Familial Amyotrophic Lateral Sclerosis

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KEYWORDS

• Amyotrophic lateral sclerosis • ALS • Familial ALS • Genetics • Phenotypes
• Genetic testing

KEY POINTS

- Amyotrophic lateral sclerosis (ALS) is genetically heterogeneous with more than 50 potential causative or disease-modifying genes identified, but *C9ORF72*, *SOD1*, *TARDPB*, and *FUS* account for greater than 50% of ALS-linked gene variants found in patients with ALS and variants in other genes are uncommon or rare.
- Genetic risk for ALS probably represents combined effects of multiple genes that establish a person's overall genetic susceptibility, acting with environmental and random effects leading to disease onset.
- Clinical features in general do not reliably separate familial from sporadic ALS (SALS) in individual patients owing to phenotypic overlap; family history, including history of frontotemporal dementia (FTD), aids in recognizing that a patient may have familial ALS (FALS).
- ALS-linked gene variants can be identified in about 60%–70% of patients with FALS, a proportion likely to grow, and a pathogenic ALS gene variant may be found in an increasing minority of patients with SALS.

BACKGROUND

Familial incidence of ALS was described in scattered publications beginning in the mid-1800s but received limited attention in the literature until the report in 1955 by Kurland and Mulder,[1,2] which suggested that ALS may be familial in nearly 10% of cases. The application of molecular genetic techniques to ALS, marked by the report in 1993 of linkage of the superoxide dismutase 1 (*SOD1*) gene in FALS, signaled an increasing focus on genetics in ALS as a means to gain insights into the pathogenesis of the disease, identify therapeutic targets, and facilitate diagnosis.[3] In recent years, a rapidly expanding list of genetic variations linked to ALS and their related clinical and pathologic correlates continues to provide key insights into the causes of ALS and inform therapy development.[4]

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This review examines genetic correlates of classic ALS demonstrating combined upper and lower motor neuron signs, but some of the genes discussed may be associated with pure lower motor neuron and pure upper motor neuron phenotypes and, in some cases, FTD and parkinsonian features. Technological developments that have facilitated advances in ALS gene discovery are briefly discussed, and efforts to translate growing knowledge of ALS genetics into patient care are noted. In line with recommendations of the International Human Genome Society, DNA sequence alterations associated with disease are referred to in terms such as genetic sequence variants or sequence variants rather than mutations, recognizing that pathogenicity of some ALS-associated gene variants is less well established than for others.[5]

RECENT TECHNOLOGICAL DEVELOPMENTS AND AMYOTROPHIC LATERAL SCLEROSIS GENE DISCOVERY

Advances in molecular genetic technology and the capacity for handling extensive data sets generated by large-scale DNA sequencing have had significant impact on the discovery of new gene mutations linked to ALS.[4,6,7] In addition to first-generation methods such as genetic linkage analysis and candidate gene analysis relying on linked DNA markers in ALS pedigrees, newer approaches including genome-wide association studies (GWAS) and next-generation sequencing techniques such as whole exome sequencing and whole genome sequencing have allowed the search for ALS-linked genes to be conducted in large sample sets derived mainly from patients with no family history of ALS and in families from which few DNA samples may be available.[6–8] GWAS optimally requires large case control sample sets, generally at least several thousand samples, and is based on the concept that variants of a given gene commonly associated with ALS may be present in a sufficient number of patients to be detectable if enough patients are studied.[6] Next-generation technology leverages high-throughput, large-scale parallel DNA sequencing of essentially all expressed coding sequences (whole exome sequencing) or the entire genome (whole genome sequencing) in conjunction with software and computing capacity able to sort and align short segments of overlapping DNA sequence and efficiently analyze the tremendous amount of sequence data produced. Whole exome or whole genome sequencing produces essentially complete data on all protein-coding genes or on the entire genetic sequence, respectively, allowing identification of wide range of DNA variants potentially associated with ALS.[6–8]

Clinical Spectrum of Amyotrophic Lateral Sclerosis Genetics

Increasing evidence from clinical and basic research suggests that ALS has multiple causes with an important, although varied, genetic component.[4,9] Genetic factors in ALS range from highly penetrant ALS-linked gene variants to sequence variants with seemingly limited impact on disease susceptibility.[6] Phenotypes associated with these sequence variants include classic ALS, primary lateral sclerosis (PLS), and progressive muscular atrophy (PMA).[4,6,8] An important extramotor feature associated with some gene variants linked to ALS is FTD, which may develop with, before, or after onset of motor signs in ALS and as FTD alone.[10,11] Less common clinical features associated with some ALS-linked gene variants include extrapyramidal features and inclusion body myopathy.[4,12] Although FALS is mainly an adult-onset disorder, a few genes associated with ALS may have phenotypes characterized by juvenile onset.[6,8] Although some clinical patterns may tend to occur in association with specific ALS gene variants, in clinical practice, significant overlap among phenotypes limits practical application as a means to ascertain patients likely to carry a specific ALS-linked gene variant.[12]

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