

The Genetics of Amyotrophic Lateral Sclerosis



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Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive, age-dependent neurodegenerative disorder of motor neurons. It causes paralysis, bulbar dysfunction and respiratory failure and is invariably fatal within 2-5 years of onset. Riluzole, the only disease modifying agent used in ALS, has only a modest effect on survival.¹ Treatment is essentially supportive and palliative and ~1200 people die of ALS annually in the UK. ALS is challenging to study as it is mostly sporadic, rapidly progressive and clinically heterogeneous. Significantly, a family history of ALS is seen in 5-10% of cases (FALS), usually with autosomal dominant inheritance.² FALS is essentially indistinguishable from the more common sporadic ALS (SALS). Identification of FALS genes offers a direct approach to elucidating common mechanisms of disease in ALS and potentially identifying therapeutic targets.

Classical Mendelian inheritance in FALS kindreds is complicated by a variable age of onset, phenotypic heterogeneity and incomplete penetrance. There is also growing evidence that SALS has a genetic basis. Environmental factors interacting with genetic variants of small effect may predispose to SALS and may also explain the heterogeneity of FALS. ALS is a complex genetic disease with sporadic and familial ALS existing at opposite ends of a genetic spectrum. Ten forms of FALS linked to separate genetic loci have been classified, six of which cause typical ALS (Table 1). Two loci linked to ALS with frontotemporal dementia (ALS-FTD) have also been characterised. ALS and FTD are recognised to be part of a clinicopathological spectrum. Up to half of ALS patients may have clinical features of FTD,³ and both conditions demonstrate characteristic pathological inclusions containing ubiquitinated TAR DNA-binding protein (TDP-43).^{4,5}

In this review we will discuss the major genetic causes of ALS, starting with genes identified by linkage analysis of FALS kindreds. The most significant genes associated with sporadic disease will also be highlighted.

FALS genes causing typical ALS

ALS1- SOD1

Autosomal dominant FALS was first linked to chromosome 21q22, and mutations in Cu/Zn superoxide dismutase (*SOD1*), an antioxidant enzyme, were subsequently identified.^{6,7} Over 120 *SOD1* mutations in all five exons affecting all functional domains are recognised. *SOD1* mutations are the commonest cause of FALS accounting for ~20% of cases. The pathogenicity of mutant *SOD1* is not fully understood but is prob-

ably due to a toxic gain of function affecting many cellular processes, including mitochondrial function and axonal transport.⁸ *SOD1* mutations are also seen in 1-7% of SALS cases.⁸¹

ALS6-FUS

Linkage of ALS to chromosome 16p (*ALS6*) was originally described in several families in 2003.^{9,10,11} The mean age of onset is ~45 years with disease duration ~33 months and lower motor neuron predominance. Mutations in fusion (*FUS*) have recently been found in these kindreds.^{12,13} *FUS* has roles in gene transcription and RNA processing. Although a predominantly nuclear protein, mutations result in cytoplasmic sequestration. *FUS* mutations cluster at the c-terminus and may account for as many as ~7% of FALS cases, though more studies are needed to accurately determine their frequency. *FUS* mutations have not been found in SALS cases.

ALS10-TARDBP

Mutations in *TARDBP* which encodes TDP-43, have been found in FALS and SALS cases. This demonstrates a mechanistic role in neurodegeneration for TDP-43, the hallmark protein of ALS.¹⁴ Around 30 *TARDBP* mutations, mostly c-terminal, have been described by various groups in ALS (Table 2). The mean age of disease onset is ~55 years with survival ~54 months. There is little evidence of cognitive dysfunction, which is surprising given that TDP-43 inclusions are also a hallmark of FTD. *TARDBP* mutations account for ~3% of FALS and ~1% of SALS, though these values vary between populations.

Genes causing rare ALS variants

ALS2-Alsin

ALS2 is a rare, recessively inherited, juvenile-onset disease characterised by slowly progressive spasticity beginning in the lower limbs and spreading to the upper limbs and bulbar musculature. Truncation mutations in the *ALS2* gene (coding for alsin) were found in Tunisian and Arab kindreds.^{15,16} *Alsin* has roles in cellular trafficking and the cytoskeleton.^{17,18,19} *Alsin* may also protect neurons against mutant *SOD1*-mediated toxicity and promote neurite outgrowth.^{20,21} Mutations are thought to result in loss of function.

ALS4-Senataxin

ALS4 is a rare, non-fatal, autosomal dominant, juvenile-onset distal hereditary motor neuropathy characterised by limb weakness, muscle wasting and pyramidal involvement. Bulbar and respiratory muscles are spared. Missense mutations in

Table 1 Genes and loci linked with ALS

| Disorder | OMIM | Locus | Gene (protein) function | Inheritance | Onset | References |
|---|--------|--------------|---|-------------|---|---|
| Typical ALS | | | | | | |
| ALS1 | 105400 | 21q22.1 | SOD1 (Cu/Zn superoxide dismutase 1) Converts superoxide to water or hydrogen peroxide | Dominant | Adult | Siddique et al., 1991 Rosen et al., 1993 |
| ALS3 | 606640 | 18q21 | ? | Dominant | Adult | Hand et al., 2002 |
| ALS6 | 608030 | 16q12 | TLS/FUS (TLS/FUS) Gene transcription, RNA processing | Dominant | Adult | Ruddy et al., 2003 Sapp et al., 2003 Vance et al., 2009 |
| ALS7 | 608031 | 20ptel-p13 | ? | Dominant | Adult | Sapp et al., 2003 |
| ALS9 | 611895 | 14q11 | ANG (Angiogenin) Angiogenesis | Dominant | Adult | Greenway et. al., 2006 Wu et. al., 2007 Gellera et. al., 2008 |
| ALS10 | 612069 | 1p36.2 | TARDBP (TDP-43) DNA/ RNA binding, splicing, transcriptional regulation | Dominant | Adult | Sreedharan et. al., 2008 Kabashi et. al., 2008 |
| ALS with frontotemporal dementia | | | | | | |
| ALS-FTD1 | 105550 | 9q21-22 | ? | Dominant | Adult ALS with FTD | Hosler et al., 2000 Ostojic et al., 2003 |
| ALS-FTD2 | 611454 | 9p21-13 | ? | Dominant | Adult ALS with FTD | Vance et al., 2006 Morita et al., 2006 Valdmanis et al., 2007 |
| Atypical ALS | | | | | | |
| ALS2 | 205100 | 2q33 | ALS2 (ALS2/Alsin) Endosomal dynamics. Guanine exchange factor for Rab5 and Rac1. Neuronal survival factor | Recessive | Juvenile – predominantly UMN (PLS, infantile-onset ascending HSP) | Hadano et al., 2001 Hentati et al., 1994 Yamanaka et al., 2006 Yang et al., 2001 |
| ALS4 | 602433 | 9q34 | SETX (Senataxin) Putative DNA /RNA helicase, RNA metabolism | Dominant | Juvenile – recessive mutations Cause ataxia- oculomotor apraxia type 2 | Chance et al., 1998 Chen et al., 2004 |
| ALS5 | 602099 | 15q15.1-21.1 | ? | Recessive | Juvenile | Hentati et al., 1998 |
| ALS8 | 608627 | 20q13.3 | VAPB (VAMP associated membrane protein B) Endosomal trafficking, calcium metabolism | Dominant | Adult – causes slowly progressive SMA phenotype, tremor or typical ALS | Nishimura et al., 2004 Nishimura et al., 2004b atypical ALS with |

SETX (coding for senataxin) have been found in three Caucasian kindreds.^{22,23} The function of senataxin is unknown, but it is notable that recessive *SETX* mutations (mostly truncations) cause ataxia-oculomotor apraxia 2 (AOA2).²⁴ This suggests that a toxic gain of senataxin function may be responsible for ALS4, while loss of function may lead to AOA2.

ALS8-VAPB

Following linkage of a large Portuguese Brazilian kindred with dominantly inherited atypical ALS to chromosome 20q13.3 (ALS8), a mutation in the *VAMP/synaptobrevin-associated membrane protein B gene (VAPB)* was identified.^{25,26,27} The same mutation was found in seven more Brazilian families with an ancient

common founder.²⁸ Three distinct phenotypes are seen: late-onset SMA, typical ALS and slowly-progressive ALS with tremor. VAPB can associate with microtubules and is implicated in axonal and intracellular transport, and may also be important as a motor neuronal survival factor.^{29,30,31} Mutant VAPB may have excitotoxic properties.^{32,33,34}

Dynactin (OMIM 601143)

A large kindred with a slowly progressive ALS-like syndrome was linked to chromosome 2p13.³⁵ The phenotype was predominantly lower motor neuron, involving the limbs and face and causing vocal cord paresis. A mutation of the axonal motor protein dynactin was identified, and further mutations found in one

SALS, two FALS cases and one ALS-FTD kindred.^{36,37} Dynactin mutations have not been formally classified as an ALS subtype.

SALS genes: candidate approaches

The search for SALS genes has frequently involved a candidate-gene approach. This has demonstrated a role for FALS genes, most notably *SOD1* and *TARDBP*, in a minority of sporadic cases. Numerous candidate-gene studies in ALS have produced conflicting results. The most significant of candidates are discussed below.

VEGF (OMIM 192240)

Vascular endothelial growth factor (VEGF) was identified as a candidate for ALS on the

Table 2 TARDBP genetic screens in ALS

| Reference | Index FALS screened (mutations) | SALS screened (mutations) | Mutation Frequency (FALS, SALS) | Ethnic origin |
|--------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------|
| Sreedharan et al., 2008 | 154 (1) | 372 (2) | 0.65%, 0.54% | UK & Australian Caucasian |
| Gitcho et al., 2008 | 8 (1) | 0 | 12.5%, - | European |
| Kabashi et al., 2008 | 80 (3) | 120 (6) | 3.75%, 5% | France/Quebec |
| Van Deerlin et al., 2008 | 65 (2) | 86 (0) | 3%, 0% | Eastern Europe, China |
| Yokoseki et al., 2008 | 16 (1) | 112 typed for mutation only (0) | 6.25%, - | Japan |
| Kuhnlein et al., 2008 | 31 (2) | 134 (0) | 6.25%, 0% | German |
| Rutherford et al., 2008 | 92 (3) | 24 (0) | 3.26%, 0% | Caucasian |
| Daoud et al., 2008 | 0 | 285 (6) | - 2.1% | French |
| Lemmens et al., 2009 | 20 (1) | 0 | 5%, - | Belgian |
| Corrado et al., 2009 | 125 (6) | 541 (12) | 4.8%, 2.2% | Italian |
| Gijselincx et al., 2008 | 0 | 237 (0) | - 0% | Belgian |
| Guerreiro et al., 2008 | 0 | 297 (0) | 0%, 0% | Caucasian & African |

basis of a mouse model displaying motor neuron degeneration following deletion of the hypoxia response element of the *VEGF* promoter.⁸⁰ However, *VEGF* mutations have not been found in ALS cases and association studies have generated conflicting results.^{40,41,42,43}

ALS9- *ANG*

Angiogenin is functionally similar to VEGF. Significant association between SALS and the angiogenin gene (*ANG*) was identified in Irish and Scottish populations.⁴⁴ Coding mutations were subsequently found in sporadic and familial cases and shown to impair the angiogenic properties of angiogenin.^{45,46} Although *ANG* mutations are a rare cause of FALS, they are classified as ALS9.

Paraoxonase (OMIM 168820, 602447)

Paraoxonases have antioxidant and detoxifying roles.^{47,48} Their candidacy in ALS stems from evidence that chemical exposure may increase the risk of ALS.^{49,50} Functional polymorphisms in the *PON* genes on chromosome 7q have been associated with susceptibility to Alzheimer's disease (AD)⁵¹ and Parkinson's disease (PD).⁵² Evidence from several groups supports an association with susceptibility to ALS, though reports are conflicting.⁵³

Neurofilaments (OMIM 162280, 162230)

Neurofilamentous aggregates within motor neurons are a neuropathological hallmark of ALS. Neurofilaments are composed of heteropolymers of light, medium and heavy subunits (NF-L, -M and -H) and are involved in maintenance of cytoskeletal and axonal architecture.⁵⁴ Rare deletions and insertions within the multi-KSP phosphorylation domain of NF-H have been found in ~1% of SALS cases and one FALS case^{55,56,57}, although functional stud-

ies of NF-H KSP variants is lacking. NF-H variants are unlikely to be a significant cause of ALS.

Peripherin (OMIM 602447)

Peripherin is another intermediate filament protein expressed in neuronal projections and is upregulated in the CNS in injury.⁵⁸ Rare mutations of peripherin have been found in ALS^{59,60} and are associated with abnormal NF assembly in vitro and marked peripherin aggregation in anterior horn cells in vivo. These data suggest that peripherin variants may play a small role in the pathogenesis of ALS.

SMN (OMIM 600354, 601627)

Spinal muscular atrophy (SMA) is an autosomal recessive lower motor neuron disorder of neonates and children usually caused by deletion of the *Survival Motor Neuron 1 (SMN1)* gene.⁶¹ Two copies of SMN exist at the chromosome 5 locus in humans, with deletions in *SMN1* causing disease. *SMN2* is only partially functional due to splice variation, but an increase in *SMN2* copy number can ameliorate the severity of SMA.⁶² SMA may result from a loss of motor neuron-specific functions of SMN, including processing and transport of RNAs.^{63,64} Although studies have not demonstrated a direct role for *SMN1* variants in ALS, copy number analysis demonstrates that ALS patients may have reduced SMN protein levels, or deletions of *SMN2*, although, reports are conflicting.^{65,66,7,68,69}

SALS genes: Genome-wide association studies

Unlike candidate approaches, genome-wide association (GWA) studies can be used to identify susceptibility genes without making assumptions about the likely disease mecha-

nisms. They have the potential to identify new mechanistic pathways. Early GWA studies did not identify polymorphisms linked to ALS, probably because they were underpowered, reporting on only a few hundred ALS individuals and controls. Evidence from other so-called complex diseases such as Type II diabetes suggests that ~2-3000 cases and controls are required to generate reliable results, when one accounts for the stringent corrections required for multiple analyses on the same data set. More recent GWA studies in ALS have been large-scale studies analyzing thousands of cases and controls using high-density mapping techniques such as DNA microarrays. These approaches have led to the identification of four significant genetic associations in SALS: *FLJ10986*⁷⁰, the inositol 1,45-triphosphate receptor 2 gene, *ITPR2*⁷⁶, the dipeptidyl peptidase 6 gene, *DPP6*⁷⁷ and the elongator protein 3 gene, *ELP3*⁷⁸. *FLJ10986* is expressed in brain, but its function and the effects of the ALS variants are unknown. *ITPR2* is involved in glutamate-mediated neurotransmission, regulation of intracellular calcium and has an important role in apoptosis. All these roles have previously been linked with ALS pathogenesis. *DPP6* is expressed predominantly in the brain, regulates neuropeptide activity and modulates voltage-gated potassium channels. *ELP3* is involved in RNA processing and gene expression, which are increasingly recognised to be important in ALS pathobiology. *ELP3* may additionally be neuroprotective.⁷⁸

Although these GWA studies suggest that there may be a significant genetic component to sporadic ALS, they have used relatively common polymorphic markers. Thus, if rarer polymorphisms account for much of the susceptibility in ALS these will be unlikely to be picked up even if several thousands of patient samples are screened.

PRESCRIBING INFORMATION – UK AND ROI REBIF 8.8 MICROGRAMS AND 22 MICROGRAMS SOLUTION FOR INJECTION REBIF® 22 MICROGRAMS SOLUTION FOR INJECTION REBIF® 44 MICROGRAMS SOLUTION FOR INJECTION. Interferon beta-1a

Presentation Rebif 8.8 and 22: Pre-filled glass syringe containing 8.8µg or 22µg of Interferon beta-1a in respectively 0.2 or 0.5ml. Rebif 22 or 44: Pre-filled glass syringe containing 22µg or 44µg Interferon beta-1a in 0.5ml. **Indication** Treatment of relapsing multiple sclerosis. Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapse activity. **Dosage and administration** Initiate under supervision of a physician experienced in the treatment of multiple sclerosis. Administer by subcutaneous injection. Recommended dose: Weeks 1 and 2: 8.8µg three times per week (TIW); Weeks 3 and 4: 22µg TIW; Week 5 onwards: 44µg TIW (22µg TIW if patients cannot tolerate higher dose). Limited published data suggest that the safety profile in adolescents aged 12–16 years receiving Rebif 22 TIW is similar to that in adults. Do not use in patients under 12 years of age. Prior to injection and for 24hrs afterwards, an antipyretic analgesic is advised to decrease flu-like symptoms. Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapse activity. **Contraindications** History of hypersensitivity to natural or recombinant interferon beta, or to any of the excipients; treatment initiation in pregnancy; current severe depression and/or suicidal ideation. **Precautions** Inform patients of most common adverse reactions. Use with caution in patients with previous or current depressive disorders and those with antecedents of suicidal ideation. Advise patients to report immediately any symptoms of depression and/or suicidal ideation. Closely monitor patients exhibiting depression and treat appropriately. Consider cessation of therapy. Administer with caution in patients with a history of seizures and those receiving anti-epileptics, particularly if epilepsy is not adequately controlled. Closely monitor patients with cardiac disease for worsening of their condition during initiation of therapy. Patients should use an aseptic injection technique and rotate injection sites to minimise risk of injection site necrosis. If breaks in skin occur, patients should consult their doctor before continuing injections. If multiple lesions occur, discontinue Rebif until healed. Use with caution in patients with history of significant liver disease, active liver disease, alcohol abuse or increased serum ALT. Monitor serum ALT prior to the start of therapy, at Months 1, 3 and 6 and periodically thereafter. Stop treatment if icterus or symptoms of liver dysfunction appear. Treatment has potential to cause severe liver injury including acute hepatic failure. Full haematological monitoring is recommended at Months 1, 3 and 6 and periodically thereafter. All monitoring should be more frequent when initiating Rebif 44. New or worsening thyroid abnormalities may occur. Thyroid function testing is recommended at baseline and if abnormal every 6–12 months. Use with caution in, and closely monitor patients with, severe renal and hepatic failure or severe myelosuppression. Serum neutralising antibodies may develop and are associated with reduced efficacy. If a patient responds poorly and has neutralising antibodies, reassess treatment. Use with caution in patients receiving medicines with a narrow therapeutic index cleared by cytochrome P450. Women of childbearing potential should use effective contraception. Limited data suggest a possible increased risk of spontaneous abortion. During lactation, either discontinue Rebif or nursing. If overdose occurs, hospitalise patient and give supportive treatment. **Side effects** In the case of severe or persistent undesirable effects, consider temporarily lowering or interrupting dose. **Very common:** flu-like symptoms, injection site inflammation/reaction, headache, asymptomatic transaminase increase, neutropenia, lymphopenia, leucopenia, thrombocytopenia, anaemia. **Common:** injection site pain, myalgia, arthralgia, fatigue, rigors, fever, pruritus, rash, erythematous/maculo-papular rash, diarrhoea, vomiting, nausea, depression, insomnia. Serious side effects include: injection site necrosis, hepatitis with or without icterus, severe liver injury, anaphylactic reactions, angioedema, erythema multiforme, erythema multiforme-like skin reactions, seizures, thromboembolic events, suicide attempt, Stevens–Johnson syndrome, dyspnoea. Consult the Summary of Product Characteristics for more information relating to side effects. **Legal category** POM **Price** Rebif 8.8 and 22: 6 (0.2ml) + 6 (0.5ml) syringes – £563.33. Rebif 22: 12 syringes (0.5ml) – £624.77. Rebif 44: 12 syringes (0.5ml) – £829.61. For prices in Ireland, consult distributors Allphar Services Ltd. **Marketing Authorisation Holder and Numbers:** Sero Europe Ltd, 56 Marsh Wall, London, E14 9TP; EU/1/98/063/007; 003 & 006 **For further information contact:** UK: Merck Serono, Bedford Cross, Stanwell Road, Feltham, Middlesex, TW14 8NX. Tel: 020 8818 7373. **Republic of Ireland:** Merck Serono, 3013 Lake Drive, Citywest Business Campus, Dublin 24. Tel: 01 4661910 **Date of Preparation:** February 2009.

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Genetic links between ALS and FTD

A genetic link between ALS and FTD is strongly suggested by linkage of families displaying inheritance of both ALS and FTD to loci on chromosome 9p⁷⁰ and 9q^{71,72,73} (Table 1). No mutations have been identified as yet. There is little evidence that pure FTD genes (*Progranulin*, *MAPT* and *CHMP2B*) are a significant cause of ALS.⁷⁴

Conclusions

The identification of SOD1 mutations in 20% of FALS kindreds and the use of SOD1 models of disease have enhanced our knowledge of motor neuron degeneration⁷⁹, but therapeutic developments have been disappointing. Several new genes have recently been identified, notably *TARDBP*, *FUS* and *ANG*, and suggest a significant role for RNA-processing abnormalities in ALS. ELP3 variants add further weight to this hypothesis. SOD1 screening has been available as a clinical test for some years. *TARDBP* and *FUS* screening should prove cost effective as most mutations cluster within a single exon. The identification of gene mutations in the remaining ~75% of FALS cases, and the characterisation of genes that contribute to SALS will add further pieces to the jigsaw puzzle that is ALS. ♦

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