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# Genetics of Familial Amyotrophic Lateral Sclerosis

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## 1. Introduction

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder caused by the selective loss of motor neurones from the cortex, brainstem and spinal cord. For the patient, this results in a progressive loss of muscle function characterised by muscle weakness, atrophy and spasticity that develops into paralysis. Onset is typically in mid-life around ages 50-60 years, however there are juvenile forms with much earlier symptom onset (below 25 years). Disease duration is heterogeneous; however the majority of patients will only survive 2-3 years following initial symptom onset, with death generally resulting from respiratory muscle failure (Worms 2001).

A recent meta-analysis of population based studies revealed that 5% of ALS cases are familial (FALS) and the remaining 95% are sporadic (SALS) with no reported family history (Byrne et al 2011). There is a broad spectrum of inheritance for FALS ranging from fully penetrant, dominantly inherited Mendelian forms to recessive disease with weak penetrance affecting only a few family members (Simpson & Al-Chalabi 2006). The majority of familial cases are clinically and pathologically indistinguishable from sporadic cases, leading to the hypothesis that they share common pathogenic mechanisms. In addition, mutations in several of the FALS genes have also been identified in apparently sporadic disease, suggesting some degree of genetic overlap (Alexander et al 2002; Chio et al 2010; Kabashi et al 2008).

In ALS, cognitive impairment has been reported in up to 51% of cases, with frontotemporal dementia (FTD) present in up to 15% (Gordon et al 2011; Lillo et al 2011; Ringholz et al 2005). In approximately a third of cases, there is a family history of ALS or FTD or both in the family, and genes initially associated with either ALS or FTD are now being found to be associated with both disease phenotypes. This genetic link, in addition to extensive neuropathological evidence (Mackenzie et al 2010) has led to the widely accepted view that ALS and FTD form part of a spectrum of the same neurodegenerative disease process (Geser et al 2010).

## 2. Overview of genetics of ALS

The inheritance of FALS in many families is atypical with one proband and one or two first/second degree relatives who also have the disease (Valdmanis & Rouleau 2008). The first big breakthrough in the genetics of FALS came in 1993 with the discovery of

pathological mutations in the Cu-Zn superoxide dismutase (*SOD1*) gene in ALS patients (Rosen et al 1993). Since then there has been an explosion of research into the mechanism(s) by which *SOD1* mutations cause ALS, however the answer remains elusive. There are now 16 genes associated with Mendelian forms of ALS (Table 1) which have mostly been identified using linkage analysis of rare families with large pedigrees affected by the disease (Lill et al 2011). More recently, studies to identify the proteins found in the ubiquitinated inclusions that are a common neuropathological feature of both ALS and FTD, have identified trans-activation response element (TAR) DNA binding protein of 43kDa (TDP-43) as the major component (Arai et al 2006; Neumann et al 2006). Mutations in the gene encoding TDP-43, *TARDBP*, were subsequently found as a genetic cause of ALS (Sreedharan et al 2008). The genetics of FALS has moved forward rapidly in recent years, providing invaluable insight into disease pathogenesis and allowing the development of animal models to further study the disease and efficacy of therapeutic compounds.

	Type	Locus	Reference
Autosomal Dominant Adult Onset			
Most common genetic causes			
<i>SOD1</i>	ALS1	21q22	(Rosen et al 1993)
<i>TARDBP</i>	ALS10	1p36.22	(Sreedharan et al 2008)
<i>FUS</i>	ALS6	16q12.1-2	(Abalkhail et al 2003)
Less frequent genetic causes			
<i>VAPB</i>	ALS8	20q13.3	(Nishimura et al 2004)
<i>ANG</i>	ALS9	14q11.2	(Greenway et al 2004)
<i>FIG4</i>	ALS11	6q21	(Chow et al 2009)
<i>OPTN</i>	ALS12	10p15-14	(Maruyama et al 2010)
<i>DAO</i>		12q22-23	(Mitchell et al 2010)
<i>VCP</i>		9p13.3	(Johnson et al 2010b)
Autosomal Dominant Juvenile Onset			
<i>SETX</i>	ALS4	9q34	(Chen et al 2004)
Autosomal Recessive			
<i>ALS2</i>	ALS2	2q33-35	(Hentati et al 1994)
<i>ALS+FTD</i>			
<i>SIGMAR1</i>		9p13.3	(Luty et al 2010)
<i>MAPT</i>		17q21	(Sundar et al 2007)
Genetic Loci Linked to Familial ALS			
<i>SPG11</i>	ALS5	15q15-22	(Orlacchio et al 2010)
Unknown	ALS7	20ptel-p13	(Sapp et al 2003)
Unknown	ALS3	18q21	(Hand et al 2002)
<i>UBQLN2</i>	ALSX	Xp11-q12	(Deng et al 2011)
<i>C9ORF72</i>	ALS-FTD1	9p21-q22	(Hosler et al 2000)
Unknown	ALS-FTD2	9p13.2-p21.3	(Vance et al 2006)

Table 1. Summary of the Genetic Causes of Familial ALS

### 3. Genetic causes of FALS

#### 3.1 Most common genetic causes of autosomal dominant, adult onset ALS

The three most common genetic causes of FALS, together accounting for approximately 30% of cases are mutation of the *SOD1*, *TARDBP* and fused in sarcoma (*FUS*) genes.

##### 3.1.1 ALS1: Cu-Zn superoxide dismutase 1 (*SOD1*)

The first genetic cause of familial ALS was identified by Rosen and colleagues (Rosen et al 1993) when, following analysis of FALS pedigrees demonstrating linkage to chromosome 21, mutations were identified in the *SOD1* gene. Since then, over 150 mutations have been described throughout the 5 exons encoding the gene consisting predominantly of missense mutations, although nonsense mutations, insertions and deletions have also been described (Lill et al 2011). The frequency of *SOD1* mutations is widely reported to be 20% of FALS cases, though this varies across European and North American populations, from 12% in Germany to 23.5% in USA (Andersen 2006). Whilst the majority of mutations are inherited in an autosomal dominant manner, in Scandinavia the p.D90A mutation is polymorphic, (0.5-5% of Scandinavian populations), with the disease manifesting only in individuals who are homozygous (Andersen et al 1995). However, this inheritance pattern is not attributable to the specific amino acid substitution, as p.D90A has been shown to be inherited as an autosomal dominant mutation in other populations. Mutations in *SOD1* have also been identified in sporadic ALS, albeit at lower frequencies, suggesting that some mutations have reduced penetrance. This has been shown in a family where the p.I113T mutation shows age-related penetrance (Lopate et al 2010).

Clinically, *SOD1* mutations are not associated with a distinctive phenotype. Individuals with *SOD1*-related ALS predominantly manifest with limb onset ALS, with symptoms more likely to start in the lower limbs (rather than upper limbs). However, bulbar onset is seen in approximately 7% of *SOD1*-related cases (ALSoD database: <http://alsod.iop.kcl.ac.uk>). Whilst duration of disease varies widely among *SOD1* mutations, even within members of the same family with the same mutation, the p.A4V mutation has been shown to be associated with a rapid disease progression and only 1-2 years survival (Andersen 2006). In contrast to the indistinguishable clinical phenotype, *SOD1*-related ALS cases appear to have a characteristic pathology distinguished by *SOD1* positive, but TDP-43 negative, protein inclusions (Mackenzie et al 2007).

The mature *SOD1* protein is a homodimer of 153 amino acid subunits. This free radical scavenging protein converts the superoxide anion to hydrogen peroxide; this in turn is converted to water and oxygen by glutathione peroxidase or catalase. Mutations in *SOD1* cause a toxic gain of function in the resulting mutant protein, though the mechanism(s) by which this brings about selective neurodegeneration of the motor neurones appears to be a complex interplay between multiple interacting pathomechanisms. The main hypotheses involve either an altered redox function or misfolding of the protein leading to aggregation (Rakhit & Chakrabartty 2006). Interestingly, not only have *SOD1* positive aggregations been seen in SALS spinal cord, recent work has also shown that a conformation specific antibody raised against mutant *SOD1* binds oxidised, but not normal, wild-type *SOD1* in a subset of SALS cases thereby linking both *SOD1*-ALS and SALS (Bosco et al 2010).

Identification of *SOD1* led to the generation of many cellular and animal models which mirror aspects of the disease process and enable mechanistic insights and therapeutic approaches to be investigated. Current pathogenic mechanisms associated with mutant

SOD1 include oxidative stress, excitotoxicity, protein aggregation, mitochondrial dysfunction, endoplasmic reticulum stress, inflammatory cascades, involvement of non-neuronal cells and dysregulation of axonal transport. Each of these mechanisms has also been shown to play a role in SALS, demonstrating the relevance of the *SOD1* models to the disease as a whole (Ferraiuolo et al 2011). Therefore, although to date therapeutic agents which have shown promising results in the *SOD1* transgenic mouse models have yet to show a beneficial effect in human trials (Benatar 2007), the generation and continued use of these models has greatly extended our knowledge of ALS.

### 3.1.2 ALS10: Transactive response (TAR) DNA binding protein (*TARDBP*)

The identification of TAR-DNA binding protein (TDP-43) as the major component of ubiquitinated cytoplasmic inclusions in ALS (and FTD) (Neumann et al 2006) led to the gene encoding this protein, *TARDBP*, to be screened in cohorts of FALS. Following the initial report of mutations being identified in exon 6 of the gene (Sreedharan et al 2008), a further 39 nucleotide substitutions have been published; the vast majority of which are in exon 6 and encode non-synonymous changes. The frequency is reported to be 4-5% of FALS cases (Kirby et al 2010; Mackenzie et al 2010), with mutations inherited in an autosomal dominant manner.

Clinically, *TARDBP*-related ALS presents as a classical adult-onset form of ALS; 73% of cases manifest with limb onset and there is a wide range in the age of onset (30-77 years) and disease duration, even in cases carrying the same mutation (e.g. p.M337V), (ALSoD database: <http://alsod.iop.kcl.ac.uk>). Perhaps the most distinctive feature commented upon, is the absence of dementia in these patients, despite several reports of *TARDBP* mutations in cases of FTD (Borrioni et al 2009; Kovacs et al 2009). Neuropathologically, there is no distinction between *TARDBP*-related ALS and SALS cases, with both showing skein and compact ubiquitinated inclusions.

*TARDBP* encodes several isoforms of a predominantly nuclear protein, of which TDP-43 is the most prevalent. TDP-43 contains 2 RNA recognition motifs (RRM), a nuclear localisation and nuclear export signal, as well as a glycine-rich region in the C-terminus, which is encoded by exon 6. TDP-43 is involved in a variety of roles in the nucleus, including regulation of transcription, RNA splicing, microRNA (miRNA) processing and stabilisation of mRNA. Reports have recently identified RNA molecules which bind to TDP-43 in whole cell extracts using cross linking and immunoprecipitation (CLIP) methodologies (Polymenidou et al 2011; Sephton et al 2011; Tollervey et al 2011; Xiao et al 2011). This has established over 4000 TDP-43 binding targets, including ALS-related genes *FUS* and *vasolin* containing protein (*VCP*), as well as other RNA processing genes. One target which has been confirmed is the *TARDBP* mRNA. TDP-43 regulates its own transcription by binding to the 3'UTR region of the *TARDBP* mRNA and promoting mRNA instability (Budini & Buratti 2011). In addition, TDP-43 has been shown to interact with mutant, but not wild-type *SOD1* mRNA, thereby linking the two distinct genetic pathogenic mechanisms (Higashi et al 2010). In ALS, both in *TARDBP*-related ALS and SALS, TDP-43 is seen to mislocalise to the cytoplasm and form either compact or skein like protein inclusions. It is currently unclear whether a loss of nuclear function or a gain of toxic function (or both) causes motor neuronal cell death. Numerous cellular and animal models for *TARDBP*-related ALS have been generated in multiple species, in order to investigate the mechanisms of TDP-43 associated neurodegeneration (Joyce et al 2011). What is evident from this body of work is



that over-expression of not only mutant, but also wild-type *TARDBP* is toxic and that TDP-43 is essential for development, as knockout models show embryonic lethality.

### 3.1.3 ALS6: Fused in sarcoma (*FUS*)

Mutations in *FUS*, also referred to as translocated in sarcoma (*TLS*), were initially identified both through linkage analysis in a large Cape Verde pedigree manifesting with autosomal recessive ALS and in several autosomal dominant ALS families linked to chr16 (Kwiatkowski et al 2009; Vance et al 2009). Similarly to *TARDBP*, mutations in this second RNA binding protein gene are clustered, rather than spread across the 15 exons encoding *FUS*; a third occur in exons 5-6 encoding the glycine-rich region and two thirds in exon 13-14 encoding the arginine-glycine-glycine (RGG)-rich domain and the nuclear localisation signal. *FUS* mutations have been shown to account for a further 4-5% of FALS cases (Hewitt et al 2010; Mackenzie et al 2010).

Clinically, *FUS* mutations are associated with limb onset ALS; no bulbar onset cases with *FUS* mutations have been reported to date (ALSoD database: <http://alsod.iop.kcl.ac.uk>). There is a large range in the age of onset, from 26-80 years and as with *TARDBP* mutations, to date no correlations are evident between specific mutations and clinical characteristics. Pathologically, however, *FUS*-related cases have shown distinctive *FUS*-positive, TDP-43 negative inclusions. Specifically, those cases with basophilic inclusions and compact neuronal cytoplasmic *FUS*-positive inclusions had an earlier onset than those ALS cases with skein-like neuronal cytoplasmic inclusions, in whom glial cytoplasmic inclusions were also seen (Baumer et al 2010; Mackenzie et al 2011).

*FUS* is an RNA/DNA binding protein, which shuttles between the nucleus and cytoplasm. The 526 amino acid protein contains multiple protein domains, including a glutamine-glycine-serine-tyrosine rich domain at the N-terminus, involved in transcriptional activation of oncogenic fusion genes involving *FUS*, a glycine-rich region, a nuclear export signal, an RNA recognition motif and two arginine-glycine-glycine motifs flanking a zinc finger motif. At the C-terminus resides the nuclear localisation signal. Mutations within this region have been shown to disrupt transportin mediated transport of *FUS* into the nucleus, and cause the formation of *FUS* containing stress granules in the cytoplasm (Dormann et al 2010; Ito et al 2011a). In contrast, mutations in the glycine-rich region of *FUS* have yet to demonstrate pathogenicity. The normal function of *FUS* is poorly understood, though there is evidence for its involvement in alternative splicing, miRNA processing and transportation of mRNA to the dendrites for localised translation. Of the animal and cellular models generated to investigate the mechanisms of mutant *FUS*, a rat model over-expressing human p.R521C shows progressive paralysis, axonal degeneration and loss of neurones in 1-2 months old rats, whilst rats over-expressing wild-type *FUS* are pre-symptomatic at 1 year, though they do show learning and memory deficits and loss of cortical neurons (Huang et al 2011). Furthermore, drosophila and yeast models demonstrate *FUS* toxicity is due to accumulation of mutant protein in the cytoplasm (Kryndushkin et al 2011; Lanson et al 2011).

## 3.2 Rarer genetic causes of autosomal dominant, adult onset ALS

### 3.2.1 ALS8: Vesicle associated membrane protein (VAMP) associated protein B (*VAPB*)

ALS8 was first described in a large Brazilian kindred comprised of 28 Caucasian affected male and female family members distributed across four generations. Patients in this family had a

characteristic clinical phenotype of a postural tremor, fasciculations and a slowly progressive upper and lower limb weakness with an unusually long duration. Linkage analysis revealed a unique locus at Chr20q13.33 and mutation screening revealed a heterozygous C>T nucleotide substitution, resulting in a p.P56S non-synonymous change within the highly conserved major sperm protein (MSP) domain of VAPB (Nishimura et al 2004).

This exon 2 variant has since been detected in 22 additional individuals from six Brazilian pedigrees in which there is evidence of a founder effect, although it has also been seen in a Japanese and European case (Funke et al 2010; Landers et al 2008; Millecamps et al 2010). The neurodegenerative phenotype associated with this mutation is variable; 3 of the families also had several confirmed cases of autosomal dominant adult onset spinal muscular atrophy (SMA). A second heterozygous point mutation (p.T46I) within the same domain of the VAPB peptide has recently been reported in a single Caucasian from the UK with classical ALS (Chen et al 2010).

VAPB is a type II integral endoplasmic reticulum (ER) membrane protein. It is involved in multiple cellular processes including intracellular trafficking, lipid transport, and the unfolded protein response (Lev et al 2008). Both mutations residing in the MSP domain result in conformational changes which lead to VAPB aggregation and an increase in ER stress (Chen et al 2010; Kim et al 2010; Suzuki et al 2009). Whilst mutations in *VAPB* are only found rarely in FALS patients, *VAPB* shows significantly decreased gene expression in SALS cases compared to age and gender matched neurologically normal controls (Anagnostou et al 2010; Mitne-Neto et al 2011).

### 3.2.2 ALS9: Angiogenin (ANG)

Chr14q11.2 was first proposed as a susceptibility locus for ALS following the strong allelic association in the Irish population with a single nucleotide polymorphism (SNP) (rs11701) residing in the single exon angiogenin (*ANG*) gene (Greenway et al 2004). Mutation screening analysis of a large cohort of Irish, Scottish, English, Swedish and North American ALS cases detected 7 missense mutations in 15 patients, 4 of whom were FALS (Greenway et al 2006). Additional screening of ALS cohorts report *ANG* mutations occurring in both FALS and SALS cases, though at low frequencies (Fernandez-Santiago et al 2009; Gellera et al 2008).

ANG is a member of the pancreatic ribonuclease A (RNaseA) superfamily whose activities are known to be important in protein translation, ribosome biogenesis and cell proliferation (Crabtree et al 2007). The ribonuclease A activity has been shown to be reduced or lost in ANG mutant proteins. ANG is a potent inducer of neovascularization *in vivo* and has been shown to play a key role in neurite outgrowth and pathfinding during early embryonic development (Subramanian et al 2008). Its structure and function are partially homologous to that of vascular endothelial cell growth factor (VEGF); a previously reported genetic susceptibility and disease modifying factor in the development of neurodegeneration (Lambrechts et al 2009), and both VEGF and ANG have been shown to be neuroprotective. A proposed mechanism by which ANG prevents cell death is through inhibiting the translocation of apoptosis inducing factor into the nucleus (Li et al 2011).

### 3.2.3 ALS11: Factor-induced gene 4 *S.cerevisiae* homolog (*FIG4*)

The Sac1 domain containing protein 3 (SAC3) *FIG4*, located on Chr6q21, was originally identified as the causative gene of Charcot Marie-Tooth disease type 4J (CMT4J); a severe autosomal recessive childhood disorder that is characterised by both sensory and motor

deficits (Chow et al 2007). However, in one CMT4J pedigree there was a later onset of disease, with predominantly motor symptoms, similar to ALS (Zhang et al 2008). Screening of a North European cohort of FALS patients revealed 5 heterozygous mutations, resulting in either complete or significant loss of protein (Chow et al 2009). In general, cases of ALS11 are associated with a rapidly progressive disease course of approximately 1-2 years, early bulbar involvement and minimal cognitive dysfunction.

*FIG4* encodes the phosphatidylinositol 3,5-bisphosphate 5-phosphatase which controls the cellular abundance of PI(3,5)P<sub>2</sub>, a signalling lipid that mediates retrograde trafficking of endosomal vesicles to the Golgi apparatus (Michell & Dove 2009). It remains unclear as to whether the deleterious variants of *FIG4* exert an effect by a dominant negative mechanism or through a partial loss of function, as seen in CMT4J patients (Chow et al 2007). Human motor neurones are considered to be particularly susceptible to disruptions in this transport network because of their high membrane component turnover demands from long axonal processes over many decades (Ferguson et al 2010).

### 3.2.4 ALS12: Optineurin (*OPTN*)

Homozygosity mapping using 4 FALS cases demonstrated linkage to chr10p13 and subsequently mutations in *OPTN*, a gene previously linked to primary open-angle glaucoma (POAG), were identified in these cases (Maruyama et al 2010; Rezaie et al 2002). Mutations were initially found in both homozygous and heterozygous states. However, mutation screening of subsequent cohorts have identified only heterozygous mutations in ALS cases, occurring at a frequency of 3.4% in Japanese populations whilst this was at much lower frequencies in European and North American populations (Belzil et al 2011; Del Bo et al 2011). Interestingly, *OPTN*-related ALS is characterised by a lower limb onset with upper motor neurone involvement and a slow clinical progression.

The gene encodes the ubiquitously expressed optic neuropathy inducing protein which localises to the perinuclear region of the cytoplasm, where it is known to associate with the Golgi apparatus, and plays a key role in a number of biological processes, including vesicular trafficking, signal transduction and gene expression (Chalasani et al 2008). It is anticipated where mutations are inherited in an autosomal recessive manner, that reduced protein levels result in neurotoxicity through a loss of function mechanism. Conversely, the heterozygous missense substitution is predicted to exert a dominant negative effect. Examination of autopsy derived spinal cord tissue revealed extensive *OPTN* staining of TDP-43 positive intracytoplasmic hyaline inclusion bodies, although this was not replicated in a subsequent study (Hortobagyi et al 2011; Ito et al 2011b).

### 3.2.5 D-amino acid oxidase (*DAO*)

Following linkage analysis, a rare heterozygous missense mutation in the *DAO* gene, located on chr12q22-23, has been reported to segregate with disease in a single three generational Caucasian pedigree, though there was evidence of incomplete penetrance (Mitchell et al 2010). Those affected showed a rapidly progressive form of classical ALS with a mean disease duration of 21 months. Early bulbar involvement was apparent with limited signs of cognitive impairment. Interestingly, post-mortem immunohistochemical analysis on spinal cord tissue revealed no evidence of TDP-43 positively labelled inclusion bodies within the nuclear or cytoplasmic fractions of residual motor neurones which are normally a distinguishing feature of ALS pathology.



DAO encodes a universally expressed 39.4kDa peroxisomal flavin adenine dinucleotide (FAD)-dependent oxidase that is enriched in the neuronal and glial cell populations of the mammalian brainstem and spinal cord. The mutation results in the formation of an aberrant peptide product proposed to exert a dominant negative effect on the function of the wild type protein; *in vitro* work showed abnormal cellular morphology in cells over expressing the mutant protein, along with reduced cell viability, the presence of large intracellular ubiquitinated aggregates and an increased rate of apoptosis (Mitchell et al 2010).

### 3.2.6 Valosin containing protein (VCP)

Whole exome sequencing of two affected individuals in a large Italian pedigree identified a single heterozygous missense mutation in the *VCP* gene, located on chr9p13.3 (Johnson 2010). Screening of an additional cohort of ALS cases detected further *VCP* mutations at a frequency of 1.74%. There was no distinct phenotype associated with *VCP*-related ALS, with both limb and bulbar onset and an average age of onset of 49 years. Mutations in *VCP* have previously been linked to the autosomal dominant disorder inclusion body myopathy, Paget's disease and FTD (IBMPFD), which is characterised by muscle wasting, associated with osteolytic bone lesions and FTD (Watts et al 2004).

*VCP* is an evolutionarily conserved AAA+-ATPase that is known to be of importance in multiple biological processes including cell signalling, protein homeostasis, organelle biogenesis and autophagy (Ritson et al 2010), through its role in identifying ubiquitinated proteins in multimeric complexes and mediating their proteasomal degradation. It has been demonstrated both *in vitro* and *in vivo* that aberrant expression of *VCP* results in the cellular redistribution and mislocalisation of nuclear TDP-43 within the cytoplasm where neurotoxic ubiquitinated and phosphorylated aggregates form (Custer et al 2010; Gitcho et al 2009).

## 3.3 Genetic causes of autosomal dominant, juvenile onset ALS

### 3.3.1 ALS4: Senataxin (*SETX*)

The locus responsible for ALS4 was mapped to chr9q34 in an 11 generation pedigree affected by juvenile ALS and later confirmed by analysis of another two families with a similar phenotype (Chance et al 1998; De Jonghe et al 2002; Myrianthopoulos et al 1964). Sequence analysis of this region revealed disease associated mutations in the Senataxin (*SETX*) gene in all three affected families that were inherited in an autosomal dominant pattern (Chen et al 2004). *SETX* mutations are rare, with only four FALS families discovered to date, although mutations in this gene are also associated with ataxia-oculomotor apraxia-2 (AOA2), an autosomal recessive cerebellar ataxia (Anheim et al 2009). ALS4 is characterised by young onset (below the age of 25 years), distal muscle weakness and atrophy, pyramidal signs, an absence of sensory abnormalities while bulbar and respiratory muscles are spared. Disease progression is slow and patients have a normal life span (Chen et al 2004).

The *SETX* gene encodes a ubiquitously expressed DNA/RNA helicase that shares high homology to the yeast Sen1p protein and is suggested to play a role in DNA repair in response to oxidative stress (Suraweera et al 2007). *SETX* interacts with several RNA processing proteins, including RNA polymerase II, and is proposed to regulate transcription and pre-mRNA processing (Suraweera et al 2009).

### 3.4 Genetic causes of autosomal recessive ALS

#### 3.4.1 ALS2: Alsin (*ALS2*)

Linkage analysis in a large, inbred Tunisian family mapped the gene responsible for an autosomal recessive form of ALS to chr2p33-q35 (Hentati et al 1994). Subsequent sequencing in this family, and a Saudi pedigree with juvenile primary lateral sclerosis (PLS), revealed mutations in the previously uncharacterised gene now known as *ALS2* (Yang et al 2001). Thus, mutations cause a spectrum of early onset motor neurone disorders including infantile ascending hereditary spastic paraplegia (IAHSP), PLS and ALS (Bertini et al 1993). To date, 19 *ALS2* mutations have been identified in ALS patients, which are characterised by a juvenile onset of limb and facial spasticity with subsequent lower motor neurone signs (Hentati et al 1994; Lill et al 2011). The milder phenotypes of PLS and IAHSP are characterised by isolated upper motor neurone degeneration without lower motor neurone signs (Bertini et al 1993).

The *ALS2* gene is ubiquitously expressed and encodes the Alsin protein which contains three putative guanine-exchange factor (GEF) domains that activate small GTPases (Yang et al 2001). Evidence suggests that loss of Alsin is responsible for motor neurone damage and several groups have now generated *ALS2* knock-out mouse models, but only mild neurological changes have been reported in these animals to date (Cai et al 2008). The pathological mechanism of *ALS2* mutations remains unknown although evidence that Alsin has a role in endosomal transport and glutamate receptor targeting at the synapse offer interesting avenues for further study (Devon et al 2006; Hadano et al 2006; Lai et al 2006).

### 3.5 Genetic causes of ALS+FTD

#### 3.5.1 Sigma non-opioid intracellular receptor 1 (*SIGMAR1*)

Following linkage analysis of a large multigenerational pedigree to chr9p, mutation screening of 34 genes in the candidate region identified a nucleotide substitution in the 3'UTR of the *SIGMAR1* gene which co-segregated with the disease (Luty et al 2010). Two further FALS cases were also identified with 3'UTR substitutions, yet none of the 3 changes were present in controls. Pathological material was available from 2 individuals carrying one of the changes and both TDP-43 and FUS positive inclusions were observed. The *SIGMAR1* protein functions as a subunit of the ligand-regulated potassium channel and regulates channel activity (Aydar et al 2002). It was suggested that the 3'UTR alterations alter the stability of the transcript, though how this subsequently causes motor neuronal cell death, is unknown (Luty et al 2010).

#### 3.5.2 Microtubule associated protein tau (*MAPT*)

Pedigrees with clinical features of FTD, ALS and Parkinsonism have been identified with pathogenic mutations in the microtubule associated protein tau (*MAPT*) gene located on chr17 (Hutton et al 1998). Over 40 mutations have been identified to date that either affect the normal function of the tau protein to stabilise microtubules or disrupt alternative splicing leading to changes in the ratio of tau isoforms (Seelaar et al 2011). Affected individuals have a variable age of onset (25-65 years) with disease duration of 3-10 years and usually show symptoms of executive dysfunction, altered personality and behaviour. Many develop a Parkinsonism phenotype and/or other clinical features of 1 or 2 syndromes that may reflect an expansion of affected brain regions over time. Cases affected by an ALS phenotype are rare and so far mutations in *MAPT* have not been described in pure FALS (Boeve & Hutton 2008).

### 3.6 Genetic loci linked to ALS

#### 3.6.1 ALS5: Spatacsin (*SPG11*)

The study of three consanguineous Tunisian pedigrees originally established linkage of chr15q15-q21 to an autosomal recessive form of ALS (Hentati et al 1998). A more recent study of 25 unrelated FALS families revealed 10 pedigrees with linkage to the same region and disease associated mutations in the spatacsin (*SPG11*) gene (Orlacchio et al 2010). Clinically, FALS patients with linkage to this region experience a juvenile onset, slowly progressive motor neuropathy associated with both upper and lower motor neurone signs. Disease duration is typically over 10-40 years without sensory symptoms and an absence of the feature of thin corpus callosum (Hentati et al 1998; Orlacchio et al 2010).

Mutations in this gene have been previously found to be the most common cause of autosomal recessive hereditary spastic paraplegia with thin corpus callosum (HSP-TCC), a condition characterised by progressive spasticity of lower limbs, mild cognitive impairment and a thin, but otherwise normally structured, corpus callosum (Abdel Aleem et al 2011). All but one of the mutations identified in FALS are also present in HSP-TCC pedigrees and the majority of these are truncating which may suggest a loss of function and a common pathological mechanism between the two conditions (Salinas et al 2008). The *SPG11* gene has 40 exons and encodes the highly conserved Spatacsin protein, which is ubiquitously expressed in the central nervous system (Salinas et al 2008). Although the function of Spatacsin remains unknown, neuropathological studies of HSP-TCC patients with *SPG11* mutations have revealed accumulations of membranous material in non-myelinated axons which are suggestive of axonal transport disturbance (Hehr et al 2007).

#### 3.6.2 ALS7

To date, only one pedigree with ALS7 and linkage to chr20ptel-p13 has been identified (Sapp et al 2003). The family included 15 siblings, two of which were affected by an autosomal dominantly inherited form of ALS with mid-life onset and a rapid disease course of less than 2 years. The authors found probable linkage to a 6.25cM region of chr20 though more individuals from this pedigree are needed to confirm the findings (Sapp et al 2003).

#### 3.6.3 ALS3

One large European kindred affected by an adult onset, autosomal dominant form of ALS has been linked to chr18q21 (Hand et al 2002). Patients in this family present with classical ALS involving progressive weakness in the limbs and bulbar regions with both upper and lower motor neurone signs. A candidate region of 7.5cM was identified on chr18, however, the pathogenic mutation is not yet known (Hand et al 2002).

#### 3.6.4 ALSX

Linkage analysis of a 5-generation pedigree identified an adult onset, dominantly inherited locus on Xp11-q12. The causative gene has very recently been found to be ubiquilin 2 (*UBQLN2*), which encodes a cytosolic ubiquitin-like protein (Deng et al 2011). Mutation screening of additional cohorts of patients found a further 4 missense mutations in

unrelated FALS cases, with all mutations affecting proline amino acids in the proline-x-x repeat region near the carboxyl end of the protein. Clinically, age of onset was variable (16-71 years) in the affected individuals, and although males were more likely to have an earlier age of onset, disease duration was similar. Some patients also showed symptoms of dementia. Post-mortem material from two unrelated FALS cases showed the classical skein like inclusions were positive for UBQLN2. The identified missense mutations lead to impairment of the protein degradation pathway in a cell model of *UBQLN2*-related ALS.

### 3.6.5 ALS-FTD1: 9p21-q22

A locus for FALS that arises in conjunction with FTD has been identified in 5 American families at chr9p21-q22 (Hosler et al 2000). Affected patients had adult onset of either: ALS and FTD, ALS alone or ALS with dementia. Disease duration was typically less than 4 years although one individual had a slow progression and survived for 15 years. No pathogenic mutations have been identified for this region to date (Hosler et al 2000).

### 3.6.6 ALS-FTD2: 9p13.2-p21.3

Linkage of autosomal dominant FALS and FTD to chr9p13.2-p21.3 has been established in two pedigrees, one large Dutch kindred and a Scandinavian family (Morita et al 2006; Vance et al 2006). Clinically, all members with ALS had definite or probable ALS by the El-Escorial Criteria with mid-life onset and a typical disease course of around 3 years. In the Scandinavian family ALS and FTD occurred separately, in contrast, affected individuals in the Dutch kindred all had features of both conditions. Linkage has been narrowed down to a 12cM (11Mb) region of chr9, however the pathogenic gene mutations have yet to be identified (Morita et al 2006; Vance et al 2006).

## 4. Conclusion

FALS accounts for 5% of ALS; an underlying mutation has been identified in approximately a third of these cases (Kiernan et al 2011). FALS causing mutations are used as a window into familial and the clinically indistinguishable sporadic disease; generating genetic models of ALS allows investigations into the mechanisms of motor neuronal degeneration, the identification of therapeutic targets and screening for candidate therapeutic agents (Van Damme & Robberecht 2009). However, the discovery of pathogenic mutations in ALS by linkage analysis is difficult because a relatively low prevalence and rapid disease course make large pedigrees difficult to obtain, therefore novel strategies to identify pathogenic mutations are essential (Hand & Rouleau 2002).

With the evolution of next generation sequencing technology, exhaustive sequencing of exonic regions of the genome has been used to identify pathogenic mutations in the *VCP* gene in ALS, and genetic mutations responsible for other diseases have also been identified from relatively few related or unrelated patients (Bowne et al 2011; Hoischen et al 2010; Johnson et al 2010a; Ng et al 2010; Ng et al 2009; Nikopoulos et al 2010; Simpson et al 2011). Exome sequencing, unlike a linkage analysis and positional cloning approach, is not targeted at a candidate region. Therefore it is likely that a large number of potential genetic variations will be discovered; the difficulty then is to determine which, if any, are pathogenic. However, next generation sequencing offers the potential for identifying at least some of the genes responsible for the remaining uncharacterised causes of FALS.



An expanded GGGGCC hexanucleotide repeat in *C9ORF72* has just been published as the cause of 9p-linked ALS-FTD, following next generation sequencing of the disease associated region (Renton et al 2011, DeJesus-Hernandez et al 2011). Expansions have been identified not only in ALS-FTD pedigrees, but also in familial FTD, familial ALS and sporadic ALS. Estimated frequencies vary from 23.5% to 46.4% for familial ALS and 4.1% to 21% for sporadic ALS. The expansion, which is non-coding, is therefore the most common genetic cause of ALS identified to date.

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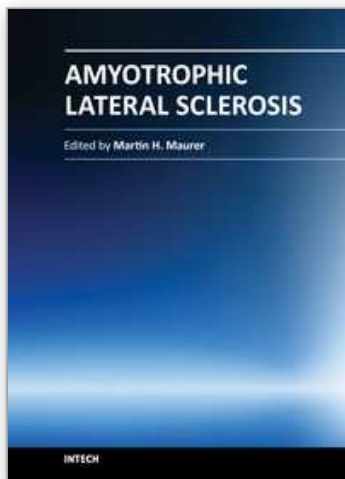


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## **Amyotrophic Lateral Sclerosis**

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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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