Familial amyotrophic lateral sclerosis/motor neurone disease (FALS): a review of current developments

J de Bellerroche, Richard Orrell, Andrew King

Amyotrophic lateral sclerosis (ALS)/motor neurone disease (MND) is a relatively common neurodegenerative condition with a prevalence of approximately 5 per 100 000 and is characterised by loss of motor neurones in the spinal cord, brain stem, and motor cortex. Approximately 5 to 10% of ALS cases are familial. The familial form is indistinguishable from the sporadic form with a mean age of onset of 50 years and a rapid progression of approximately three years duration. Recently, mutations in Cu/Zn superoxide dismutase (SOD-1) have been identified in a subpopulation of familial cases and this has stimulated an enormous amount of interest. This finding has opened the way to investigating potential pathogenic mechanisms and developing treatment rationales. However, the picture is still incomplete as SOD-1 mutations have only been detected in a minority of cases (fig 1) and the value of identifying subjects at risk in the subgroup is debatable. The aim of this review is to provide a summary of the most recent developments in FALS research which give an insight into the possible mechanisms underlying the disease and their implications and expectations for affected subjects.

Clinical and pathological features of FALS

PHENOTYPIC HETEROGENEITY AND SIMILARITIES WITH SPORADIC ALS

Familial ALS (FALS) is expressed as an age dependent autosomal dominant trait. There is incomplete penetrance being 0·8 at the age of 85 years. It is therefore not uncommon to see obligate carriers in a family who die without manifesting the disease (see pedigrees 5, 6, and 7, fig 2). The phenotypic heterogeneity seen in sporadic forms of ALS are also common within families, for example, age of onset may vary over 30 years within a family as can duration of illness (for example, 0·5 to 5 years) and signs at onset. The initiation of the disease is usually focal and asymmetrical, for example, wasting of muscles of one hand, and then spreads in a contiguous way. Lower motor neurone involvement is usually conspicuous in most cases whereas involvement of upper motor neurones is less marked. Pathologically, the disease starts with shrinkage of motor neurones and leads to extensive loss of motor neurones in the spinal cord and degeneration in the corticospinal tract.

DIAGNOSTIC CRITERIA

The diagnostic features of FALS are common to those for ALS. It is a progressive neurodegenerative disease, affecting primarily motor neurones. It mainly affects adults but there are rare juvenile cases which have autosomal recessive inheritance. ALS occurs in sporadic, familial, and Western Pacific forms. It may present as a predominantly lower motor neurone form (progressive muscular atrophy), predominantly upper motor neurone form (primary lateral sclerosis), or predominantly affect bulbar muscles (progressive bulbar palsy). The clinical diagnosis of ALS in a person requires the presence of both upper and lower motor neurone features and progression of disease.

Clinical features of lower motor neurone disease include weakness and wasting of the muscles of the limbs, face, tongue, and throat, muscle cramps, and fasciculations. Upper motor neurone involvement causes weakness and spasticity of similar muscle groups, with brisk responses and extensor plantar responses. The condition results in difficulty in walking, use of the arms and hands, speaking, and swallowing.

Figure 1 Proportion of ALS cases which are familial and have mutations in SOD-1.
A patient with a familial form of ALS will be clinically indistinguishable from one with the sporadic form. Especially at onset of the disease, the clinical picture may be incomplete and varied and there is often some delay in reaching a final clinical diagnosis, as there is no specific diagnostic test. Within multigeneration families, where at least one member has full features of ALS, others may have an incomplete form, including largely lower motor neurone features or progressive muscular atrophy (which is often termed spinal muscular atrophy when in a familial form). In some families, extreme forms resembling infantile spinal muscular atrophy may be found. Within families, there is also a wide variation in age at presentation, disease duration, and site of onset.

The disease is present worldwide but with an increased incidence in regions of the Western Pacific, among the Chamorros of Guam, the Auyu and Jakei of West New Guinea, and the Japanese in the Kii peninsula. Within these areas a high incidence of ALS and Parkinsonism-dementia is found within the same families. It is now felt that much of the familial clustering is accounted for by environmental factors, but a genetic component remains possible. SOD-1 mutations have not been identified in these patients.

Linkage analysis and superoxide dismutase (SOD-1) mutations

The diagnosis of ALS is based on the clinical history and findings on examination and may be supported by electrophysiological and imaging studies which may also exclude other potentially treatable conditions. The disease is progressive, resulting in death in 50% of patients within three years of onset. A proportion of patients have a much more protracted course, over decades. Significant disability and dependence may result in the later stages of the disease from muscular weakness and spasticity, and death often results from respiratory failure owing to muscle weakness. Although there is at present no cure, much support and symptomatic treatment may be provided through multidisciplinary medical teams and voluntary organisations. These include management of spasticity, mobility, dysarthria, dysphagia, respiration, and psychological problems.

The earliest evidence of linkage in FALS came from studies using restriction fragment length polymorphisms (RFLPs) when Siddique et al mapped a FALS locus to chromosome 21q22.1. Multipoint analysis indicated that the locus was 10 cM distal to D21S58, but at this time no significant two point lod scores were obtained. Since then a number of microsatellite markers have been identified in this region which give significant two point lod scores, for example, D21S235, D21S223, and D21S224.

Identification of SOD-1 mutations

Subsequent studies were carried out on a candidate in proximity to the FALS locus which was cytosolic copper zinc dependent superoxide dismutase (SOD-1). This is a well characterised enzyme which exists as a homodimer whose sequence of 153 amino acids is remarkably well conserved across species from man to plants, such as tomato, and microorganisms, such as yeast. The enzyme is present in virtually all animal cells and in man is especially highly concentrated in the liver, erythrocytes, and brain. A number of mutations were identified initially in two out of five of the exons encoding this protein. This study was extended by Deng et al who identified a total of 14 different mutations affecting 12 different amino acids in SOD-1 present in exons 1, 2, 4, and 5 and also showed evidence of an associated reduction by approximately 50% in SOD-1 enzyme activity in the six mutations studied. Mutations in SOD-1 were found in 23 families but some families were clearly not linked to chromosome 21 markers and showed no evidence of SOD-1 mutations.

To date there are 31 reported SOD-1 mutations in FALS and these are summarised in the table.

Structural localisation of SOD-1 mutations

The elucidation of the structure of the SOD-1 dimer by x ray crystallography permits the
**Missense mutations in SOD-1 ALS**

<table>
<thead>
<tr>
<th>Exon</th>
<th>Amino acid affected</th>
<th>Nucleotide change</th>
<th>Reference</th>
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<tr>
<td>Exon 1</td>
<td>Ala4Val</td>
<td>GCC→GTC</td>
<td>16, 17</td>
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<tr>
<td></td>
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<tr>
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<td>Val7Glu</td>
<td>GTG→GAG</td>
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<td></td>
<td>Gly41Ser</td>
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<td>Gly41Asp</td>
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<td>His46Arg</td>
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<td>His48Gln</td>
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<td>Gly85Arg</td>
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<td>GGT→GAT</td>
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<td>Gly100Gly</td>
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<td></td>
<td>Val148Gly</td>
<td>GTA→GGA</td>
<td>17</td>
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<tr>
<td></td>
<td>Ile149Thr</td>
<td>ATT→ACT</td>
<td>26, 35</td>
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**Deletion mutation**

| Exon 5 | Leu126 | TTG→**G | 35 |

Copper binding site which is essential to the catalytic activity of the enzyme. The His46 and His48 are highly conserved residues. An important feature of the His46 mutation, however, is the relatively severe nature of the disease, having a rapid course of eight months' duration, which contrasts with the benign course of the His48 mutation. As the number of families with each mutation increases, any consistent phenotypic features will emerge. However, it is already apparent that considerable phenotypic variation occurs within a family among affected members bearing the same mutation. We have recently described a family with the Ile113Thr mutation where affected subjects show a very different course of disease with one case within the family dying after short progression and the other member surviving more than 20 years. This draws attention to the fact that it will not always be possible to offer prognosis for a given mutation in SOD-1. Thus understanding of the pathogenic mechanisms may not depend exclusively on effects on superoxide dismutase activity as currently measured.

**WHAT DO SOD-1 MUTATIONS TELL US ABOUT THE PATHOGENIC MECHANISM?**

In the original studies on SOD-1 mutations and their effects on enzyme activity, enzyme activity was seen to be reduced by approximately 50% in the six mutations studied and similar reports on other mutations have shown similar results. However, even more interesting has been the observation that in the case of some mutations enzyme activity is only minimally affected despite a normal clinical presentation of the disease. Three examples of this effect are Gly37Arg, Gly43Ser, and Gly93Ala. In the case of Gly37Arg it has been shown from transient expression of this mutant in primate cells that the mutation leads to full activity, in contrast to other SOD mutants studied under similar conditions. However, in all cases, including Gly37Arg, polypeptide stability was found to be reduced. Thus for mutants like Gly37Arg there is only modest loss of activity which only affects the mutant subunit. The Gly93Ala mutation, although only producing a modest effect on enzyme activity, has been shown in transgenic studies to yield a “motor neurone syndrome”. A third mutation only producing a modest decrease in enzyme activity of approximately 27% is Gly41Ser.

The original demonstration of SOD-1 mutations led Rosen et al to hypothesise that FALS could arise either by an increase in SOD-1 monomer activity (dominant gain of function) or the heterozygous mutation could cause mutant monomers to be functionally defective and inhibit wild type monomers in the heterodimer (dominant negative effect). A third possibility was that the mutation could cause a simple loss of function without any effect on the wild type monomer. More recently a further explanation has been proposed, and that is that the mutant could cause a gain of new function. No evidence has yet been obtained that gain

**localisation of the mutations in FALS.** The majority of mutations detected to date lie in regions outside the active site affecting conserved regions of the enzyme at turns in the backbone of the protein (beta strands, Greek key connections, turns, and loop 5) or in regions involved in the dimerisation of the two subunits. The position of mutations and nature of the amino acid change is important in determining their potential effects on enzyme function; a charge change at a key site involved in maintenance of the conformation of the active site, Cu$^+$ binding, or dimerisation would have more severe effects than a neutral charge in the peripheral part of the molecule. A mutation has been identified at the active site in codon 125 which leads to a major charge effect replacing the negatively charged aspartate residue with histidine. However, this mutation is associated with a classical form of ALS with no evidence that this location of mutation has a greater effect on the course of the disease.

**DOES DEFINITION OF THE MUTATION DEFINE THE CLINICAL OUTCOME?**

A clinically distinct form of FALS has been described in Japan in two families where the disease is relatively late in onset with slow progression of muscle weakness and atrophy and only rare involvement of bulbar muscles. The mutation in exon 2, His46Arg associated with a more benign form of disease with an average duration of 17 years, had only slightly reduced levels of SOD-1 enzyme activity, being reduced by approximately 20%. This was the first mutation to be detected in the active site, the residue histidine being important in copper binding. We have recently reported a second mutation, His48, in close proximity to that reported in Japanese families in the region of the...
of potentially cytotoxic activity occurs in association with SOD-1 mutations. In most cases mutations are associated with a loss of enzyme activity to approximately 50 to 80% of wild type activity. A range of enzyme activity has been shown by Borchelt et al.\(^9\) who have additionally clearly shown an increased peptide instability in all six mutants that were studied. Coexpression of a mutant protein with the wild type provides no evidence that mutant protein affects the activity of the wild type.\(^{29}\) More recently, in studies of SOD-1 enzyme activity in 27 UK families with FALS, we have found one mutant, Gly93Arg, that does show evidence of a dominant negative effect where enzyme activity is reduced to 30% of normal and the activity of the wild type protein is affected.\(^{29}\)

Support for the idea that the mutation may be associated with a gain of new function has come from transgenic studies in which mice from a Gly93Ala transgene but not an Ala4Val line that express the largest amounts of SOD enzyme activity in brain developed a syndrome “suggestive of MND”. The disease was only in one line of mice and it is possible that the site of integration of the transgene may have contributed to disease development. Mice bearing the normal human SOD gene as well as the wild type murine SOD-1 do not develop neurodegeneration.\(^{41}\) As pointed out above, the mutation involved in this study, Gly93Ala, does not perturb enzyme activity to a significant level. Thus a gain of function mutation may have occurred in this case which is not associated with a reduction in SOD enzyme activity. Alternatively, only a minimal effect on enzyme activity may be sufficient to cause the disease.

SOD-1 is highly abundant in neurones accounting for up to 1% of the total protein. Most types of neurone possess similar levels of SOD-1 immunoreactive protein\(^{22}\) but differences are, however, seen when levels of SOD-1 mRNA are quantitated and in this case motor neurones are seen to possess very high levels of SOD-1 mRNA.\(^{22}\) Neurones with high concentrations of the enzyme which may be critically dependent on SOD-1 for protection against superoxide may potentially become susceptible to mutants for additional adverse effects of the protein. On the other hand the selective vulnerability of motor neurones in the disease may depend on another feature of motor neurones. One popular hypothesis is that the activation of nitric oxide synthase by N-methyl-D-aspartate (NMDA) glutamate receptors leads to the generation of nitric oxide (NO) which reacts readily with superoxide to produce the toxic species peroxynitrite, which in turn releases hydroxyl free radicals.\(^{43}\) The simultaneous availability of both high levels of superoxide from reduced SOD-1 activity and NO from NMDA receptor activation provides the conditions giving rise to free radical damage which is localised to the nervous system.

SOD-1 MUTATIONS IN SPORADIC CASES OF ALS

The same SOD-1 mutation lle113Thr has been detected in three out of 56 sporadic cases in the population based study of Scotland.\(^{44}\) However, the full family history was not available on at least one of these cases and a familial basis cannot be excluded. A single case of an exon 1 mutation, Glu21Lys, has been detected in this cohort as well.\(^{21}\) There are no other published reports of SOD-1 mutations in sporadic cases, although several hundred cases have been screened to date in North America, and the possibility that these reflect incomplete penetrance within the families together with incomplete family history cannot be ruled out.

SOD-1 POLYMORPHISMS

A polymorphism in intron 3 of SOD-1 has recently been reported\(^{50}\) which is present in seven out of 157 FALS cases and 11 out of 100 normal controls. DNA sequence analysis of the proximal segment of intron 3 showed an A-C substitution 34 base pairs downstream of exon 3.

HOMOZYGOUS MUTATIONS IN SOD-1

A possible exonic polymorphism has recently been identified in Finnish and Swedish communities which has no effect on enzyme activity. However, although subjects heterozygous for the mutation do not develop FALS, a high proportion of homozygotes for the mutation (Asp90Ala) studied in four families were shown (10/14) to manifest the disease and a recessive mode of inheritance may be responsible for this form of the disease.\(^{27}\) The site of this mutation is distant from the active site in a region which is not highly conserved in evolution and would not be expected to have a major effect on enzyme activity.

Other disease loci

OTHER FALS LOCI

There is no evidence of SOD-1 abnormalities in a proportion (up to 80%) of FALS families from linkage analysis, sequencing of SOD-1 exons, and assays of SOD-1 enzyme activity.\(^{45-48}\) Currently the more extensive pedigrees in this group are being systematically screened by linkage analysis for other FALS loci in laboratories in North America and our own in the UK. Ideally this should be carried out with highly polymorphic di-, tri-, and tetra-nucleotide microsatellite polymorphisms distributed across the genome at 10 cM intervals. Once positive lod scores have been obtained, the region can then be saturated with closely spaced markers and the job of positional cloning begins, that is if the gene does not turn out to be a previously identified gene as happened with SOD-1.

EXCLUSION OF CANDIDATE GENES INVOLVED IN HANDLING FREE RADICALS

Alternative strategies which have proved successful in studies on Alzheimer’s disease are to concentrate on candidate genes or risk factors where more of the smaller families may be used and the analysis carried out by sib pair analysis and related statistical methods.
Using linkage analysis we have used flanking markers around candidates of interest to exclude a number of candidate genes. A number of potential candidates are implicated from the studies on SOD-1 that are involved in handling free radicals, in particular, SOD-2, a mitochondrial enzyme and SOD-3, an extracellular form of this enzyme. Preliminary linkage analysis of markers flanking the SOD-2 locus (6q25), ESR (6q25.1) and D6S290 (6q21-25.2) and markers flanking the SOD-3 locus (4p16.2-q21), D4S230 (4p16.1-p11), and D4S189 (4p15-q23) provide evidence for a significant exclusion of both of these loci in these families. Other candidate loci involved in free radical handling such as catalase and glutathione peroxidase can be investigated similarly.

**NEUROFILAMENTS**

A number of cytoskeletal abnormalities have been detected in the spinal cord in ALS which has stimulated interest in these proteins as candidate genes in FALS. Overexpression of both the light and heavy chain neurofilament wild type genes have been shown to produce neurodegenerative changes in motor neurones in mice. Some of these mutants have a base pair deletion in four sporadic cases with loss of a lysine residue. This deletion was not present in parents where available for analysis, in 80 familial cases, or 106 controls. This observation suggests a potential mechanism whereby a repetitive sequence within a structural protein may be the focus for the generation of an abnormal protein that could accumulate, giving rise to cell disruption with an analogous development to that occurring in the transgenic studies. A 106 base pair deletion has also recently been reported in an ALS case.

**MOTOR NEURONE DISEASES**

We have investigated a number of key loci implicated in diseases of motor neurones and affecting motor neurone survival as candidate genes for FALS. Spinal muscular atrophy (SMA) has features in common with ALS when presenting as an adult onset lower motor neurone syndrome and could potentially represent a phenotypic manifestation of ALS. As the SMA locus has been mapped (5q11.2-13.3), we were able to use close markers to investigate this candidate gene but found no evidence of linkage in FALS families.

A rare juvenile onset, slowly progressive form of ALS (juvenile onset ALS: FALS-2), with autosomal recessive inheritance has been recognised and linkage analysis in a large Tunisian family has recently shown linkage to chromosome 2q33-3q35 (2q57-2q25). A rare form of spinal muscular atrophy manifesting as a slow, progressive atrophy and weakness of the limbs and tongue and normal life span is Kennedy's disease (X linked recessive bulbospinal neuronopathy) which is the result of a polyglutamine expansion in the androgen receptor caused by an increase in the number of CAG repeats in exon 1 of the gene. This form of motor neurone disease can usually be distinguished clinically from ALS owing to the absence of upper motor neurone involvement, benign course, and additional features such as gynaecomastia and testicular atrophy, and the X linked inheritance of the disease.

**NEUROTROPHIC FACTORS**

A key factor regulating motor neurone viability may be the availability of one or more growth factors such as ciliary neurotrophic factor (CNTF), which has survival promoting effects on spinal motor neurones and prevents genetically determined and lesion induced motor neurone degeneration. Abolition of CNTF by homologous recombination in adult mice results in progressive atrophy and loss of a proportion of motor neurones with some reduction in muscle strength. The inactivation of CNTF did not reduce motor neurone number during embryogenesis or the first postnatal weeks, which suggested that CNTF plays a role mainly in the postnatal period. These properties of CNTF have prompted the initiation of CNTF trials for the treatment of ALS.

The human gene encoding CNTF is located on chromosome 11 and a null mutation in the human CNTF gene has recently been identified, which produces aberrant RNA splicing and abolishes expression of the normal protein. The frequency of mutant homozygotes and heterozygotes in 391 Japanese (240 neurological cases and 51 normals) was 2% and 36%, respectively, compared to 62% for normal homozygotes. The distribution of the three genotypes was similar in the neurological and control group. The neurological cases included 47 ALS cases, only two of whom were homozygous mutants. We confirmed the conclusion that CNTF deficiency is not causally related to the disease in 52 separate familial cases taking advantage of the fact that this mutation results in the loss of a HaeIII site that can be detected in restriction enzyme digests of a region of the CNTF gene amplified by PCR using flanking primers. No mutant homozygotes were found in these UK families, 67% were normal homozygotes, and 33% were heterozygotes.

Other aspects of neurotrophic function may turn out to be more relevant to ALS treatment; while CNTF is present mainly in Schwann cells and a subpopulation of astrocytes, the receptor is more widely expressed in neuronal tissue. To date the therapeutic trials using CNTF have been largely ineffective, but targeting drug treatment is still likely to present a major problem with this approach.

**Diagnostic testing**

**SOD-1 TESTING: CAUTIONARY THOUGHTS**

The identification of SOD-1 mutations in FALS received much publicity in the general press, some of which was reported accurately and some exaggerated. As a result public expectation was raised about the immediate benefits of diagnostic testing and treatment.
Because of this, there was initially some demand for SOD-1 mutation screening in relatives of both familial and sporadic cases. Since only about 20% of ALS cases result from SOD-1 mutations, screening of at risk subjects is of limited value. Even where SOD-1 mutations are known to be present within a family, the value of screening is again debatable as penetrance is incomplete, age of onset is not reliably predictable, and treatments are not established. Correction of a SOD-1 deficiency may be difficult to achieve without perturbing the balance maintained by free radical handling enzymes and may have little effect on as yet unidentified effects of a toxic mutated protein. A further complication of the media publicity of SOD-1 mutations relates to procedures used when blood samples are taken for research. All patients and relatives give their informed consent for the use of blood samples for research purposes without the expectation of a specific result on their sample. However, they may at some stage wish to explore the possibility of a predictive test and will need to be counselled appropriately at this time and separate samples taken for this purpose.

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