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Genetics of Amyotrophic Lateral Sclerosis

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INTRODUCTION

ALS was first described by Charcot in 1869 as what we would now call a sporadic disease; that is, a disease thought to occur without a strong genetic influence. By 1880 Sir William Osler recognized that the Farr family of Vermont had a dominantly inherited progressive muscular atrophy, one phenotypic variation of ALS.¹ It took another 100 years to develop the tools of molecular biology that allowed examination of the clearly inherited forms of the disease. Only within the past ten years has it been possible to fully explore genetic influence on disorders that appear to occur “sporadically,” but which are in fact quite complex, those that likely result from the convergence of multiple genetic and environmental factors. The roughly 90% of ALS that occurs in individuals with no family history of ALS is called sporadic ALS (SALS), while the remaining 10% of ALS which has at least two affected persons in the same family is considered familial ALS (FALS).¹

We will review the genetics of FALS and summarize current investigations of genetic influence in SALS.

FAMILIAL ALS

FALS can be transmitted as a dominant or a recessive trait, but is most commonly an adult-onset disorder of autosomal dominant transmission. Autosomal recessive inheritance is rare and appears limited to persons with juvenile onset ALS or persons with a double dose of particular mutations in the SOD1 gene. We have reported a single family with X-linked dominantly inherited ALS, a rarely observed phenomenon in neurogenetics.²

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In 1991 positional cloning identified linkage of familial ALS to the SOD1 locus on chromosome 21q22 and demonstrated genetic locus heterogeneity in FALS.³ Two years later mutations in SOD1 were linked to FALS, establishing SOD1 as the first causative gene for ALS (genetic nomenclature, ALS1).^{4,5} Subsequently, homozygosity mapping of highly consanguineous families identified the gene ALSIN causing autosomal recessive ALS2⁶ and the locus for ALS5.⁷ Since then five additional genetic loci for FALS and seven for related motor neuron degenerations have been identified (Table 1 and Table 2), establishing multi-etiological basis for FALS.¹

SOD-ALS (ALS1)

The SOD1 gene is around 11kb, with five exons, four introns and several alternatively spliced forms. Over 100 mutations, predominantly missense, have been reported in 68 of the 153 codons, spread over all five exons. (<http://alsod.iop.kcl.ac.uk/index.aspx>) The SOD1 protein is a 32 kilodalton homodimeric protein consisting of 153 highly conserved amino acids. Each monomer has a Greek key β -barrel fold that binds to one copper and one zinc ion.^{8,9} The dimer interface is stabilized by hydrophobic interactions, with dimerization doubling the dismutase activity of SOD1. An electrostatic guidance channel shepherds superoxide ions to the active Cu^{2+} containing site.⁹ In human SOD1 two cysteine residues are oxidized as a sulphydryl bridge (C₅₇, C₁₄₆), which provides stability and increases melting temperature with the aid of the zinc ion. The dismutase reaction is likely limited only by substrate availability.⁹ The size- and charge-selective access to the active site specifically allows in the negatively charged superoxide ion, while excluding larger and positively charged ions.⁹

There are three superoxide dismutases (SOD1, 2 and 3), all three of which are isoenzymes which play major roles in reducing free radical induced cellular damage. They scavenge superoxide free radicals that are by products of oxidative respiration and the cytochrome P450 system. SOD1, the only one of the three implicated in FALS, is primarily a cytosolic enzyme, but small amounts are also present in mitochondria and other organelles.^{8,9}

Human SOD-ALS (ALS1)

A typical presentation of FALS, particularly ALS1, is one of early monomelic weakness without significant loss of muscle bulk which may persist for many months before significant weakness or muscle wasting is noted at the site or elsewhere. In 2000, the Escorial Criteria were revised in recognition of this phenomenon. "Clinically Definite Familial ALS – Laboratory Supported" can be diagnosed if a pathogenic mutation has been identified in the presence of progressive upper and/or lower motor neuron signs in at least a single region in the absence of another cause for the abnormal neurological signs.¹⁰ In practice though, lower motor neuron (LMN) features predominate in ALS1 with the first sign frequently being mild weakness in calf muscles accompanied by loss of the S₁ glutamate-mediated monosynaptic Achilles reflex, calling in question the role of glutamate toxicity. (T. Siddique, unpublished observation)

Age of onset does not correlate with mutation, ranging from 15–81 years, with mean onset at age 47 ± 13 years. Extremity onset, particularly in the legs, is much more common than bulbar onset and both genders are equally affected. However, disease duration or rate of disease progression does correlate with some mutations, with particularly the A4V mutation that causes about 50% of ALS1 in North American families being consistently associated with a rapid course of $1.0 \pm .4$ years from symptom onset until death.¹¹ A few other mutations confer a disease duration of 10 years or more, while some others exhibit extensive variability.¹ Penetrance of SOD1 mutations is variable and mutation specific, with the I113T and D90A mutations markedly reduced compared to the generally high A4V mutation.¹

The dosage of certain SOD1 mutations, particularly D90A, appears to affect age of disease onset as well. Generally individuals of Scandinavian origin who are D90A heterozygotes do not develop ALS. However, more than 80 cases with homozygous D90A mutations from 40 independent pedigrees originating in Northern Scandinavia developed ALS. A slowly progressive form, often presenting as SALS, has been identified in homozygotes of other populations. Dominant pedigrees have also been reported.^{1,12,13} SOD1 enzyme activity is not associated with disease severity, with mutations that provide even marginally reduced activity producing disease.¹

Animal, biochemical and cellular studies in SOD-ALS

The first mouse model overexpressing SOD1 was constructed in 1994 using the G93A mutation.⁸ The model has since been replicated with other SOD1 mutations in both mouse and rat and extensively studied.¹ Transgenic mice or rats overexpressing mutant SOD1 develop an ALS-like phenotype, while those overexpressing wild-type SOD1 remain unaffected. SOD1 knockout mice show axonal damage although, while their muscles show fiber type grouping characteristic of denervation/reinnervation, they do not develop motor neuron degeneration or obvious clinical weakness. Despite the varied pathology described in animals with ALS overexpressing mutant SOD1, the central lesson is that onset of disease correlates with levels of protein expression, which in turn is related to copy number of the transgene.^{1, 15} This suggests that mutant SOD1 must reach a critical threshold in its expression, above which it causes disease by gain of a toxic property which triggers degeneration of motor neurons.^{1, 15} Two major hypotheses have been proposed. One is that while normal SOD1 activity serves as an antioxidant defense, the peroxidase, superoxide reductase and superoxide generating properties of mutant SOD1 lead to the formation of toxic species, including peroxynitrite, superoxide and decomposition products of hydrogen peroxide.¹⁶ However, removal of copper essential for these reactions with copper chaperone of SOD or copper chelators did not ameliorate disease in mutant SOD1 transgenic mice,¹⁷ which makes it unlikely the basis for disease.

We propose that formation of aggregates of SOD1 identified in brain and spinal cord of both SOD1 transgenic mice and ALS1 patients, like the mutant prion aggregates of Creutzfeldt Jakob disease, are the toxic mechanism in SOD-ALS. Investigations with double transgenic mice in our laboratory established that wild-type SOD1 is recruited in the presence of mutant SOD1, not only hastening disease onset in G93A and L126Z mutant mice, but also converting the otherwise unaffected A4V mice into diseased mice. Analyses of spinal cord tissue of these double transgenic mice revealed this phenomenon is accompanied by conversion of both mutant and wild-type SOD1 from a soluble form to an aggregated and detergent-insoluble form. This conversion, observed in the mitochondrial fraction of the spinal cord, involved formation of insoluble SOD1 dimers and multimers that are cross-linked through intermolecular disulfide bonds. The dimers act as seed in forming toxic intermediate species with possible membrane disrupting properties. Therefore, SOD1, normally an important protein in cellular defense against free radicals, is converted to an aggregated and apparently toxic species by redox processes, demonstrating direct links between oxidation, protein aggregation, mitochondrial damage and SOD1-mediated ALS.¹⁸ We have observed SOD1 protein levels are highest in spinal cord of G93A mutants, with lesser amounts in brain and liver and least in kidneys, and increased accumulation occurs with age (N. Cole and T. Siddique, unpublished). These studies, taken together, suggest that the spinal cord and brainstem are unable to effectively deal with the mutant protein load, leading to the region specific pathology and dysfunction noted in ALS mice, and probably in humans. This is important because rational therapy based on these observations can now be developed and tested.

ALSIN-ALS (ALS2)

Mutations in the ALSIN gene, which encodes the protein alsin, produce either a recessive juvenile onset primary lateral sclerosis (PLS) or a juvenile onset upper motor neuron (UMN)-predominant ALS.¹⁹ The alsin sequence contains three domains with homology to GTPases, proteins with roles in axonal outgrowth, signaling cascades and vesicular trafficking.¹⁹ ALSIN makes both a short and long transcript by alternate splicing. We hypothesize a loss of normal function resulting in an ALS phenotype occurs from mutations that affect domains close to the N-terminal region of ALSIN, rendering both long and short transcripts nonfunctional. The milder PLS occurs from more distal mutations that leave the short transcript intact, so perhaps a short protein may allow preservation of some function.¹⁹ ALSIN set the precedent that proteins related to the function of small GTPases and proteins involved in vesicular trafficking are determinants of motor neuron viability.

Knockout models of the ALSIN gene do not exhibit a robust phenotype of motor neuron degeneration, although special copper-silver staining demonstrates distal axonal degeneration in the corticospinal tracts of knockout mice.²⁰ Corticospinal tracts in rodents are small and lie behind the central cord, raising concern whether rodents are appropriate models of UMN disease and spinal cord injury. Cross-breeding experiments using G93A-SOD1 mice and ALSIN knock-out mice did not alter the onset or survival of G93A mice, which may indicate that alsin-related UMN neurodegeneration utilizes a different pathway than SOD1-related neurodegeneration.²⁰ In vitro experiments suggest a protective role for alsin in SOD1 linked cell death.²¹

TDP43-ALS

There has been much discussion recently over the relationship between ALS and frontotemporal dementia (FTD), with frontal temporal impairment being increasingly recognized as clinically associated with ALS.²² A commonality between a subset of ALS cases and FTD cases is the presence of ubiquitinated inclusions comprised of the transactive response (TAR)-DNA-binding protein with a molecular weight of 43 kDa (TDP-43).^{23, 24} Mutations in TDP-43 have recently been identified in several affected persons in families with FALS, both with and without FTD, as well as a number of patients with apparently sporadic ALS.^{25, 26, 27, 28}

Locus Heterogeneity—With three ALS genes and five additional ALS loci identified, it is apparent that virtually identical clinical and pathological phenotypes can arise from multiple causes (Table 1). Related disorders involving motor neuron degeneration also have demonstrated locus heterogeneity, including ALS with frontotemporal dementia.²⁹ (Table 2). Therefore, it is crucial that additional ALS genes and loci be identified to further the understanding of the multiple pathways involved in the pathogenesis of ALS.

SPORADIC ALS (SALS)

SALS is believed to be a multifactorial disease, likely produced by multiple genes interacting with multiple environmental factors, with its complex etiologies still undetermined. Identification of susceptibility genes may provide clues to pathogenesis and point to intersecting environmental factors. Some polymorphisms may not influence susceptibility, but rather may affect onset, severity and duration, thus influencing the phenotype. Successful gene mapping in complex diseases depends on many factors, including appropriate study design, adequate statistical power, extent of genetic heterogeneity and appropriate mechanisms for verification of the susceptibility genes. Association studies using population based case-control samples or family-based samples determine whether a specific allele of a given genetic marker

is found with increased frequency in individuals with disease compared to the frequency of the marker in individuals without disease. We will highlight a number of association studies.

The APOE gene polymorphisms, alleles 2, 3 and 4, have been the focus of at least five association studies with ALS, in which early reports of associations were not replicated with larger sample sizes. Our recent, larger study, which identified the E2 allele as protective against an early onset of ALS, was the first subclassification of the role of an APOE in ALS.³⁰

Three studies have looked at SMN2 copy number or deletions within SMN1 gene and SALS, with one demonstrating deletions of SMN do not predispose one to ALS, another reporting modest differences in SMN2 copy numbers in SALS patients, and the third identifying homozygous deletion of SMN as a prognostic factor. None of the results has yet been replicated.¹

A case control meta-analysis of three Belgian, Swedish and British populations demonstrated an association with three polymorphisms known to affect vascular endothelial growth factor expression. However, no association was found in a different subset of the British population, a Dutch cohort or our own North American cohort.^{1, 31, 32} Interestingly, a single nucleotide polymorphism of the related protein angiogenin was associated with SALS in an Irish population.³³

Associations have been reported in polymorphisms of the heavy neurofilament subchain³⁴ and a frameshift mutation was identified in peripherin, a type III intermediate neurofilament protein expressed predominantly in the peripheral nervous system, in one individual with ALS.³⁵

The paraoxonase cluster, PONs1, 2 and 3, are enzymes involved in detoxification of organophosphate pesticides and chemical nerve agents. Our investigation of a large North American Caucasian family-based and case-control cohort (n=2008) demonstrated significant evidence of association of variants in the PON cluster with SALS, indicating environmental toxicity in a susceptible host may precipitate ALS.³⁶ Importantly, these results have been replicated in Polish and Irish populations.^{37, 38}

The first reported whole genome association study (WGAS) identified SNPs of interest, but none survived Bonferroni correction. However, the more than 300 million genotypes it produced have been made available on the Internet, which is the first time such data has been so easily accessible.³⁹ TGen's larger series identified 10 loci significantly associated with SALS in all three of their data sets, and 41 others that had significant association in two. Their most significant association was near the uncharacterized gene FLJ10986, which codes for a protein expressed in spinal cord and CSF of patients and controls.⁴⁰ The 19 SNPs that showed a trend toward association in a large British pathway-based, candidate gene, case-control association study were not associated with a moderately sized German replication group.⁴¹ A three armed European GWAS reported a variant in the inositol 1,4,5-triphosphate receptor 2 gene (ITPR2) is significantly associated with SALS, with combined analysis of all samples confirming this association. Additionally, ITPR2 expression was greater in the peripheral blood of 126 ALS patients compared to 126 healthy controls.⁴² Recently, examination of publicly available data identified SNPs within guidance pathway genes as highly predictive of ALS susceptibility, survival free of ALS, age at onset of ALS, and overlap with genes associated with Parkinson disease, which may indicate they are involved more broadly in neurodegeneration.⁴³ As mentioned above, mutations in TARDBP have been recently identified in ten SALS patients.^{25,26}

While genetic study clearly offers the potential for identification of molecular targets that would allow development of rational therapies for various forms of ALS, but much work remains.

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Table 1

ALS Genes and Loci¹

Frequency of cases	Genetic Nomenclature	Inheritance Pattern	Disease Name	Gene	Locus	Protein Product
20%	ALS1	AD	SOD-FALS	SOD1	21q22.1	Cu-Zn Superoxide Dismutase
Rare	ALS2	AR	Juvenile ALS Type 3	ALS2	2q33	Alsin
Single family	ALS3	AD	FALS		18q21	Unknown
Rare	ALS5	AR	Juvenile ALS Type 1		15q15.1-q21.1	Unknown
Three families	ALS6	AD	FALS		16q12	Unknown
Single family	ALS7	AD	FALS		20p11	Unknown
Rare		AD	FALS and FALS/FTD	TDP-43	1p36	TAR DNA binding protein
Single family	XALS	X - dominant	FALS		X	Unknown

Table 2
ALS-related Motor Neuron Disorders with upper and lower motor neuron involvement¹

Frequency of cases	Genetic Nomenclature	Inheritance Pattern	Disease Name	Gene	Locus	Protein Product
Rare	ALS4*	AD	Distal hereditary motor neuropathy with pyramidal features	SETX	9q34	Senataxin
Rare	ALS8**	AD	SMA IV, Finkel type SMA	VAPB	20q13	VAPB
Rare	ALS/FTD1	AD	ALS with FTD	Unknown	9q21-q22	Unknown
More common	ALS/FTD2	AD	ALS with FTD	Unknown	9p21	Unknown
Rare	FTDP17	AD	disinhibition-dementia-parkinsonism-amyotrophy complex	Unknown	17q	Unknown
Uncommon	SPG17	AD	Silver Syndrome	Unknown	11q12-q14	Unknown
Old order Amish	SPG20	AR	Trover Syndrome	SPG20	13q12:3	Spartin
Rare		AD	Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia	VCP	9p21.1-p12	Valosin Containing Protein

* No bulbar involvement. Long, slow progression, distal wasting with pyramidal signs and sensory loss, previously called axonal CMT with pyramidal signs.

** This is a disorder that appears to be proximal SMA IV (Finkel type) with some UMN findings.