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Genetics of Amyotrophic Lateral Sclerosis

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive muscle weakness caused by loss of central and peripheral motor neurons. Symptoms typically have a localized limb or bulbar onset and progress to other muscle groups of the body. Denervation of respiratory muscles and dysphagia leading to respiratory complications are the most common causes of death. There is no cure for this rapidly progressive disease.

Approximately 5% of patients have a family history of ALS (fALS) (Byrne et al., 2011). All other cases are considered to have a sporadic form of the disease (sALS). A twin study of sALS patients has estimated hereditability to be considerable (0.38-0.76), indicating an important genetic component in disease etiology (Al-Chalabi et al., 2010). sALS, therefore, is considered to be a disease of complex etiology with both genetic and environmental factors contributing to disease susceptibility.

This chapter will provide an overview of the current knowledge of the genetics of both fALS and sALS. There will be, however, particular emphasis on two sALS associated regions identified in a large genome wide association study namely, chromosomal region 9p21.2 and 19p13.11. Evidence for the association with these regions as well as the function of the relevant genes in these regions will be discussed.

2. Genetics of familial amyotrophic lateral sclerosis

Familial ALS is a genetically heterogeneous group of diseases for which linkage has been found for over 13 different loci (Table 1). These loci account for approximately 25-30% of all fALS cases. In addition, variants in several other genes have been implicated in fALS but most of these data are still inconclusive. All currently known fALS loci and the genes involved will be briefly discussed in this section.

2.1 ALS1 (SOD1)

Linkage analysis in autosomal-dominant fALS pedigrees associated the copper-zinc superoxide dismutase (*SOD1*) gene on chromosome 21q to ALS. Several point mutations in

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Name of Disease	*Locus*	*Gene*	*Protein*	*Inheritance*	*Clinical features*
ALS1	21q22	*SOD1*	Cu/Zn superoxide dismutase	AD/AR	Typical ALS
ALS2	2q33	*ALSin*	ALSin	AR	Juvenile onset, slowly progressive, predominantly upper motor neuron signs
ALS3	18q21	N.K.	-	AD	Typical ALS, disease onset in legs
ALS4	9q34	*SETX*	Senataxin	AD	Childhood/Adolescent onset, slowly progressive, no respiratory and bulbar involvement
ALS5	15q15-21	*SPG11*	Spatacsin	AR	Juvenile onset, slowly progressive
ALS6	16p11.2	*FUS*	Fused in sarcoma	AD/AR	Typical ALS
ALS7	20p13	N.K.	-	AD	Typical ALS
ALS8	20q13	*VAPB*	VAMP-associated protein B	AD	Typical ALS, SMA and atypical ALS
ALS9	14q11	*ANG*	Angiogenin	AD	Typical ALS, frontotemporal dementia, Parkinson's disease
ALS10	1q36	*TARDBP*	TAR-DNA binding protein	AD	Typical ALS
ALS11	6q21	*FIG4*	PI(3,5)P(2)5-phosphatase	AD	Adult onset, prominent corticospinal tract signs
ALS12	10p13	*OPTN*	Optineurin	AD/AR	Adult onset
ALS14	9p13-p12	*VCP*	Valosin-containing protein	AD	Adult onset with or without FTD
ALS-FTD1	9q21-22	N.K.	-	AD	ALS, FTD
ALS-FTD2	9p13.2-21.3	*C9ORF72*	Chromosome 9 open reading frame 72	AD	ALS, FTD
ALS-FTDP	17q21.1	*MAPT*	Microtubule-associated protein tau	AD	Adult onset with FTD
ALS-X	Xcen	N.K.	-	XD	Adult onset

AD = Autosomal dominant, AR = Autosomal recessive, XD = X-linked dominant, FTD = frontotemporal dementia, SMA = spinal muscular atrophy, N.K. = not known, FTDP = frontotemporal dementia with parkinsonism

Table 1. Classification of familial ALS.

SOD1 that co-segregated with the disease were identified in several of these pedigrees (Rosen et al., 1993). To date, over 150 different mutations in *SOD1* have been identified (see http://alsod.iop.kcl.ac.uk). Mutations have been reported in ~20% of fALS patients and in 1-4% of sALS patients (Pasinelli and Brown, 2006; Valdmanis and Rouleau, 2008).

The SOD1 protein is a cytoplasmic enzyme that converts superoxide radicals, a by-product of oxidative phosphorylation, to hydrogen peroxide and molecular oxygen. The exact mechanism by which *SOD1* mutations lead to ALS pathology is unknown although several toxic properties of mutant SOD1 such as aberrant oxidative stress, protein instability, and mitochondrial damage have been proposed to be causative (reviewed in Pasinelli and Brown, 2006). Interestingly, the presence of mutant SOD1 in non-neuronal cells contributes to pathogenesis and is needed for disease progression (Ilieva et al., 2009). *SOD1* mutations most likely result in a toxic gain of function pathology since *SOD1* knockout mice do not develop motor neuron degeneration whereas transgenic mice overexpressing mutant SOD1 show motor neuron degeneration and ALS-like pathology (Gurney et al., 1994; Reaume et al., 1996).

2.2 ALS2 (ALSin)

ALS2 is an autosomal recessive form of juvenile ALS that was first reported in a large consanguineous Tunisian kindred and linkage analysis in this family associated locus 2q33-q35 to ALS (Hentati et al., 1994). This led to the discovery of causal mutations in the gene encoding ALSin (Hadano et al., 2001; Yang et al., 2001). Mutations in *ALSin* have been scarcely reported and do not appear to be a common cause of ALS.

ALSin is a Rab5 and Rac1 guanine exchange factor that acts as a regulator of endosomal/membrane trafficking. The protein is able to promote neurite outgrowth in neuronal cultures through activation of the small GTPase Rac1 (Otomo et al., 2003; Topp et al., 2004). Overexpression of ALSin protects cultured motor neuronal cells from mutant SOD1 toxicity suggesting a neuroprotective role. Mutations in *ALSin* may induce a loss of this neuroprotective function (Kanekura et al., 2004). *ALSin* knockout mice do not develop overt motor neuron disease but degeneration of the corticospinal tract has been reported (Cai et al., 2008; Hadano et al., 2006).

2.3 ALS3 (18q21)

Linkage to chromosome 18q21 was identified in a large European family of which 20 members had autosomal-dominant ALS (Hand et al., 2002). This region contains 50 genes but the causal mutation at this locus remains to be identified.

2.4 ALS4 (SETX)

ALS4 is a rare, childhood- or adolescent-onset, autosomal dominant disease, which is also known as distal hereditary motor neuronopathy with pyramidal features. Linkage to chromosome 9q34 was found in a large family from the USA with 49 affected members (Chance et al., 1998). Sequencing of 19 genes in this locus revealed that missense mutations in the senataxin (*SETX*) gene were the cause of ALS4 in several families (Chen et al., 2004). Since then, mutations have been identified in additional ALS patients from China, Italy and the USA (Avemaria et al., 2011; Hirano et al., 2011; Zhao et al., 2009). Interestingly, mutations in *SETX* leading to a premature termination in the protein product have also been identified in ataxia oculomotor apraxia 2 (Moreira et al., 2004).

Senataxin contains a seven-motif domain characteristic for DNA/RNA helicases. It displays strong homology to several genes involved in RNA processing such as the immunoglobulin mu binding protein 2 gene (*IGHMBP2*), in which mutations are known to cause spinal muscular atrophy with respiratory distress type 1 (Grohmann et al., 2001). SETX was shown to be involved in the termination of RNA transcription (Skourti-Stathaki et al., 2011). It is therefore possible that mutations in *SETX* cause neuronal degeneration due to aberrant RNA processing. Overexpression of wild-type senataxin in primary hippocampal neurons is sufficient to trigger neuronal differentiation by protecting cells from apoptosis and promoting neuritogenesis (Vantaggiato et al., 2011).

2.5 ALS5 (SPG11)

This is the most common form of recessive fALS and is characterized by a juvenile onset. In seven families from Tunisia, Pakistan, and Germany, linkage to chromosome 15q15-21 was found (Hentati et al., 1998). Recently, 12 mutations in the spatacsin (*SPG11*) gene were identified in 10 unrelated pedigrees from Italy, Brazil, Canada, Turkey, and Japan (Orlacchio et al., 2010). Ten out of 12 mutations are frameshift or nonsense mutations. Mutations in *SPG11* are known to cause autosomal recessive hereditary spastic paraplegia with a thin corpus callosum (Stevanin et al., 2007).

Spatacsin contains four putative transmembrane domains, a leucine zipper and a coiled-coil domain. The exact function of spatacsin is unknown although it may play a role in axonal transport (Salinas et al., 2008).

2.6 ALS6 (FUS)

Linkage to a 42-Mb region containing more than 400 genes on chromosome 16 was reported in several families (Sapp et al. 2003). Recently, mutations in the fused in sarcoma/translated in liposarcoma (*FUS/TLS*) gene were shown to cause ALS6 (Kwiatkowski et al., 2009; Vance et al., 2009). Several subsequent studies have identified additional mutations in *FUS* in ALS cohorts from different populations with an overall frequency of ~4% in fALS and ~1% in sALS (Belzil et al., 2009; Corrado et al., 2010; Hewitt et al., 2010; Groen et al., 2010). *FUS* mutations have also been detected in fALS patients with frontemporal dementia (FTD) and patients with juvenile ALS with basophilic inclusions (Bäumer et al., 2010; Huang et al. 2010; Yan et al., 2010).

The *FUS* gene encodes for a DNA/RNA binding protein that is involved in several cellular pathways including the splicing, transport and maturation of RNA (Lagier-Tourenne et al., 2010). FUS positive ubiquitinated cytoplasmic inclusions have been observed in spinal cord tissue of sALS and fALS patients without *SOD1* and *FUS* mutations (Deng et al., 2010). The majority of *FUS* mutations identified reside in its C-terminal nuclear localization signal which results in an abnormal cytoplasmic localization of FUS and localization to stress granules (Bosco et al., 2010; Dormann et al., 2010; Ito et al., 2010). In yeast, overexpression of human FUS leads to toxicity, cytoplasmic inclusions and FUS localization to stress granules as can be seen in ALS patients (Ju et al., 2011; Sun et al., 2011). In addition, transgenic rats overexpressing ALS mutant FUS develop progressive paralysis due to motor axon degeneration as well as neuronal loss in the cortex and hippocampus which are phenotypes seen in ALS and FTD (Huang et al., 2011).

2.7 ALS7 (20p)

Linkage to chromosome 20p was found in a large autosomal dominant fALS pedigree from the USA. A 5-Mb segment was identified that was shared between two affected

siblings (Sapp et al., 2003). This region contains 24 genes but no causal mutation has been identified.

2.8 ALS8 (VAPB)

In a large family from Brazil with 28 affected members across 4 generations, linkage was found at chromosome 20q13.3. Sequencing identified a mutation (P56S) in the vesicle associated membrane protein (VAMP)/synaptobrevin-associated membrane protein B (*VAPB*) gene in all affected members of this family (Nishimura et al., 2004). The same mutation was also identified in six additional families with different clinical courses including, ALS8, late-onset spinal muscular atrophy and typical severe ALS with rapid progression. A different mutation (T46I) was detected in a family from the UK (Chen et al., 2010).

The VAPB protein has been implicated in various cellular processes including the formation of the presynaptic terminal in neurons, vesicle trafficking and the unfolded protein response (Chen et al., 2010). Transgenic mice overexpressing ALS mutant VAPB or wild-type VAPB do not develop an overt motor neuron phenotype. However, transgenic mice overexpressing ALS mutant but not wild-type VAPB show TAR DNA-binding protein 43 (TDP-43) positive cytoplasmic inclusions, a pathological hallmark of ALS (Tudor et al., 2010). It has been suggested that mutant VAPB exerts a dominant-negative effect by forming dimeric complexes with wild-type VAPB thereby recruiting it into aggregates (Teuling et al., 2007).

2.9 ALS9 (ANG)

Angiogenin (*ANG*) was identified as a candidate gene for ALS because it is located 237kb downstream of apurinic endonuclease, multifunctional DNA repair enzyme (*APEX*) and because of its functional similarity to vascular endothelial growth factor (VEGF) (Greenway et al., 2004). Both *APEX* and *VEGF* are candidate genes for sALS and will be discussed in the next section. A single nucleotide polymorphism (SNP) in *ANG* was associated with ALS in patients from Ireland and Scotland (Greenway et al., 2004). Missense mutations in *ANG* were found in 4 fALS cases and 11 sALS cases (Greenway et al., 2006). Subsequent sequencing in populations from Europe and the USA identified additional mutations in approximately 2% of fALS cases and 1% of sALS cases (Conforti et al., 2008; Fernández-Santiago et al., 2009; Gellera et al., 2008; Paubel et al., 2008; Wu et al., 2007). However, *ANG* mutations have also been observed in healthy controls suggesting that not all mutations are pathogenic (Corrado et al., 2007). A K17I mutation was identified in a 4-generation family of which one patient presented with ALS, FTD, and Parkinsonism (Van Es et al., 2009a). An obligate carrier did not develop the disease suggesting incomplete penetrance. Two *ANG* mutations (K17I and K54E) were identified in two fALS cases from France who also had a mutation in FUS (Millecamps et al., 2010). An R145C mutation has been observed in a sALS patient with a G93D SOD1 mutation (Luigetti et al., 2011). A recent study showed a significantly higher frequency of *ANG* variants in both ALS and Parkinson's disease (PD) patients which could reflect a genetic susceptibility to widespread neurodegeneration (Van Es et al., 2011).

The ANG protein is a member of the pancreatic ribonuclease superfamily and a potent mediator of new blood vessel formation. In endothelial cells, the protein can promote ribosomal RNA (rRNA) production and cellular proliferation and is able to cleave transfer

RNA which results in inhibition of protein translation (Yamasaki et al., 2009). ANG is also expressed in spinal motor neurons (Sebastià et al., 2009). It is thought that *ANG* mutations cause ALS due to a loss of function and it has been shown that wild-type but not mutant angiogenin is neuroprotective and that mutant angiogenin impairs neurite outgrowth *in vitro* (Sebastià et al., 2009; Subramanian et al., 2008; Wu et al., 2007).

2.10 ALS10 (TARDBP)

TDP-43 was identified as one of the main components of ubiquitinated cytoplasmic inclusions in ALS and FTD (Neumann et al., 2006). Sequencing of the gene encoding this protein (*TARDBP*) identified mutations in ALS patients (Kabashi et al., 2008; Shreedharan et al., 2008). To date over 40 mutations in *TARDBP* have been identified in several different populations with a frequency of ~5% of fALS cases and up to 2% of sALS cases (Corrado et al., 2009; Iida et al., 2010; Millecamps et al., 2010; Ticozzi et al., 2009; Van Deerlin et al., 2008). *TARDBP* mutations have also been observed in ALS-FTD and FTD patients (Benajiba et al., 2009; Gitcho et al., 2009b). Despite the presence of *TARDBP* mutations in only a portion of ALS and FTD patients, TDP-43-positive cytoplasmic inclusions are found in almost all ALS patients but they are also seen in other neurodegenerative diseases such as FTD, Huntington's, Alzheimer's, and Parkinson's disease (Da Cruz and Cleveland, 2011).

TDP-43, like FUS, is a DNA/RNA binding protein that is part of the heterogeneous ribonucleoprotein family. It has a role in gene transcription, regulation of splicing, and mRNA transport and stabilization (Buratti and Baralle, 2010). Except for one truncation mutation, all *TARDBP* mutations identified in ALS patients are missense mutations clustered in the glycine-rich C-terminal region which is involved in protein-protein interactions (Lagier-Tourenne et al., 2010). *TARDBP* mutations lead to an abnormal distribution of the protein to the cytoplasm.

2.11 ALS11 (FIG4)

Mutations in the PI(3,5)P(2)5-phosphatase (*FIG4*) gene on chromosome 6q21 are known to cause a severe form of Charcot-Marie-Tooth (CMT) disease with early onset and loss of sensory and motor neurons, CMT4J (Chow et al., 2007). In a screen for *FIG4* mutations in a large cohort of sALS and fALS patients, several variants were detected that were unique to fALS and sALS patients (Chow et al., 2009). Two mutations were identified in patients diagnosed with primary lateral sclerosis. To date, no other studies have replicated the finding of ALS-associated FIG4 mutations in other cohorts and it is unclear whether *FIG4* mutations are pathogenic in ALS patients.

FIG4 is a phosphoinositide 5-phosphatase that regulates PI(3,5)P2 abundance. PI(3,5)P2 is a signalling lipid that mediates endosomal trafficking to the trans-Golgi network (Rutherford et al., 2006). Pale tremor mice, which are homozygous for null mutations in *FIG4*, show neurodegeneration in sensory and autonomic ganglia, motor cortex, striatum, and cerebellum. Motor neurons in the ventral spinal cord contain vacuoles (Chow et al., 2007). Mutant mice lacking *Vac14*, a gene encoding for a FIG4 interactor, show a similar neurodegeneration (Zhang et al., 2007).

2.12 ALS12 (OPTN)

Using homozygosity mapping in six ALS patients from consanguineous marriages, an overlapping region on chromosome 10 was identified as the candidate region. Screening of

17 genes in this region revealed a homozygous deletion in the gene for optineurin (*OPTN*), a gene known to cause primary open-angle glaucoma, in two siblings and an individual from a different family (Murayama et al., 2010; Rezaie et al., 2002). In addition, a homozygous nonsense (Q398X) mutation was identified in one fALS case (Murayama et al., 2010). Subsequent screening in a larger cohort of fALS and sALS patients identified a heterozygous missense mutation (E478G) in a four individuals with ALS from two families (Murayama et al., 2010). A homozygous E478G mutation was identified in a Japanese fALS case in a different study (Iida et al., 2011). One additional nonsense mutation and one missense mutation in *OPTN* were identified in fALS cases from Italy (Del Bo et al., 2011). Two separate studies identified novel variants in fALS patients but the authors state that these variants may be a genetic predisposition to glaucoma instead of causing ALS (Belzil et al., 2011; Millecamps et al., 2011). One study also detected mutations in sALS patients with a rapid disease progression (van Blitterswijk et al., 2011). Another study could not identify *OPTN* mutations in fALS and sALS patients (Sugihara et al., 2011).
OPTN is a multifunctional protein involved in membrane trafficking, maintainance of the Golgi complex, and exocytosis (Sahlender et al., 2005). OPTN can inhibit the activation of NFκB and it has been proposed that mutations in *OPTN* causing ALS may relieve this inhibition and cause neuronal death (Murayama et al., 2010).

2.13 ALS14 (VCP)

Recently an exome sequencing study detected a mutation in the gene encoding valosin-containing protein (*VCP*) in an Italian family. Subsequent screening in 210 ALS cases from unrelated families identified four mutations in *VCP* in four different families from Italy and the USA (Johnson et al., 2010). Mutations in the gene for *VCP*, located on chromosome 9p13.3, are a known cause for the multi-system degenerative disease inclusion body myopathy with Paget's disease and frontotemporal dementia (IBMPFD) (Watts et al. 2004). IBMPFD, like ALS, is characterized pathologically by TDP-43 inclusions (Weihl et al., 2008).
VCP is an AAA+-ATPase that mediates ubiquitin-dependent extraction of substrates from multiprotein complexes for subsequent recycling or degradation by the proteasome. It plays a role in a variety of cellular functions including Golgi biogenesis, cell cycle regulation, DNA damage repair and protein homeostasis through the ubiquitin-proteasome system (Ju and Weihl, 2010). It is thought that *VCP* mutations result in the impairment of protein degradation trough both the ubiquitin-proteasome system and autophagy leading to the formation of inclusions. *VCP* mutations found in FTD and ALS have been shown to disrupt TDP-43 localization from the nucleus to the cytoplasm which could be caused by the disruption in protein homeostasis (Gitcho et al, 2009a; Ju and Weihl, 2010). In mice, a missense mutation in vacuolar sorting protein 54, the mouse homologue of VCP, causes motor neuron degeneration (Schmitt-John et al., 2005).

2.14 Other fALS associated genes

In addition to the genes listed in the previous sections, several other genes have been implicated in fALS.
Dynactin 1 (*DCTN1*) was discovered as a candidate gene for ALS when a G59S mutation in this gene was identified in a family with a slowly progressive, autosomal dominant form of lower motor neuron disease without sensory symptoms (Puls et al., 2003; Puls et al., 2005). Subsequent sequencing of the *DCNT1* gene in 250 ALS patients revealed the presence of

three heterozygous missense mutations in one sALS and three fALS cases with typical ALS (Münch et al., 2004). An additional mutation was detected in a patient with ALS and his brother who had FTD (Münch et al., 2005). The pathogenicity of these variants has however not been established. Screening for *DCTN1* mutations in a cohort of ALS, FTD or ALS-FTD patients did not result in the identification of disease segregating variants (Vilariño-Güell et al., 2009). One of the missense variants identified in a sALS case was also found in controls in the same study (Vilariño-Güell et al., 2009). Interestingly, five mutations in *DCTN1* were found in eight families with Perry syndrome, a disease that is characterized by Parkinsonism and TDP-43- and ubiquitin- positive inclusions (Farrer et al., 2009).

In a 3-generation family with typical ALS, a mutation in the D-amino acid oxidase (*DAO*) gene was identified (Mitchell et al., 2010). However, screening of an additional 322 unrelated fALS cases did not reveal any other causal mutation in this gene (Mitchell et al., 2010). Additional screening will be needed but *DAO* mutations seem to be very rare in ALS.

Because of their structural and functional similarities to FUS, the genes encoding TAF15 RNA polymerase II, TATA box binding protein associated factor (*TAF15*) and Ewing sarcoma breakpoint region 1 (*EWS*) were screened in fALS cases (Ticozzi et al., 2010). Two missense mutations in *TAF15* (A31T and R395Q) were identified in three fALS cases and not in 1159 controls. However, one of the fALS cases with an R395Q mutation also carried a mutation in *TARDBP*. Moreover, the R395Q is in close proximity to two non-pathogenic variants, suggesting it is a benign polymorphism (Ticozzi et al., 2010).

Recently, a mutation in the sigma non-opioid intracellular receptor 1 (*SIGMAR1*) gene was identified in an autosomal recessive family with juvenile ALS (Al-Saif et al., 2011). Interestingly, variants in the 3'UTR of *SIGMAR1* were described in three ALS-FTD families (Luty et al., 2010).

An X-linked dominant ALS locus has been reported but has not been further described (Siddique et al., 1998). Recently, mutations in the gene encoding ubiquitin-like protein ubiquilin 2 (*UBQLN2*) were identified as the cause of dominantly inherited X-linked ALS and ALS/dementia (Deng et al., 2011).

Several family pedigrees contain individuals affected by ALS, FTD or both. The first linkage study performed in 16 of these ALS-FTD families found linkage to chromosome **9q21-q22**, designated as ALS-FTD1 (Hosler et al., 2000). This association has thus far not been replicated in other ALS-FTD families. Linkage to chromosome 9p in ALS-FTD families (ALS-FTD2) has also been reported. A hexanucleotide repeat expansion in the chromosome 9 open reading frame 72 (*C9ORF72*) gene was recently identified as the causal genetic defect of ALS-FTD2 and will be discussed in a next section (Dejesus-Hernandez et al., 2011; Renton et al., 2011). Mutations in the gene encoding microtubule-associated protein tau (*MAPT*) have been reported in patients with ALS or FTD (Hutton et al., 1998).

Finally, mutations in the neurofilament heavy (*NEFH*) gene and the paraoxonase genes (*PON1, 2, 3*) have been identified in fALS cases and these genes will be discussed in more detail in the following section.

3. Genetics of sporadic ALS

Sporadic ALS is considered to be a complex disease, where both genetic and environmental factors contribute to pathogenesis. Several association studies have been performed to identify the genetic contribution in sALS with mixed success, possibly due to the small sample sizes in many of these studies. Although their precise contribution to sALS is often unclear, a few of

the risk factors identified to date have been consistently replicated. Furthermore, several of these associated genes have overlapping cellular functions such as in RNA metabolism, vesicle trafficking, and axonal transport. In this section, genes that have been associated with sALS will be discussed (Table 2). In addition to these genes, mutations in several fALS associated genes that were discussed in the previous section have been found in a portion of sALS cases.

Associated Gene	*Protein*	*Positive studies*	*Negative studies*	*Type of association found*	*Additional information*
APEX	Apurinic endonuclease, DNA repair enzyme	2	2	SNP association	Protein has a role in oxidative stress
ATXN2	Ataxin-2	6	0	PolyQ repeats	Intermediate polyQ repeats increase risk for sALS/interaction with TDP-43
CHMP2B	Chromatin modifying protein 2B	2	0	Mutations	Mutations are known to cause FTD. All patients have lower motor neuron signs consistent with PMA.
HFE	Haemo-chromatosis	5	1	SNP association	Mutations cause hereditary haemochromatosis
NEFH	Neurofilament-heavy	5	3	Deletions/ insertions/ mutations	Neurofilament-containing inclusions are a pathological hallmark of ALS
SMN1	Survival motor neuron 1	3	1	Abnormal copy number	*SMN1* deletions cause SMA
SMN2	Survival motor neuron 2	1	5	Deletions	*SMN2* copy number variation affects SMA disease severity
PON1, 2, 3	Paraoxonase	7	3	SNP association/ mutations	Possible gene-environment interaction
PRPH	Peripherin	3	0	Mutations	Peripherin-containing inclusions are a pathological hallmark of ALS. Possible involvement of abnormal splice forms.
VEGF	Vascular-endothelial growth factor	2	6	SNP association	Deletion of HRE in promoter results in an ALS phenotype in mice. Possible gender association.

Table 2. Genes associated with sporadic ALS

3.1 Apurinic endonuclease, multifunctional DNA repair enzyme (APEX1)

A study in 117 Scottish sALS patients showed association of a common SNP resulting in a D148E amino-acid change with ALS (Hayward et al., 1999). This finding was replicated in 169 Irish sALS patients (Greenway et al., 2004). In one study, DNA extracted from CNS tissue from 81 sALS patients was screened but the D184E SNP was not associated with ALS (Tomkins et al., 2000). A different study assessing 134 Italian sALS patients also failed to detect significant association between this SNP and ALS (Coppedè et al., 2010). These inconsistent association results might reflect a population-specific effect of the *APEX1* D184E allele.

APEX1 is involved in DNA repair and maintains and stimulates the DNA binding activity of transcription factors (Fishel and Kelley, 2007). Frontal cortical levels and activity of APEX1 were significantly reduced in 11 ALS patients as compared to six controls (Kisby et al., 1997). However, in a different study, increased expression levels and activity in ALS brain and spinal cord motor neurons were observed (Shaikh and Martin, 2002).

3.2 Ataxin-2 (ATXN2)

In a screen for toxicity modifiers of TDP-43 in yeast, ataxin-2 (ATXN2) was identified (Elden et al., 2010). ATXN2 and TDP-43 form a RNA-dependent complex and are mislocalized in spinal cord motor neurons in ALS patients. *ATXN2* has a polyglutamine (polyQ) region which is normally 22-23 repeats long. Expansion of this region of the protein to 34 repeats causes spinocerebellar ataxia type 2 (SCA2) (Imbert et al., 1996; Pulst et al., 1996; Sanpei et al. 1996). The polyQ repeat length of *ATXN2* was determined in 915 ALS patients and 980 controls and intermediate length polyQ repeats (23-34) were found to be more common in ALS patients and thus may be a risk factor for ALS (Elden et al., 2010). This finding was replicated in several studies with ALS patients from different populations. Interestingly, the exact length of the polyQ repeat region seems to vary between populations (Chen et al., 2011; Daoud et al., 2011; Lee et al., 2011; Ross et al., 2011; Van Damme et al., 2011).

Longer polyQ repeats in ATXN2 possibly stabilize the protein and enhance its interaction with TDP-43. Under stress conditions, increased mislocalization of TDP-43 to the cytoplasm was observed in cells harbouring expanded polyQ repeats in ATXN2 (Elden et al., 2010). ATXN2 was shown to be part of stress granules and interacts with poly-A-binding-protein 1 (PABP), which is involved in poly(A) shortening and translation initiation (Ralser et al., 2005). ATXN2 was also shown to interact with endophilin A1 and A3, which are involved in synaptic vesicle endocytosis (Nonis et al., 2008).

3.3 Chromatin modifying protein 2B (CHMP2B)

A mutation in a splice-site of *CHMP2B* was first identified in a large Danish family with FTD and mutations have since been detected at low frequency in other FTD patients (Skibinski et al., 2005). Screening of the *CHMP2B* gene in ALS patients identified two mutations in two fALS patients. These patients displayed a predominant lower motor neuron phenotype and one of the patients showed signs of FTD (Parkinson et al., 2006). Sequencing of the *CHMP2B* gene in 433 ALS patients identified three missense mutations in one fALS case and three sALS cases (Cox et al., 2010).

The exact function of CHMP2B is unknown but its yeast homologue, vacuolar protein sorting 2 (VPS2), is a component of the ESCRTIII complex (Skibinski et al., 2005). This complex is involved in the trafficking of proteins between plasma membrane, trans-Golgi network, and lysosomes. The *CHMP2B* mutation identified in FTD results in dysmorphic endosomal structures similar to what is seen in ALSin overexpression (Skibinski et al., 2005). In cortical neurons, overexpression of the FTD related CHMP2B splice-site mutant leads to dendritic retraction prior to cell death and the accumulation of autophagosomes (Lee et al., 2007). In hippocampal neurons, the same FTD related CHMP2B mutant causes a decrease in large dendritic spines suggesting that CHMP2B is needed for dendritic spine growth and maturation (Belly et al., 2010).

3.4 Haemochromatosis (HFE)

Mutations in the *HFE* gene are a cause of hereditary haemochromatosis and have been associated with Alzheimer's disease and PD (reviewed by Nandar and Connor, 2011). The first report examining the presence of *HFE* mutations in ALS found no association between two mutations (H63D and C282Y) and ALS patients from the USA (Yen et al., 2004). However, several subsequent studies in a total of 1133 ALS patients and almost 7000 controls individuals from the USA, Ireland, UK, Italy, The Netherlands, and China reported association between the *HFE* H63D polymorphism and an increased risk for ALS (Goodall et al., 2005; He et al, 2011; Restagno et al., 2007; Sutedja et al., 2007; Wang et al., 2004).

The most important function of HFE is the regulation of iron homeostasis by binding to the transferrin receptor and reducing the transport of iron molecules (Feder et al., 1998). When HFE with the H63D mutation binds to the transferrin receptor, iron transport is reduced leading to iron accumulation and increased oxidative stress. In addition, it has been shown that in neuronal cell lines the H63D mutation induces increased oxidative stress, altered glutamate regulation and prolonged ER stress, all cellular processes affected in ALS (Liu et al., 2011; Mitchell et al. 2011).

3.5 Neurofilaments (NEFL, NEFM, NEFH)

One of the pathological hallmarks of ALS is the presence of neurofilament-containing inclusions in the cell body and proximal axon of spinal motor neurons (Delisle and Carpenter, 1984). Neurofilaments are intermediate filaments that constitute the most abundant cytoskeletal element in large myelinated axons. Neurofilaments are formed by the co-polymerization of light (NEFL), medium (NEFM), and heavy (NEFH) subunits, which are each encoded by different genes.

Several lines of evidence suggest a role for neurofilaments in neurodegeneration. Initial evidence came from mouse models overexpressing or deficient for neurofilaments (reviewed in Lariviere and Julien, 2004). Overexpression of NEFL or NEFH resulted in an abnormal accumulation of neurofilaments, as seen in ALS patients, and in axonal atrophy and motor dysfunction but not degeneration. Surprisingly, both overexpression and knockout of neurofilaments in transgenic mutant SOD1 mice increases life span (Couillard-Després et al., 1998; Williamson et al., 1998). This indicates that the role of neurofilaments in ALS is complex and more research is needed to examine the possible contribution of neurofilaments to ALS pathogenesis.

Additional evidence for a role for neurofilaments in ALS comes from genetic studies. Mutations in *NEFL* have been identified in some forms of the sensory and motor neuropathy Charcot-Marie-Tooth disease (Mersiyanova et al., 2000; Shin et al., 2008). The C-terminal tail region of NEFH contains phosphorylation motifs known as KSP repeats. In humans there are two common polymorphic variants of 44 (short) or 45 (long) repeats. Homozygosity for the short repeat allele is associated with Russian sporadic motor neuron disease patients (Skvortsova et al., 2004). Deletions and insertions in the KSP repeats of *NEFH* were detected in ALS patients (Al-Chalabi et al., 1999; Figlewicz et al., 1994; Tomkins et al., 1998). However, another study in 117 unrelated fALS patients could not identify deletions or insertions in the KSP repeats of *NEFH* (Rooke et al., 1996). A missense mutation in the *NEFH* gene was identified in a sALS case and not in controls (Garcia et al., 2006). Moreover, in a recent candidate gene sequencing study, three missense mutations were identified in the *NEFH* gene in two sALS and one fALS case. However, co-segregation of the mutation in the

fALS case could not be tested and none of the missense mutations were predicted to be deleterious (Daoud et al., 2011). One study did not identify ALS specific variation in the *NEFH* gene in fALS and sALS samples (Vechio et al., 1996).

3.6 Paraoxonase genes (PON)

The paraoxonase gene cluster consists of 3 genes (*PON1, PON2,* and *PON3*) and is located in an 80-kb block on chromosome 7q21.3-22.1. PON1 and PON3 are primarily expressed in liver where they are associated with high-density lipoproteins, whereas PON2 is ubiquitously expressed (Costa et al., 2005; Draganov et al., 2000; Ng et al., 2002). Both PON1 and PON2 expression has been shown in mouse brain (Giordano et al., 2011). All PON proteins are able to hydrolyze lactones and PON1 is able to detoxify organophosphate pesticides and neurotoxins. Since neurotoxins are not normally present in the body the biological function of PON1 is thought to be protection of low-density lipoproteins from oxidation (Mackness et al., 1991). PON2 and PON3 share this function (Draganov et al., 2000; Ng et al., 2001). A higher incidence of ALS among Gulf war veterans and farmers suggested that chemical exposure may be a risk factor for ALS (Chió et al., 1991; Horner et al., 2003). Because PON proteins reduce oxidation and are able to detoxify neurotoxins these proteins have been investigated for association with ALS.

Polymorphisms in *PON1* and *PON2* as well as a haploblock spanning *PON2* and *PON3* were found to be associated with sALS (Saeed et al., 2006; Slowik et al., 2006). Since then several other studies in different populations have reported association of SNPs in the *PON* genes with sALS (Cronin et al., 2007; Landers et al., 2008; Morahan et al., 2007; Valdmanis et al., 2008). However, a meta-analysis including 4037 cases and 4609 controls from five case-control studies and several genome-wide association studies showed no significant association between *PON* polymorphisms and ALS (Wills et al., 2009). More recently, two other studies failed to detect association between *PON* polymorphisms and ALS (Ricci et al. 2011; Zawislak et al., 2010). In a recent sequencing study, eight mutations in all three *PON* genes were identified in fALS and sALS patients (Ticozzi et al., 2010). Mutations in the *PON* genes might play a role in ALS but additional sequencing is needed to confirm this.

Interestingly, PON1 activity can vary greatly depending on polymorphisms in its coding region (Costa et al., 2005). Thus, mutations in the *PON* genes could affect PON activity and thereby contribute to ALS pathogenesis. Toxicity in neurons caused by oxidative stress was higher in cells from PON2 knockout mice than in wild-type mice, suggesting that PON2 has a protective effect against neurotoxicity caused by oxidative stress (Giordano et al., 2011).

3.7 Peripherin (PRPH)

Peripherin is an intermediate filament similar to neurofilaments and is also associated with axonal spheroids in the proximal axon of spinal cord motor neurons of ALS patients (Corbo and Hays, 1992). It is also present in Lewy body-like inclusions and Bunina bodies that are seen in a portion of ALS patients (He and Hays, 2004; Mizuno et al., 2011). Peripherin is predominantly expressed in the peripheral nervous system and in spinal motor neurons in the central nervous system. After neuronal injury, peripherin expression is upregulated in spinal motor neurons and this upregulation has been linked to axonal regeneration (Troy et al., 1990). However, transgenic mice with wild-type overexpression of peripherin develop a late-onset and selective motor neuron disease characterized by intermediate filament inclusions (Beaulieu et al., 1999). For these reasons, the possibility of *PRPH* mutations in

ALS patients was investigated. Two missense mutations and a frameshift deletion in the PRPH gene have been identified in sALS patients (Corrado et al., 2011; Gros-Louis et al., 2004; Leung et al., 2004). Additional screening of the *PRPH* gene for mutations in larger cohorts of ALS patients and controls is needed to determine the frequency and pathogenecity of *PRPH* mutations.

Expression of abnormal peripherin splice variants has also been suggested to play a role in ALS pathogenesis. A toxic splice variant of peripherin (Per61) was found in motor neurons of mutant SOD1 transgenic mice but not wild-type mice (Robertson et al., 2003). Expression of Per61 has more recently also been observed in mutant TDP-43 transgenic mice but not in wild-type TDP-43 transgenic mice (Swarup et al., 2011). In addition, Per61 specific antibodies stain aggregates in human ALS but not in control spinal cord (Swarup et al., 2011). The presence of abnormal peripherin splice variants (Per28) has also been shown in humans (Xiao et al., 2008). Per28 overexpression results in peripherin aggregation and an upregulation of peripherin expression at the mRNA and protein levels in ALS patients as compared to controls (Xiao et al., 2008). A different study showed expression of Per28 in lumbar spinal cord lysates of ALS patients but not control cases (McLean et al., 2010). Although the functional significance of these abnormal splice forms is unknown they seem to play a role in the development ALS.

3.8 Survival motor neuron (SMN) 1 and 2

Two highly homologous copies of the survival motor neuron gene exist in humans, telomeric *SMN1* and centromeric *SMN2*. *SMN2*, which lacks exon 7 due to a nucleotide difference in a splice enhancer site, produces a less stable SMN protein and has only 20% of the biological function of SMN1 (Lorson et al., 1998). It has been shown that TDP-43 overexpression regulates the inclusion of exon 7 during pre-mRNA splicing of *SMN2* (Bose et al., 2008).

Deletions or mutations in *SMN1* cause the autosomal recessive disorder spinal muscular atrophy (SMA), whereas variation in *SMN2* copy number affects SMA disease severity (Lefebvre et al., 1997). SMA patients with a higher copy number of *SMN2* generally have a milder form of the disease (Gavrilov et al., 1998). SMN1 is widely expressed and functions in the assembly of the spliceosome as part of the SMN complex. SMN1 also interacts with several proteins involved in mRNA editing, transport, splicing, transcriptional regulation, and post-transcriptional processing and modification of rRNA (Eggert et al., 2006). The impaired assembly of the spliceosome could lead to neuronal degeneration.

Thus far, five different studies have failed to detect homozygous *SMN1* deletions in ALS patients (Gamez et al., 2002; Jackson et al., 1996; Moulard et al., 1998; Orrell et al., 1997; Parboosingh et al., 1999). However, an increased frequency of abnormal copy number (one or three copies) of *SMN1* was found in ALS patients compared to controls (Corcia et al., 2002). However, these results were inconsistent with other reports (Corcia et al., 2006; Veldink et al., 2001; Veldink et al., 2005). Recently, a large study was published including new samples of 847 sALS patients and 984 controls, showing that *SMN1* duplications were associated with ALS susceptibility (odds ratio [OR] = 2.07, 95% confidence interval [CI] = 1.34 - 3.20. (Blauw et al, 2011)). A meta-analysis of all previously published data, taking possible heterogeneity between studies into account, confirmed this association with *SMN1* duplications. Other work has shown that homozygous deletions of *SMN2* are associated

with sporadic adult-onset lower motor neuron disease (Echaniz-Laguna et al., 2002; Moulard et al., 1998). Homozygous deletions of *SMN2* were also found to be overrepresented in 110 ALS patients (16%) compared to 100 controls (4%) (Veldink et al., 2001). *SMN2* deletions were associated with shorter survival in this study. However, a study by the same group using more ALS and control samples and several other studies did not find a higher frequency of *SMN2* deletions in ALS patients versus controls (Corcia et al., 2006; Gamez et al., 2002; Moulard et al., 1998; Parboosingh et al., 1999; Veldink et al., 2005). The recent meta-analysis showed that there is no increased frequency of homozygous *SMN2* deletions in ALS patients, and that neither *SMN1* nor *SMN2* appear to influence survival or age at onset of disease (Blauw et al. 2011).

Homozygous deletions in *SMN1* or *SMN2* do not play a role in ALS but an abnormal copy number in *SMN1* could increase risk for ALS and it is important to study the consequences on protein level in brain and spinal cord of having three copies of *SMN1* in order to determine the potential damaging effect.

3.9 Vascular endothelial growth factor (VEGF)

VEGF, a protein that stimulates angiogenesis in response to hypoxia, was identified as a candidate gene for ALS based on the finding that a deletion in the hypoxia response element (HRE) in the promoter of this gene in mice, resulting in decreased VEGF expression, led to progressive motor neuron degeneration (Oosthuyse et al., 2001). In addition, *VEGF* gene delivery in muscle and VEGF overexpression prolongs survival in mutant SOD1 transgenic mice. Furthermore, intracerebroventricular VEGF administration prolongs survival in mutant SOD1 transgenic rats (Azzouz et al., 2004; Storkebaum et al., 2005; Wang et al., 2007). Finally, decreased expression of VEGF and its receptor VEGFR2 is observed in spinal cords of ALS patients (Brockington et al., 2006).

Sequencing of the *VEGF* gene and its promotor in ALS patients failed to identify ALS specific mutations (Brockington et al., 2005; Gros-Luois et al., 2003; Lambrechts et al., 2003). However, a large study in 750 ALS patients and over 1200 controls from Sweden, Belgium, and England found association between two haplotypes determined by three SNPs and an increased risk for ALS (Lambrechts et al., 2003). These haplotypes lowered the circulating levels of VEGF and *VEGF* transcription (Lambrechts et al., 2003). This association was replicated in a study with small sample size (Terry et al., 2004). In contrast, subsequent studies could not confirm the association between *VEGF* and ALS in Dutch, British, American, Italian, Polish and Chinese populations (Brockington et al., 2005; Chen et al., 2006; Del Bo et al., 2008a; Golenia et al., 2010; Van Vught et al., 2005; Zhang et al., 2006). Furthermore, a meta-analysis on several of these studies found no association between *VEGF* polymorphisms and ALS (Lambrechts et al., 2009). A study in German ALS patients identified an association of a *VEGF* SNP with sALS in women (Fernández-Santiago et al., 2006). A different SNP was associated with ALS in male patients in a large meta-analysis (Lambrechts et al., 2009). This suggests that the role of *VEGF* in ALS may be gender dependent. An association of *VEGF* SNPs with age of onset in ALS was also reported although no such association was observed in the meta-analysis (Chen et al., 2007; Lambrechts et al., 2009).

In summary, studies in rodent models suggest a role for VEGF in ALS, possibly as a therapeutic target. However, genetic studies do not yet provide conclusive evidence for a genetic role for VEGF in ALS, although gender dependent effects may exist.

3.10 Genome wide association studies in sporadic ALS

Several genome-wide association studies (GWAS) have been performed in sALS patients. These studies have generated association results that have been replicated in the same study but rarely in independent studies. Although several of the associated genes discussed below are plausible to contribute to ALS considering their functional roles, the lack of consistent replication results makes it difficult to firmly establish their role in sALS.

A GWAS in 276 ALS patients and 271 healthy controls identified 34 possible associated SNPs but none of these reached genome-wide significance after Bonferroni correction (Schymick et al., 2007). A SNP near the gene FGGY carbohydrate kinase domain containing (*FGGY*) was reported to be associated in a GWAS in 1152 ALS patients with an odds ratio of 1.35 (Dunckley et al., 2007). However, two replication studies in a total of 2478 sALS patients and 2744 controls did not detect this association (Fernández-Santiago et al., 2011; Van Es et al., 2009b). No mutations in *FGGY* were found by sequencing in 190 ALS patients (Daoud et al., 2010).

A GWAS in 461 ALS patients and 450 controls found a variant in the inositol 1, 4, 5-triphosphate receptor 2 gene (*ITPR2*) to be associated with ALS. This association was replicated in the same study in a cohort of 876 patients and 906 controls and in the combined analysis (Van Es et al., 2007). ITPR2 has a role in glutamate-mediated neurotransmission, regulation of calcium concentration and apoptosis. However, the *ITPR2* association has not been found in a replication study and in subsequent GWAS (Chiò et al., 2009; Cronin et al., 2008; Fernández-Santiago et al., 2011; Laaksovirta et al., 2010; Shatunov et al., 2010; Van Es et al., 2009c).

Variation in the dipeptidyl-peptidase 6 (*DPP6*) gene was found to be significantly associated with sALS in a GWAS performed in a combined GWA data set from the USA and the Netherlands (Van Es et al., 2008). This association was replicated in three additional independent populations from The Netherlands, Sweden, and Belgium (Van Es et al., 2008). The same variant was the top hit in a joint analysis of GWA data sets in an Irish population and the same Dutch and American populations, although it did not reach genome-wide significance (Cronin et al., 2008). Upon addition of a Polish data set the association could not be replicated which could point to a population-specific effect (Cronin et al., 2009). In an Italian cohort of 266 ALS patients association of the same SNP was replicated (Del Bo et al., 2008b). However, subsequent replication studies and GWAS could not find evidence for a role of *DPP6* in ALS (Chiò et al., 2009; Daoud et al., 2010; Fogh et al., 2011; Laaksovirta et al., 2010; Li et al., 2009; Shatunov et al., 2010; Van Es et al., 2009c). Interestingly, in a genome scan for copy number variations, including 4434 ALS patients and over 14000 controls, a suggestive association was found for the *DPP6* locus (Blauw et al., 2010). Not much data is available on the function of DPP6, but it is expressed in brain and able to regulate the activity of neuropeptides and to bind A-type neuronal potassium channels (Nadal et al., 2003).

Another two-stage GWAS in sALS patients was unable to find any associated SNPs that reached genome-wide significance, although suggestive association was found on **chromosome 7p13.3** (Chiò et al., 2009).

Survival analysis in a GWAS using samples from the USA and Europe revealed that a CC genotype of a SNP in the kinesin-associated protein 3 (*KIFAP3*) gene conferred a 14-month survival advantage on ALS patients (Landers et al., 2009). Expression data using RNA from brain tissue and lymphoblasts of patients showed that the favorable genotype significantly

decreased KIFAP3 expression (Landers et al., 2009). However, two subsequent studies in two Italian cohorts could not replicate the finding that the CC genotype had a beneficial effect on survival or decreased KIFAP3 expression in ALS patients (Orsetti et al., 2011; Traynor et al., 2010). KIFAP3 is part of the trimeric kinesin 2 motor complex KIF3 which mediates binding between proteins and their cargo. It serves multiple functions including a role in mitosis and intracellular transport of organelles and proteins in various tissues including neurons (Haraguchi et al., 2006; Takeda et al., 2000).

The largest GWAS to date identified two loci, on **chromosome 9p21.2** and **19p13.11**, to be associated with sALS. The genetic variant in 19p13.11 maps to a haplotype within the boundaries of the *UNC13A* gene. Two studies failed to replicate this finding, but were underpowered, and more studies are needed to firmly establish genetic variation in *UNC13A* as being causative to sALS.

The association to chromosome 9p21.2 will be discussed in more detail in the following sections.

4. ALS-FTD2 (9p13.2-21.3)

Several linkage studies associated **chromosome 9p** to ALS-FTD, designated as ALS-FTD2 (Table 3). The first two independent studies found linkage to locus 9p13.2-21.3 in a Dutch and a Scandinavian family (Morita et al., 2006; Vance et al., 2006). Subsequently, eight other linkage studies in families from Canada, France, Belgium, North-America, Australia and Wales showed association to regions on chromosome 9p13.1-q21 (Boxer et al., 2010; Gijselinck et al., 2010; Le Ber et al., 2009; Luty et al., 2009; Momeni et al., 2006; Pearson et al., 2011; Valdmanis et al., 2007; Yan et al., 2006). Individuals in these families were diagnosed with ALS, FTD, and ALS-FTD. However, dementia, psychosis and Parkinsonism were also seen. Besides the co-occurrence of ALS and FTD in families, there is also considerable clinical overlap between ALS and FTD, i.e. mild cognitive abnormalities occur in up to 50% of ALS patients and in approximately 5% of ALS patients FTD is present with marked behavioral changes and language impairment (Elamin et al., 2011; Ringholz et al., 2005). Furthermore, ALS and FTD are both characterized by TDP-43 positive ubiquitinated cytoplasmic inclusions (Neumann et al., 2006). This strongly supports the idea that there is a common genetic contribution to the pathogenesis of both diseases.

A total of 41 genes, four micro RNAs, two pseudogenes, and a non-coding RNA in the associated chromosome 9p region have been screened for mutations but only in one study a premature stop codon in the intraflagellar transport 74 gene (*IFT-74*) was identified in two brothers from one family (Momeni et al., 2006). However, no mutations in *IFT-74* were identified in any of the other ALS-FTD families that were linked to chromosome 9p and it is therefore unlikely that this mutation is the underlying cause in these families.

Interestingly, a recent GWAS in sALS patients found association between ALS and chromosome 9p21.2. 2323 ALS patients and 9013 controls were genotyped and genome-wide significance was found for SNPs on these two loci (van Es et al., 2009c). This finding was replicated in a second, independent cohort of 2532 ALS patients and 5940 controls. The associated SNPs are in a 80-kb linkage disequilibrium (LD) block on chromosome 9 which overlaps with the common region found in the ALS-FTD linkage studies (Figure 1).

Study	*Linkage region*	*Families*	*Country/ Region*	*fALS*	*FTD*	*ALS-FTD*	*Genes screened*	*Mutations*
Yan et al. 2006	9p13.3-p22.1 (D9S1684-D9S1678)	15	N.K.	N.K.	N.K.	N.K.	27	None
Morita et al. 2006	9p13.2-p21.3 (D9S1870-D9S1791)	1	Scandinavia	5	9	-	2	None
Vance et al. 2006	9p13.2-p21.2 (D9S2154-D9S1874)	1	The Netherlands	7	2	3	3	None
Momeni et al. 2006	9p13.2-p22.2 (D9S157-D9S1874)	2	North-America	1	-	9	14	p.Q342X in *IFT-74*
Valdmanis et al. 2007	9p13.3-p22.2 (D9S157-D9S1805)	2	Canada/ France	14	3	4	4	None
Le Ber et al. 2009	9p11.2-p21.2 (AFM218xg11-D9S301)	6	France	9	10	12	29 + 4 miRNAs	None
Luty et al. 2008	9p21.2-q21 (D9S169-D9S167)	1	Australia	2	5	2	11	None
Gijselinck et al. 2010	9p22.3-q21 (D9S235-D9S257)	1	Belgium	1	8	-	17	None
Boxer et al. 2010	9p21.2-p23 (D9S1808-D9S251)	1	USA	2	5	3	10	None
Pearson et al. 2011	9p21.2-p21.2	1	Wales	2	5	1	8	None

Table 3. Overview of linkage studies in ALS-FTD families. N.K. = not known

Fig. 1. Schematic overview of the associated regions found by linkage studies and GWAS.

Since this initial report several other GWAS in ALS patients have replicated the association to chromosome 9p21.2. In a GWAS performed on 405 Finnish ALS patients, of whom 93 patients had fALS, and 497 control individuals two association peaks were identified (Laaksovirta et al., 2010). One peak corresponded to the autosomal recessive D90A allele of the SOD1 gene. The other was identified in a 232-kb LD block on chromosome 9p21.2. The association signals in this study were mainly driven by the 93 fALS patients. A 42-SNP risk haplotype across the chromosome 9p21 locus was shared between 41 fALS cases with an odds ratio of 21.0 (Laaksovirta et al., 2010). In another GWAS in an ALS cohort from the UK

consisting of 599 ALS patients and 4144 control individuals two SNPs on chromosome 9p21.2 were found to be associated with ALS (Shatunov et al., 2010). A joint analysis including 4132 ALS patients and 8425 controls from this UK cohort and from previously published data from the UK, USA, Netherlands, Ireland, Italy, France, Sweden, and Belgium also showed significant association to the locus on chromosome 9p21.2 (Shatunov et al., 2010). In addition, replication of one of the associated SNPs on chromosome 9p21.2 was found in a GWAS performed in FTD patients when analyzing the ALS-FTD patients only. A different SNP in this locus was significantly associated with FTD (Rollinson et al., 2011). A trend towards significant genome-wide association between chromosome 9p21.2 and FTD was found when analyzing 426 FTD patients with TDP-43 pathology without mutations in the progranulin gene and 2509 control individuals (Van Deerlin et al., 2009). A replication study in Chinese and Japanese sALS patients failed to find association to one of the previously associated SNPs on chromosome 9p21.2 but this might be due to a lack of power (Iida et al., 2011).

In summary, linkage studies in ALS-FTD families and GWAS in sALS, ALS-FTD and FTD patients provide compelling evidence for a role of chromosome 9p21.2 in ALS and/or FTD.

As mentioned, recently two studies identified a GGGGCC hexanucleotide repeat expansion in intron 1 of the *C9ORF72* gene as the cause of chromosome 9p-linked ALS-FTD (Dejesus-Hernandez et al., 2011; Renton et al., 2011).

5. Gene function

A hexanucleotide repeat expansion in the *C9ORF72* gene has recently been identified as the cause of chromosome 9p-linked ALS-FTD. The mechanism as to how this expanded repeat causes ALS is unknown. No causal mutations in *UNC13a* have been identified in ALS patients to date. Close examination of the reported function(s) of the proteins encoded by the *C9ORF72* and *UNC13a* gene may help to design strategies for determining the functional role of these loci in ALS and/or FTD.

In this section the current knowledge of the function of these genes will be discussed in light of a possible contribution to ALS pathogenesis.

5.1 Chromosome 9 open reading frame 72

The *C9ORF72* gene encodes a protein of 481 amino acids. Alternative splicing of this gene is thought to produce five isoforms of which three are protein coding. Isoform 1 contains the entire sequence and consists of 481 amino acids, while isoform 2 and 3 have an asparagine to lysine change at amino acid 222 which results in the truncation of amino acids 223 to 481. Thus far, no C9ORF72 protein has been detected and nothing is known about the function of C9ORF72.

The *C9ORF72* gene has been sequenced in four linkage studies in 39 patients from different families, but no mutations have been identified. No changes in splicing, small deletions or duplications were detected in patients from an ALS-FTD family (Boxer et al., 2010). The gene has been sequenced in 16 sALS patients and 16 controls but no variants specific for sALS were identified (Laaksovirta et al., 2010). Hexanucleotide repeat expansions were recently found to be the most common cause of fALS and familial FTD and were also identified in sALS patients (Dejesus-Hernandez et al., 2011; Renton et al., 2011). The functional consequence of these repeat expansions are however unknown.

Further studies will be needed to characterize the C9ORF72 protein and to establish the consequences of the intronic repeat on ALS pathogenesis.

5.2 UNCoordinated 13 homolog A (UNC13a)

UNC13a is a member of UNC13 family of presynaptic proteins. The protein consists of 1791 amino acids but several isoforms exist. It contains a zinc-finger like C1 domain that is homologous to a diacylglycerol and phorbol ester binding region of protein kinase C (PKC), three C2 domains that are similar to the calcium binding regulatory regions of PKC and synaptotagmin, a calmodulin binding domain and two Munc homology domains (Basu et al., 2005).

In mammals, the Munc13 family comprises four homologous members, Munc13-1, Munc13-2, Munc13-3, and Munc13-4. Deletion mutants of Munc13-1 in mice, the murine homologue of UNC13a, shows that the protein is needed for presynaptic vesicle maturation and fusion competence in glutamergic hippocampal neurons (Augustin et al., 1999). GABA-ergic neurons in the hippocampus show no spontaneous or evoked synaptic transmission in absence of both Munc13-1 and Munc13-2 (Varoqueaux et al., 2002). Neuromuscular junction (NMJ) axon terminals contain Munc13-1 and a splice variant of Munc13-2 (Varoqueaux et al., 2005). Mice deficient in Munc13 due to a double knockout of Munc13-1 and Munc13-2 form specialized neuromuscular endplates. However, the distribution, size and shape of these synapses are altered. Also, muscle morphology is abnormal and a larger number of motor neurons is present in the spinal cord in Munc13-1/2 knockout mice, probably as a result of defective apoptosis. Furthermore, evoked synaptic transmission is impaired in these mutants but spontaneous transmission is unchanged (Varoqueaux et al., 2005). This indicates that vesicle priming in NMJs is partially independent of Munc13-1 or Munc13-2. However, despite the unchanged spontaneous transmission, muscle innervation is aberrant in Munc13-1/2 knockout mice (Varoqueaux et al., 2005).

As exemplified by the defects observed in Munc13-1 and Munc13-1/2 knockout mice, it is plausible that a disruption in UNC13a expression affects motor neurons and muscle innervation. The effect of UNC13a on glutamate exocytosis is also interesting since Riluzole, the only drug with a proven effect on ALS, is a glutamate release inhibitor. Therefore, *UNC13a* is an interesting candidate gene to be investigated further for a role in ALS pathogenesis.

6. Conclusion and future research

The use of linkage analysis, candidate gene studies, and GWAS has led to the identification of several causal loci and genes for fALS and sALS. The overview above clearly shows the extent of heterogeneity in genes that underlie fALS, let alone sALS, illustrating the complex molecular basis of this disease. There is not one dominant biological process that is represented by these genes, although RNA-processing, axonal transport and synaptic dysfunction appear to emerge as being relevant in ALS etiology. Interestingly, several of the genes implicated in these processes are already known to be causal or have been implicated in other neurodegenerative diseases which suggests that there is, at least in part, a common underlying mechanism.

Since these findings explain only about a third of the genetic variability in fALS and a small percentage of the genetic contribution to sALS, there is a clear need for the identification of additional causal loci. This would require the collection of large family pedigrees with many affected individuals, which is difficult in ALS considering the adult onset with rapid disease progression. However, the development of next generation sequencing techniques provides a possible solution to this problem. Using exome and whole-genome sequencing, causal genes can be identified with a small number of affected and unaffected individuals as has been shown in several, mostly autosomal recessive disorders (Choi et al., 2009; Ng et al., 2009). Recently, exome sequencing in two affected individuals from the same family identified *VCP* as a causal gene for fALS, illustrating that this technique is a promising tool for gene identification in ALS as well (Johnson et al., 2010). In addition, the repeat expansion in C9ORF72 was also discovered with the use of whole-genome sequencing (Renton et al., 2011).

The identification of causal genes for ALS has broadened our understanding of this motor neuron degenerative disease. Studying the function of associated genes in neurons and animal models has revealed several possible processes underlying ALS such as RNA processing, axonal transport, glutamate regulation, oxidative stress and synaptic dysfunction. However, the contribution of most genes to ALS pathogenesis has not been resolved. SOD1 and TDP-43 transgenic animal models have provided valuable insights into ALS pathogenesis. Further research using existing animal models of ALS associated genes and the generation of new animal models are needed to further determine their role in the disease. Generation of animal models harbouring repeat expansions in C9ORF72 and ATXN2 could help to reveal the pathogenic mechanisms behind these repeats. The effect of overexpression or knockdown of ALS associated genes and the expression of repeat expansions in motor neurons or motor neuron-like cell lines on protein aggregation and cell survival could also help to unravel the contribution of these genes to ALS. In addition, some associated genes (e.g. *DCTN1*, *PON1/2/3*, *TAF15*, and *VCP*) remain to be sequenced in larger cohorts from different populations in order to determine the actual contribution of these genes to ALS.

Additional new strategies in sALS include a more network oriented approach to gene identification. It is possible to detect networks of genes, proteins and metabolites that are misregulated in ALS, or that determine disease progression. By searching for subtle genetic variation that drives these network perturbations, new genes might be identified that are hard to detect with GWAS. Also, the focus in ALS genetics thus far has been on common variation in exonic DNA. The regulatory part of the genome is challenging to study, but might be relevant as well. This also requires the combined analysis of gene-expression and protein data with data on genetic variation. In addition, recent studies show that tandem repeats in DNA might be also relevant, as exemplified by the ATXN2 and C9ORF72 findings. Typically, this type of variation is hard to detect by current high-throughput methods. Lastly, the type of copy number variation that has not yet been covered very well to date, including variation in microRNAs or inversions, deserves more attention.

In summary, impressive progress in the understanding of the genetics of ALS has been made over the past several years with the identification of several causal genes. However, most of the genetic variability underlying ALS remains to be identified. The use of deep sequencing techniques and functional research will be needed to further broaden our understanding of ALS pathogenesis.

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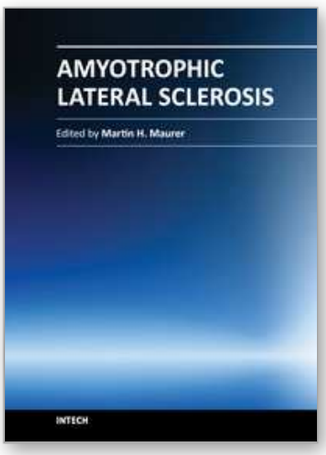

Amyotrophic Lateral Sclerosis

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Though considerable amount of research, both pre-clinical and clinical, has been conducted during recent years, Amyotrophic Lateral Sclerosis (ALS) remains one of the mysterious diseases of the 21st century. Great efforts have been made to develop pathophysiological models and to clarify the underlying pathology, and with novel instruments in genetics and transgenic techniques, the aim for finding a durable cure comes into scope. On the other hand, most pharmacological trials failed to show a benefit for ALS patients. In this book, the reader will find a compilation of state-of-the-art reviews about the etiology, epidemiology, and pathophysiology of ALS, the molecular basis of disease progression and clinical manifestations, the genetics familial ALS, as well as novel diagnostic criteria in the field of electrophysiology. An overview over all relevant pharmacological trials in ALS patients is also included, while the book concludes with a discussion on current advances and future trends in ALS research.

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