoralists living in the semiarid **Sahel region of sub-Saharan Africa**, consanguineous marriage is frequent, with first or second cousin marriage preferred [18]. Arranged first marriages are accompanied by the payment of bridewealth, ideally in the form of cattle, and it is suggested that inbreeding may be more frequent when there is a scarcity of cattle available, since bridewealth demands are thought to be reduced with close-kin marriage. Among women's marriages, 66% were consanguineous up to and including second cousins, and 33% were non-consanguineous. Corresponding rates among men's marriages were 71.0% and 28% respectively. It was noted that a significantly higher rate of consanguineous marriage was found in families owning the fewest cattle [18].

Saha and Sheikh conducted a survey in **Sudan** of 4833 marriages comprising 345 from three Nilotic tribes, 302 from two indigenous Negroid tribes, and 4186 from several Arab and other tribes. They found that first cousin unions constituted about half of all the consanguineous marriages, and that the pattern of first cousin marriages was similar in all three groups [19]. In a further study by Saha *et al*. in Sudan in 1990 to study the inbreeding effects on reproductive profiles and morbidity of offspring, it was noted that 49.5% of the women had married their first cousins and 13.8% had married more distant relatives [20].

Also in Sudan, Bayoumi *et al*. tested 298 subjects from the Fur and Baggara tribes of Western Sudan for polymorphism of hemoglobins, seven red cell enzymes, and four serum proteins. They describe both these tribes as being "highly consanguineous", with inbreeding coefficients of 0.04167 and 0.04450, respectively. The authors commented that despite the high degree of inbreeding, no significant deviation from the Hardy-Weinberg equilibrium was observed in either tribe, and the effects of inbreeding appeared to be offset by mixing between the two tribes [21].

In **Mauritania**, a country in the Maghreb bordered by the Atlantic Ocean in the west, Western Sahara in the north, Algeria in the northeast, Mali in the east and southeast, and Senegal in the southwest, consanguineous marriages are extremely frequent, ranging from 30.5% among members of one group to 74.5% among members of a different group [22].

A study in 1974 of the Oka Akoko, a community of approximately 60,000 Yoruba-speaking Nigerians in the Western State of **Nigeria** who practice polygamy and preferentially include both consanguineous and unrelated spouses within each household, found that each man was married to about three wives, of whom about 51% were consanguineous. It is required by custom that at least one wife in each household should be a close relative, and most of the men conform. The relationship of the consanguineous spouse ranges from niece to half first cousin once removed [23]. Consanguinity in Nigeria is also discussed by Olusanya and Okolo in a study of hearing-impaired children [24].

The Middle East and North Africa

In the **Middle East** and **North Africa**, the prevalence of consanguineous marriages is generally high, especially among the Arab communities. Table **1** shows the percentages of consanguineous marriages in countries with high frequencies in Asia and Africa.

In **Morocco** there is a high frequency of consanguineous marriages. Jaouad *et al*. studied the rate of consanguineous marriage in families with autosomal recessive diseases and compared this with the average rate of consanguinity in the Moroccan population. They found that among 176 families with autosomal recessive disorders, consanguineous marriages comprised 59.09% of all marriages, whereas the overall prevalence of consanguinity in Morocco was found to be 15.25% with a mean inbreeding coefficient of 0.0065 [25].

In **Algeria** in 1984, the prevalence of consanguineous marriages was noted by Benallègue and Kedji to be between 22% and 25%, the majority of which were between first cousins [26]. In a more recent survey in the Tlemcen area (West Algeria), unions between cousins represented 34.0% of the marriages. The

frequency of such unions was lower in the urban areas than in the rural areas (30.6% and 40.5% respectively) [27].

A study in **Tunisia** carried out between 1989 and 1990 found that consanguineous marriages represented 24.8% of the unions. Of these, 70.13% were between first cousins [28].

It is estimated that 48% of marriages in **Libya** are consanguineous, and that 30% of the total marriages are between first cousins [29].

In **Egypt**, the practice of not only consanguineous marriages, but also incestuous unions, goes back to the pre-Christian era, and a detailed account can be found in a fascinating paper by Ruffer, written in 1919 (described in more detail in Chapter 1) [30]. In somewhat more modern times, a survey by Hafez *et al*. in 1983 found that the incidence of consanguineous matings in the general Egyptian population was 28.96%, with an average inbreeding coefficient of 0.010. The highest incidence was in the rural areas, and first cousin marriages occurred more often than other types [31]. Another survey found that in Alexandria the prevalence of consanguineous marriages was 22.8%, with the highest frequency being those between first cousins (15.8%) [32].

Khoury and Massad conducted a survey in 1992 in **Jordan**, in which they found that 51.25% of all marriages were consanguineous: 32.8% were among first cousins, 6.8% among first cousins once removed or second cousins, and 10.6% among more distant relatives. The proportion of first cousin marriages was significantly higher among the rural population, where almost 38% of the marriages fell into this category. In urban areas and semi urban areas the rates were 29.8% and 31% respectively. They also noted that comparison with trends in the 1920's indicated that the rate of first cousin marriages has remained stable [33].

A study by al-Gazali *et al*. examined the frequency of consanguineous marriage and the coefficient of inbreeding in the **United Arab Emirates** (**UAE**). The study was conducted between October 1994 and March 1995 and a total of 2033 married women aged 15 years and over participated. The degree of consanguinity

between each couple, and also that between their parents, were recorded. The rate of consanguineous marriage was 50.5%, with the commonest type being that between first cousins (26.2%). Double first cousin marriages were also common (3.5%) in comparison to other populations. The consanguinity rate in the UAE increased from 39% to 50.5% in one generation [34].

Othman and Saadat carried out a survey in order to identify the prevalence and types of consanguineous marriages in **Syria** [35]. A total of 67,958 couples participated, of whom 36,574 were from urban areas and 31,384 from rural areas. The authors found that the overall frequency of consanguinity was 30.3% in urban areas and 39.8% in rural areas, giving a total rate of 35.4%. Lower levels were recorded in the western and north-western provinces as compared with the central, northern and southern provinces. The commonest type of consanguineous marriage was that between first cousins (20.9%), followed by double first cousins (7.8%) and second cousins (3.3%). More distant than second cousins was the least common type [35].

Among **Palestinians**, the rates vary widely according to the country of residence. Table **2** shows the frequencies in the countries surveyed by Pedersen *et al.,* (2002). It is interesting to note that in both Lebanon and Syria, the rate of consanguineous marriages among Palestinians is approximately one third of all marriages in that community, whereas the comparable figure for Palestinians in the West Bank and Gaza is about two thirds of all the marriages – in other words, double the rate in Lebanon and Syria. The rate in Jordan is around 50%, and thus is halfway between the rates in the other areas [36]. A later paper gives the rates for the West Bank and Gaza as being 45% in 2004, with 28% first cousin marriages [37].

Regarding **Kuwait**, Al-Awadi *et al*. surveyed 5,007 Kuwaitis in order to study the incidence of consanguineous marriages during 1983 [38]. They found that the rate of consanguineous marriages of all types was 54.3%, with 30.2% being between first cousins. Double first cousins accounted for 2%, first cousins once removed for 1.32%, and second cousins for 0.77%. The rate for more remote than second cousins was 20.1%. Al-Nassar *et al*. investigated a random sample of 2200 individuals for consanguineous relationships up to the level of second cousins

[39]. Of the participants, 46.8% were Kuwaitis, 20.5% Egyptian, 19.1% Jordanian, and the rest were of various other nationalities. Among the Kuwaitis the rate of consanguinity was found to be 37.8%, whereas among the Egyptians it was 23.3% and the Jordanians 36.2%. In the Kuwaiti population, 2.3% of the marriages were between double first cousins. It was also found that the rate was higher among the younger Kuwaitis. Teebi noted that the most frequent form of consanguineous marriage among Kuwaiti citizens was that between first cousins, particularly paternal first cousins, but that double first cousin marriages also exist [40].

Table 2: Rates of consanguineous marriages among Palestinians according to country of residence (Figures from Pedersen [36])

	Double First Cousins (%)	**First Cousins (%)**	**More Distantly Related (%)**	**Unrelated (%)**
Lebanon	2.9	16.9	12.5	67.7
Jordan	3.8	22.3	20.9	52.9
West Bank (Judea & Samaria)*	27.2		38.9	33.7
Gaza*	31.6		31.9	36.5
Syria	3.1	15.2	12.3	69.5

*The surveys for the West Bank and Gaza did not differentiate between double first cousins and first cousins, so the figures for those areas are for both of these types of marriages combined.

In the Dohuk region of Northern **Iraq**, a study of the mutations found in patients with β-thalassemia noted that the rate of consanguineous marriages in that area was estimated at 25.3%, according to a recent unpublished regional health survey [41]. Another study reported the overall consanguinity rate in Iraq as being around 57.9% [42].

A survey carried out in Western Iraq in order to study the association of consanguinity as a risk factor for congenital heart disease found that this was indeed the case. Overall, consanguinity was found in 78% of cases and 43.3% of controls, of which first cousin marriages comprised 66.2% in cases and 35.6% in controls [43].

A study of the genetic diseases prevalent in **Bahrain** included a survey in which a group of 500 young, married Bahraini women each completed a standard questionnaire, which included questions about the relationship of the husband and wife and also about the relationship of their parents. The rate of cousin marriage was 39.4% in the current generation and 45.5% in the previous generation, indicating a high rate of consanguinity that decreased significantly over time. The rate of first-cousin marriage was 21% [44].

In a study in **Lebanon**, Barbour and Salameh gave questionnaires to 1556 women in order to determine the prevalence of consanguineous marriages in Beirut and in other parts of Lebanon [45]. They found that overall 35.5% of all marriages were consanguineous, with first-cousin unions accounting for 31.6% and second-cousin marriages for 3.9%, while 2.3% were between partners with lower degrees of consanguinity. The highest rates of consanguineous marriages were found among people living in suburbs of Beirut, those in which the women worked in the home, and non-Christians. The rates among the Muslim and Druze communities (approximately 46%) were significantly higher than those among the Christian community (approximately 20.5%).

A recent report by Medlej-Hashim *et al*. [46] described a very large consanguineous Lebanese family – comprising the entire population of one village – in which 461 family members are descendants of four brothers who settled in the village around 500 years ago. The village is, in fact, a sort of genetic isolate due to the frequent consanguineous marriages. In this family the prevalence of familial Mediterranean fever (FMF) is 1:7. Among 31 FMF patients and 32 healthy individuals from this family who were studied, five different mutations were detected. Reasons suggested for the co-occurrence of this relatively high number of mutations in one family include multiple founder effects, fusion with additional groups and subpopulations or "*de novo*" mutations [46].

A survey in **Qatar** by Bener and Alali (2006) found that the rate of consanguinity in the present generation was high (54.0%) with a coefficient of inbreeding of 0.02706. The commonest type of consanguineous marriage was between first cousins (34.8%); double first cousin marriages, which comprised 3.1%, were also

common compared with other populations. In one generation the consanguinity rate in the State of Qatar increased from 41.8% to 54.5% [47].

A study carried out in **Iran** by Akrami *et al*. (2008) surveyed 400 individuals attending the diabetes and osteoporosis clinic in Shariati Hospital, Tehran [48]. The purpose of the study was to examine the trend in consanguineous marriage across three generations of Iranians. The authors studied data on consanguinity status for 1789 marriages within the index cases' families; generation 1 consisted of marriages contracted before 1948, generation 2 comprised marriages contracted between 1949 and 1978, and generation 3 consisted of marriages contracted after 1979. The prevalence of consanguineous marriages within these three generations was reported as 8.8%, 16.6% and 19%, respectively, and represented a significant trend ($p<0.001$). The commonest type of consanguineous marriage was that between first cousins (69%) [48].

In a recent study in **Afghanistan** of the prevalence and types of consanguineous marriages among populations from different regions of the country, Saify and Saadat reviewed by means of a questionnaire data on the types of marriages contracted by 7140 couples [49]. The authors found that the overall frequency of consanguineous marriages was 46.2%, ranging from 38.2% in Kabul province to 51.2% in Bamyan province. First cousin marriages, which accounted for 27.8%, were the most common type, followed by double first cousin (6.9%), second cousin (5.8%), beyond second cousin (3.9%) and first cousin once removed (1.8%).

In **Oman**, consanguinity is very common. In a study to determine whether consanguinity played a significant role in the etiology of recurrent spontaneous miscarriage, Gowri *et al*. studied 141 patients [50]. They ascertained that 53% of the women had a consanguineous marriage, 42% were non-consanguineous, and in 5% the marital interrelationship was not known.

A study was conducted between 2004 and 2005 by El-Mouzan *et al*. in 13 regions of **Saudi Arabia** in which the mother of each household was asked about the relationship to her husband [51]. She was asked to choose one of three answers: first cousin, more distant relationship, or no relation. The authors found that the

overall prevalence of consanguinity was 56%, with first-cousin marriages, which were 33.6% of the total, being more common than all the other types of relationships (22.4%). The overall prevalence was more common in rural (59.5%) than in urban (54.7%) areas. The prevalence was high in some regions, such as Madina (67.2%), and lower in others, such as Al-Baha (42.1%).

The situation in **Turkey** was analyzed in detail by Koc [52]. The overall rate of consanguinity according to the latest available figures (2003) was 22% for the country as a whole, but this varied from region to region. The lowest rate was in West Marmara (9.8%) and the highest in south-east Anatolia (41.6%). Regarding ethnicity, when both spouses were of Kurdish origin the frequency of consanguineous marriages was higher – 45% – as compared with couples where either both spouses were Turkish (18%), or one of the spouses was Turkish (19%). Among the consanguineous marriages, 16.8% were between first cousins, 3.3% between second cousins, and 1.9% between more distant relatives [52].

In **Yemen**, consanguinity rates appear to be increasing in the current generation. In a survey conducted in 1997 by Jurdi and Saxena, the overall consanguinity rate was 39.9%; first-cousin marriages accounted for 33.9%, while the remaining 6.0% were marriages between more distant relatives [53]. A more recent survey was carried out in 2000 by Gunaid *et al*. in order to ascertain the rate of consanguineous marriages in Sana'a City, the capital of Yemen. The authors interviewed a total of 1050 couples regarding their relationship to each other, and found that the total incidence of consanguinity was 44.7%, with first-cousin marriages constituting 71.6% of the total consanguineous marriages and 32% of all marriages [54].

The situation in **Israel** is interesting as the rates of consanguineous marriages vary markedly among the different religious groups that make up the population of that country (Table **3**). A survey conducted in 1992 by Jaber *et al*. found that among **Muslim Arabs** 44.3% of all marriages were consanguineous, with 23% being between first cousins or closer [55]. Another study carried out in the same year by Vardi-Saliternik *et al*. found a similar rate (42% of all marriages) [56]. A later study by Jaber *et al*. determined the rate of consanguineous marriages in four Arab residential locations in Israel, and found that during the period 1981 – 1990

the rate was 36.0%, whereas by the period 1991 – 1998 this had fallen to 32.8% [57]. A more recent study by Sharkia *et al*. compared the rates in four Arab villages in Israel over two time periods and found that the average rate in the period 1980 – 1985 was 33.1% (range over the four villages 18.8% – 44.9%), while during the period 2000 – 2004 it had decreased to 25.9% (range 13.5% – 40.3%) [58].

Among **Christian Arabs** in Israel, the rate of consanguineous marriages is and has always been lower than that among Israeli Muslims. According to a study by Jaber *et al*. in 1992, the rate was 32% [55], while Vardi-Saliternik *et al*., in a survey carried out between 1990 and 1992, found a rate of 22% [56]. The rate among the **Druze** population was 47% [56].

The **Samaritan** community is a distinct religious and cultural sect, which traces its ancestry back over more than 2000 years. It is one of the oldest and smallest ethnic minorities in the world, with only around 650 individuals in the entire community today [59]. The numbers declined over the years and in the mid-nineteenth century there were only 122 individuals. However, the numbers then started to increase again, and they now live in two localities situated about 20 miles apart in the same geographical region where they have always lived and never left.

Throughout their history, the Samaritans have maintained an endogamous marriage system practiced both within the limits of the community and also often within the family. The community is highly inbred with 84% of marriages being between either first or second cousins, and their mean inbreeding coefficient, 0.0618, is the highest recorded for any human population [60]. The gene pool of the present day population derives from only 45 founders.

Among the Israeli **Jewish** population, the rate of consanguineous marriages is very much lower, and approximates that in Western countries. A survey by Cohen *et al*. carried out between 1990 and 1992 found that the overall rate was 2.3%, of which 0.8% were between first cousins [61]. However, there were wide differences between the various sub-divisions of the Jewish community; among

Jews who originated in the Middle Eastern countries the overall rate was 7.1%, whereas among Ashkenazi Jews, who are of European origin, the overall rate was 1.5%.

Table 3: Rates of consanguineous marriages among Israelis according to religion

Israeli Population	First Cousins and Closer (%)	More Distantly Related (%)	References
Muslim Arabs (1980-1985)	18.8 – 44.9		[58]
Muslim Arabs (1992)	23	21.3	[55]
	42		[56]
Muslim Arabs (2000-2004)	13.5 – 40.3		[58]
Christian Arabs (1992)	32		[55]
	22		[56]
Druze (1992)	47		[56]
Samaritans (1980)	84		[60]
Jews (1992)	0.8	1.5	[61]

The general rates of consanguinity among those populations in whom such marriages are preferred are still extremely high. Chapters 7 and 8 describe future strategies for attempting to reduce these rates.

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CONFLICT OF INTEREST

The authors confirm that this chapter contents have no conflict of interest.

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CHAPTER 3

General Health Topics Associated with Consanguinity; Genetic Disorders and Congenital Malformations; Benefits

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Abstract: In the main, the detrimental health effects associated with consanguinity are caused by the expression of rare, recessive genes inherited from a common ancestor(s). The closer the biological relationship between the parents, the greater is the probability that their offspring will inherit identical copies of disease-causing recessive genes. However, in spite of all the potential health problems associated with consanguineous marriages, in the vast majority of the societies where these are common, it is generally accepted that the advantages of consanguinity outweigh the disadvantages. The rate of congenital malformations among the offspring of consanguineous marriages is approximately 2.5 times higher than that among the offspring of unrelated parents. First cousin consanguinity has been shown to be significantly associated with an increased risk of congenital heart defects, congenital hydrocephalus and neural tube defects, susceptibility to infectious diseases, underweight, and having an adverse effect on cognitive performance in some consanguineous populations. Another disadvantage is the high rate of hospitalization and utilization of the health care facilities in consanguineous communities, causing a major financial burden, much of which could be saved if the rate of consanguineous marriages were lower. However, in certain situations consanguineous marriages can actually be advantageous. The culture of consanguineous marriages and the genetics of protection against malaria may have co-evolved by fostering survival against malaria through better retention of protective genes in the extended family, and also the circle of family members who can act as successful tissue donors is significantly extended. There are also many social advantages.

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Keywords: Advantages, congenital malformations, consanguineous marriages, disadvantages, recessive genes, socioeconomic.

INTRODUCTION

In the main, the detrimental health effects associated with consanguinity are caused by the expression of rare, recessive genes inherited from a common ancestor(s) [1]. The amount of genetic material shared by first cousins is four times higher than that shared by second cousins. First cousins once removed have half the amount of shared DNA as full first cousins. The closer the biological relationship between the parents, the greater is the probability that their offspring will inherit identical copies of disease-causing recessive genes – *i.e.* two alleles that are identical by descent because they are inherited from the same ancestor as a result of consanguineous mating.

CONSANGUINITY AND AUTOSOMAL RECESSIVE DISEASES

Inbreeding depression is the reduced survival and fertility of offspring of related individuals [2], and can be defined as the deleterious effects that result from mating related individuals. Biémont suggested that this probably results from epigenetic mechanisms – that is, chromosomal events in which DNA sequence is not altered [3]. Epigenetic mechanisms include RNA interference, histone modifications, cell-specific DNA hyper- and hypomethylation, chromatin remodeling, and canalization/decanalization. The expression of recessive deleterious alleles is likely to be the main mechanism of inbreeding depression, in addition to interactions between inbreeding and environment.

Offspring of consanguineous marriages have segments of their genomes that are homozygous as a result of inheriting identical ancestral genomic segments through both parents [4, 5]. One consequence of this is an increased incidence of recessive diseases in these families. Woods *et al*. performed theoretical calculations that predicted that 6% (1/16) of the genome of a child of first cousins will be homozygous and that the average homozygous segment will be 20 cM in size [4]. The authors assessed whether these predictions held true in populations that have practiced consanguineous marriage for many generations. They found

that in individuals with a recessive disease whose parents were first cousins, approximately 11% of their genomes were homozygous, with each individual having 20 homozygous segments exceeding 3 cM, and that the size of the homozygous segment associated with recessive disease was 26 cM. In fact, first-cousin offspring had as much homozygosity as would have been expected for double-first cousin offspring. These data suggest that prolonged parental inbreeding leads to a background level of homozygosity increased ~5% over and above what would be predicted by simple models of consanguinity [4]. Certain ethnic groups have long genomic stretches of homozygosity – 67% of Native Americans from Central and South America have at least one homozygous segment longer than 10 Mb. This is consistent with considerable inbreeding [5]. The term "autozygosity" is also used – this occurs when two alleles in the same individual are identical by descent – *i.e.* they are inherited from the same ancestor as a result of consanguineous mating.

Thus it can be seen that there is a difference in the risk for first-time cousin couples with no background of consanguinity among their parents, grandparents *etc.*, compared with couples whose family history on both sides includes multiple consanguineous marriages going back through many generations [4, 6]. First-cousin couples with no family background of multiple consanguineous marriages have a lower risk of affected offspring. This is partly because the likelihood that both spouses will inherit the same deleterious gene from the common ancestor is lower because there will be fewer common genes than in cousin couples with a family background of multiple consanguineous marriages. Also, in first-time cousin couples, there is no founder effect operating with regard to deleterious mutations.

Teeuw *et al*. designed a future case-control study that will establish whether consanguineous parents of a child affected by an autosomal recessive disease have more DNA identical-by-descent than similarly-related parents with healthy offspring [7]. The purpose of this study is to investigate whether affected children have more homozygous DNA than healthy children of consanguineous couples who do not have affected children. The authors expect that the results of this study will assist in designing future research, such as the recruitment of a large, possibly international, cohort of consanguineous couples before reproduction. This cohort

will enable different risk estimates to be obtained for the different proportions of DNA that is identical-by-descent. Once such estimates are available, couples will benefit by having reproductive options once they are informed more precisely about their risk status.

Consanguinity by itself does not alter the allele frequencies of recessive disorders, but increases the probability of a mating between two individual heterozygotes for the identical recessive mutant allele. The relatively frequent existence of an autosomal recessive disease in an isolated population suggests a founder effect.

Autosomal recessive diseases are common in populations with a high rate of consanguinity [8-11]. In these populations, increased levels of morbidity and mortality caused by the action of detrimental recessive genes can be predicted. Empirical studies on the progeny of first cousins indicate morbidity levels to be some 1% to 4% higher than in the offspring of unrelated couples. The less common a disorder, the greater the influence of consanguinity on its prevalence – in other words, the level of inbreeding is expected to be much higher in a rare disease than in a common disease – a generalization that applies to recessive multigene disorders as well as to single gene conditions [12]. For this reason, many previously unrecognized genetic diseases have first been diagnosed in highly endogamous communities (endogamy is the practice of seeking a mate or marriage partner from within a group defined by social status, ethnic identity, family relationship or area of residence or some other distinct social characteristic), and in a significant proportion of cases the underlying mutation may be unique to the community [1]. In these communities, rare autosomal recessive diseases are relatively frequent and can be limited to one village [13]. In many isolated inbred communities the inhabitants are descendants of a limited number of ancestors, and hence some conditions are confined to specific villages or even specific families. This leads to an unusually high frequency of genetic diseases in these communities [14-16]. A good example of such a situation is an Israeli Arab town in central Israel in which a considerable number of the inhabitants suffer from Arthrogryposis Multiplex Congenita [17].

Certain population groups that practice endogamy can be broadly considered as one large family from a genetic point of view. Jewish populations, and

particularly the large Ashkenazi Jewish population, exhibit a high degree of endogamy. Other groups with high levels of consanguinity include the Amish community in Pennsylvania, Ohio and Indiana, and the Hutterian Brethren, or Hutterites, also in the North American continent. These groups are described in more detail in Chapter 1.

In communities with a high frequency of consanguineous marriages, the existence of a recessive disorder in one or more members of the same family is generally indicative of a recent mutation, whereas the presence of a rare disorder in several families suggests either an older mutational event or one previously introduced *via* marriage with a person from another community [18, 19].

Genetic heterogeneity (a situation in which a genetic disorder may be caused either by different mutations within a single gene locus, forming multiple alleles of that gene, or by mutations in completely unrelated gene loci), may occur even where a recessive disorder is known to be common within a particular inbred subpopulation, with no certainty that all affected members are homozygous for the same mutation. Also, in many consanguineous isolates, two or more mutant alleles may be segregating within the same family, and the possibility of the presence of multiple genetic conditions, especially rare autosomal recessive disorders, must be carefully considered. This can greatly complicate diagnosis and genetic counseling [20-24].

Frishberg *et al*. offered several possible explanations to delineate the mechanism responsible for the phenomenon of multiple mutations in rare recessive disorders among the Arab population in Israel [25]. They note that spontaneous mutations occur constantly in all genes, but these are only detectable because of the changes they cause in the phenotype. Also, even if the *de novo* mutation rate is normal, a new deleterious recessive allele will probably become homozygous because of the high rate of consanguinity. Alternatively, the mutation rate may be higher, and this will obviously lead to a significant number of affected individuals. Finally, it is possible that a heterozygote may have an as yet unidentified advantage that is combined with the unique structure of the community involving high consanguinity and large families [25].

The excessive number of deaths in consanguineous families is attributed to the homozygosity of lethal recessive alleles, although, with the death of each homozygote, the number of disease-causing genes in the gene pool is reduced. This beneficial effect of inbreeding is, however, offset by an increased number of offspring in consanguineous families, who replace some of the lost lethal genes; in every extra pregnancy there is a 50% probability of transmission of a lethal recessive gene to the next generation. The purging of lethal genes from a population is further counteracted by the occurrence of spontaneous mutations and immigration of people from outside populations [26].

Interestingly, countries with high rates of consanguinity often report smaller effects of inbreeding on mortality than countries with low rates of consanguinity [27]. This finding can be explained by the fact that these studies often did not consider different socio-demographic variables, thereby exaggerating the adverse effect of consanguinity [28]. Bittles concluded that offspring of first cousin marriages experience 4.4% more deaths than the offspring of non-consanguineous families [29]. Another study, which examined the progeny of first-cousin marriages in Italy, estimated an excess of deaths of 3.5% [30]. Most other studies conducted on Arab populations have also found that postnatal mortality is higher among offspring of consanguineous parents than among unrelated parents [31]. A meta-analysis comparing prereproductive mortality from 6 months gestation to an average of 10 years of age, in first-cousin *versus* non-consanguineous progeny within specific populations found 3.5% excess deaths among first-cousin progeny [19]. It has been estimated that among first-cousin progeny there is a mean excess of only 1.1% deaths during the neonatal period, and a similar amount for infant deaths [32].

Nevertheless, in spite of all the potential health problems associated with consanguineous marriages, in the vast majority of the societies where these are common, it is generally accepted that the advantages of consanguinity outweigh the disadvantages [33].

CONSANGUINITY AND CONGENITAL ANOMALIES

A higher prevalence of congenital anomalies in general has been reported among first cousin couples in all populations. Several studies have shown that the rate of

congenital malformations among the offspring of consanguineous marriages is approximately 2.5 times higher than that among the offspring of unrelated parents [8, 33-35]. However, Hamamy suggests that if there is no known genetic disorder in the family, first cousin marriages are generally given a risk for congenital anomalies in the offspring that is double that in the general population. Among closer consanguineous couples, such as double first cousins, the risk for their offspring is estimated at triple the rate in the general population [36]. The main cause appears to be the expression in the offspring of autosomal recessive disorders, although congenital malformations that are structural in nature and that have not been classified as typical autosomal recessive conditions have also been demonstrated [8, 33]. Whether these malformations are due to a single autosomal recessive gene, or to other mechanisms, such as increased homozygosity in several loci, is not known. It should be emphasized, however, that while consanguineous marriage facilitates the expression of rare recessive disease genes, it does not actually cause genetic disease [32]. The malformations that have been found to be especially more common are: cardiovascular, central nervous system, urogenital, ophthalmic, gastrointestinal, skeletal, cutaneous, and also multiple malformations. Studies of anthropometric parameters revealed no differences between children born to consanguineous parents as compared to those born to unrelated parents except for birth weight, which was significantly lower in the consanguineous group ($p < 0.035$) [34, 37].

About 3-5% of all live newborns have a medically significant congenital anomaly. There are two possible explanations for the increased risk of major malformations in consanguineous families; the first is that some of the malformations are due to monogenic disorders, and the second is that the threshold of disease penetrance is reached more easily if both parents share the same genetic predisposition factors inherited from a common ancestor. Therefore, clear separation between major malformations due to Mendelian and non-Mendelian causes is difficult. Many studies examining the frequency of congenital anomalies in consanguineous populations have been conducted; these are heterogeneous in terms of the different types of anomalies included, the method of obtaining data (personal examination *versus* registries), and whether the data were collected during pregnancy, at birth or during childhood. The common finding in all these studies

was that higher rates of congenital anomalies were observed among offspring of first cousins as compared to offspring of unrelated parents. It appears that the frequency of malformations during pregnancy and at birth, including or excluding conditions diagnosed in early childhood, is approximately two-three times higher among the offspring of first cousins than among the offspring of unrelated couples from the same population. It has been suggested that the relative risk is not significantly different from that observed for first-cousin marriages in non-inbred populations [38].

In a study by Jaber *et al*., 610 families were prospectively ascertained through infants who were routinely seen in the local "Well Baby Clinics" [8]. The authors found a significant increase in the incidence of major malformations in relation to the closeness of the parental relationship; the prevalence of individuals with major malformations was 5.8% in the offspring of inter-village marriages, 8.3% among the offspring of intra-village non-related unions, 15.1% in the offspring of distantly consanguineous couples, and up to 15.8% among the progeny of first-cousin marriages. Among the siblings of these index cases, the frequencies of major malformations were 4.3%, 4.5%, 10.5%, and 10.3%, respectively. Analysis of the major malformations in each body system showed the same trend [8].

In a study by Bundey and Alam (1993), which described the prevalence of congenital malformations and genetic disorders in the offspring of 4,886 women during childhood, the prevalence was 4.3% among the North European sub-population (0.4% related) and 7.9% among the British Pakistani children (57% first cousins) [39]. In a recent study by Zlotogora and Shalev (2010), 6% offspring of first cousins or double first cousins in an isolated village had a major malformation detected at birth or during pregnancy; in 7.77% of children a significant medical condition was diagnosed before the age of 5 years [40].

The Catalogue for Transmission Genetics in Arabs (CTGA) is a database of genetic disorders in Arab populations maintained by the Centre for Arab Genomic Studies in Dubai in the UAE (http://www.cags.org.ae/ctga_search.html). Analysis of the list of diseases in this database indicates that in contrast to international databases, a large proportion of the disorders consists of autosomal recessive

diseases (63%), compared to a smaller proportion of dominant diseases (27%) [31]. In a study by Zlotogora, the frequency of consanguineous marriages among the parents of individuals affected with dominant and X-linked disorders or with chromosome rearrangements was shown to be close to that observed in the general population, while among the rare autosomal recessive disorders the frequency of consanguineous marriages was 92.5% as opposed to 44.3% in the general population [13]. In a recent study by Jaouad *et al.*, among 176 families with autosomal recessive disorders in Morocco, consanguineous marriages comprised 59.09% of all marriages, while the prevalence of consanguinity in Morocco generally is 15.25% [41]. The influence of first cousin marriage on the prevalence of autosomal recessive Mendelian disorders was examined in a 5-year prospective study in a Pakistani community in the United Kingdom [39]. It was calculated that there would be a ~7/1,000 increase in autosomal recessive disorders per 0.01 increase in the mean coefficient of inbreeding.

The frequency of consanguineous marriages has been shown to be higher among parents of offspring with congenital malformations compared with the figures for the general population in all studies reported among Arabs [31], including in the UAE [42], Kuwait [43], Oman [44], Iraq [10], Jordan [45], Egypt [46], Lebanon [47], Tunisia [48], Saudi Arabia [49], and Arabs in Jerusalem [50].

A report by the March of Dimes Birth Defects Foundation estimated congenital anomalies to be >69.9/1000 live births in most Arab countries, where consanguinity is common, as compared to <52.1/1000 live births in Europe, North America and Australia [31, 51]. According to the Latin American Collaborative Study of Congenital Malformations, in which the congenital anomalies affecting 34,102 newborn infants born between 1967 and 1997 were analyzed, a significant association with consanguinity was found only for hydrocephalus, postaxial polydactyly and bilateral cleft lip with or without cleft palate [52].

The comparison between the rates of congenital anomalies among the offspring of first cousin marriages and those of unrelated couples in several studies from inbred communities are shown in Table **1** [6].

Table 1: Congenital malformations and/or genetic diseases among first cousins and other consanguineous parents in different populations. (Copyright (2002) Wiley. Used with permission from Zlotogora J. What is the birth defect risk associated with consanguineous marriages? Am J Med Genet. 2002;109:70–71) [6]

Population	First Cousin	Related	Not Related
Norway, Norway [38]	3.4%	1.6%	1.5%
Norway, Pakistani [38]	4.5%	3.8%	2.1%
Turkey [53]	2.7%	2.2%	0.8%
Israel [8]	15.8%	15.1%	5.8%
Israel [6]	6.4%	6%	2.5%

Congenital Cardiac Defects

The role of consanguinity in common congenital cardiac defects, some of which are multigenic in etiology, has been studied by several researchers. Elevated rates of consanguinity have been consistently reported for congenital heart defects, in particular, atrial septal defect and ventricular septal defect, suggesting the involvement across populations of recessive gene variants with similar phenotypic outcomes. Yunis *et al*. found a significantly increased risk of specific congenital heart defects in first cousin offspring, suggesting a recessive mode of inheritance [54]. Shieh *et al*. performed a systematic review of consanguinity in congenital heart disease, focusing on non-syndromic disease, in which they compared the methodologies and results from studies of different ethnic populations [55]. Overall the results suggested that the risk for congenital heart disease is increased in consanguineous unions in the studied populations, principally at first-cousin level and closer. Similarly, in a study by Tadmouri *et al*., after controlling for confounders, first cousin consanguinity remained significantly associated with an increased risk of congenital heart defects (CHD) [31].

Chehab *et al*., in a study in Lebanon, found that congenital heart defects associated with hypoplasia of the left heart, such as tetralogy of Fallot, valvar aortic stenosis, and atrial septal defect, were associated with parental consanguinity, but conditions such as atrioventricular septal defect, common atrioventricular junction ("atrioventricular canal"), and discordant ventriculo-arterial connections ("transposition") were not [56]. Seliem *et al*. conducted a

similar study in Saudi Arabia and found that cardiomyopathy was much more prevalent among children born to consanguineous parents, while septal defects and conotruncal lesions, both of which could be considered flow lesions, were more prevalent in the non-consanguineous group [57].

In a survey in Western Iraq, Al-Ani studied 86 patients with CHD and 258 controls [58]. The commonest types of CHD were ventricular septal defect, atrial septal defect and tetralogy of Fallot. Consanguinity was present in 78% of cases and 43.3% of controls, with first cousin marriages accounting for 66.2% of cases and 35.6% of controls. The author concluded that consanguinity was a significant risk factor, mainly in the patients with ventricular septal defects and atrial septal defects.

Earlier studies also found that infants born to consanguineous parents had a higher risk of having a CHD diagnosed at birth compared to those born to unrelated parents in Lebanon [54], Saudi Arabia [59], Egypt [60], and Israel among Israeli Arabs [61]. Conversely, the overall incidence of CHD among 140,000 newborns in Oman, a country with a high consanguinity rate, was similar to that reported from developed countries in Europe and America, insinuating that consanguinity is not a risk factor for CHD [62].

Congenital Hydrocephalus and Neural Tube Defects

Some studies found that consanguinity rates were higher among parents of newborns with congenital hydrocephalus and neural tube defects than in the general population, but other studies did not reach the same conclusion [31]. Congenital hydrocephalus was found not to be significantly associated with consanguinity in a study by Murshid *et al*. in Saudi Arabia [63], although in a survey in Oman all the 11 children with congenital hydrocephalus came from consanguineous families (45% first cousins, 27% second cousins, 28% distant relatives), and all six of the patients with encephalocele were from first cousin marriages [64]. In another study by Murshid in Saudi Arabia, among children with spina bifida, 89% of the spina bifida parents were consanguineous, but only 67% of the controls; from this the author concluded that parental consanguinity was a significant risk factor for spina bifida [65].

Childhood Deafness

Childhood deafness has been commonly associated with consanguinity. In a study of hearing-impaired children in Lagos, Nigeria, Olusanya and Okolo reported that consanguineous marriage was one of many risk factors for permanent hearing loss [66]. In the UAE, Al-Gazali conducted a study among children from four schools for the deaf in four different Emirates [67]. A detailed history was obtained including, among other parameters, the level of consanguinity between the parents. He found that 98% and 57%, respectively, of cases of nonsyndromic and syndromic deafness were attributed to autosomal recessive inheritance. This association has also been described in a paper by Feinmesser *et al*., who reported that the prevalence of moderate-to-severe bilateral sensorineural hearing loss among 147 Jewish children born in the Jerusalem area between 1968 and 1985 declined during the years 1977-1985, in parallel with a decline in the rate of consanguinity of their parents [68]. However, this decline was evident only among the non-Ashkenazi children, among whose parents the rate of consanguineous marriages at the beginning of the period studied was around 10% and which decreased considerably in the later years studied. Among the Ashkenazi children there was no decline in the incidence of hearing loss and no recorded parental consanguinity.

Another study was performed on a similar group of children, who were also born in the Jerusalem area between 1978 and 1991 [69]. The authors studied 150 Jewish children with hearing loss from 139 families and found that 16% (8/49) of the families with autosomal recessive deafness were consanguineous – six were first cousins or closer and two were more distantly related. The consanguinity rate among the non-Ashkenazi families was 21%, among the Ashkenazi families 12%, and zero among the four families of mixed Ashkenazi/non-Ashkenazi origin. Overall among the 139 families the consanguinity rate was 7.2%, which, according to the authors, was high compared with the rate of 2.3% among a sample of the Israeli Jewish population in 1991. This study also noted a decline in the incidence of hearing loss in the children of non-Ashkenazi families over time, which they attributed to the decrease in the rate of consanguineous marriages in this population.

Congenital Eye Diseases

Autosomal recessive retinitis pigmentosa is reported to occur more commonly in populations where consanguineous marriages are preferred [70-73]. Increased rates of congenital cataracts and other congenital eye malformations have also been reported in several populations [74]. In a study in Kuwait, blindness was found not to be commoner among consanguineous families than among non-consanguineous ones [75], although a study in Saudi Arabia found that the opposite was true; Tabbara and Badr found that the incidence of parental consanguinity among blind students with genetic diseases was significantly higher than among the parents of the students in the group with acquired diseases [76].

Down Syndrome

An elevated frequency of Down syndrome has been reported in some populations, for example in an Arab village in Israel. However, most of the literature on the effects of parental consanguinity on Down syndrome has concluded that no such association exists. A recessive gene coding for non-disjunction of chromosome 21 was proposed to explain the apparent excess of Down syndrome babies born to younger consanguineous parents in Kuwait [77], but the existence of such a predisposing gene for trisomy 21 has been disputed in other populations [13].

Infectious Diseases

Consanguinity has been shown to have an effect on susceptibility to certain infectious diseases. Lyons *et al*. showed that genetic heterozygosity is a key predictor of fitness in natural populations, partly as a result of inbreeding depression, because inbred individuals have low heterozygosity [78]. They studied 148 children who died of invasive bacterial disease (bacteremia, bacterial meningitis or neonatal sepsis), and 137 age-matched healthy children in Kenya. They genotyped samples for 134 microsatellite markers and analyzed these for an association between homozygosity and mortality. They found that at five markers homozygosity was strongly associated with mortality. In another study by Lyons *et al*., the authors showed that there is a strong association between consanguinity and susceptibility to both tuberculosis and persistent hepatitis B virus infection in West Africans, indicating that consanguinity is an important risk factor in susceptibility to infectious diseases in humans [79].

Other Conditions

A positive association of consanguinity with cleft lip and/or palate has been reported among Palestinians [13] and the Lebanese [80], but not in studies in Kuwait [81] and Saudi Arabia [82]. Consanguinity has also been identified as a risk factor for underweight, showing that couples who were first cousins were 1.5 times more likely to have an underweight child as compared to those couples who were not first cousins [83]. Consanguinity can also have an adverse effect on cognitive performance, which has been shown to be significantly lower in the children of consanguineous marriages [84-86].

BENEFICIAL EFFECTS – GENETIC AND SOCIAL

Genetic

The hypothesis has been put forward that, in contrast to the harmful effects of consanguinity, in certain situations consanguineous marriages can actually be advantageous. Denic and Nicholls suggested that in the case of the most common monogenetic conditions in humans, α-thalassemia, glucose-6-phosphate dehydrogenase (G6PD) deficiency, hemoglobin C, and Duffy antigen negative red blood cells, which have evolved under pressure from malaria, their survival and selection have been enhanced by consanguineous marriages in malaria-infested regions of the world [87]. The authors postulated that there are various reasons for this. Firstly, the presence of two mutations in homozygotes of the above-mentioned conditions (except G6PD deficiency) confers better protection against malaria than the presence of one or no mutation (heterozygous or normal genotypes, respectively), and consanguinity increases the number of homozygotes, especially at low allele frequency. For G6PD deficiency, inbreeding may increase the allele frequency of the G6PD-deficient allele. Secondly, there is an overlap between the geographic distributions of malaria, thalassemias, and other red blood cell conditions that protect against malaria, and consanguineous marriages. Thirdly, the distribution of different intensities of malaria infestation matches the frequency of human inbreeding. The authors concluded that these observations taken together strongly support the hypothesis that the culture of consanguineous marriages and the genetics of protection against malaria have co-evolved by fostering survival against malaria through better retention of protective genes in the extended family [87].

Denic *et al*., in a further study on consanguinity and malaria, noted that when the mortality from malaria is low, consanguinity lowers the population with α+-thalassemia by causing an excessive number of deaths *via* recessive lethal alleles and by negligibly slowing down the selection of the α+-thalassemia allele [88]. They also found that an enhanced speed of selection of the α+-thalassemia allele in inbred populations increases the relative fitness against malaria, and commented that when mortality from malaria is high, this increase in fitness could offset the loss of life resulting from inbreeding. Therefore, they suggest, consanguinity augments the fitness of a population with endemic malaria through its effect on the α+-thalassemia allele [88].

Inbreeding depression (described above) is the reduced survival and fertility of offspring of related individuals [2]. Nebert *et al*., however, observed the opposite phenomenon, a situation they described as "inbreeding de-repression", which they defined as the beneficial effects that result from mating related individuals [89]. By inbreeding a freshly generated knockout mouse line, the authors found that subsequent generations produced much healthier viable offspring compared with the F1 generation. The authors suggested that these findings represent the action of natural selection, where only the healthiest animals survived and were able to breed the subsequent generation. Because this inbreeding de-repression phenomenon happened within just two to four generations, the authors presumed it reflected epigenetic rather than genetic changes in the genome.

Consanguinity can also result in the homozygous expression of beneficial recessive genes. Another notable advantage is that in populations with high frequencies of consanguineous marriages, the circle of family members who can be successful tissue donors is significantly extended, thus reducing reliance on sibling donors [32].

Social

The fact that consanguineous marriage has been practiced for centuries worldwide indicates that the advantages of this type of union greatly outweigh the disadvantages in the societies in which it is prevalent. The main reasons for the continuation of these unions are social and economic. Factors contributing to the

high incidence of these marriages include a lack of suitable mates outside the family as a result of geographical, tribal or cultural isolation, so that marriage to a relative may be the only sort that is possible. Preservation of property, especially land, and the desire to keep this within the family is another important reason [33]. Other reasons include the popular belief that intrafamilial marriage offers advantages in terms of compatibility of the bride with her husband's family, where the bride herself finds it reassuring to marry into a known family background; tradition, strengthening of family ties, maintenance of family structure, a closer relationship between the wife and her in-laws, greater marital stability and durability, ease of prenuptial negotiations, enhanced female autonomy, and the desire to avoid hidden health problems and other undesirable traits in a lesser-known spouse [90]. Care for people in old age has been suggested as a reason [91], and lower domestic violence and divorce rates have also been claimed [92]. In traditional Arab societies, marriage outside the family may be perceived as an insult by the family head [93]. Furthermore, a man usually has the right to claim marriage to his father's brother's daughter. Economic considerations also are important and, in countries where dowry or bridewealth payments are the norm, arranging marriage within the family reduces or even obviates the potential financial costs [20, 94]. Dowry, according to Hussain, is the major economic transaction that determines marriage decision-making [94]. He suggests that it is generally true that the size of the dowry is a consideration in opting for cousin marriages, because the demands and expectations of the potential in-laws, who are also close relatives, are likely to be lower and more realistic. Also, and perhaps more importantly, the bride and her family are less likely to be 'penalized' for any perceived shortcomings in the expected dowry.

The family is the main source of social security for most people worldwide [91]. In communities that prefer consanguineous marriage, the close family structure offers protection for socially or medically disadvantaged members, and as a result relatively less stigma might be attached to inherited conditions. Therefore, any attempt to alter the marriage pattern on medical grounds could undermine the very support systems that help people to cope with genetic disadvantage.

Religious reasons for preferring consanguineous marriages have been cited; however, Hussain commented that the suggestion that Islam favors marriage

between close relatives other than the proscribed ones such as siblings, parent and child, uncle and niece or aunt and nephew, is, in fact, erroneous [94]. He pointed out that there are actually no passages in the Koran that can be interpreted as encouraging consanguineous marriages. Indeed, the Islamic faith discourages consanguineous marriages, and Muhammad, the prophet of Islam, in his Traditions in fact stated: "Alienate the sibling spousal" [8].

Khlat *et al*., in a survey conducted in 1984 and 1985 in Beirut among 100 women who had married relatives and a matched group of 100 women who had married non-relatives, found that some of the women in consanguineous marriages (and a few of the matched women) as adolescents were contemplating marriage to a relative [95]. The authors suggest that this indicates that the acceptance of consanguineous marriage is rooted in the system of values prevailing in the upbringing of girls. Interviewees often commented that they would rather have their son/daughter marry his/her cousin than a stranger. This attitude has to be seen in the wider context of intra-familial preference that is prevalent in the Middle East. A mother feels better about her son marrying his cousin rather than someone else because she knows her niece's personality and family background well. With a daughter the motivations are slightly different; by marrying her cousin, she is protected from any possible mistreatment to which she might be exposed in an unfamiliar setting. It is particularly important to note that "protection of the woman" was the most frequently quoted as an advantage of cousin marriage, while "economic benefits" was mentioned only twice. The favorable perception of in-laws and their greater involvement in the family life of the women who marry relatives fits well in this framework by highlighting the continuation of common family interests that existed before marriage. Thus, whereas the economic argument may have been decisive in rural situations, it is of much lesser importance in an urban setting where the family is no longer the major unit of production; there, the maintenance of family cohesion takes precedence over financial concerns [95].

Bhopal *et al*. conducted a survey between 2007 and 2010 in Bradford, a city in West Yorkshire, England, in which 20.5% of the population are Asian or Asian British, and where in one specific district 73% of the population are of South Asian origin [96]. They compared Pakistani and other ethnic groups in

consanguineous marriages with Pakistani, other ethnic groups (mainly Indian and Bangladeshi) and white British groups not in consanguineous relationships in order to determine whether there were any social or economic benefits associated with consanguineous marriages. A total of 11,396 pregnant women at 26-28 weeks' gestation completed a questionnaire, including questions about their relationship to their baby's father. The authors found that among the Pakistani group, 37.5% were in first-cousin marriages, 21.8% were in more distantly related marriages, and 39.2% were not related to their partner (information was missing for 1.4%). In the group of subjects from other ethnic origins, 5% were in first-cousin marriages, 2.3% were in more distantly related marriages, while 92.5% of the marriages were non-consanguineous (information was missing for 0.3%). In the white British group, 99.7% of the marriages were non-consanguineous; there were no first-cousin marriages, 0.1% more distantly related marriages, and 0.1% where information was missing. The authors determined that even though people in consanguineous relationships were generally less educated and economically less well-off than their counterparts in non-consanguineous marriages, they were not disadvantaged, and in certain cases were actually advantaged, in a wide range of other factors that were important in their lives and relevant to their health. These included financial, marital and mental well-being, such as capacity to pay bills (similar), divorce (rarer), warmth and trust in the marital relationship (similar), enjoying ordinary activities (similar) and mothers' smoking (rarer). The authors concluded by commenting that "the danger of stigmatizing and alienating ethnic minorities who practice consanguinity can be countered by public health policy that reconsiders the balance of harms and potential benefits" [96].

IMPACT OF CONSANGUINITY ON THE PROVISION OF MEDICAL AND GENETIC COUNSELING SERVICES

In the last approximately 60 years there has been a significant decline in developed countries in childhood illness caused by infections and malnutrition. The widespread implementation of vaccination programs, better nutrition and the development of antibiotics to treat infectious diseases have resulted in a shift in emphasis in the provision of medical care in these countries, and nowadays a far higher proportion of all hospitalizations in childhood is for chronic and congenital diseases [33, 97]. For example, in the Israeli Arab community, approximately

16% of the children of first-cousin marriages, which account for nearly one quarter of all the marriages in this population, have major malformations [8]. This results in a high rate of hospitalization and utilization of the health care facilities in this community, causing a major financial burden, much of which could be saved if the rate of consanguineous marriages were lower.

A study by Hall *et al*. in 1973 found that 53.4% of admissions to a large general pediatric hospital in Seattle, Washington, were for diseases with a genetic component. The authors noted that patients with genetic disorders had many more admissions that were slightly more expensive, that they stayed longer in hospital, that they traveled further, and that their families paid the bill more often [97].

The 1991 population-based hospital discharge data from California and South Carolina formed the basis for a study by Yoon *et al*., which found that nearly 12% of pediatric hospitalizations in the two states combined were related to congenital anomalies and genetic diseases [98]. The children were, on average, about 3 years younger, stayed in hospital 3 days longer, incurred 184% higher charges, and had a 4.5 times greater in-hospital mortality rate than children who were hospitalized for other reasons.

McCandless *et al*. reviewed the records of 5,747 consecutive admissions (4,224 individuals), representing 98% of patients admitted in 1996 to Rainbow Babies and Children's Hospital in Cleveland, Ohio [99]. They found that 34% of admissions had a clearly genetic disorder, although an underlying disorder with a significant genetic component was present in 71% of admitted children. Disorders with a genetic determinant accounted for 81% of the total hospital charges for 1996, and the 34% of admissions with clearly genetic disorders accounted for 50% of the total hospital charges. The mean length of stay was 40% longer for individuals with an underlying disease with a genetic basis than for those without an underlying disease.

While the above papers do not specifically discuss the impact of children of consanguineous marriages, probably because in the communities studied the frequency of such marriages was negligible, by extrapolation it can be assumed that in communities where these marriages are common, the burden on the genetic

services will be correspondingly greater [33]. For example, among inpatients in a large tertiary children's hospital in central Israel, the consanguineous marriage rate in the parents of Israeli Arab children with severe congenital malformations was around 50% in 2010 [100], whereas the frequency of such marriages in the general Israeli Arab population in the same year was about 29% (personal communication).

The effects of consanguinity on common diseases will be discussed in detail in chapter 4.

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CONFLICT OF INTEREST

The authors confirm that this chapter contents have no conflict of interest.

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CHAPTER 4

Consanguinity and Susceptibility to Common Diseases

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Abstract: Offspring of consanguineous parents have an increased risk for congenital anomalies and major malformations. This is mainly due to the expression of recessive diseases, since when the parents share a common ancestor, the offspring are more likely to inherit the same variant/mutation that originated from their common ancestor. Although it is well known that offspring of consanguineous parents have an increased risk for monogenic autosomal recessive diseases, the contribution of parental consanguinity to the development of common multifactorial diseases is controversial. Most of the common diseases are multifactorial in etiology, *i.e.* the disease will manifest only after the risk factor level, both genetic and environmental, has exceeded a certain cut-off point. Coronary artery disease (CAD) is caused by numerous genetic and environmental factors, and a small proportion of cases are due to rare, highly penetrant variants in single genes. CAD is known to cluster in families, and early-onset CAD has a particularly strong genetic component. Hypertension is influenced by hundreds of loci, and consanguinity influences not only the blood pressure levels but also their reactivity. Asthma is primarily a multifactorial polygenic disease, although it is possible that homozygous mutations in specific genes may result in the "asthma phenotype". There are conflicting reports as to whether consanguinity plays a role in the etiology of diabetes mellitus – some studies have found an association while others have not. A possible association between consanguinity and psychiatric disorders is explored, and the possible effect of consanguinity on cancer is also discussed.

Keywords: Congenital anomalies, consanguineous parents, major malformations, multifactorial diseases, recessive diseases.

INTRODUCTION

Offspring from consanguineous relationships, *i.e.* unions between individuals who

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are genetically related, have long been known to have an increased risk for congenital anomalies [1-5], poor growth [6], infant mortality [5, 7-9] and major malformations [10-12]. Because their parents share a common ancestor or ancestors, these offspring are more likely to inherit the same variant/mutation in one or more genes that originated from their common ancestor(s). Although the probability of the common ancestor having a mutation in any one disease-associated gene is extremely low, such a risk exists for each of the over 20,000 genes in the human genome. Therefore, these offspring are at an increased risk for having homozygous mutations for disease-associated genes compared to offspring of non-consanguineous parents. However, consanguineous marriages continue to be prevalent mainly because of the socioeconomic benefits such as similar cultural values and maintaining the family's wealth [13]. These marriages are particularly common in the Middle East among the Arab communities where they are practiced by both Muslims and Christians [11].

Although it has been well-established that offspring of consanguineous parents have an increased risk for monogenic autosomal recessive diseases, the contribution of parental consanguinity to the development of common multifactorial diseases is controversial. Most of the common diseases such as coronary artery disease (CAD), asthma and type 2 diabetes mellitus are multifactorial in etiology, *i.e.* the disease will manifest only after the risk factor level, both genetic and environmental, has exceeded a certain cut-off point. This is known as the **threshold phenomenon** [14]. For each of these conditions there are many loci in the genome that contribute to the disease and there is no single genetic test at present that can establish a person's risk for any of these diseases.

COMMON DISEASES AND CONSANGUINITY

Roberts showed an increase in susceptibility to multiple sclerosis in offspring of consanguineous parents [15]. It has been suggested that consanguinity may also have an adverse effect on cognitive performance, which has been shown to be significantly lower in the children of consanguineous marriages [16-18]. However, this might be due to an undiagnosed autosomal recessive syndrome that results in MR.

The role of consanguinity in multifactorial common adult diseases has yet to be established and several studies have reported conflicting results. Jaber *et al*. investigated the effects of consanguinity on the prevalence of diabetes mellitus, myocardial infarction, bronchial asthma, and duodenal ulcer in the Israeli Arab population [19]. The consanguinity rate was 33% and there were no differences between the male and female offspring of consanguineous *versus* non-consanguineous marriages in the prevalence of diabetes mellitus (consanguinity: 4.3% in males, 1.5% in females *vs*. non-consanguinity: 2.9% in males, 1.6% in females), myocardial infarction (2.7%, 0.03% *vs*. 2.3%, 0.03%), bronchial asthma (2.4%, 2.0% *vs*. 3.7%, 2.3%), or duodenal ulcer (7.0%, 3.0% *vs*. 7.8%, 2.9%) (the first percentage in each pair is the prevalence of the disorder in males, and the second percentage is the prevalence of the disorder in females in consanguineous *versus* non-consanguineous matings). Moreover, the overall prevalence of these diseases among Israeli Arabs was not higher than that in the Israeli Jewish population, in which the rate of consanguineous marriages is extremely low.

In their study of consanguinity and adult morbidity among outpatients presenting to the Pakistan Institute of Medical Sciences and the Nuclear Oncology and Radiotherapy Institute, Shami *et al*. also did not demonstrate an association between cardiovascular, liver, kidney, or thyroid diseases and consanguinity, but the rate of consanguinity was higher among patients with cancer, suggesting that some Pakistani adults might be at risk for specific cancers due to homozygous mutations in autosomal recessive genes [20]. However, a study of the Qatari population, in which 51% of marriages were consanguineous, found that the offspring of such marriages had a higher risk for many common diseases, including cancer, blood disorders, mental disorders, heart disease, bronchial asthma, gastrointestinal disorders, hypertension, and diabetes mellitus; the odds ratio ranged from 2.65 for heart disease ($p = 0.002$) to 9.23 for hypertension ($p < 0.001$) [13].

Coronary Artery Disease

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in industrialized countries. It is a multifactorial disease caused by numerous genetic and environmental factors [21]. While some of the environmental risk factors for

CAD can be modulated through lifestyle modifications such as diet and exercise, the genetic factors are not modifiable. A small proportion of CAD cases are due to rare, highly penetrant variants in single genes such as *ALOX5AP* [22, 23], but many instances of CAD are caused by variants in a large number of genes. Many association studies have identified multiple genomic loci associated with CAD, of which the most strongly associated is the locus on chromosome 9p21 [24-26]. However, in most patients, CAD is due to the cumulative effect of multiple susceptibility alleles (*i.e.* genetic variants) together with adverse environmental factors (the threshold phenomenon, as described above).

CAD is known to cluster in families, and early-onset CAD has a particularly strong genetic component [27]. A family history of CAD is considered a major risk factor in disease development, not only due to susceptibility genes that are inherited through the generations, but also due to shared lifestyles that may exacerbate individual susceptibility to CAD [28, 29]. Indeed, Yasar *et al*. demonstrated that a family history of CAD is the third most important risk factor for CAD in both genders aged 45 years and younger after cigarette smoking and hypercholesterolemia in men and hypercholesterolemia and hypertension in women [30].

There is conflicting evidence for the role of consanguinity in the development of CAD. As mentioned, the offspring of a consanguineous marriage are more likely to inherit the same gene variants from each of their parents, and thus are more likely to have similar "gene determined" health outcomes [31]. It is unclear whether parental consanguinity contributes to the risk for CAD, the age of onset, or both. Ismail *et al*. assessed 193 subjects between 15 and 45 years old who had their first acute myocardial infarction (MI) and 193 age, sex and neighborhood matched controls from Karachi, Pakistan [32]. They showed that environmental risk factors such as tobacco use, ghee intake, elevated blood glucose, high cholesterol, low income, and low level of education, as well as a paternal history of CAD, were associated with premature acute MI in South Asians. This was the first published study on the association between parental consanguinity and acute MI in the absence of a family history of CAD. The authors suggested that this might be a true association, or it could possibly be explained by dietary patterns that are more likely to have been shared within the family and would therefore be

more pronounced in consanguineous marriages. They speculated that consanguinity may have a confounding effect on the risk factors thought to be specific to the South Asian population. Abu-Amero *et al*. also showed that enhanced inheritance of susceptibility alleles for autosomal recessive diseases increases the likelihood of developing these diseases independent of the family history [33].

Youhanna *et al*. examined the role of consanguinity in CAD in 4284 patients [34]. They found that while consanguinity itself did not increase the risk of CAD ($p = 0.38$), it did significantly lower the age of diagnosis ($p < 0.001$). The mean age at disease diagnosis was lowest – 54.8 years – in those with both a family history of CAD and consanguineous parents, compared to 62.8 years in those without any risk factors ($p < 0.001$).

Mani *et al*. described a family of Iranian descent with autosomal dominant early CAD, features of the metabolic syndrome (hyperlipidemia, hypertension, and diabetes), and osteoporosis [35]. They identified a missense mutation in *LRP6*, which encodes a co-receptor for WNT ligands in the Wnt signaling pathway; this mutation reduces Wnt signaling *in vitro*. The index case, whose deceased parents were affected first cousins, was homozygous for the mutation, but his clinical presentation was similar to that of the affected heterozygotes, both in presentation and age of onset.

In summary, there are studies suggesting that consanguinity decreases the age of onset of CAD although it does not influence its risk; however, there are also reports like that of Mani *et al*. [35] that do not support this. Further studies are needed to establish the role of, and relationship between, consanguinity and CAD.

Hypertension

Hypertension is a common chronic disease that leads to severe morbidity and mortality through heart disease, stroke, congestive heart failure, end stage renal disease and peripheral vascular disease. In the United States, heart disease and stroke are two of the leading causes of death [36, 37]. Hypertension, like other common diseases, has complex heritability that is influenced by both environmental and genetic factors [38, 39]; however, apart from isolated

successes in mapping rare monogenic loci, which account for about 5% of cases of hypertension, no major progress has been made in defining the genetic basis of essential hypertension [40]. The system of blood pressure (BP) control is complex and genetically highly variable and is dependent on various factors including cardiac output, blood vessel structure, renal function, and central nervous system control [40, 41]. Support for a polygenic model for the inheritance of hypertension also derives from animal models [40].

To study the influence of gender on BP, McArdle *et al*. carried out a genome wide homozygosity by descent mapping scan of the Old Order Amish of Lancaster, PA [42]. The Amish are a closed founder population where all the members of the community have a similar lifestyle with similar environmental factors associated with high BP, such as a high fat diet and low levels of physical activity. Two genomic loci were identified as being suggestive of linkage to systolic blood pressure (SBP) and five loci to diastolic blood pressure (DBP) in either the overall or gender-specific analyses. Sex specific analysis identified linkage to a specific region of chromosome 4 in men only, and to a region on chromosome 2 where men accounted for most of the linkage. The authors concluded that their results added evidence to a sex specific genetic architecture to BP related traits [42].

Twin studies have shown that at least 50-79% of BP variation can be attributed to genetic factors [43, 44]. Hassan *et al*. in 2001 studied 135 boys aged 9-10 years in order to ascertain whether children of first cousin parents where one or both were hypertensive have a higher BP reactivity as a result of having their BP measured for the first time as compared to the offspring of first cousin parents whose BP was normal [45]. The authors found that the reaction of the offspring of first cousin hypertensive parent(s) had significantly higher systolic and diastolic BP readings than did the offspring of first cousin parents with normal BP.

In another study Rudan *et al*. examined whether recessive alleles contributed to hypertension in humans by investigating the effects of inbreeding on BP in 2760 adults from 25 villages in Croatian island isolates [46]. They found a strong linear relationship between the inbreeding coefficient (*F*) and both systolic and diastolic BP, indicating that recessive or partially recessive quantitative trait locus (QTL) alleles accounted for 10% in females and 15% in males of the total variation in BP

in this population. The authors established that each village has its unique *F* and every increase in *F* of 0.01 corresponded to an increase of ~3 mm Hg in SBP and 2 mm Hg in DBP. Regression of *F* on BP indicated that at least 300-600 recessive QTL contributed to BP variability. Eight to sixteen QTL accounted for a maximum of 25% of the dominance variation, and the authors inferred from this that in the population studied, inbreeding accounted for 36% of all hypertension. The magnitude of the inbreeding effect on BP is large – equivalent to a rise of about 20 mm Hg in SBP and about 12 mm Hg in DBP in offspring of first-cousin marriages – and is consistent with the results of previous studies in other isolate populations. The population prevalence of hypertension among individuals with no known inbreeding in their recent ancestry is about 20%, similar to most outbred populations, but it increases markedly among 50-year-olds as the inbreeding coefficient rises.

These studies show that hypertension is influenced by hundreds of loci, and that consanguinity influences not only the levels of SBP and DBP but also their reactivity. Furthermore, the inbreeding coefficient has a linear effect on both SBP and DBP.

Asthma

Asthma is a clinically heterogeneous group of disorders that has been defined by the National Asthma Education and Prevention Program Expert Panel of the National Heart, Lung, and Blood Institute (National Institutes of Health, USA) as a "common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyper-responsiveness, and an underlying inflammation" [http://www.nhlbi.nih.gov/guidelines/asthma/]. Clinically, asthma can be diagnosed based on the presence of: (i) recurrent respiratory symptoms such as wheezing, cough, and dyspnea, and (ii) expiratory airflow obstruction that is reversible with the use of bronchodilators. Other causes of expiratory airflow obstruction and wheezing must be excluded. There is, however, no universally-accepted working definition of asthma, which has complicated attempts to identify the genes contributing to the development of this disease [47]. Nevertheless, genome-wide association studies as well as linkage studies have identified more than 40 genes that

contribute to the asthma phenotype. It is believed that asthma is a multifactorial polygenic condition, involving both genetic and environmental factors. The extent of contribution of each gene to the phenotype remains unknown; however, it is believed that each gene only has a small effect on the overall phenotype [48, 49].

Various authors have attempted to determine whether parental consanguinity increases the risk for the development of asthma. Shirakawa *et al*. genotyped a variant of the β-subunit of the high-affinity IgE receptor FcεRIβ – Val183Leu – and showed, in a small group of patients, an association with atopy [50]. Hijazi and Haider examined the prevalence of two variants of FcεRIβ – Leu 181/Leu 183 – in consanguineous and non-consanguineous families in Kuwait who had at least one asthmatic child aged between 4 and 12 years [51]. Although the authors concluded that the Ile181Leu/Val183Leu genotype was more prevalent among the offspring of consanguineous compared with non-consanguineous families, this was not statistically significant. The authors found a higher prevalence of the homozygous Ile181Leu/Val183Leu variant amongst severe asthmatic patients compared to moderate asthmatic patients ($p < 0.018$). Although the authors suggested that consanguinity might contribute towards the high prevalence of the FcεRIβ polymorphism in the Kuwaiti families with asthma, our re-analysis of the data presented in their paper does not support this conclusion. In fact, we opine that data from this paper suggest that consanguinity does not contribute to the risk of developing asthma.

Gürkan *et al*. in 2002 studied 140 children with asthma and 96 healthy control children, aged 3-15 years, in Turkey and found that there was no difference in the rates of consanguinity between the two groups [52]. Similarly, in a study of 103 families with 140 asthmatic children and 103 families with 295 healthy non-asthmatic children in Saudi Arabia, it was found that there was no statistically significant difference in the prevalence of consanguinity between the two groups (71/140 *vs*. 163/295 respectively; $p = 0.43$) [53].

On the other hand, a structured face-to-face survey conducted by nurses of Qatari women attending primary health centers or gynecological or antenatal clinics in hospitals found that 189/818 women (23.1%) in consanguineous relationships had at least one offspring with asthma compared to 84/697 women (12.1%) who were

not in consanguineous relationships ($p < 0.001$) [54]. Although two recent studies, one conducted in south India [55] and the other in Abu Dhabi (United Arab Emirates) [56], concluded that parental consanguinity increases the risk of developing asthma, methodological issues limit our ability to draw any definitive conclusions from either study.

Asthma is believed to be primarily a multifactorial polygenic disease, although it is possible that homozygous mutations in specific genes, the risk for which is increased among offspring of consanguineous relationships, may result in the "asthma phenotype".

Diabetes Mellitus

There are conflicting reports as to whether consanguinity plays a role in the etiology of diabetes mellitus (DM). In a study carried out in 1947-1948, Harris investigated 1241 diabetics at the Juvenile and Adult Diabetic Clinics at King's College Hospital, London, England [57]. Each patient was asked whether his or her parents were first cousins and, if not, whether they were related in any other way. Analysis of the data showed that there was an increase in the incidence of parental consanguinity in a series of patients with diabetes in whom the disease developed in early life, but no increase in the incidence of parental consanguinity in those in whom the disease developed later in life. It was concluded that there are genetic differences between the early onset and late onset forms of the disease and that at least some, and possibly all, the early onset cases are associated with one or more recessive genes. Anokute studied 210 male patients with DM who attended the diabetes clinic at the King Khalid University Hospital in Riyadh, Saudi Arabia [58]. One of the factors he investigated was consanguinity and questions about this were included in the detailed questionnaire given to both patients and controls. He found a positive family history of diabetes in 79.5% of all consanguineous marriages compared with 21.3% of non-related marriages. The difference was highly significant ($p < 0.0001$). The author commented that this high level of risk could be avoided by a cultural change.

However, El-Mouzan *et al*., in a survey in Saudi Arabia in 2004-2005, found no significant association between consanguinity and type 1 DM [59].

One factor that should be borne in mind when considering the validity of these papers is the huge discrepancy between the percentages of consanguineous marriages. In England in 1948 there were 18 such marriages out of a total of 1241 (1.45%), whereas in Saudi Arabia in 2005, 6470 of 11554 marriages (56%) were consanguineous. Whether the very small percentage of these marriages in the English sample affects the validity of the author's conclusions is not discussed.

Psychiatric Disorders

There are several studies on a possible association between consanguinity and psychiatric disorders. In a study of first-cousin marriages among the parents of a group of randomly selected patients with schizophrenic and affective disorders, Prasad found that there were a significant number of such marriages in the schizophrenic group [60].

Schizophrenia

Three studies found that consanguinity rates were significantly elevated among the parents of schizophrenic patients. Dobrusin *et al*. compared the prevalence of consanguinity in the parents of Bedouin schizophrenic inpatients in a specific catchment area of southern Israel to a control group of parents of all infants born to Bedouin mothers in the same catchment area [61]. Among the schizophrenic patients, 79% of the parents were in consanguineous marriages – 51% of these were between first cousins. In the control group, 58% of parents were in consanguineous marriages, of which 40% were between first cousins. The authors suggested that this small but significant increase in the rate of consanguineous marriages among the parents of schizophrenic patients was consistent with claims that consanguinity can contribute to the risk of schizophrenia, even though it is a polygenic illness. However, the authors stated that the absence of a better matched control group limited confidence in the results.

Bener *et al*. conducted a survey in Qatar between January 2009 and December 2010 in order to examine the impact of consanguinity on the risk for developing schizophrenia and to investigate the consanguinity characteristics of the schizophrenic patients [62, 63]. The 1184 patients completed a questionnaire that included sociodemographic characteristics and genetic and other biological

factors such as obstetric complications. They also completed a diagnostic screening questionnaire consisting of six questions on the symptoms of schizophrenia. The degree of consanguinity between the patient's parents was noted. The authors found that parental consanguinity was higher among the schizophrenic patients (41.3%) than among the non-schizophrenic subjects (28.7%), and a diagnosis of schizophrenia was more frequent among the offspring of consanguineous parents than among the offspring of non-consanguineous parents. The authors concluded that consanguinity is an important risk factor for schizophrenia in Qatar.

Mansour *et al*. conducted a study among a group of schizophrenic patients in Mansoura, the capital city of Dakahlia province in the Northern Nile Delta region of Egypt, and compared these with a group of controls [64]. The patients were 75 unrelated outpatients with a clinical diagnosis of schizophrenia, and the control group consisted of 126 adults residing in the same geographic areas as the patients and in whom a history of psychosis or bipolar disorder had been excluded. In both groups available parents were also recruited. The prevalence of consanguinity was initially estimated from family history data, and this was followed by DNA analysis using short tandem repeat polymorphisms. The authors found that self reported consanguinity was significantly elevated among the patients (46.6%) compared with the controls (19.8%) ($p = 0.000058$) and these differences were confirmed by DNA analysis. The authors concluded that consanguinity rates were significantly elevated among schizophrenic patients in the Northern Nile Delta region of Egypt.

In contrast, a study by Ahmed concluded that consanguinity rates were not significantly elevated among the parents of schizophrenic patients [65]. He compared the rate of first-cousin marriages among the parents of schizophrenic patients with a control group in an isolated, highly inbred Sudanese community where the rate of first-cousin marriages was 44% and found that among the schizophrenic patients, 43.7% of the parents were in first-cousin marriages, whereas in the control group the corresponding figure was 44.1%. He thereby concluded that there was no significant difference.

Bipolar 1 Disorder

Two studies found that consanguinity rates were elevated among bipolar 1 patients. Mansour *et al*. carried out a study to contrast the rates of consanguinity among patients with bipolar 1 disorder and controls [66]. This study was conducted in the same setting as their schizophrenia study – in Mansoura in the Dakahlia province of Egypt. The patients were unrelated outpatients in the psychiatric clinic who had received a clinical diagnosis of bipolar 1 disorder, and the controls were adults residing in the same geographic areas as the patients. The control sample included pregnant women admitted for normal delivery or their spouses, and donors at the hospital blood bank. The authors conducted two parallel studies – the first was a case-control study comprising 93 patients with bipolar 1 disorder, 90 adult controls and available parents. The consanguinity rate was estimated by using 64 DNA polymorphisms, and also from family history data ("self report"). The second study was an epidemiological survey in which a total of 1,584 individuals were screened. Self-reported consanguinity rates were obtained for identified bipolar 1 patients (n = 35) and 150 randomly selected, unaffected controls. The authors found that the self-reported consanguinity rates were elevated among bipolar 1 patients in both surveys and concluded that their studies indicated increased consanguinity among Egyptian bipolar 1 patients in the Nile delta region [66].

Mechri *et al*. conducted a study in Tunisia in order to determine the rate of consanguinity in patients with bipolar 1 disorder and to compare the clinical characteristics and the frequency of affective disorders in first and second degree relatives of probands with and without consanguinity [67]. A total of 130 patients with bipolar 1 disorder participated. The rate of consanguinity was estimated to be 28.5%, and was higher in patients with a family history of affective disorders: 34.2% *versus* 20.4% ($p = 0.08$). Bipolar 1 patients with consanguineous parents had a high frequency of affective episodes, which themselves were more severe, but the difference was not significant. However, the frequency of affective disorders was significantly increased in first and second degree relatives of probands with consanguineous parents. The authors concluded that consanguinity has an influence on the clinical characteristics and the frequency of affective

disorders in first and second degree relatives of bipolar patients, which is consistent with recessive polygenic transmission of bipolar disorders.

Another study found differing effects of consanguinity. Saadat carried out a study in 2012 in Shiraz, Iran, to investigate the association between parental consanguineous marriages and the age at onset of bipolar disorder [68]. Out of the 195 patients in the study, 25.6% were the offspring of first-cousin parents and 15.4% were offspring of parents who were more distantly related. The authors found that among patients with early onset of bipolar disorder, the age at onset was higher for offspring of consanguineous than unrelated marriages, whereas among patients with late onset bipolar disorder the age at onset was lower for offspring of consanguineous than unrelated marriages. However, the authors found no difference between consanguineous and unrelated marriages for intermediate age of onset.

Cancer

Several studies have shown that in populations with a high frequency of consanguineous marriages, there is a significant increase in the prevalence of cancer. Single nucleotide polymorphism (SNP) array data analysis has found long regions of homozygosity in genomic DNA from tumor and matched normal tissues of patients with colorectal cancer [69]. The presence of these regions may indicate consanguinity in the individual's family tree. These autozygous regions are referred to as identity-by-descent segments (for a description of homozygosity and autozygosity in offspring of consanguineous marriages, see Chapter 3).

One survey that investigated the effects of consanguinity on the incidence of cancer and other late-onset complex diseases studied individuals from genetically isolated islands in middle Dalmatia, Croatia [70]. The investigators determined that consanguinity can be a positive predictor for a number of late-onset diseases such as heart disease, stroke, and cancer. Similar observations were noted in a study in Pakistan where, on average, cancer patients were found to have a higher coefficient of inbreeding compared with the general population [20].

In a study in Wisconsin involving descendants of an Italian immigrant group, 94% of the subjects with reported adenocarcinomas (mostly colorectal) were offspring

of consanguineous marriages [71]. The authors surmised that in the extended family they surveyed, the occurrence of adenocarcinoma appeared to segregate as an autosomal recessive trait and that, in some family members, consanguineous unions led to homozygosity for the deleterious gene.

The effect of consanguinity on cancer is likely to be more complex than simple Mendelian genetics, with many additional genetic components involved. Nevertheless, studying genetically isolated populations may eventually lead to the discovery of other genes that contribute to predisposition to cancer.

Examples of cancer predisposition syndromes include Nijmegen breakage syndrome, ataxia telangiectasia, Bloom syndrome and Fanconi anemia (all types), all of which are autosomal recessive diseases. *MYH*-associated polyposis is transmitted by autosomal recessive inheritance and homozygotes have a very high risk (43-100%) for colorectal cancer, compared to the general population. However, it is unclear whether heterozygotes also have an increased risk for colorectal cancer, and if so, it is not as high (OR 1.1-3). Another example is hereditary nonpolyposis colorectal cancer HNPCC (Lynch syndrome), which is transmitted by autosomal dominant inheritance and heterozygotes are at increased risk mainly for colorectal cancer, uterine cancer and other gastrointestinal malignancies in adulthood.

Lynch syndrome is caused by heterozygous germline mutations in any of the four mismatch repair genes – *MLH1, MSH2, MSH6* and *PMS2*. Offspring of couples where both spouses have Lynch syndrome have a 1:4 risk of inheriting biallelic MMR gene mutations; these cause constitutional MMR deficiency (CMMRD) syndrome, a severe recessively inherited childhood cancer syndrome with a very broad tumor spectrum including mainly hematological malignancies, brain tumors and childhood colon cancer. Café-au-lait spots are also present. The age of presentation of these patients can also extend into young adulthood. In a recent report by an international CMMRD consortium from Toronto, Canada, 23 children with CMMRD from 14 families were studied [72]. One patient, who was aged 21 at the time of diagnosis of an oligodendrioglioma, had also had gastrointestinal polyposis and diffuse large B cell lymphoma in childhood. This patient was a compound heterozygote for two mutations in *PMS2*, suggesting that

the parents were more likely to be non-consanguineous. This patient's sibling was 24 years old at the time of presentation of a glioblastoma multiforme, but he/she had also had rectal cancer and gastrointestinal polyposis in childhood. Another patient was 17 years old when he/she presented with a glioblastoma multiforme and 17.5 years old when he/she was found to have gastrointestinal polyposis. This patient was homozygous for a mutation in *PMS2*, suggesting that the parents were probably consanguineous. Eleven of the 14 families were consanguineous, but unfortunately the authors did not elaborate on the type of consanguinity in these families. Since in 11 families the mutations the patients carried were all homozygous, even though it is not stated, it is likely that these 11 families are the consanguineous ones. In the three remaining families, the patients were compound heterozygotes for two different mutations, so these families were probably not consanguineous. The authors commented that a family history of consanguinity and a history of various malignancies combined with the presence of café-au-lait spots should raise a high index of suspicion for CMMRD [72].

In another survey, five families with CMMRD who were seen in the genetics departments of one or other of two large tertiary medical centers in Israel were studied (unpublished data). Two of the families (both Ashkenazi Jewish) were not consanguineous, but the other three were. Of these families, one was of Iranian Jewish descent; the proband, who presented at the age of 22 years with colon cancer, was the daughter of healthy first-cousin parents, each of whom was found to carry a mutation in *PMS2*. In another family, Bedouin Arabs from southern Israel, the proband, who presented at the age of 46 years with colon cancer, had Lynch syndrome. His 2-year-old niece, the third child of consanguineous parents, presented with a grade IV glioma in the left parietal region; both parents were found to be carriers of a mutation in *MSH6*. In addition, two of the proband's grandchildren, a five-year-old girl and a four-and-a-half-year-old boy of consanguineous parents, developed medulloblastomas; each of their parents was also a carrier of the same *MSH6* mutation. In the fifth family in the series, the proband was the daughter of first-cousin parents of Palestinian origin. She presented at the age of 17 years with anaplastic astrocytoma and died at age 19; both parents, who were healthy, were found to carry a mutation in *PMS2*.

More studies are needed to establish the exact role of consanguinity in common diseases.

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CONFLICT OF INTEREST

The authors confirm that this chapter contents have no conflict of interest.

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CHAPTER 5

Consanguinity and Fertility and Reproductive Issues

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Abstract: The effects of inbreeding on reproductive outcome have been extensively studied. Previously it had been considered that inbreeding contributed to increased mortality and morbidity with detrimental effects on reproductive outcome; however, some studies have shown only a moderate to slight impact. The fertility of consanguineous couples and infant and childhood morbidity and mortality in their progeny have also been extensively studied and numerous reports have concluded that consanguinity is not associated with either a significant positive or negative effect on fertility. The majority of studies found that first cousin couples produce more children. In many cases the mean number of live births to women in consanguineous marriages has been reported as being higher than that in non-consanguineous unions, although several studies found that mean fertility rates may be lower in consanguineous couples. Other reports suggested that lower fertility was possibly due to a failure to initiate pregnancy when the couple shared specific HLA haplotypes, or because of the expression of deleterious genes acting during early embryonic or fetal development that resulted in periconceptual losses. In general, higher total fertility rates have been reported in consanguineous marriages. Reports regarding the association of consanguinity and fetal wastage are conflicting, with some reporting that the total prenatal losses were essentially the same for consanguineous and non-consanguineous couples. A higher prevalence of congenital anomalies in general has been reported among first cousin couples in all populations.

Keywords: Congenital anomalies, consanguinity, fertility, fetal wastage, human leukocyte antigen, reproductive outcome.

INTRODUCTION

Clinically, a consanguineous marriage means the union between couples who are

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second cousins or more closely related [1]. This includes double first cousins, first cousins, first cousins once removed, and second cousins. Uncle-niece marriages are prohibited in Islam but are permissible in the Hindu and Jewish religions. Consanguinity may also refer to unions of individuals with at least one common ancestor, such as those occurring within population isolates, for example, the Amish in Lancaster County, Pennsylvania [2], small towns, tribes, intra-community, or endogamous marriages, as is frequently the case among Arab Muslim communities [3].

Over the past approximately 40-50 years, simultaneously with the decline in the prevalence of infectious diseases and malnutrition due to the widespread implementation of vaccination programs, antibiotic use and better nutrition, childhood illnesses caused by genetic diseases have assumed far more significance [4].

The biological effects of consanguineous marriages have been studied extensively in almost all populations throughout the world [5-11]. Previously it had been considered that inbreeding contributed to increased mortality and morbidity with detrimental effects on reproductive outcome [5, 7, 12]. However, studies conducted in Japan and other countries many years ago showed only a moderate to slight impact [6]. It has been suggested that the adverse consequences of inbreeding may have been eliminated by the eradication of deleterious recessive genes in earlier generations [13]; however, unfortunately, not all published studies have taken into account possible sources of bias – mainly socioeconomic status, but other confounding factors as well, such as maternal age, maternal education, birth intervals and birth order [4, 5, 14-17]. These variables have been shown to have an adverse impact on infant and 5 year survival [17]. The influences of consanguinity on reproduction are shown in Table **1**.

CONSANGUINITY AND FERTILITY

The association of congenital malformations and consanguinity is well known and in the main is caused by the expression of rare recessive genes inherited from a common ancestor(s) [5]. However, little is known about the effects of inbreeding on reproduction and fertility in modern human societies; the majority of the

studies were carried out over 30 years ago and not much in the way of follow-up has been conducted since. It appears that biological effects are masked by socioeconomic factors, which are the major determinants of fertility [19].

Table 1: Reproduction and consanguinity [18]

Characteristic	**Consanguineous *vs.* Non-Consanguineous**
Mean maternal age	Lower
Mean maternal age at birth of first child	Generally lower
Time-span of child bearing years	Longer partly due to lower contraceptive usage
Maternal-fetal genetic compatibility	Enhanced and essential for fetal growth and development
Rates of rhesus incompatibility	Lower
Pre-eclampsia	Equivocal
Successful pregnancies and surviving children	Larger number
Mean number of live births in 40 studies	First cousin couples had a larger mean number of live births in 33 studies, which is an additional 0.08 birth per family

The aspects that have been the most extensively studied are the fertility of consanguineous couples and infant and childhood morbidity and mortality in their progeny. Reports in the literature on fertility and consanguinity are contradictory [20-36]. Hussain and Bittles reviewed 21 studies performed in India and Pakistan that found substantial variations in mean fertility levels [23].

In general, higher total fertility rates have been reported in consanguineous marriages [32-47]. The majority of studies found that first cousin couples produce more children – a finding explained partly by lower parental age at marriage and partly by the ages of the parents at the birth of their first child [5, 47] (Table **1**). In addition, the time interval between the marriage and the first pregnancy is often longer in consanguineous unions, possibly due to gynecological immaturity in women who marry at a young age. Subsequent intervals between births are usually shorter, and consanguineous couples may continue to have children to

comparatively advanced ages [48]. Another reason is that consanguineous couples may be less likely to use reliable methods of contraception [37]. An additional factor is "reproductive compensation", which is a compensatory mechanism for infant and childhood losses (*i.e.* the replacement of children who die at an early age) [20].

Other studies found that mean fertility rates may be lower in consanguineous couples [19, 33, 34, 37, 49-51]. Some reports suggested that lower fertility was possibly due to a failure to initiate pregnancy when the couple shared specific HLA haplotypes [52], or because of the expression of deleterious genes acting during early embryonic or fetal development that resulted in periconceptual losses [53]. Mechanisms such as greater genetic compatibility between the mother and the developing fetus in a consanguineous pregnancy may lead to reduced rates of involuntary sterility and prenatal losses [48, 54, 55]. The association of consanguinity and fertility is shown in Table **2**.

Table 2: The effect of consanguinity on fertility – study populations and consanguinity

Location	**Study Population**	***CM (%)**	**No. of Women**	**Fertility**	**Reference**
South India	Muslims, Hindus, Christians	41.4	377	Higher fertility in consanguineous couples	[32]
Andhra Pradesh	3 caste groups	46	2524	Higher fertility in consanguineous couples	[40]
Ladakh region in Jammu and Kashmir	Indian Muslim population groups	14.8-21.8	503	Higher fertility in consanguineous couples	[41]
Seven cities in the Pakistani province of Punjab	Residents of 7 cities in Punjab	66.9	3329	Higher fertility in consanguineous couples	[46]
Eleven cities in the Pakistani province of Punjab	Women, household and hospital-based	50.3	9520 (44,474 pregnancies)	Higher fertility in consanguineous couples	[47]

Table 2: contd….

Pakistan Karachi and the 1990-91 Pakistan Demographic & Health Survey (PDHS)	Multi-ethnic communities		4679 (PDHS) and 913 (Karachi)	Women in first cousin marriages in Karachi had a higher mean number of children ever born. The number of pregnancies in the PDHS were the reverse	[37]
Turkey	Different nationwide surveys	20-25		Higher fertility and infant and child mortality in consanguineous couples	[43]
Los Nogales, Galicia, Spain	Rural community	5.15	2347	Complete fertility was slightly higher in consanguineous couples	[38]
Mauritania	Various Mauritanian ethnic groups	30.5-74.5	2413		[45]
Qatar	Qatari women	54.0	1515	Number of pregnancies and live births higher in first cousin couples	[35]
Monastir, Tunisia	Live-births from November 1989 to October 1990	24.81	1741	Higher fertility in consanguineous couples	[36]
Iceland	Icelandic population born between 1800 and 1965	There is a significant positive association between consanguinity and fertility	160,811	Higher fertility in consanguineous couples, with the highest in couples related at the level of third and fourth cousins	[39]
Denmark	Danish population			Superposition of effects of inbreeding and outbreeding depression on human fertility	[34]

Table 2: contd….

South India	Women belonging to 3 endogamous communities	50.0	1,500	Negative aspect of reproduction in the inbred group.	[33]
Canada	Cohort of Canadian women born in the late 19th century			High levels of close father inbreeding are associated with reduction of the productivity of parents during the second half of their reproductive period, compared with the first half	[19]
Lebanon	Muslims Christians	29.6 16.5		Significant association between consanguinity and family clustering of male factor infertility cases	[51]

*CM = consanguineous marriage.

Numerous studies have concluded that consanguinity is not associated with either a significant positive or negative effect on fertility [20-32]. Tadmouri *et al*. [3] reported that in the **Arab population**, higher rates of both fertility and live births were found among first cousin couples as compared with among non-consanguineous couples in Qatar [35], Kuwait [56], Saudi Arabia [57], and Tunisia [36]. In various ethnic groups in Mauritania, it was found that consanguineous couples had significantly higher averages of fertility as compared with non-consanguineous couples [45].

Khlat investigated the effects of consanguineous marriages on fertility and mortality of offspring in Beirut through a population-based health survey of 2,752 households [21]. The total number of pregnancies, live births and living children were significantly higher among consanguineous than non-consanguineous couples, and no difference was found either in fertility or mortality when allowance was made for socioeconomic status, religious affiliation and marriage duration. The lack of a significant pattern in the final analysis was attributed to the

long-term practice of consanguineous marriages. A more recent study from Lebanon suggested a positive association between consanguinity and male factor infertility among 120 infertile males, indicating the important contribution of recessive genetic factors to the etiology of male infertility [51].

As is the case with studies from other parts of the world, in **India** as well there is no complete consensus concerning the effect of consanguinity on fertility. There are two conflicting opinions – firstly that consanguinity is associated with an increased fertility rate [32, 40-42], and secondly that there is no clear association [20, 29-31]. Twenty-one studies in India and Pakistan revealed that in most cases the mean number of live births reported by women in cousin marriages was higher than that in non-consanguineous unions. Notably, in 19 of the 21 studies, women in first cousin unions had a higher mean number of live births compared to women not married to a relative [23].

Bhasin and Nag evaluated the incidence of consanguinity and its effects on fertility and child survival among the Muslims of the Ladakh region of Jammu and Kashmir. They compared the study populations with other Indian Muslim population groups and found that the incidence of consanguinity was relatively low. They also reported increased fertility and a lower proportion of surviving children in consanguineous compared with non-consanguineous marriages [41].

Asha Bai *et al*. found that fertility in southern India was higher in consanguineous than in non-consanguineous marriages, but the number of living children was approximately equal in both groups because of increased child mortality in the consanguineous group ($p<0.05$) [32]. The frequencies of abortion and stillbirth were also approximately equal in both groups, but the frequency of congenital anomalies was significantly higher among the offspring of consanguineous parents.

Reddy *et al*. investigated the association between consanguineous marriages and fertility and mortality among offspring in 1,500 women belonging to three endogamous communities within the Chittoor District, Andhra Pradesh, India. There were 500 women from each community [33]. Overall, the consanguineous marriages were significantly more fertile than the non-consanguineous ones. The mean number of pregnancies, live births and surviving offspring was higher

among consanguineous couples. On the other hand, the authors found a significant difference in the mortality rates among the offspring between consanguineous and non-consanguineous marriages when all the marriages (those of the women, the women's parents and the women's husbands' parents) were considered in all three communities. They postulated that due to inbreeding, the offspring of earlier generations may have passed on deleterious genes to later generations, resulting in problems among the offspring of the present couple [33].

Yasmin *et al*. [42] collected data on patterns of marriage, differential fertility and mortality from 211 Kotia women living in the Visakhapatnam district of Andhra Pradesh, India. Women in consanguineous marriages had a lower mean number of total conceptions, live births and living offspring (net fertility) as compared with women in non-consanguineous marriages.

In a study in Bangalore, Karnataka, in southern India, Devi *et al*. did not find any significant differences between the consanguineous and non-consanguineous groups regarding the numbers of live born or living children [30]. Verma *et al*. reported a study conducted in 1978 in which data on 1,000 mothers in the Indian district of Pondicherry were analyzed [31]. Their findings revealed that consanguinity did not affect fertility but contributed considerably to infant mortality and morbidity.

Basu studied endogamous Muslim groups in Delhi and Lucknow, India. Certain groups had a much higher incidence of parental consanguinity than others, and different varieties of inbreeding occurred among the various groups [29]. In all of the groups the fertility rate was higher in consanguineous than in non-consanguineous marriages, although the net fertility rate was not higher.

Bittles *et al*. performed a systematic review of the literature and collated data on 30 populations resident in six countries [20]. They found a positive association between consanguinity and fertility at all levels of inbreeding, reaching statistical significance at first cousin level ($p < 0.0001$). Fertility in first cousin marriages was positively influenced by a number of variables, including illiteracy, earlier age at marriage and lower contraceptive uptake, but the most important factors were duration of marriage and reproductive compensation. The authors

determined that in net terms, consanguinity was not associated either with a significant positive or negative effect on fertility.

In summary, most studies have shown similar or higher fertility rates among consanguineous as compared with non-consanguineous couples. This may be attributed to the younger age of women at marriage, leading to a longer maternal reproductive span, and compensation for the higher infant mortality among consanguineous couples and lower prenatal losses among non-consanguineous couples.

HUMAN LEUKOCYTE ANTIGEN (HLA) GENES AND PREGNANCY

Pregnancy can be considered as an example of a successful host-parasite interaction where the type of the immune interactions changes over the lifecycle of the parasite [58]. Because of the expression of paternal genes, the fetus and placenta have always been considered to be analogous to an allograft [59]. Allograft rejection is mediated by genes of the major histocompatibility complex (MHC), which include the human leukocyte antigen (HLA) genes, but maternal-fetal HLA incompatibility is not deleterious during pregnancy [60]. The placenta is not an immunologically inert barrier; maternal and fetal cells are reciprocally transported across the placenta, and a state of mutual tolerance exists between mother and fetus during normal gestation. The classic HLA antigens that are responsible for the rapid rejection of allografts in humans are not present on placental cells at the maternal-fetal interface, and, in addition, maternal-fetal incompatibility, with respect to HLA, may actually be beneficial during pregnancy.

The fetal cells that are in direct contact with maternal tissues in the pregnant uterus are the extravillous cytotrophoblasts, which invade the maternal decidua [60]. These cells do not express any HLA class II genes, which are strongly immunogenic cell-surface markers in allogeneic transplants. Class I loci *HLA-A* and *HLA-B*, which are expressed in nearly all other nucleated cells, are not expressed in trophoblast-cell populations. However, maternal antibodies against paternally derived HLA that are inherited by the fetus are detectable in the circulation of ~20% of primigravidae and ~40% of multigravidae [61, 62]. The

presence of anti-HLA antibodies in a significant number of healthy pregnancies has demonstrated that sensitization to paternal HLA during pregnancy is not harmful, and, on the contrary, it has been suggested that these antibodies may in fact be beneficial. Paternal minor H antigens, peptides that are presented by Class I MHC, appear to play an important role in ensuring pregnancy success and blocking of activated abortogenic NK-lineage cells. Identifying such molecules could lead to a new approach to the diagnosis and treatment of infertility and pregnancy loss [58].

Human leukocyte antigen-G (HLA-G) is a human non-classical MHC class 1b antigen. Production of HLA-G by trophoblast cells derived from the external trophectoderm layer of the blastocyst appears to be of major importance as a mechanism of tolerance because it impairs both natural killer (NK) and T cell functions [63, 64]. The expression of HLA-G in placental tissue decreases with gestational time. The activity of the enzyme nitric oxide synthase (NOS), which synthesizes the free radical nitric oxide (NO), is also higher in first trimester trophoblast and lower in third trimester. NO can affect the immune system, either directly or by interacting with other factors. The relation between NO and HLA-G has not yet been proven; however, considering the important role of NO in the immune system and the abundance of NOS in the placenta, its role in the materno-fetal tolerance seems highly probable. It is possible that NO interacts with several mechanisms at the same time [64].

Indoleamine-2,3-dioxygenase (IDO) is an enzyme present in placental trophoblast that initiates the degradation of tryptophan, and is very important in maintaining maternal tolerance [64].

No pregnancies have been reported in which all of the proteins derived from *HLA-G* are absent [63]. To date, seven alternatively spliced variants of *HLA-G* have been identified, consisting of four membrane-bound and three soluble isoforms [65].

NK cells are large granular lymphocytes whose function is the direct killing of virus-infected cells and production of cytokines, which are small cell-signaling protein molecules used extensively in intercellular communication [59, 66]. NK

cells thus provide a rapid but relatively nonspecific response to infection, and, in addition, they also appear to play a role in immune surveillance against the development of metastatic spread of certain tumors [66].

It has been found that NK cells are present in abundance in the uterus at the time of implantation, and it has been suggested that they may play a role in the implantation process and the subsequent orderly growth and development of the placenta. The number and activity of NK cells appear to be altered in women with reproductive failure, although it is unclear whether the difference is a cause or effect of reproductive failure [66]. It is possible that maternal allo-recognition may be mediated by the interaction of uterine NK cells with unusual trophoblast MHC class 1 molecules [59].

Ober *et al*. studied the records of the Hutterite community [67, 68]. The Hutterites are Anabaptists who originated in the Tyrolean Alps in the 1500s. Approximately 400 Hutterites migrated to the United States in the 1870s and established three colonies in what is now South Dakota. As a result of rapid population growth, today there are more than 30,000 contemporary Hutterites living in about 300 colonies in the northern United States and western Canada. Virtually all are descendants of the founding population, who were themselves descendants of less than 90 independent genomes [69]. The average relatedness between spouses in the population studied (>1000 individuals) was greater than that of first cousins once removed (kinship coefficient = 0.0369). Because of the small number of independent genomes and paucity of HLA haplotypes, there was a greater likelihood that many Hutterite couples would share HLA antigens. In addition, Hutterite couples sharing HLA also shared alleles at nearby loci, allowing the effects of sharing alleles at undefined MHC loci to be evaluated [67].

The results of an earlier survey by Ober *et al*. in the Hutterite community showed that the intervals from marriage to each birth were no longer among couples sharing HLA compared with couples not sharing HLA, although differences did become significant at the second birth and remained so through the sixth birth ($p < 0.05$) [70]. When effects of individual loci on interval lengths were examined, HLA-DR was the only one whose effects on interval lengths were statistically significant, while sharing at other loci (HLA-A or HLA-B) had a smaller effect. It

may be that the longer intervals to pregnancy among Hutterite couples sharing HLA-DR may result from recurrent peri-implantational losses [67].

Fetal loss rates were not different among couples sharing and not sharing HLA-DR, but were increased among couples sharing HLA-B as compared with couples not sharing HLA-B, suggesting that HLA-B or a closely linked locus influences fetal loss rates [52].

FETAL WASTAGE

Reports regarding the association of consanguinity and fetal wastage are conflicting, according to studies from Sudan, Saudi Arabia and Jordan. In Saudi Arabia and Jordan the total prenatal losses were essentially the same for consanguineous and non-consanguineous couples [22, 28, 71]. Other studies reported similar results [21, 24, 35, 36, 72-74]; however, a higher rate of prenatal losses among consanguineous couples was observed in the Palestinian Territories [75]. The possible effects of consanguinity on abortion rate, stillbirths and neonatal deaths are shown in Tables **3, 4** and **5**.

Table 3: Rates of abortion associated with consanguinity according to previous studies

Location	**Abortion Rates %**			**References**
	First Cousins	**Distantly Related**	**Unrelated**	
Van region Eastern Turkey 2005-2006	High rate of abortion was found in families with *CM			[76]
Lebanon	21.5		16.1	[77]
Palestinian Territories	Consanguinity is a significant risk factor for reproductive wastage			[75]
Qatar	16.8		14.5	[35]
Qatar	No association between CM and recurrent miscarriages in a population with a high rate of consanguineous couples			[24]
Turkey, Kahramanmaras City	The rate of spontaneous abortion was similar in the consanguineous and non-consanguineous groups			[78]
Egypt, Alexandria	Consanguinity increased the relative risk of recurrent abortion			[74]

Table 3: contd….

Rural upper Egypt	Abortion and recurrent abortion is significantly associated with consanguinity			[28]
Karachi	The risk of an adverse pregnancy outcome was higher among the progeny of couples who were not only themselves consanguineous but also products of consanguineous unions			[79]
Dammam city, Saudi Arabia	No significant relationship was demonstrated between CMs and reproductive wastage			[57]
Israel (Arab)	19.0	12.6	17.6	[73]
Sudan	No significant difference was observed between consanguineous and non-consanguineous			[22]
Turkey	9.3	8.2	4.0	[80]
Kuwait	12.4	11.6	11.7	[72]
South India	20.4 (includes uncle/niece unions)	20.8	18.9	[81]
Japan	No significant difference was observed between consanguineous and non-consanguineous			[82]
Chicago, USA	14.5		12.9	[83]

*CM = consanguineous marriage.

Table 4: The rates of stillbirths associated with consanguinity found in previous studies

Location	**Stillbirth Rates %**			**References**
	First Cousins	**Distantly Related**	**Unrelated**	
Van region eastern Turkey 2005-2006	High stillbirth rate found in consanguineous marriages (*CM)			[76]
Turkey	There was an effect of consanguinity on stillbirth rate			[78]
Egypt, Alexandria	Consanguinity increased the relative risk of stillbirth			[74]
Oslo, Norway	The risk of recurrence of stillbirth and infant death is higher for offspring of first cousin parents compared with offspring of unrelated parents.			[84]
Norway	Consanguinity influences stillbirth and infant death independent of maternal education			[85]
Saudi Arabia	8.3		8.9	[71]
Israel (Arab)	1.5	1.1	0.9	[73]

Table 4: contd….

Sudan	No significant difference was observed between consanguineous and non-consanguineous			[22]
Turkey	2.3	2.1	1.2	[80]
Kuwait	2.0	2.7	2.6	[72]
South India	2.0 includes uncle/niece unions	2.9	2.1	[81]
Japan	No significant difference was observed between consanguineous and non-consanguineous			[82]
Japan	3.8	3.8	3.6	[6]
Chicago, USA	1.4		1.2	[83]

*CM = consanguineous marriage.

Table 5: The rates of neonatal deaths associated with consanguinity found in previous studies

Location	**Neonatal Death Rates %**			**References**
	First Cousins	**Distantly Related**	**Unrelated**	
Karachi, Pakistan	Consanguinity is a risk factor for neonatal mortality			[79]
Saudi Arabia	2.7		2.2	[71]
Israel (Arab)	1.6	0.6	0.9	[73]
Sudan	No significant difference was observed between consanguineous and non-consanguineous			[22]
Turkey	18.9	14.9	10.8	[80]
Egypt, Alexandria	Consanguinity increased the relative risk of neonatal death and total reproductive losses			[74]
Kuwait	3.1	2.7	2.5	[72]
South India	5.2 (includes uncle/niece unions)	3.7	4.0	[81]
Japan	No significant difference was observed between consanguineous and non-consanguineous			[82]
Japan	17.3	13.4	13.2	[6]
East Jordan	17.1 (all deaths in the first year of life)	15.1 (all deaths in the first year of life)	12.9 (all deaths in the first year of life)	[86]
Chicago, USA	1.9		1.8	[83]

A consanguinity study group of international experts and counselors met at the Geneva International Consanguinity Workshop in 2010 [11], and their deliberations on the known and presumptive risks and benefits of consanguineous marriages indicated that:

1. Consanguinity does not seem to be associated with elevated rates of miscarriages, and in general, abortion rates among consanguineous and non-consanguineous couples are comparable.

2. A large majority of studies have failed to detect any significant increase in the rates of fetal loss among consanguineous couples (Table **3**). Available data suggest that stillbirth rates are either similar in consanguineous and non-consanguineous couples, or slightly higher among consanguineous couples. A meta-analysis of stillbirths showed a mean excess of 1.5% deaths among the progeny of first-cousin couples [11].

3. First-cousin couples had a higher mean number of live births in 33 of 40 studies, which represented a mean 0.08 additional births per family [18].

4. Studies of the offspring of first-cousin couples also indicated a mean excess of 1.1% in infant deaths compared with those of non-consanguineous couples with an equivalent excess of 3.5% in overall prereproductive mortality [18].

Bittles and Black investigated the impact of consanguinity on death from ~6 months gestation to an average of 10 years of age [87]. Using a meta analysis they compared the prereproductive mortality in first-cousin *versus* non-consanguineous progeny within specific populations. The study sample consisted of 69 populations resident in 15 countries located in four continents, giving a total sample size of 2.14 million. The results revealed a mean excess mortality at first cousin level of 3.5% ($p < 0.00001$). This estimate of 3.5% excess deaths among first cousin progeny was comparable with a previous estimate of 4.4% excess mortality calculated from 38 studies, each of which was included in the 1994 analysis [88] (Table **6**).

Table 6: The rates of infant deaths associated with consanguinity found in previous studies

Location	Infant Death Rates (%)			References
	First Cousins	**More Distantly Related**	**Unrelated**	
The Netherlands – Native and Migrants.	Between a quarter and a third of marriages are between first cousins. Hereditary causes of death in the Moroccan and Turkish populations are 4-5 times higher than in the Surinamese/Antillians and indigenous Dutch			[89]
Mauritanian ethnic groups	The death rate among infants and young children in the Soninkes and Poulard groups is higher among consanguineous than non-consanguineous couples			[45]
Abu Dhabi	Consanguinity is significantly associated with mortality in infants and children aged under 5 years but not with neonatal mortality			[90]
Israel	The incidence of congenital malformations and Mendelian diseases correspond to the differences in the consanguinity rates between the Jewish and Arab populations			[91]
Egypt, Alexandria	Consanguinity increased the relative risk of post-neonatal death and total reproductive losses			[74]
Jordan	Consanguineous marriages showed significantly higher rates of stillbirths and infant mortality in general. Within the consanguineous group, female infant mortality rates were significantly higher than those of males			[28]
Norway	The risk of recurrence of stillbirth and infant death is higher for offspring of first cousin parents compared with offspring of unrelated parents			[84]
Israel (Arab)	6.3	0	1.3	[73]
Sudan	No significant difference was observed between consanguineous and non-consanguineous			[22]
South India – Post neonatal deaths	6.2 (includes uncle/niece unions)	5.7	5.3	[81]
South India – Infant deaths	11.3 (includes uncle/niece unions)	9.2	9.3	[81]
Japan	No significant difference was observed between consanguineous and non-consanguineous			[82]
Chicago, USA	6.3		0.6	[83]

CONSANGUINITY, BIRTH OUTCOMES AND MEASUREMENTS

Few studies have been conducted into possible associations between consanguinity and neonatal distress as measured by Apgar scores, and the results of investigations into the relationship between consanguinity and birth

measurements have been mixed [18]. Some authors have reported that babies born to consanguineous parents are smaller and lighter than those born to non-consanguineous couples, and therefore less likely to achieve developmental milestones or survive, while an approximately equal number found no significant consanguinity-associated difference. These contradictory findings may be a result of variability of the investigative protocols used, the use of simple "consanguineous" *versus* "non-consanguineous" comparisons, and limited or no control for possible confounding factors, such as socioeconomic status, maternal age, nutrition, health status and disease. The importance of these latter factors was shown in a study in Jordan [92]. While univariate analysis suggested a highly significant positive association between consanguinity and low birth weight, when the authors used multivariate analysis to control for age, body mass index, occupation, education, smoking, gravidity, parity, medical problems during pregnancy, and a family history of premature deliveries, the statistical significance of the association with consanguinity disappeared [92].

INFANT MORTALITY

In 2004 Tarabeia *et al*. investigated the difference in infant mortality rates (IMR) between the Arab and Jewish populations in Israel, and found that, similar to the Jewish population, the IMR in the Arab community has decreased over the years, although it is still much higher than that in the Jewish community [93] (Fig. **1**). The continuing difference is attributed to the constantly high frequency of consanguineous marriages in the Arab Israeli population [8], together with a high rate of major congenital anomalies, many of which affect the central nervous system [94].

CONGENITAL ANOMALIES AND CONSANGUINITY

Approximately 3-5% of all live newborns have a medically significant congenital anomaly. A report published in 2006 by the March of Dimes estimated birth defects to be >69.9/1000 live births in most Arab countries, as opposed to <52.1/1000 live births in Europe, North America and Australia [95]. These anomalies are mostly attributable to autosomal recessive diseases [3, 96, 97].

The association between consanguinity, genetic disorders and congenital malformations is discussed in Chapter 3, while the relationship between consanguinity and adult diseases is addressed in Chapter 4.

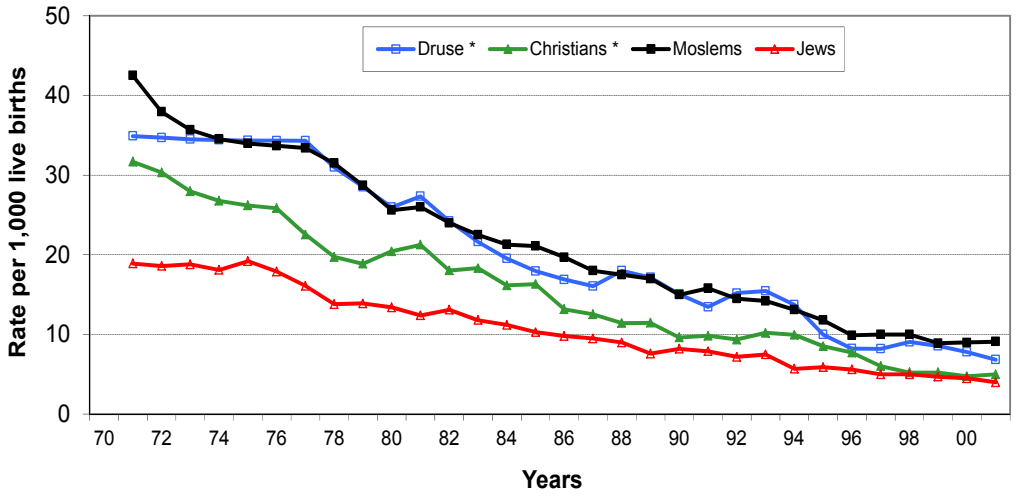

Figure 1: Trends in IMR by religion, 1970 – 2000 (rate per 1,000 live births). (Copyright (2004) Israel Medical Association Journal (IMAJ). Used with permission from Tarabeia J, Amitai Y, Green M, *et al.* Differences in infant mortality rates between Jews and Arabs in Israel, 1975-2000. Isr Med Assoc J 2004; 6: 403-7 [93]).

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CONFLICT OF INTEREST

The authors confirm that this chapter contents have no conflict of interest.

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CHAPTER 6

Awareness and Knowledge about Consanguinity-Related Problems among Members of Communities Where the Custom is Prevalent

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Abstract: Consanguineous marriages constitute over 50% of all marriages in many countries of the Middle East and Asia, and in most of these populations at least half of such unions are between first cousins. In the main, the detrimental health effects associated with consanguinity are caused by the expression of rare, recessive genes inherited from a common ancestor(s), and the closer the biological relationship between the parents, the greater is the probability that their offspring will inherit identical copies of disease-causing recessive genes. In many traditional Arab societies, in which the frequency of consanguineous marriages is very high, there is generally a low level of genetic literacy among the public and most health care providers, and therefore the need for education is of vital importance in such communities before any programs can be established that aim to reduce the rates of these marriages. The main factor in establishing educational and counseling programs aimed at reducing the frequency of consanguineous marriages is to identify the target group(s) who would benefit most from such programs. We report here several studies carried out in different countries with high rates of consanguineous marriages that aimed to assess the levels of awareness among various groups, both general public and health care professionals, regarding the health problems associated with such marriages. The information gained from these surveys was used in each case to establish educational and counseling programs geared to that specific society.

Keywords: Awareness, consanguineous marriages, counseling, education, high frequency, low genetic literacy, recessive genes, target groups.

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INTRODUCTION

Consanguineous marriages constitute over 50% of all marriages in many countries of the Middle East and Asia, and over 20% in several other countries (see Chapter 2). Throughout the world, more than 1,000 million people live in countries where between 20% and 50+% of marriages are consanguineous [1]. In the main, the detrimental health effects associated with consanguinity are caused by the expression of rare, recessive genes inherited from a common ancestor(s), and the closer the biological relationship between the parents, the greater is the probability that their offspring will inherit identical copies of disease-causing recessive genes. In many traditional Arab societies, in which the frequency of consanguineous marriages is very high, there is a low level of genetic literacy among the public and most health care providers [2, 3], and this constitutes an enormous stumbling block when attempts are made to reduce the burden of consanguineous marriages, since if the members of the community have no knowledge about the problems associated with such marriages, or indeed are not even aware that problems exist at all, they will not be willing to change the marital pattern of hundreds of years and will strongly resent any attempts to do so. The need for education is of vital importance in such communities before any programs can be established that aim to reduce the rates of these marriages (see Chapter 7).

ESTABLISHMENT OF EDUCATIONAL AND COUNSELING PROGRAMS – IDENTIFICATION OF TARGET GROUPS

The main factor in establishing educational and counseling programs aimed at reducing the frequency of consanguineous marriages among the members of those communities in which it is high is to identify the target group(s) who would benefit most from such programs, with success being measured by a reduction in the rate of these marriages among the participants of the programs. In order to identify the target group(s) in a specific community, preliminary studies have to be carried out to assess the levels of awareness about problems associated with consanguineous marriages among the people in the community.

An example of this is the survey carried out by Jaber *et al*. in 1999 in which the level of knowledge about the issues associated with consanguinity was evaluated

among adolescents (tenth grade students) in the Israeli Arab community in order to try to obtain information about which groups should be targeted for educational programs [4]. This age group was selected because these youngsters would be thinking about choosing a partner in the near future. The schools that participated in this survey were chosen randomly, and since attendance at high schools is compulsory in Israel, the group of students included in the survey was representative of this age group. A total of 2933 Israeli Arab students aged 15-16 years were interviewed by means of a written questionnaire, which included questions on demographic characteristics, questions that assessed the level of knowledge of the respondents regarding the issue of consanguinity, and questions that addressed the students' attitudes and behavior toward the question of consanguinity. The list of conditions given in the questionnaire that it is possible for a baby to be born with or that children of consanguineous parents are more likely to suffer from compared with children of unrelated parents intentionally included "throat infection". This, of course, is not congenital, and the reason for including it was to distinguish between those students who did not know what congenital disorders were, and answered "yes" to this question, and those who did know that throat infection was not a congenital disorder.

The percentage of girls with a high level of knowledge was significantly higher than the percentage of boys (27.9% compared with 22.3%), but no significant differences were found between the responses of the Muslim students as compared with those of the Christian students. Students living in urban areas had a lower level of knowledge than those from the rural and suburban areas. There was no association between the age of the students' parents at marriage and the level of knowledge of the students. The level of education of the parents was significantly associated with the level of knowledge of the students; children of parents with lower levels of education had a lower level of knowledge. The level of knowledge was also lower among students whose parents were consanguineous compared with those whose parents were unrelated. A comparison of the level of knowledge between students with siblings married to relatives *vs*. those whose siblings were not married to relatives found no significant difference.

The students were asked whether any of their brothers or sisters suffered from congenital disorders such as deafness, mental retardation, or blindness. Those

students who had siblings with congenital disorders demonstrated a significantly lower level of knowledge about consanguinity.

The students were asked the following question in order to assess their awareness of an association between consanguinity and specific congenital disorders: "Is it more likely that children of consanguineous parents will suffer from congenital disorders such as deafness, mental retardation, blindness, heart defect, anomalies of extremities, or throat infection, compared with children of unrelated parents?" According to their answers it was possible to assess the percentage of students who knew what was meant by the term "congenital disorders", and who understood the association between such disorders and consanguinity. The percentages of students giving correct answers to this question were: deafness, 43.8%, mental retardation, 58.6%, blindness, 31.0%, heart defect, 45.5%, anomalies of extremities, 53.3%, and throat infection, 48.2%. Among the students who knew what congenital disorders were, a higher percentage knew that there was an association between these and consanguinity compared with students who did not know what congenital disorders were.

The overall results of this survey revealed that almost half (45.8%) of the respondents to the questionnaire had a low level of knowledge about consanguinity, and only 24.5% had a high level of knowledge [4]. The rest (29.7%) had a moderate level of knowledge. There was a generally low level of knowledge among male students, among the offspring of parents with low levels of education, among the offspring of consanguineous parents, and among students with extreme religious attitudes. These factors should be taken into account when planning the educational programs in the schools.

ACCEPTANCE OF PRENATAL DIAGNOSIS AND TERMINATION OF PREGNANCY

Another important consideration is the acceptance by the community of prenatal diagnosis and termination of pregnancy in the case of an affected fetus. In a survey in the Israeli Arab community, 231 women of childbearing age were interviewed three days postpartum to assess their knowledge of prenatal diagnosis and termination of pregnancy, their willingness to undergo prenatal diagnosis, and

their attitudes towards termination of pregnancy in the event that the fetus was affected with a severe congenital malformation or genetic disease [5]. Half the women believed that prenatal testing was not an accurate or effective method for diagnosing an affected fetus. A quarter had poor knowledge about prenatal diagnosis, and a quarter believed that prenatal diagnosis does provide the correct diagnosis. Ninety-five percent said they would agree to undergo prenatal diagnosis, and in the event of a severely affected fetus, 36% said they would agree to a termination of pregnancy, 57% said they would not, and 7% were undecided. The authors pointed out that there is a need for special intervention programs, with guidance by health professionals, geneticists and religious authorities, to educate this population about the increased risk associated with consanguinity, to stress the importance and effectiveness of prenatal testing, and to encourage them to accept prenatal diagnosis and termination of pregnancy if indicated [5].

Zahed *et al*. conducted two studies in Lebanon, the first [6] involving 83 couples at risk for a hemoglobin disorder, mainly beta-thalassemia, and the second [7] comprising 90 couples at risk for various genetic disorders, in order to assess their acceptance of prenatal diagnosis and the factors that may influence their decision. In each survey, of those who refused, a large majority said that the reason for their refusal was because of religious conviction against termination of pregnancy. Only 12 percent of the couples understood and were aware of their genetic risk, and the authors commented that for prevention of genetic disorders, the emphasis in countries such as Lebanon should be placed on public awareness about genetic risks, the risks of consanguinity and availability of services, while taking into account the personal beliefs of the individuals [7].

In a survey in Saudi Arabia, Babay investigated the attitude of 550 pregnant women aged >35 years to prenatal screening for chromosomal anomalies [8]. Even though chromosomal anomalies are not connected with consanguinity, the results of this survey shed light on the general attitudes of Saudi women regarding prenatal screening and termination of pregnancy. A total of 336 women (61.1%) accepted the general idea of prenatal screening, 160 (29.1%) did not, and 54 women (9.8%) were undecided. Non-invasive methods such as ultrasound and biochemical screening were well accepted (61.35% and 53.0% respectively), but invasive methods less so (34.2%). Seventy-six percent would not agree to

termination of pregnancy in the event of an abnormal result, 22% did not accept screening in general as they doubted that the tests were accurate, 19% did not believe that they would have an abnormal child, and 6% did not believe that screening should be carried out for chromosomal anomalies. The main reason why they refused screening was the unacceptability of termination of pregnancy as a treatment option [8].

Tsianakas and Liamputtong examined how immigrant Muslim women living in Australia perceived and experienced prenatal testing [9]. They also looked at the opinions of the women's partners. The authors conducted in-depth interviews with the women and found that they had, in general, positive attitudes toward prenatal testing, particularly ultrasound, although some were ambivalent about amniocentesis. In spite of their doubts, the women tended to agree to prenatal testing as they believed it was a routine part of antenatal care and "confirmed their own perceptions of being a 'normal mother', who should accept advice from their doctors". The partners of the women in the study also played an important role in the acceptance of prenatal testing. The authors suggested that women should be given a choice rather than being pressured and "made to conform to the routinization of prenatal testing", and this would enable sensitive health care to be provided for women in general and for Muslim immigrant women in particular [9].

Durosinmi *et al*. examined the acceptability of prenatal diagnosis for sickle cell anemia (SCA) as a means of controlling sickle cell disorder in Nigeria by means of a structured questionnaire [10]. The respondents were 92 adult female patients with SCA, 53 carrier mothers (*i.e.* who had sickle-cell trait), and 48 carrier fathers. More than 85% of the respondents said they would like prenatal diagnosis to be offered in Nigeria; 92% of the mothers and 86% of the fathers said they would like to undergo, or would like their wives to undergo, this procedure. However, only 35% of the patients as opposed to 63% of the mothers and 51% of the fathers would opt for termination of an affected pregnancy. The main reasons given for refusing termination were religious convictions and the fear of the complications of abortion. The high percentage of parents who would opt for termination of pregnancy was connected with the general desire in the community for "perfection" and on their previous experience of managing a patient with SCA.

Most of the respondents considered effective genetic counseling as the best means of controlling SCA. When the respondents were asked their views about the transmission of SCA, 68% of the patients and 79% of the fathers knew it was from both parents, but only 47% of the mothers knew this. In fact, 30% of the mothers attributed SCA to an "act of God", while only 8% of the fathers and none of the patients gave this as the cause.

ATTITUDES TO CONSANGUINITY

In a survey by Jaber *et al*. in the Israeli Arab community, respondents (mostly fathers, occasionally mothers if fathers were unavailable, of second-graders) were asked to rate their opinion of consanguineous marriage according to a 5-point scale. Those whose own marriages were consanguineous were considerably more likely to strongly encourage such a union, and therefore this group should also be a main target group for counseling and education [11]. A similar result was obtained by Khlat *et al*. among a sample of women in a hospital setting in Beirut [12], and in a review of the spectrum of genetic diseases in Bahrain, al-Arrayed found that 53% of respondents were in favor of consanguineous marriage, 62% agreed it could cause genetic disease, and 47.8% agreed it could cause social problems [13].

A survey in Saudi Arabia among 32 families with children affected with hemoglobinopathies found that 17 (53.1%) participants had a negative attitude towards consanguinity [14]. Among these, five (15.6%) participants continued to have a negative attitude towards consanguinity and 12 (37.5%) changed their attitude from positive or ambivalent to negative or less positive after their experience with their own affected children, *i.e.* they would no longer encourage consanguineous marriages. Eleven (34.4%) participants had a positive attitude towards consanguinity, four (12.5%) would encourage consanguineous marriage provided premarital screening would be carried out, while four (12.5%) remained ambivalent.

SURVEYS AMONG SPECIFIC ETHNIC GROUPS

A paper by Shaw and Hurst describes in detail the results of an investigation into the understanding of genetics, illness causality and inheritance among British

Pakistanis referred to a genetics clinic in England [15]. The participants were interviewed either in English or Urdu, and the sessions revealed that a wide selection of environmental, behavioral and spiritual factors were perceived as being the causes of medical and intellectual problems. Misconceptions about where in the body genetic information is located and of genetic mechanisms of inheritance were common and included the belief that a child receives more genetic material from the father than from the mother. Despite the "conversational" use of genetic terminology by some participants, it was apparent that some patients had absorbed genetic information in ways that were at variance with genetic knowledge with potentially serious clinical consequences. Moreover, the patients were skeptical of genetic theories of illness, thus reflecting their rejection of the prevailing opinion that cousin marriages do carry a genetic risk. The authors remarked that patients referred to genetics clinics may not easily dispense with their personal theories about the causes of their own or their child's condition and their understandings about genetic risk. This paper provides a wealth of evidence that genetic counselors, and indeed other health professionals as well, who work in Western countries and for whom consanguinity might previously have been merely something they may have read about but not personally encountered, need to become experts when working with immigrant communities such as Pakistanis in order to be able to identify, work with, and possibly challenge patients' understandings of illness causality and inheritance [15].

In another study carried out among the Pakistani community in England, Ahmed *et al*. interviewed after they had received their results 43 pregnant women who were tested for thalassemia carrier status [16]. One purpose of the survey was to determine the women's awareness of and attitudes towards prenatal diagnosis and how this affected their attitudes towards the termination of an affected fetus. The survey also examined whether the women's religious beliefs influenced their attitudes towards termination of pregnancy, how they perceived the severity of the condition, the influence of other people important to them, and gestational age at the time that termination was offered. Analysis of the results revealed that most women who decided to undergo prenatal diagnosis did so not because they wanted to terminate an affected fetus, but because they wanted to know whether

their baby had thalassemia, in order to be able to prepare themselves emotionally and physically and make financial arrangements for caring for the child. They would also be able learn about the condition that the child has and the treatment(s) available.

The authors also commented that sometimes women at-risk refused prenatal diagnosis or agreed to terminate an affected fetus because they did not feel that they could agree to prenatal diagnosis without concomitantly agreeing to undergo termination in the event of an affected fetus. To enable couples to make informed decisions, it should be made clear to them that the offer of prenatal diagnosis is not dependent on their agreement to terminate an affected pregnancy [16].

The findings of this study also showed that religion was an important factor in the decision-making about termination of pregnancy. Information about Islam's position on termination for a serious disorder enables parents to consider this more favorably. There is a difference of opinion between Islamic scholars as to whether "ensoulment" occurs at 40 or 120 days, depending on different interpretations of a specific Hadith. However, all the scholars agree that embryonic life is entitled to respect even before "ensoulment", and even more so afterwards [17]. Muslim religious teaching allows termination of pregnancy within the first 120 days after conception in the event of a severely affected embryo, but abortion after 120 days is considered a criminal offense and is prohibited by all Islamic scholars. Because of this, in the study by Ahmed *et al*. [16], the timing of the offer of termination of pregnancy was important; the women were more likely to agree if it were offered in the first trimester and the authors therefore recommended that prenatal diagnosis should be made available to all at-risk couples in the first trimester.

Many of the women considered that their risk of having a child with β-thalassemia major was "fate". Such beliefs may have been influenced to some extent by their Islamic faith, but also by their social class, educational background and age. The findings also showed that religion was not always the major factor in the women's decisions about prenatal diagnosis and/or termination of pregnancy, but that their perceptions of the severity of β-thalassemia major were also likely to be an important consideration. In other words, the more severe their perceptions of

β-thalassemia major, the more likely they were to agree to termination of an affected fetus [16].

Another factor revealed by this study was that family members were also involved in the decision-making process and tended to encourage prenatal diagnosis and termination of pregnancy, especially if they were aware of the problems associated with β-thalassemia major. The positive aspect of involving other family members in the decision making process is that the couple would not have to worry about the consequences of their decision alone. If the decision is made collectively with a supportive family, the couple will feel more comfortable with the decision to terminate an affected fetus, or to continue the pregnancy knowing that the family will be involved in helping to care for a child with β-thalassemia major [16].

Another study describing lay perceptions of genetic risks attributable to consanguinity among Pakistanis was carried out by Hussain over a 7 month period in 1995 [18]. This study, however, was conducted in Pakistan, in four low-income, multi-religious, and multi-ethnic squatter settlements in Karachi. The study was carried out in two stages, the first of which consisted of a demographic survey of a random sample of 1,011 ever-married women aged between 15 and 49 years. The second comprised focus-group discussions and in-depth, semi-structured, face-to-face interviews. The participants were 294 women who had ever been married and who were 30 years of age or older at the time of the study. The questions focused on the women's perceptions and experiences of close consanguineous marriages, including social and health advantages and disadvantages of such marriages. Only those respondents who knew that consanguineous marriages could increase the risk of health problems were asked to list the type of conditions associated with consanguinity.

The main religions of the participants were Muslim (71%), Christian (24.5%) and Hindu (4.5%). Among the Muslims, 65.1% were in consanguineous marriages, among the Christians the figure was 38.9%, and among Hindus 23.1% were married to a relative. Over 80% of the consanguineous couples were married to first cousins, and approximately 55% of respondents reported that their parents had also been close cousins [18]. When the group discussion participants were

asked to describe the advantages and disadvantages of consanguineous marriages for the health of their offspring, most of them said that such unions did not lead to adverse health effects in the offspring. Many agreed with the commonly held belief that "illness comes from God" or was a result of "nazar" ("evil eye"). However, some of the participants did acknowledge that if one or both parents were affected by a particular illness there was an increased likelihood of their children being affected by the same disease. By comparison, approximately one-half of the respondents (51%) from the in-depth interviews understood that consanguineous marriages increased the risk of inherited disorders. Responses included statements such as "illness came from God" (4%) and "no knowledge on the issue" (7%). The fact that most children, except those with gross malformations, appeared normal at birth and later became ill was frequently cited in group discussions as evidence for the influence of the "evil eye". Some of the participants said that although they themselves were not convinced that consanguineous marriages had an adverse effect on the health of the offspring, medical doctors often emphasized the fact that several illnesses could be attributed to the practice of cousin marriage. Nevertheless, very few women said that they would reconsider their decision of a consanguineous marriage for their children on the basis of health problems in the parental generation [18].

Their perceptions of risk varied according to the educational status of the respondents. Among women with no formal education, there was little difference in the proportion of participants reporting an association between inbreeding and risk of ill-health in the offspring between women who were in consanguineous marriages and those who were not. However, among participants with primary or secondary education, more consanguineously married participants said that the risk of genetic disorders was higher among children of consanguineously married parents. There was no appreciable difference in perceptions about adverse effects of consanguineous marriage by religious affiliation of the respondents [18].

The absence of observable defects in all the children of consanguineous marriages appeared to create much confusion with regard to the genetic origins of disease. A common question was "if the problem (medical condition) is genetic in origin, then why are not all the children of a consanguineously married couple affected?" The lack of a uniform outcome across families was very frequently given as an

example of how "doctors have got it all wrong". Furthermore, the respondents appeared confused that some of the diseases that the doctors said were due to the practice of marrying within the family did not appear until later in life, "which made little sense as the illness must have been in the 'blood' all along and should have manifested much earlier" [18].

Respondents who knew that consanguinity increased the risk of inherited disorders were asked which types of illness might affect the offspring of consanguineous marriages. Most of the responses fell into three broad categories: infections – for example tuberculosis, chronic diseases such as diabetes, hypertension and asthma, and malignancies. Many participants thought that disability in the offspring resulted from problems with compatibility of the husband and wife's blood groups, and therefore perceptions of genetic risk were considered to be insignificant as long as the couple had compatible blood groups [18].

This study underscores the need for additional research in order to quantify the health risks associated with consanguineous marriages in Pakistan and to determine community perceptions of these risks among different population subgroups. The author described as equally important the need for the Pakistani medical community also to understand these issues, both from a medical point of view and according to the prevailing socio-cultural norms. Furthermore, given the general level of confusion among general practitioners regarding medical conditions associated with consanguinity, the author suggested that there is an urgent need to include the basics of genetic counseling in the medical curriculum and to provide appropriate information through continuing education workshops. The author also pointed out that it is important to determine the attitudes of the community towards premarital and prenatal screening, especially among high-risk families, and to assess the acceptability of pregnancy termination services. Because of the complexity of these issues, in addition to the medical personnel, the active engagement of religious and community leaders would be required to formulate policies that are both religiously appropriate and culturally sensitive. While it is acknowledged that consanguineous marriages offer many social advantages in the Pakistani setting, as in all the communities in which this type of marriage is prevalent, it is essential to balance these benefits against the health

costs, both social and economic, so that the communities can make informed choices about consanguineous marriages [18].

Like the Pakistani interviewees in the paper by Hussain [18], a group of Saudi Arabian parents also had difficulty accepting a genetic explanation for diseases that did not affect all the children at the time of birth and they also expressed religious or folk beliefs to account for illness [19]. Thirty-six Saudi families with children who suffered from neuro-metabolic disorders were interviewed at a specialist hospital in Riyadh in order to assess parental understanding of disease and attitudes towards future births and consanguineous marriages. At the time the survey was performed (1988), the frequency of consanguineous marriages in Saudi Arabia was 54.3% overall, 31.4% for first cousins, and in general the rates were higher among the Bedouin [20]. A more recent assessment of the frequency of consanguineous marriages puts those between first cousins at 33.6% and those between more distant relatives at 22.4%, giving an overall rate of 56% [21], indicating that in the intervening years no significant changes in the frequency have taken place.

The survey by Panter-Brick [19] focused only on families with children with metabolic disorders and thus was not representative of the general spectrum of diseases in the Saudi-Arabian population; however, the attitudes and opinions of the families can be regarded as representative since these were not specific to specific illnesses. The parents were interviewed by semi-structured questionnaires. Knowledge about the disease was ascertained from the family's belief in its underlying cause, recognition of symptoms, expectation of progress or fatal outcome, and awareness of specific treatment, and then the social, financial and emotional burden of caring for the sick child was discussed. The parents' attitudes towards marriage and family planning were explored by asking them whether they wished to have more children, preferred consanguineous marriages to non-consanguineous ones, and would want their children to marry a close relative. Parental explanations for disease included statements such as: "God's will", "genetics", "I don't know", the "evil eye", and "illness during childbearing". All the parents believed that "God determined their fate in granting health or illness". Some acknowledged that the disease had a genetic basis without really accepting or understanding it. Many said they had no idea what could be a

possible cause, mainly because they did not believe the medical explanations they had been given or because they did not want to reveal beliefs of a non-medical nature [19].

Parents only acknowledged that a disease was inherited if this was clearly the case according to the family history. They thought that if a disease was genetic then all the children should be affected and not just some, and that the illness should manifest immediately after birth rather than some time later. They stressed the fact that they had relatives who had married cousins but who had normal children, and conversely that brothers who had married outside the family had affected children. However, they did acknowledge that they were carriers where the disease was clearly apparent in the husband's or the wife's pedigree. The risks to future pregnancies were poorly understood; of eight parents who stated what they thought was a probability for future children being affected, only four did so correctly [19]. Two-thirds of the respondents acknowledged that the disease might have a genetic basis, but only a third of them were certain.

Parents centered their explanations for the occurrence of the disease around religious belief, whether or not they had acknowledged heredity, because to them this provided a better reason. One mother expressed this as follows: "the disease runs in my family. But only God knows why some children are fine and others are not". Some parents said that they believed "their burden was willed by God and should be borne patiently". This helped the parents to overcome their feelings of anger or helplessness and they would say "I must accept His will". The more religiously devout families regarded their suffering as a test of their faith. Religion also allowed them to deny responsibility; unlike in the West, only a few of the parents felt a sense of guilt for having given birth to a child who had to suffer. While most mothers worried that future offspring might be affected, others did not, since "God would provide". Religious beliefs also enabled the parents to hope that the child would survive, since Islam accepts that surrendering to God's will does not prevent people from seeking a cure. Religion offers them a more acceptable explanation for the disease; parents prefer to relate the reason for individual suffering to "God's will rather than chance events: there is a purpose to God's action that cannot be attributed to 'blind' probability" [19].

Many of the parents said that belief in the "evil eye" was also a factor in explaining why some children who were perfectly healthy at birth and growing normally were suddenly afflicted with a serious illness. The "eye" – also known as the "look" – "is cast by females, who may be jealous, envious or simply wicked, and who intentionally or unintentionally harm a child at a glance". Some parents cited infectious illnesses (*e.g.* meningitis) and taking the contraceptive pill during pregnancy or early lactation as causes for a child's failure to thrive. Consistent with the variety of explanations, families sought a combination of cures among Quranic readers, local healers and empirical medicine [19].

The attitudes of the respondents towards marriage between close relatives were approximately equally divided between those who were in favor and those who were against. Thirteen parents thought that cousin marriages were preferable to those between non-relatives because the families knew one another and this strengthened the relationships between them. Fourteen parents stated that they would discourage their children from marrying a close relative, while another three said that they would merely advise them against doing so. One father suggested banning all consanguineous marriages for the next several generations, while two mothers said "the modern way" was to undergo testing before marriage to determine whether a prospective couple carried any diseases [19].

Slightly more than half of the parents said they had a good understanding of heredity and as a result of this awareness they had a cautious attitude towards future births and marriages. There was a significant association between the consistency of their responses and the education of both husbands and wives. However, contrary to expectation, the type of response was not significantly associated with their past experience of the disease. The author commented that Saudi parents may well have difficulty in comprehending the complex rules of genetic inheritance, especially if they have had little schooling. She also pointed out that women in particular felt unable to question male physicians. In addition, parents may be unwilling to accept a genetic explanation for something that is a very sensitive family matter [19].

A survey of childhood blindness in Saudi Arabia, which showed significant association with consanguinity, recommended "a comprehensive program of

religious and governmental intervention to discourage marriage between persons having the same grandfather or grandmother" [22]. However, it is difficult to implement such a program in Saudi Arabia as this involves a very sensitive issue which most people consider lies solely in the family domain. At the present time, general education in genetics is available only to those who attend high school. However, local newspapers and some television programs have begun to draw public attention to the subject [19].

The establishment of a screening program for identifying families at particular risk of genetic disease is a realistic objective in Saudi Arabia [19]. In meetings, parents showed great interest in the rules of genetic inheritance and the possibilities for screening relatives before marriage. Awareness of medical facts may not offer much emotional comfort to parents, but it does allow for future preventive measures through pre-marital screening to identify adult carriers and the early diagnosis of affected infants.

Khlat *et al*. conducted a survey in 1984 and 1985 in Beirut among 100 women who had married relatives and a matched group of 100 women who had married non-relatives [9]. One purpose of the questionnaire was to assess the women's perception of consanguineous marriages, and a second was to evaluate their awareness of the genetic risks to which these expose the offspring. Among the women in consanguineous marriages, 72% thought that marrying a relative was advantageous, while only 12% of the matched women agreed (the remainder may not have wanted to appear to underrate their own marriage as one of lower quality). Furthermore, 48% of the women who had married a relative, as compared with 12% of the matched women, indicated a preference for cousin marriage rather than marriage between non-relatives. The women in consanguineous marriages cited "ill-effects on offspring's health" as the main argument against cousin marriage, while the matched women said that the main one was "does not extend family". For them, "ill-effects on offspring's health" was the second argument. Nearly twice as many of the matched women (66%) compared with the women who had married a relative (36%) were aware of the increased risk of inherited disease among offspring of consanguineous marriages. However, both groups recognized to a similar extent the importance of counseling by a physician before a marriage between relatives. Even though only 12% of the

matched women expressed a favorable attitude towards marriages between relatives, almost half of them (49%) would still advise their son/daughter to marry his/her cousin, while 53% of the women who had married a relative would do likewise [9].

Kisioglu *et al*. carried out a study in 2007 to examine the effects of a formal training program on consanguineous marriages on the knowledge of, and attitudes towards, consanguineous marriage of high school students in the Mediterranean region of Turkey [23]. Prior to and after completion of the training program, questionnaires were administered to the participants in order to assess the effectiveness of the program. The program was aimed at educating the students about consanguineous marriages.

The questionnaire consisted of 37 questions, of which 7 were descriptive questions (name, gender, school name, *etc.*), 15 were about sociodemographical features of the students and their families (birth place, educational status, job, monthly income, number of siblings, consanguinity), and 15 were designed to assess the students' knowledge of consanguineous marriage and their attitudes towards the issue. Prior to the program, the general level of awareness of the role of heredity in the causation of thalassemia was low – only 39% of the students thought that this was the cause – whereas after the program this figure increased to 96.3%. Other questions about thalassemia revealed a similar lack of knowledge before the program, with a significant improvement after. Asked whether they would consider consanguineous marriage for the future, before education 83.5% said no, while after education 93.9% said they would not consider this [23].

In a survey conducted in Qatar, a higher proportion of respondents reported that they were aware that the risk of congenital anomalies and genetic problems were increased with consanguinity [24]. Seventy percent of the offspring of non-related parents knew of the risk of blood diseases such as thalassemia and sickle cell anemia, whereas only 54% of consanguineous and 60% of tribal offspring knew this. Fifty-two percent of offspring of non-related parents knew of the increased risk for inborn errors of metabolism in consanguineous offspring, and similar results were found regarding the risk of deafness, anomalies of extremities and heart conditions, all of which can be associated with autosomal recessive

transmission and consanguinity. More than 50% of the participants thought that the occurrence of Down syndrome could be increased with consanguinity, although the evidence to support such an association has been conflicting.

Overall, there is still much work to be done to increase knowledge and awareness of the problems associated with consanguinity among the majority of the members of the communities in which consanguineous marriages are still the preferred type of union. Education, discussed in chapter 7, and genetic intervention, discussed in chapter 8, offer the best prospects for future management.

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CONFLICT OF INTEREST

The authors confirm that this chapter contents have no conflict of interest.

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CHAPTER 7

Future Strategies 1 – Educational and Counseling Programs

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Abstract: Even though most people accept that consanguinity can have a deleterious effect on the health of the offspring, the fact that such marriages have been practiced worldwide for many hundreds of years indicates that the advantages are generally perceived as greatly outweighing the disadvantages. The detrimental health effects are mainly caused by the expression of rare, recessive genes inherited from a common ancestor(s), and the closer the biological relationship between the parents, the greater is the probability that their offspring will inherit identical copies of disease-causing recessive genes. In most families where the parents are first cousins this added risk is estimated to be about 2-4% above the background risk in the general community. In recent years there has been a general overall reduction in the frequency of consanguineous marriages worldwide, although the current rates in most of the countries where they are practiced are still unacceptably high. Attempts to reduce the incidence of consanguineous marriages should be undertaken with tact and diplomacy together with an insight into and knowledge of the cultural and societal norms of the communities concerned. We describe attempts in various countries to offer training, educational and counseling programs aimed at reducing the incidence of consanguineous marriages. We also discuss whether religious intervention to discourage the practice of consanguineous marriage would be effective, and whether the participation of a Muslim cleric or physician might influence the decision-making process among women (and their husbands) with regard to their acceptance of prenatal diagnosis and termination of pregnancy.

Keywords: Consanguineous marriages, counseling, education, frequency, recessive genes, religious intervention.

INTRODUCTION

Even though most people accept that consanguinity can have a deleterious effect

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on the health of the offspring, mainly due to the expression of rare, recessive genes inherited from a common ancestor(s), the fact that such marriages have been a deeply ingrained part of the social, cultural and religious fabric of the communities in which they have been practiced worldwide for many hundreds of years indicates that the advantages of this type of union are generally perceived as greatly outweighing the disadvantages [1]. The main reasons for the continuation of the practice are preservation of property, especially land, and the desire to keep this within the family, and the popular belief that intrafamilial marriage offers advantages in terms of compatibility of the bride with her husband's family, where the bride herself finds it reassuring to marry into a known family background. A more detailed account is given in Chapter 3.

Generally worldwide, for most people the family remains the main source of social security [2]. In communities in which consanguineous marriages are common, the existence of multiple family ties confers strong reciprocal obligations on family members to assist each other when in need. The large, close family structure offers protection for socially or medically disadvantaged members, and as a result relatively less stigma might be attached to inherited conditions. Because of this, efforts to alter the marriage pattern on medical grounds could undermine the very support systems that enable people to cope with genetic disadvantage. Prosperity and social stability can reduce the need for strong family ties and economic development might eventually reduce the frequency of marriage between cousins. However, such changes have to be allowed to take place in their own time, as external efforts to accelerate them might be particularly harmful for the less advantaged members of society. Indeed, the loosening of family ties is a recognized social problem of modern societies [2].

MEDICAL RISKS OF CONSANGUINEOUS MARRIAGES

One factor that should be borne in mind is that a certain degree of over-reaction has over the years accompanied discussions about the medical dangers of consanguineous marriages. There is no doubt that couples who are close biological relatives are at a higher average risk than non-related spouses of giving birth to a child who has inherited a genetic disorder that otherwise is very rare in the general population, but in a large majority of families where the spouses are first cousins this

extra risk is small, and comparable to other non-genetic risk factors, such as maternal alcohol ingestion during pregnancy [3]. When the actual increase in the risk over the background risk in the general community is computed, it is estimated to be about 1.7-2.8% above the background [1, 4], although other studies put the risk somewhat higher; Bittles and Neel, in a multi-national meta-analysis of deaths from late pregnancy to approximately 10 years of age, found there was a 4.4% excess in early mortality among first cousin offspring [5].

There is also a difference in the risk for first-time cousin couples with no background of consanguinity among their parents, grandparents *etc.*, compared with couples whose family history on both sides includes multiple consanguineous marriages going back through many generations [6, 7]. First-cousin couples with no family background of multiple consanguineous marriages have a lower risk of affected offspring. This is partly because the likelihood that both spouses will inherit the same deleterious gene from the common ancestor is lower because there will be fewer common genes than in cousin couples with a family background of multiple consanguineous marriages. Also, in first-time cousin couples, there is no founder effect operating with regard to deleterious mutations.

The argument has also been put forward that the risk to the offspring born to a woman over the age of 40 is of similar magnitude to that for consanguineous couples, yet such women are not prevented from childbearing, nor is anyone suggesting they should be, despite the equivalent risk for congenital anomalies [8].

Bittles and Black made the point that consanguineous marriage remains a subject that arouses fierce debate in many parts of the world, with opinions expressed on all sides [9]. They noted that unfortunately, and far too often, these opinions are based more on prejudice than fact, and that the highly publicized interventions of possibly well-meaning, but certainly under-informed, politicians have also been notably unhelpful in promoting informed discussion. An example of such interference is the case of the British environment minister Phil Woolas, who, in 2008, sparked a major row in the United Kingdom when he attributed the high rate of congenital anomalies in the Pakistani community to the practice of marriages between first cousins. He told one of Britain's most popular Sunday

newspapers: "If you have a child with your cousin, the likelihood is there'll be a genetic problem". While a Muslim activist group demanded that Woolas be fired, most of his constituents would certainly have shared Woolas' view that the risk to offspring from first-cousin marriage is unacceptably high – as would many Americans [8].

Over-emphasis on the contributory role of consanguinity alone to ill-health has resulted in numerous misconceptions among health care practitioners and also among the general public. It also has caused unease and upset in communities that have traditionally favored consanguineous marriage [9].

A dramatic account of one American woman's experience when she told her doctor that she was pregnant by her first cousin confirms that in some cases a lack of knowledge of the actual situation regarding consanguinity can have severe consequences. This woman was an anonymous participant in an on-line support group for cousin romances in August 2000, and was quoted by Bennett *et al*. [4]. She described how she was "madly in love" with her first cousin and became pregnant by him. She went to see her gynecologist, who was "stunned" and said that he had never come across such a situation in all his years of practice. He informed her that the baby would be "sick all the time" and suggested that she have an abortion. She was horrified at the idea. He later informed her that it was illegal for them to be married, but it was legal to have the baby. Her cousin then told his mother about the pregnancy, and she went "nuts", saying that the baby would be retarded. The woman then went ahead and had an abortion, since she reasoned that if that was what the doctor recommended, it must be the right thing to do. However, she described this as "the worst mistake of my life", especially after she watched a program on television a year later about cousin couples, in which it was stated that such couples only have a 3% higher chance of something being wrong with the baby than that of "normal" couples. The poor woman was absolutely distraught, and said that "if only I had seen this show a year sooner my doctor would have known the facts".

This is a stark illustration that even as relatively recently as about 15 years ago, this experienced gynecologist in the United States apparently did not have the first idea about the real facts of consanguineous unions, resulting in the totally

inaccurate and devastating advice that he gave to the patient. The attitude of her boyfriend's mother could possibly be partially excused on the grounds that she would not be expected to have any scientific knowledge, although she apparently also overreacted in a somewhat hysterical manner.

The main point that the above example illustrates is that in countries such as the USA, where the incidence of consanguinity is generally extremely low, even highly qualified professionals lack knowledge and experience of what is an everyday event in, for example, most of the Arab countries. It is this that gave rise to the wholly out-of-proportion reaction of this gynecologist. While this particular gynecologist is just one of millions, if his reaction is the norm among American (and other Western) gynecologists, this is an indication that there is an urgent need for education and dissemination of information about the true facts of consanguinity in Western countries, especially with regard to the future as immigrants from countries in which it is common are in increasingly large numbers making their homes in European countries and the United States.

Notwithstanding the above comments, even though the risk to the offspring of individual first-cousin couples is not so high when compared to the general background risk, when the frequency of consanguineous marriages in a community is high, with the majority of these marriages being between first cousins, the overall risk in the community as a whole can reach an unacceptably high level – especially when there is one (or more) specific genetic disease(s) segregating in that specific population.

In recent years there has been a general overall reduction in the frequency of consanguineous marriages worldwide, although the current rates in most of the countries where this type of marriage is traditionally prevalent are still unacceptably high, and therefore strategies to reduce these rates are essential.

OVERVIEW OF THE GENERAL TREND OF A DECLINE IN THE WORLDWIDE RATES OF CONSANGUINEOUS MARRIAGES

In the **Indian subcontinent**, a definite decline has been observed in the past three or four decades in Andhra Pradesh and Tamil Nadu, and due to recent changes in

the demographic and social situation in these states, this decline in consanguinity is thought likely to continue [10]. There has also been a general trend of decline in consanguineous marriages in the southern part of West Bengal and eastern part of Assam among the Bengalee Muslims [11], and among the Kamma of Andhra Pradesh from 1950 [12]. The decline in uncle-niece marriages has contributed heavily to the decline in consanguinity, which may be due to shifting from agriculture to other occupations like government service and the rapid growth of industrialization. More recently, the tendency toward a lower consanguinity rate has been strengthened by a reduction in the number of children per marriage, which reduces the number of eligible cousins. Marriages beyond first cousin have on the whole remained constant [12].

A decrease in the incidence of consanguineous marriages was observed in **Japan** during the period from 1942 to 1983, based on the observed decrease in the incidence of major autosomal recessive disorders by between 40 and 80% during this period [13].

In the **Arab countries**, similar trends have become apparent. A study in **Jordan** found that the first-cousin marriage rate among a representative population from Amman showed a significant decline among marriages contracted after 1980 compared to marriages contracted between 1950 and 1979, but not to marriages contracted before 1950. The proportion of first-cousin marriages between paternal parallel first cousins showed a steady decline from one generation to the next [14]. Another study showed that in **Bahrain**, the rate of cousin marriage was 39.4% in the present generation, whereas it had been 45.5% in the previous generation, indicating a high rate of consanguinity that decreased significantly over time [15]. In **Lebanon**, Khlat also found a decrease over time in the rate of consanguineous marriages; the mean percentage dropped from 30% before 1950 to 25% between 1950-69, and to about 20% starting from 1970 [16].

A survey conducted in the **Israeli-Arab** community revealed a similar pattern [17]. Four Arab towns were studied and the trends in the rates of consanguineous marriages analyzed. Even though these four locations may not have been completely representative of the situation in the country as a whole (all were in the same geographical area in the center of the country), nevertheless the findings

do reflect a trend that is consistent in at least the larger Arab towns and villages in Israel (personal communication). The frequency of consanguineous marriage in these four locations was highest in the period 1961–1965 (50.6%), but by the period 1981–1985 it had decreased to 40.6%.

In another survey within the Israeli-Arab community, statistically significant declines in consanguinity were found for the Muslim populations of northern Israel, since 1965, and for Jerusalem, since 1949. However, for the Bedouin of southern Israel only a temporary decline was found. Significant declines in consanguineous marriages were also found among the Druze of northern Israel after 1982. It is thought, though not definitively proven, that the declining rates are associated with the increasing levels of education and urbanization that are known to have occurred in these populations [18].

A third survey in the Israeli Arab community explored the frequency of consanguineous marriages during two periods (1980 – 1985 and 2000 – 2004) in relation to the socioeconomic status of four selected Arab villages in northern Israel, two of which have high socioeconomic status and two of which have low socioeconomic status [19]. The authors found that the average incidence of consanguineous marriages slightly decreased from 33.1% in the first period to 25.9% in the second period in all four villages. Interestingly, marriages between first cousins showed a more significant decrease, from 23.9% in the first period to 13.6% in the second period.

A study in the **Palestinian Territories** also showed a reduction over time – prior to 1983 the rate of total consanguineous marriages was 54.1% and of first cousin marriages 32.7%, whereas in 2004 the total rate was 36.4% with first-cousin marriages 22.2% [20].

The reasons given for the decline in the frequency of consanguineous marriages in the majority of the populations in which this is prevalent are many. These include the transition from agriculture to other occupations and the rapid growth of industrialization, more mobility from rural to urban settings, and the improving economic status of families. Others are a greater awareness among the population generally of the association between genetic diseases and consanguinity,

increasing higher levels of female education, and a decline in fertility, resulting in lower numbers of suitable relatives to marry [21].

STRATEGIES TO REDUCE THE PROBLEMS ASSOCIATED WITH CONSANGUINITY

Attempts to reduce the incidence of consanguineous marriages should be undertaken with tact and diplomacy together with an insight into and knowledge of the cultural and societal norms of the communities concerned. Such programs should be cognizant of the needs of the community and be sensitive to its traditional values [22]. As mentioned above, efforts to alter the marriage pattern on medical grounds could undermine the support systems that are so essential in the event of genetic (or indeed any) illness in the family [2]. Also, Jaber *et al*. pointed out that to suggest to the young generation that the norms of their parents are bad could lead to all kinds of intrafamilial strife, with the children losing respect for their parents and possibly even blaming them for causing illness in siblings and other relatives [1]. The authors also commented that such a situation could result in the break-up of not only the families, but of the community as well. Additionally, as has been mentioned above, although most people do accept that the practice of consanguineous marriage has disadvantages, many feel that these are greatly outweighed by the advantages, and that to stop the practice on the grounds of possible medical problems would deprive them of all the benefits [1].

EDUCATIONAL PROGRAMS

The main factor in establishing educational and counseling programs aimed at reducing the frequency of consanguineous marriages among the members of those communities in which it is high is to identify the target group(s) who would benefit most from such programs – this is discussed in more detail in Chapter 6. The success of the programs is measured by a reduction in the rate of these marriages among the participants. The programs should be based on educating the populations in question about the risks of congenital malformations, with a basic description of genetics and the biological process that results in the transmission of autosomal recessive diseases. While it is reasonable to convey the message that consanguineous unions are not discouraged when love is involved, it should nevertheless be emphasized that this type of marriage should not be encouraged.

Educational programs should be prepared bearing in mind the specific cultural and social norms of the target group(s). They should be planned at a level of complexity that the participants can understand and identify with; there is no point in being over-scientific if the audience will have no idea what the speaker is talking about. It is also extremely important to take great care to avoid any controversial or contentious material, since this would cause the participants to take offense and result in their not taking any interest in the main thrust of the subject matter, thereby defeating the whole purpose of the exercise. Inaccurate information can also do more harm than good and would eventually interfere with the successful implementation of the program [23].

Kisioglu *et al*. carried out a study in 2007 to determine the effects of a formal training program on consanguineous marriages on the knowledge of, and attitudes towards, consanguineous marriage of high school students in the Mediterranean region of Turkey [24]. The training program included a 45 minute presentation and handouts about the subject prepared by two medical doctors who were specialists in public health education. This was followed by a 30 minute discussion session to improve the effectiveness of the program. Prior to the commencement of the program, a questionnaire was given to the students consisting of 37 questions, and after completion of the program, post-tests were administered.

Students who received the training were compared with those who did not receive any formal training about the subject. After the post-tests were administered, data were collected and analyzed statistically. Significant differences in knowledge and attitudes were demonstrated among the students who had received the formal training program compared with those who had not. Also, the results suggested possible peer influence between the students who had received the program and those who had not. This study offers strong evidence that educational programs can and do make a difference to the students' level of knowledge, but since this is a recent study, it is still too early to know whether or not there has been a reduction in the frequency of consanguineous marriages among the students who underwent the training program [24].

Hamamy *et al*. reported a proposal for a national strategy for the care and prevention of congenital anomalies in Jordan [23]. This was based on the

workshop: "National strategies for the prevention of genetic and congenital disorders" held by the Jordanian Ministry of Health in collaboration with the World Health Organization in October 2005. While the recommendations detailed in this paper are set out with respect to the circumstances in and requirements of Jordan, they could very well apply to most, if not all, of the countries in which the rate of consanguineous marriages is high.

The authors point out that the magnitude of the problem of genetic and congenital disorders in Jordan can be attributed to several factors, including the high consanguinity rate, the lack of public health measures directed at the prevention of congenital and genetically determined disorders, the dearth of genetic services, and an insufficient number of trained health professionals in the area of medical genetics. There is low genetic literacy among both the health sector and the public, and a lack of awareness about genetic risks and possibilities for care and prevention of congenital anomalies. Community services may be restricted by cultural, legal and religious limitations, such as the fear of families with genetic diseases to be stigmatized within their community, as well as by the legal and religious restrictions on selective abortion of an affected fetus [23].

Consanguineous marriages are common in Jordan – 20-30% of all marriages are contracted between first cousins. The Jordanian public is generally becoming more aware of effective services like genetic testing and risk assessment, and many of the families seen at the genetic clinics request better access to effective facilities for diagnosis, care and prevention. Increased awareness among the general public about the role of genetics in disease and the tremendous advances in medical genetics in recent years have had a considerable impact on the practice of medical genetics in Jordan [23].

The authors note that prevention of congenital and genetic disorders at the population level depends on a combination of basic public health measures and the education and involvement of the primary health care network. Such measures include interventions to reduce the burden imposed by genetic and congenital disorders and consist of premarital screening and counseling, preconception counseling, and prenatal counseling, screening, and testing with the option of the termination of an affected fetus or prenatal and neonatal management [23].

The strategies described by the authors for the care and prevention of congenital anomalies include commitment of policy makers, education and training in the context of community genetic services, education of the public, consideration of ethical, legal, religious and cultural issues, population screening programs, the creation of a birth defects Registry, and the establishment of genetics centers and introduction of new technology. Planned prevention programs should be cost effective and should take into consideration local beliefs and social attitudes. In Jordan, premarital screening and preconception counseling as preventive measures are more acceptable than therapeutic abortion. Primary health care workers are not adequately trained to deal with common genetic disorders and therefore need to be educated in both basic scientific principles of genetics and in the ethics and practice of genetic counseling. Genetic counseling for high-risk individuals or families or people with unfavorable test results is provided by specialists [23].

The authors point out that an essential component of any community genetics program is to define ethical standards. The public in general, religious leaders, many politicians and some health professionals may not feel comfortable with the very rapid advance in the science of genetics and molecular biology, and it is therefore important to alleviate fears so that community genetic services become widely acceptable and sought. Generally the main ethical standards required are that genetic services should reach all those in need, education of the public should be addressed, and the services should not contradict cultural and religious beliefs. Definition of guidelines are essential, including for prenatal genetic diagnosis, selective therapeutic abortion of an affected fetus, premarital screening programs, newborn screening programs, premarital counseling, and counseling and media messages on consanguinity [23].

Hamamy *et al*. consider education of the public to be of vital importance, since ignorance and misconceptions could be barriers to the implementation of community genetic programs [23]. Organized information, education and communication need to be disseminated to the population in general through different channels that include school curricula and media messages. Education is a prerequisite to screening programs, since a well-informed individual is able to

take responsible decisions. School curricula could include basic principles of human genetics, and information about both common genetic disorders in the community and screening programs. Education of the population in general could be overseen by trained primary health care workers. Health pamphlets addressing methods for the prevention of genetic and congenital disorders could be published, and mass media educational campaigns must be scientifically based and appropriately delivered. As always, these campaigns must respect local cultural and religious beliefs and avoid controversial issues.

Education in basic scientific principles of genetics and in the ethics and practice of genetic counseling should be provided for health workers. This should include training in recording a basic genetic family history, taking account of the complexities of large families with multiple consanguineous marriages. Guidelines in counseling on consanguineous marriages are of paramount importance, particularly as consanguinity is a sensitive issue in communities where half of all marriages are consanguineous. Evidence-based guidelines regarding consanguinity in genetic counseling settings should be developed and educational material should be prepared to clarify these guidelines [23].

That educational programs can be at least partially responsible for achieving the desired outcome and reducing the rates of consanguineous marriages in certain populations has been borne out by the fact that the practice has declined over the years in some communities in which it used to be very common. For example, the frequency of these marriages in certain parts of the Israeli Arab community has been reported to have declined from 52.9% in 1970 to 32.8% in 1998 [17], and it continues to drop (personal communication). During the 1990's there was a concerted effort to make health education regarding the genetic disadvantages of consanguineous marriages available to the whole Israeli Arab population, especially *via* the media. However, no studies were carried out either before or after the media campaign to assess the general level of awareness within the population as a whole with regard to the possible health problems associated with consanguineous marriages. Therefore it is not possible to assess accurately what impact, if any, the educational efforts had on the incidence of these marriages [17].

THE ROLE OF RELIGIOUS LEADERS

Another important factor to consider for Muslim couples is the effect of involving a Muslim cleric. There are two aspects – whether religious intervention to discourage the practice of consanguineous marriage would be effective, and whether the participation of a Muslim cleric or physician might influence the decision-making process among women (and their husbands) with regard to their acceptance of undergoing prenatal diagnosis and, in the event of a severely affected fetus, termination of pregnancy (TOP).

Ahmed *et al*. conducted a study based in northern England among members of four faith communities – Pakistani Muslims, Indian Hindus, Indian Sikhs, and African-Caribbean Christians [25]. The aim of the study was to explore the views of members of these communities towards TOP for sickle cell disorders and thalassemia major, and to determine the influence of faith and religion, the perceived severity of the conditions, and the role of religious and community leaders in the decision-making process.

TOP is not specifically prohibited in the Indian Sikh and Indian Hindu religions, and for followers of these religions such a decision can be made by the individual. Sikhism specifically teaches "prevention of suffering", and this is an important factor in making decisions about terminating an affected pregnancy. The other groups considered that TOP was prohibited both in Islam and Christianity; however, like the Indian Sikh and Indian Hindu groups, most of the Muslim and Christian participants said that their reproductive decisions would be based on their personal moral judgments and beliefs. In the Pakistani Muslim groups, following information about Fatwas permitting TOP for thalassemia, some people said that they would still not consider it because of their own moral beliefs. They added that Fatwas could be interpreted in various ways; for example, they had been produced in developing countries (Lebanon, Saudi Arabia, Pakistan) and may not be applicable to Western countries for thalassemia, since treatment there is more readily available and children are therefore less likely to suffer in the same way as in developing countries. Most of the parents of children with thalassemia major stressed a preference for prenatal diagnosis and TOP within the first trimester because of their religious beliefs [25].

The authors noted that the Indian Hindu, Pakistani Muslim and Indian Sikh groups generally believed that thalassemia major resulted in a lifetime of suffering for the affected child and, therefore, TOP was justified. These groups also thought that a child with thalassemia was perceived to have an adverse impact on parents and siblings. For them, therefore, the prevention of a child's suffering was perceived as more important than becoming a "sinner" through opting for TOP. Similarly, the African-Caribbean Christian participants said they were more likely to opt for termination if they were certain that the baby would have a form of sickle cell causing the child to "suffer". However, they commented that the decision about TOP was complicated by the uncertain prognosis of sickle cell, and would decide against it if there was a possibility that the child may not have the serious form of the condition [25].

Regarding the role of religious leaders, all the participants said that they would not consult a religious leader for advice on prenatal diagnosis and TOP. They said that this was because religious leaders were more likely to give biased opinions than advice based on medical knowledge, and were unlikely to understand the severity of the conditions and their impact on the affected child and family. Most of the participants believed that religious leaders would advise against TOP and state that religion prohibits it, rather than provide information that would allow people to make their own decisions. They also believed that different religious leaders were likely to give different advice, possibly because they were from different countries and/or sects of Islam. Religious leaders were also perceived to be "out of touch" with young people's needs. The authors found that overall, none of the groups believed that there was a role for religious leaders in the reproductive decision-making process because this was a very personal issue that was between the individual and God [25].

A service for prenatal diagnosis of β-thalassemia was introduced in Pakistan in May 1994 [26]. Two renowned Islamic scholars, who were consulted before the service was introduced, ruled that it is permissible to terminate a pregnancy if the fetus is affected by a serious genetic disorder and if termination is carried out before 120 days (17 weeks) of gestation. During the first 3½ years of the service 300 couples asked to be tested. Most diagnoses were made between 10 and 16 weeks of gestation, and only 15 (5%) after the 16th week.

In a study published in 2005, Neter *et al*. examined attitudes towards TOP among Israeli Arab-Muslims who were or were not at high-risk for cystic fibrosis (CF), and they also examined the effect of intervention, which among other things related specifically to TOP [27]. The study consisted of three groups: an intervention group at high risk for CF – these participants received community genetic counseling – a control group at high risk for CF, and a control group from the general population. The latter two groups received only minimal intervention. Attitudes were measured two or three times during a 1-year period. Predictors that an affected fetus would be considered a legitimate cause for TOP included religiosity and familiarity with an affected child. Predictors that an individual would choose abortion in the case of an affected fetus were education and age. No change occurred in the attitudes of any of the participants over the course of one year.

The intervention consisted of lectures given by a nurse educator, a geneticist and an imam. The nurse educator and the geneticist talked specifically about hereditary diseases, CF and its effects, carrier screening tests, consanguinity and prenatal diagnosis, while the imam focused on Islamic rulings regarding genetic counseling and specifically TOP. He informed the participants that a Fatwa that was first issued by the Islamic Jurisprudence Council in 1990 and re-issued by the Mufti of Jerusalem allowed TOP in the first 120 days after conception if the mother's life is in danger or the fetus is affected by a disease. He also discussed the situation of a family having children affected by diseases. The lectures were followed by a question-and-answer session, and the participants completed self-administered questionnaires before the intervention, immediately after it, and a year later [27].

Analysis of the reactions of the participants to the possibility of having an affected fetus found that only a minority would not consider abortion (11.8%), and an additional 8.5% did not know how they would react. Most of them would consider abortion (42.4%) or consult with others – family members, a physician or a cleric (76.9% of responders and 55.1% of responses). The person they would consult with most frequently was the family physician. The participants who were more religious were less inclined to consider that the fact a fetus was affected was a reason for abortion, whereas participants who were familiar with the situation of

an affected child or saw more benefits in a diagnostic test for CF were more inclined to accept that an affected fetus did justify abortion [27].

Bedouin Arabs constitute a Muslim traditional ethnic minority in Israel. Shoham-Vardi *et al*. carried out a study in 2000 among Bedouin living in southern Israel, in which they conducted semistructured interviews with 83 women in order to study their attitudes towards and practice of TOP following an unfavorable prenatal diagnosis [28]. Most of the women had low levels of education and approximately half were in consanguineous marriages. About half the women said that in the case of a severely affected fetus, termination would be permitted. One rationale given was that this would spare the suffering of both the child and the mother, while another was that a sick child would "interfere with the mother's obligations to her family". About half the women thought that termination is never permitted, while smaller numbers said that it is not permitted after the fourth month (36%), or that it is only permitted in the first three months (9%). Just over half said they thought it was permitted at any time [28].

Those women who did not anyway mention whom they would consult before making a decision were asked that question. About one-quarter said that they would decide without consulting anyone. The most common attitude was that the decision should be made on the basis of a proper medical opinion, by which they meant a unanimous opinion given by more than one physician. The rationale for desiring several medical opinions was to avoid wrong diagnoses, which, they thought, were very common [28]. This attitude was based on the previous experience either of the woman herself or of her family members or neighbors. While some of these experiences might have been true false-positives, most of them reflected failures of the medical system to communicate risk information properly, resulting in the women's interpreting risk, on the basis of screening, as a definite diagnosis. Therefore, when a diagnostic test showed that the fetus was, in fact, healthy, the women were convinced that this meant that the result they had been given after the screening test was "wrong", because they were interpreting that as the actual diagnosis [28].

Very few women said that they would consult a religious figure regarding the decision to terminate in the event of a severely affected fetus, and even fewer

mentioned extended family members. Consulting with a religious authority was more likely to be associated with a decision not to terminate, whereas requesting a second medical opinion was usually associated with an intention to terminate an affected pregnancy [28].

The authors pointed out that offering prenatal screening becomes a real challenge when information is to be given to populations with low levels of education, where there are language and sociocultural barriers between the providers and the patients, and where termination is believed to be forbidden by religion. Overcoming language barriers was one of the reasons why many Bedouin women expressed a wish to consult an Arab physician [28]. The authors commented that the main issue is to inform patients clearly and fully in their own language about the multistage process of prenatal diagnosis and of the decisions to be made at each stage. For Muslim populations, a culturally acceptable screening program must be based as far as possible on tests that can be performed in the early stages of pregnancy. The program should actively involve local religious authorities who will inform the families about the Fatwa that allows termination of pregnancies of severely affected fetuses up to 120 days gestation [28].

A recent study by Jaber *et al*. analyzed the possible impact of the involvement of a Muslim cleric or a Muslim physician in the decision-making process among Israeli Arab Muslim mothers of children with severe defects regarding prenatal testing and termination of future pregnancies [29]. The authors investigated: 1) How many of 250 Israeli Arab mothers of babies with severe congenital anomalies had undergone prenatal testing during pregnancy, and how many had refused TOP when this had been recommended; 2) Why they had refused TOP; 3) Their attitudes regarding prenatal testing and TOP in future pregnancies; and 4) Whether the women would have changed their decision if they had been able to talk to a Muslim cleric or Muslim doctor in addition to the regular personnel.

Among the 250 women interviewed, 50% were married to a relative, of whom 32.4% were married to a first cousin. These figures showed that the rate of consanguineous marriages among the families with genetic disorders was considerably higher than the average in the Israeli Arab population as a whole, which, at the time of the study – 2007 – was ~32% [17].

The results of the interviews showed that 87 women (35%) refused to even consider TOP, 55 (22%) agreed to undergo TOP, and 87 (35%) agreed provided the procedure would be performed before 120 days gestation. The remaining 21 women (8%) were undecided. When the 55 women who agreed to TOP were excluded, the remaining 195 (78%) were asked whether the addition of a Muslim religious cleric or Muslim physician to the Hospital Committee for TOP would influence them to change their opinion. With the addition of a Muslim cleric, 89 women (46%) said they would now agree if it were recommended, 74 (38%) said that this would make no difference and they would still refuse, 26 (13%) agreed only on condition that it would be carried out prior to 120 days of gestation, and six (3%) were still undecided. With the addition of a senior Muslim physician to the Hospital Committee for TOP, 55 women (28%) said they would then agree to TOP if recommended, 128 (66%) said they would not change their opinion and would continue to refuse, and 10 (5%) would agree only on condition that it would be carried out prior to 120 days gestation; two (1%) were still undecided. These responses indicated that from the religious angle they would trust the opinion of a religious cleric more than one-and-a-half times as much as that of a physician [29]. This response is interesting, as it is in direct contrast to that of the participants in the survey by Ahmed *et al*. [25], all of whom said that they would not consult a religious leader for advice on prenatal diagnosis and TOP for the reasons detailed above. This difference may partly be due to the fact that all Ahmed's participants were resident in England, a western country with western attitudes and values which, in spite of the fact that the participants were all immigrants, must nevertheless have influenced them to a significant extent, whereas the participants in the survey by Jaber *et al*. [29] were resident in Israel and were guided by the prevailing values and mores of their community that had remained constant for centuries.

This study [29] indicated that among Arab Muslim mothers of severely affected children there was a high degree of opposition to TOP in the event of a subsequent severely affected fetus, even when the existing children had been hospitalized for prolonged periods of time or had undergone major surgical procedures. In general, those women who underwent any part or all of the triple test, early ultrasound examination or the extended ultrasound examination were

more likely to be willing to agree to consider TOP, as were women who underwent amniocentesis. The authors commented that it might be useful if the Hospital Committees for TOP, which currently comprise a gynecologist, neonatologist and a social worker, were to ask the Muslim couples appearing before them whether they would consider it valuable to include a Muslim cleric in order to help them with any queries or doubts of a religious nature that they may have, and, if they agree, to invite such a cleric to sit on the committee during the interview.

A similar study in Saudi Arabia examined the attitudes of Saudi families affected with hemoglobinopathies towards prenatal diagnosis and abortion, and evaluated the influence of religious rulings on such attitudes [30]. Alkuraya and Kilani interviewed 32 families, 23 (71.9%) of whom were consanguineous, using a pre-structured questionnaire, which covered sociodemographic data, degree of suffering, prior genetic-related knowledge, attitudes towards prenatal diagnosis and factors influencing it, attitudes towards abortion, practice of family planning, and attitudes towards consanguinity. The authors then examined the effect of knowledge about the religious ruling (Fatwa) that indicated that abortion is permissible if a diseased fetus is diagnosed in the first 120 days. The parents were not aware of this Fatwa and were informed about it at the end of the first part of the questionnaire. They were then asked the same questions again regarding their attitudes towards prenatal diagnosis and abortion.

Twenty-six families (81.3%) accepted prenatal diagnosis, whereas four (12.5%) refused it and two (6.3%) were not sure. Twenty (62.5%) agreed to preimplantation genetic diagnosis. Four participants (12.5%) said they would abort the affected fetus regardless of gestational age and even before the Fatwa was discussed with them. In all, 28 (87.5%) participants refused the idea of abortion; 27 (96.4%) of them stated religious reasons for their rejection. Of these 28 participants, 13 (46.4%) changed their minds after they were told about the Fatwa on abortion, 14 (50%) did not, and one (3.4%) was undecided. All of the 13 participants who changed their minds after being informed about the Fatwa agreed to prenatal diagnosis, as compared to nine of the 14 (64.3%) of those who refused the idea of abortion even after the Fatwa had been explained to them ($p = 0.017$). Similarly, all four (100%) of those who agreed to abortion prior to learning about

the Fatwa agreed to prenatal diagnosis. Of interest is that the Fatwa education resulted in more participants accepting abortion, but did not increase the overall number of participants who accepted prenatal diagnosis. Of the four families who refused prenatal diagnosis, two attributed their refusal to the fact that it is "all in the hands of God", and they should "not interfere with God's will". The reason given by the other two was they did not want to be worried. All four families continued to reject abortion even after knowing about the Fatwa [30].

Overall, the implementation of educational and counseling programs is beginning to have an effect on reducing the frequency of consanguineous marriages. However, fundamental changes to the way of life that has been the norm for generations occur slowly and efforts to try to speed up the process could cause societal and familial disruptions. It is better, therefore, to allow these changes to take place at their own pace, and meanwhile and in parallel to promote genetic intervention in order to reduce the number of births of children with genetic disorders to consanguineous families. This topic is addressed in chapter 8.

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CONFLICT OF INTEREST

The authors confirm that this chapter contents have no conflict of interest.

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CHAPTER 8

Future Strategies 2 – Genetic Perspectives – Counseling, Screening, Testing, Research, and Intervention

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Abstract: Premarital and preconception genetic counseling are very important in highly consanguineous populations. In many traditional Arab societies, family-oriented genetic counseling offers an excellent approach in the prevention of genetic disorders. In most of the Arab countries, many of the towns and villages are, in effect, closed communities, in which the residents mainly marry within their own community. Within each town or village there can be at least one, and often more, autosomal recessive disease(s) that is/are exclusive to the residents of that specific location. Identifying the molecular basis of these diseases can enable genetic counseling and genetic screening, and therefore may greatly reduce the number of affected infants born. Methods used to identify the genes responsible for causing specific diseases include sequencing of specific genes, linkage analysis, homozygosity mapping and exome sequencing. Homozygosity mapping aims to identify the candidate region in which the causative gene is situated. Next generation sequencing techniques include exome sequencing; this focuses on only the protein-coding portion of the genome and is a powerful and cost-effective method for elucidating the genetic basis of Mendelian disorders with hitherto unknown etiology. Once the causative gene for a specific disease has been identified, prenatal diagnosis by mutation testing in CVS or amniocytes can be carried out and termination of pregnancy offered in the case of an affected fetus. Preimplantation genetic diagnosis is described; this is a technique used to analyze embryos genetically before their transfer into the uterus in order to enable only unaffected embryos to be transferred.

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INTRODUCTION

The adverse health effects associated with consanguinity are in the main caused by mutations in rare recessive genes inherited from a common ancestor(s). The closer the biological relationship between the parents, the greater is the probability that their offspring will inherit identical copies of disease-causing mutated recessive genes. As a result, autosomal recessive diseases are common in populations with a high rate of consanguinity, and the prevention of these diseases in consanguineous populations is of great importance.

GENETIC COUNSELING AND SCREENING OF CONSANGUINEOUS COUPLES

Preconception genetic counseling for consanguineous couples is considered very important amongst the community genetic services in highly consanguineous populations [1]. Premarital counseling is another service that is increasingly demanded in some countries and communities where consanguinity rates are still high and termination of the pregnancy of an affected fetus is not feasible and/or not acceptable. Marriage in many such countries is considered to be a family decision and not just the couple's decision, although the frequency of "arranged marriages" may be declining in recent years because an increasing number of women are reaching university level education, which gives them a wider choice of marriage partner.

In many traditional Arab societies, there is a low level of genetic literacy among the public and most health care providers [2]. In such communities, family-oriented genetic counseling offers an excellent approach in the prevention of genetic disorders, and family members understand the condition better if they have had direct contact with an affected child. The aims of this counseling are to inform relatives of their at-risk status, and genetic registers incorporating long-term follow-up and a proactive approach to at-risk subjects have been

recommended as a means of improving access to genetic counseling for affected families. An additional aim is to inform families what the implications of a carrier status are, and where the carrier status cannot be diagnosed, to advise them of the possibility that future affected pregnancies could be circumvented by avoidance of marriage with close biological relatives. However, the right of family members to have access to this information may conflict with the proband's right to confidentiality. Initial World Health Organization (WHO) guidelines on ethical issues in medical genetics suggested that, where appropriate, counselors should inform clients that genetic information could be of importance to their relatives and under these circumstances, individuals might reasonably be invited to request their relatives to seek genetic counseling [3]. However, a more recent WHO report proposed that respect for patient confidentiality may need to be considered alongside the rights of other family members for whom information about genetic risk could influence decision-making on their own health or reproductive choices [2, 4].

In offering preconception counseling for consanguinity, it is essential to distinguish between families with a known genetic or inherited disorder and those with no known such disorder by taking a detailed family history and constructing a four-generation pedigree [1]. Specific questions addressed to the couple could help in determining whether a genetic or hereditary disorder was present in the extended family. These could include inquiry about certain conditions in blood relatives, such as birth defects or congenital anomalies, early hearing or vision impairment, intellectual disability, learning disability or developmental delay, failure to thrive, inherited blood disorder, unexplained neonatal or infant death in offspring, and any other undiagnosed severe condition.

A paper by Shaw and Hurst describes in detail the results of an investigation into the understanding of genetics, illness causality and inheritance among British Pakistanis referred to a genetics clinic in England [5]. The results, which are discussed more fully in Chapter 6, revealed widespread misconceptions about genetic mechanisms of inheritance and skepticism of genetic theories of illness. This paper provides a wealth of evidence that genetic counselors, and indeed other health professionals as well, who work in Western countries and for whom consanguinity might previously have been merely something they may have read

about but not personally encountered, need to become experts when working with immigrant communities such as Pakistanis in order to be able to identify, work with, and possibly challenge patients' understandings of illness causality and inheritance. If current demographic trends continue, and more and more people from countries where consanguineous marriages are common migrate to Western countries, the onus on health professionals, especially those in genetic units, to be able to understand, empathize and work with the immigrants on a level with which the immigrant feels comfortable will be enormous and extremely challenging. It is particularly important for counselors to avoid the pitfalls of appearing to be paternalistic or judgmental when dealing with individuals from backgrounds where consanguineous marriage is the norm, and to remember that for these immigrants, one of the main pillars of the lifestyle of their community is being called into question by denying the validity of these marriages.

A study by Fathzadeh *et al*. investigated the reasons for referral to a genetic counseling center in Shiraz, southern Iran [6]. During a 4-year period, 2,686 couples came for genetic counseling. Of these, 85% were in consanguineous relationships (1.5% double first cousin, 74% first cousin, 8% second cousin, 1.5% beyond second cousin). The main reasons for referral were premarital counseling (80%), with 89% consanguinity, followed by preconception (12%), postnatal (7%), and prenatal counseling (1%), and a family history of medical problem(s) and/or consanguinity was the main indication for referral in nearly all the families.

In this study, the majority of the couples were premarital, and therefore they were not yet actually consanguineous. The authors commented that it might be argued that premarital genetic counseling would involve a decision about whether or not to marry, but they pointed out that in their experience familial and social ties compel the vast majority of couples to go ahead and marry anyway, despite the genetic risk. In other words, couples in Iran who receive premarital genetic counseling have already decided to marry, and therefore the genetic counseling service does not involve this type of decision. Some consanguineous couples are aware of the risk, and they request genetic counseling in order to find out whether there is treatment for the genetic condition in their family [6]. The authors suggest that since these couples seek a genetic consultation as a result of societal awareness and/or physician recommendation, follow-up studies of premarital

couples would be worthwhile in order to assess whether or not they go on to marry. If some couples decide not to marry, it would be interesting to determine whether their decision was based on information obtained through genetic counseling about the risk to offspring.

The authors noted that the efficacy of genetic counseling services in Iran depends on several factors. There should be intensive public education concerning consanguinity and genetic counseling, including incorporation of educational materials relevant to premarital consanguinity and genetic counseling into the high school curriculum. Preventive genetic counseling should be undertaken at premarital referral together with determination of genetic diagnoses for common abnormalities, and the data from the genetic counseling services should be included in national genomic and epidemiologic research programs [6].

In Tunisia, consanguineous marriages constituted 32% of all marriages contracted between 1983 and 1985, with the rate of first-cousin marriages being 23% [7]. The national program of mandatory premarital medical investigation that was implemented in Tunisia in 1964 has included genetic counseling since 1986, and this is obligatory for all couples with a history of genetic complications and in cases of consanguinity. Partners who are both carriers of a specific recessive disease are counseled about the risk of having an affected child and are told about the available measures for prevention. Separation of the couple is an exceptionally rare consequence of premarital medical genetic counseling.

General recommendations for genetic counseling and screening of consanguineous couples and their offspring have been published by the US National Society of Genetic Counselors [8]. The authors of this document concluded that the most useful tool for genetic screening for consanguineous couples and their offspring is a thorough medical family history. In order to enable the early detection of congenital malformations, high-resolution fetal ultrasound should be offered at 20-22 weeks with maternal serum marker screening at 15-18 weeks. For newborns resulting from unions of second cousins or closer, supplemental neonatal screening by tandem mass spectrometry by age 1 week, if not routinely implemented, should be offered in addition to the standard neonatal screening tests, with the goal of identifying potentially treatable inborn

errors of metabolism. Likewise, hearing screening should be offered by age 3 months to identify hearing loss and to implement subsequent language intervention.

GENETIC TESTING AND MOLECULAR ANALYSIS

Genetic screening tests are offered to couples who are at an increased risk for specific disorders based on the ethnic group to which each spouse belongs. In the various isolated consanguineous communities, the molecular bases of the local autosomal recessive diseases should be investigated and the information systematically collected [9]. Once the relevant information is available, genetic carrier screening for specific diseases in these isolated populations can be implemented, if feasible and if accepted by the at-risk population. It is known that genetic screening for monogenic disorders, such as thalassemia, is well accepted in the Israeli Arab population [10, 11]. Once the molecular basis of a specific condition has been identified, prenatal diagnosis by mutation testing in chorionic villi or amniocytes can be carried out and termination of pregnancy offered in the case of an affected fetus, and this may greatly reduce the number of affected infants born. In recent years the rapid expansion and availability of genomic resources together with the employment of advanced technologies has greatly facilitated the process of identification of disease-causing genes. Identification of the exact genetic basis of phenotypically similar diseases in specific populations facilitates the development of customized genetic services aimed at effective prevention of diseases that cause high morbidity and mortality.

In most, if not all, of the Arab countries, many of the towns and villages are, in effect, closed communities, in which the residents of each town or village mainly marry within their own community and only rarely have partners from outside. Within each town or village there can be at least one, and often more, autosomal recessive disease(s) that is/are exclusive to the residents of that specific town or village (see chapter 3 for a more detailed account). Basel-Vanagaite *et al*. described the results of a genetic screening program for Spinal Muscular Atrophy (SMA) and Spinal Muscular Atrophy with Respiratory Distress 1 (SMARD1) as well as for mutations causing a specific type of autosomal recessive nonsyndromic intellectual disability in just such a closed community – an Israeli

Arab village in northern Israel [12, 13]. This coastal village, a little south of Haifa, is home to approximately 10,500 inhabitants who can be grouped into several clans of various origins. The village founders include families whose ancestors migrated from Sudan and descendents of families who came to Palestine from Egypt along with Muhammad Ali's troops in 1834 [13]. Today over 50% of the population have one or other of two family names, demonstrating the high frequency of consanguineous marriages among the residents – in all, almost 40% of the marriages are consanguineous, of which about 50% are between first cousins. However, these figures do not take into account the possibly more distant degrees of consanguinity, since this is a closed community and practically all the marriages take place between residents of the village. This means that there is probably some degree of consanguinity in the vast majority of the couples living there and therefore the inbreeding coefficient among the population of this village is extremely high.

The screening program in this village revealed a carrier frequency of 1:7.6 for SMA, 1:10.1 for SMARD1, and 1:11 for a specific form of autosomal recessive intellectual disability among individuals born in the village, demonstrating the very high carrier frequency of several disorders among this population. The high rate of intellectual disability within this village has been known for decades, and because of the high heterogeneity of this condition it was thought that it may be due to different causes. However, using homozygosity mapping and linkage analysis in several families with affected children, linkage of the intellectual disability-related gene to a specific locus was established. Initially seven affected children were tested and all were found to be homozygous for the same allele for a specific marker on chromosome 19. The finding of complete homozygosity with certain specific markers in all affected individuals strongly suggested that there was a single founder mutation in all the families [14]. Later a protein truncating mutation was identified in the gene *CC2D1A* [15]. The carrier frequency of ~1/11 among individuals born in the village is consistent with the high frequency of the disorder.

The authors found that all the carriers belonged almost exclusively to the two families whose ancestors migrated from Sudan in the 19th century, and the mutation was not found in members of other families in the village. This means

that the mutation must have occurred in a common ancestor of these two families before they settled in the village over 150 years ago, and that the basis of the high frequency of the mutation is therefore mainly a founder effect resulting from the high rates of intermarriage among the members of these two families [13]. An additional reason for the very high carrier rate is that these same two extended families have a large number of intellectually disabled individuals, and therefore members of other families are unwilling to marry into these two families. As a result, therefore, the members of these families have no choice other than to marry among themselves.

Following the identification of the causative gene and mutation the screening program was established in the village; this also includes screening for SMA and SMARD1. The identification of carrier couples of any of these conditions has enabled early prenatal testing by CVS or amniocentesis. Once a month a clinic is held in the women's health station in the village, and the same medical geneticist and genetic counselor provide carrier testing counseling in each visit. It has been found that the residents of the village are far more likely to participate in the program if they can do so in the village – having to travel to the hospital where the testing is carried out, which is a long way from the village, would result in hardly anybody coming to be tested. This way the screening program can reach out to all the residents, although compliance from spouses of carriers has at times been somewhat less than satisfactory. Nevertheless, the program overall is an ongoing success story (personal communication).

METHODS USED FOR THE IDENTIFICATION OF DISEASE-RELATED GENES IN CONSANGUINEOUS POPULATIONS

Genetic Linkage Analysis

Genetic linkage analysis is aimed at identifying a polymorphic DNA sequence that is close enough to the disease gene to escape recombination and to "travel" together with it to the offspring, and it can be used to identify regions of the genome that contain genes that predispose to disease [16]. Linkage analysis is often the first stage in the genetic investigation of a trait, since it can be used to identify genomic regions that might contain a disease gene. The main quantity of interest is the recombination fraction θ, which is the probability of recombination

between two loci at meiosis. Genotyping genetic markers and studying their segregation through pedigrees can enable their position relative to each other on the genome to be deduced. This process can be used to map genetic markers or to map disease or trait loci [16].

Linkage is usually reported as a logarithm of the odds score (LOD – logarithm (base 10) of odds; "logarithmic odds"). The LOD score is the total relative probability, expressed on a logarithmic scale, that a linkage relationship exists among selected loci. Positive LOD scores support the presence of linkage, whereas negative LOD scores indicate that linkage is less likely. Computerized LOD score analysis is a simple way to analyze complex family pedigrees in order to determine the linkage between Mendelian traits, between a trait and a marker, or between two markers. By convention, a LOD score greater than 3.0 indicates 1000 to 1 odds that the linkage being observed did not occur by chance, and is therefore considered as evidence for linkage. On the other hand, a LOD score of less than -2.0 is considered as evidence to exclude linkage. It is a function of the recombination fraction θ or the chromosomal position measured in centimorgans (cM). A centimorgan is a unit that measures genetic linkage and it is defined as that distance between chromosome positions (also termed loci or markers) for which the expected average number of intervening chromosomal crossovers in a single generation is 0.01. It is often used to deduce distance along a chromosome.

Microsatellites (synonyms: satellite DNA, short tandem repeats) are repetitive segments of DNA two to five nucleotides in length (dinucleotide/ trinucleotide/tetranucleotide/pentanucleotide repeats) that are scattered throughout the genome in non-coding regions between genes or within genes (introns), and which are surrounded by unique sequences. Microsatellite sequences are extremely useful for genetic mapping; they are often used as markers for linkage analysis because the number of repeats is variable and highly polymorphic between individuals. (Polymorphisms are natural variations in a DNA sequence that have no adverse effect on the individual and occur with fairly high frequency in the general population). These very short, simple microsatellite repeats are uniformly spaced every 30 – 60 kilobases and they are distributed along the different chromosomes. These regions are inherently unstable and susceptible to mutations.

Single nucleotide polymorphisms (SNPs) are abundant polymorphic markers that are uniformly distributed throughout the human genome [17]. They are single base pair positions in genomic DNA at which different alleles exist in normal individuals, and are the most common DNA sequence variations among individuals. They are more frequent than microsatellite markers in the human genome, although they are also much less polymorphic. They are widely used for genetic mapping and genetic association studies using SNP array technology. Genomewide linkage searches aimed at identifying disease susceptibility loci are no longer carried out using microsatellite markers, but with high density SNP arrays.

Homozygosity Mapping

Homozygosity mapping is a highly efficient method for the discovery of autosomal recessive disease loci; homozygosity is the term applied to stretches of the two homologous chromosomes within the same individual that are identical by descent. The term "autozygosity" is also used when two alleles in the same individual are identical by descent – *i.e.* they are inherited from the same ancestor as a result of consanguineous mating. In homozygosity mapping, the methodology looks for homozygous regions in consanguineous families. The greater the number of affected individuals who have a shared homozygous region defined by informative markers mapping to the region, the more likely the region is to harbor the disease-causing mutation within the family [17].

Homozygosity mapping utilizing founder groups provides an extremely powerful strategy for the identification of genes that cause diseases, particularly in consanguineous families [18, 19]. This approach relies on the fact that in inbred families, children with rare recessive diseases usually inherit both copies of the disease gene, along with markers on adjacent chromosomal intervals, from a common ancestor. Hence, it may be possible to map a recessive disease gene with a panel of such individuals by searching for the area of overlap among homozygous chromosomal intervals.

If analysis of the SNP data reveals a large continuous segment of homozygosity in all the patients between specific polymorphic markers on a specific chromosome,

this is indicative that this is the most likely region to harbor the underlying disease gene. This candidate region will usually contain several known or predicted genes, and the next stage is to narrow down both the candidate interval and the number of candidate genes in order finally to identify the gene and the mutation(s) responsible for causing the disease under investigation. An illustration of this is described in a study by Gal Tanamy *et al*. on the search for the gene responsible for causing arthrogryposis multiplex congenita neuropathic type in a highly consanguineous Israeli Arab kindred [20]. The gene had already been mapped to 5qter between markers D5S1456 and D5S498 [21, 22], and in the later study haplotype sharing studies revealed complete homozygosity in all the affected individuals with marker D5S394, thus providing significant evidence in favor of linkage. Further fine mapping of this region of chromosome 5qter and the examination of several additional markers revealed that all the affected individuals showed complete homozygosity for marker D5S394, and also for three additional markers that were telomeric to marker D5S394. Analysis of the recombinant individuals enabled the narrowing down of the critical region from 2.85 Mb to 0.442 Mb between markers D5S394 and D5S2069. As a result, all the genes situated outside the boundaries of this new critical region could be excluded as being candidate genes for causing the specific form of arthrogryposis multiplex congenita neuropathic type in this kindred.

Once a candidate region has been delineated in the search for the causative gene for a specific disease, sequencing of the genes situated within the boundaries of this region ("candidate genes") will usually reveal a mutation in one of them.

Homozygosity mapping has been used with a considerable degree of success in the mapping and identification of genes that cause non-syndromic autosomal recessive intellectual disability (NSARID), especially in consanguineous families. In a study published in 2007, Najmabadi *et al*. studied 78 consanguineous Iranian families with NSARID [23]. They performed homozygosity mapping in each of these families and thus were able to determine the chromosomal localization of at least 8 novel gene loci for this condition. The authors suggested that in the Iranian population NSARID is very heterogeneous, and the data argue against the existence of frequent gene defects that account for more than a few percent of the cases. In a further study, Najmabadi *et al*. performed homozygosity mapping,

exon enrichment and next-generation sequencing in 136 consanguineous families with autosomal recessive intellectual disability from Iran and elsewhere [24]. This study revealed additional mutations in 23 genes previously implicated in intellectual disability or related neurological disorders, as well as single, probably disease-causing variants in 50 novel candidate genes. Proteins encoded by several of these genes interact directly with products of known intellectual disability genes, and many are involved in fundamental cellular processes such as transcription and translation, cell-cycle control, energy metabolism and fatty-acid synthesis, which appear to be pivotal for normal brain development and function.

Abu Jamra *et al*. performed homozygosity mapping in 64 Syrian consanguineous families with NSARID and found 11 novel loci [25]. They also noted that their study further highlights the extreme heterogeneity of NSARID and suggested that no major disease gene is to be expected. Rafiq *et al*. studied 50 Pakistani consanguineous families with NSARID [26]. They selected nine of these families with multiple affected individuals for molecular genetic studies and carried out SNP array analysis and genome-wide homozygosity mapping on members of six families. They were thus able to map three novel loci for NSARID in different families originating from different areas of Pakistan.

Occasionally homozygosity mapping may give misleading findings. An example of such a situation is described by Frishberg *et al*., in 12 Israeli Arab children living in a village near Jerusalem [27]. Most of the inhabitants of the village are descendants of one Muslim family, who have remained isolated from the rest of the community by the practice of consanguineous marriages. All of the 12 children suffered from congenital nephrotic syndrome and the authors sought to confirm that the type in the family was congenital nephrotic syndrome of the Finnish type (CNF, NPHS1), caused by mutations in *NPHS1,* which encodes nephrin. Haplotype analysis revealed several different haplotypes, leading the authors to assume that there was genetic heterogeneity. They performed direct sequencing of all DNA samples, which yielded three novel mutations. The patients were either homozygous for one of these mutations or compound heterozygotes, with differing phenotypes.

Miano *et al*. (2000) discussed some of the pitfalls they encountered while carrying out homozygosity mapping of autosomal recessive disorders in consanguineous

pedigrees [28]. They used homozygosity mapping to study a rare autosomal recessive disorder in three consanguineous pedigrees from North America and found several unexpected events. The first was the occurrence of allelic heterogeneity within a single consanguineous kindred; this can result in loss of homozygosity in flanking markers and failure to detect linkage. The second was the detection, in affected members of at least one of the families they studied, of homozygosity that was unrelated to the disease. The presence of "hidden" consanguinity in pedigree founders may have added to the likelihood of detection of such regions. Third, the usual safeguards against detecting false-positive linkage failed to prevent such an occurrence in their study. The reassurance provided by the detection of large regions of homozygosity flanking the linked marker also proved to be misleading. The probability of detecting such a region, which cosegregates with the disease in a small family, is high in the context of a whole-genome scan, so, therefore, caution is required in equating homozygosity with linkage. Finally, underestimation of the extent of inbreeding can potentially increase the chance of a false-positive linkage.

Another example of homozygosity mapping giving misleading results was described by Benayoun *et al*. [29]. They reported two extended and highly consanguineous families segregating early onset retinitis pigmentosa. Despite the consanguinity, allelic heterogeneity was found in one of the families, in which affected individuals were compound heterozygotes for two different mutations in *CRB1*. In the second family there was evidence of locus heterogeneity. A novel homozygous mutation in *RDH12* was found in only 14 of 17 affected individuals in this family, indicating that in the other affected individuals the disease was caused by a different gene(s). These findings again demonstrate that while homozygosity mapping is an efficient tool for the identification of the underlying mutated genes in inbred families, both locus and allelic heterogeneity may occur even within the same consanguineous family.

Exome Sequencing

As a result of recent developments in high-throughput sequence capture methods and next-generation sequencing technologies, exome sequencing is now a viable approach to elucidate the genetic basis of Mendelian disorders with hitherto

unknown etiology [30, 31]. Exome sequencing is the targeted sequencing of the subset of the human genome that is protein coding, *i.e.* it focuses on only the protein-coding portion of the genome. It is generally carried out using an array that captures the DNA containing the coding sequence from the patient's sample; this captured DNA is then sequenced. Exome sequencing is powerful and cost-effective [32, 33], and is less costly than whole genome sequencing because the exome represents only about 1% of the genome [33]. However, as sequencing costs decrease, more and more researchers are using whole-genome sequencing instead of whole-exome sequencing [34]. The main difference between the two techniques is that for whole-genome sequencing a capture step is not necessary, and therefore fewer biases are introduced into the sample.

Recent successes using exome sequencing have revealed genetic mutations with a limited number of probands regardless of shared genetic heritage, and are changing the approach to Mendelian disorders where soon all causative variants, genes and their relation to phenotype will be revealed. The expectation is that, in the very near future, this technology will enable the identification of all the variants in an individual's personal genome and, in particular, clinically relevant alleles [35].

Al-Romaih *et al*. studied two apparently unrelated consanguineous families from Saudi Arabia in which various family members had severe kidney disease [36]. They performed whole-genome SNP analysis and homozygosity mapping on both families; they assumed recessive inheritance and searched for identical-by-descent homozygous regions shared among the affected family members. In the first family they genotyped the three affected members and the two unaffected parents and identified a single common homozygous run of SNPs in the three affected members. They then genotyped the three affected members, the two unaffected parents and one unaffected sibling from the second family and found a homozygous run in the affected members in the same location as that found in the first family. They next performed exome sequencing in order to identify the possible genetic defects associated with the clinical and pathologic findings in one affected individual from these families. This detected a deletion in *NPHP1*, which causes nephronophthisis, a recessive disorder characterized by medullary cysts and progressive kidney failure.

Exome sequencing can serve a dual role in diagnosis and discovery, but this dual role is only applicable for disorders in which a proportion of the cases have not yet been accounted for by known mutations [30]. Exome sequencing represents a universal diagnostic tool for most genetic disorders, and thus it dispenses with the logistical challenge of performing a large number of diagnostic tests specific to each disorder. However, various ethical concerns must be given serious consideration; these are discussed in detail by Ku *et al*. [30].

PREIMPLANTATION GENETIC DIAGNOSIS

Preimplantation genetic diagnosis (PGD) is a technique that is used to analyze embryos genetically before their transfer into the uterus in order to enable only unaffected embryos to be transferred. It is used in situations where there is severe genetic disease in a family, and the indications are chromosomal abnormalities or single gene disorders [37]. It offers couples at risk the chance to have an unaffected child without facing termination of pregnancy (TOP), and therefore is particularly suitable for families who have religious (or other) objections to TOP since the procedure is carried out at a very early stage after fertilization of the ovum.

Religious Attitudes to PGD

Muslim

There is a difference of opinion between scholars as to whether "ensoulment" occurs at 40 or 120 days depending on different interpretations of a specific Hadith. However, all scholars agree that embryonic life is entitled to respect even before "ensoulment", but becomes more so after it occurs [38]. Muslim religious teaching, however, allows termination of pregnancy within the first 120 days after conception in the event of a severely affected embryo. PGD is performed three days after fertilization, when embryos are only at the eight cell stage, and the fetus has not yet become "ensouled". *In vitro* fertilization (IVF), on which PGD is based, is permissible in Islam if the sperms and oocytes are from the husband and wife [39]. Islam does not approve of the use of PGD for sex selection for non-medical reasons.

Jewish

The view of the Jewish religion is that an unborn fetus is regarded as a part of the mother's body and not a separate being until it begins to emerge from the uterus during parturition. Some Rabbinical authorities consider that prior to 40 days after conception, the fertilized egg is "mere fluid", and, as such, it has no status at all; it is not a person or "nefesh" (soul), and so can be disposed of. Therefore, for Jews, PGD is an ideal method for genetic diagnosis compared with other prenatal diagnostic methods [40].

Christian

The Roman Catholic Christian view is that the fetus attains its status as a human being at conception, and thus PGD is not permitted (John Paul II, 1995). However, other Christian denominations, especially Protestant, do accept early abortion as they do not view the embryo as a person, and therefore these groups do allow PGD [40].

The ethical aspects are also pertinent. PGD raises several significant ethical issues, of which the main one is the sanctity of human life. While PGD does not result in the loss of biopsied healthy embryos, it does involve the discarding of those that are affected. PGD also has implications on a societal level, and there is a danger of using it for eugenics [38, 41].

Methodology

Embryos are created by IVF, and are biopsied usually on day 3; blastocyst biopsy can be a possible alternative (the blastocyst is a very early stage in the development of the embryo). The genetic analysis is performed on one or two blastomeres (undifferentiated cells formed by cleavage of the fertilized ovum), by polymerase chain reaction (PCR) for molecular diagnosis, or fluorescent *in situ* hybridization (FISH) for cytogenetic diagnosis. Genetic analysis of the first or second polar body can be used to study maternal genetic contribution (meiotic division of the oocyte leads to the formation of one large cell, the ovum, and one small cell, known as the polar body). To improve the accuracy of the diagnosis, new technologies are emerging, such as comparative genomic hybridization (CGH). Only healthy, unaffected embryos are transferred into the uterus [37].

PGD requires close collaboration between obstetricians, fertility specialists, the IVF laboratory and geneticists. It needs intensive effort, expensive techniques, and is demanding for the patients, but it offers tremendous opportunity for couples who have had a previous child or children with genetic abnormalities, or who are known to be carriers of a monogenic disease (or diseases) even before they have had affected children [37].

As a result of the continuing advances in genetic research and the application of the new techniques in the management of the problems associated with consanguineous marriages, hopefully over time, as these new techniques gain acceptability among the health care providers, the religious establishment and the general public, the number of children born with severe genetic conditions will be considerably reduced. The ideal future goal will be a balance between a significant decline in the prevalence of consanguineous marriages (chiefly accomplished both by the active use of educational programs and the natural evolution of society) combined with the promotion and utilization of the new genetic techniques, especially PGD.

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CONFLICT OF INTEREST

The authors confirm that this chapter contents have no conflict of interest.

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