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Familial ALS

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Synopsis

Genes linked to ALS susceptibility are being identified at an increasing rate owing to advances in molecular genetic technology. Genetic mechanisms in ALS pathogenesis appear to exert major effects in ~10% of patients, but genetic factors at some level may be important components of disease risk in most ALS patients. Identification of gene variants associated with ALS has informed concepts of the pathogenesis of ALS, aided the identification of therapeutic targets, facilitated research to develop new ALS biomarkers, and supported the establishment of clinical diagnostic tests for ALS-linked genes. Translation of this knowledge to ALS therapy development is ongoing.

Key terms

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

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, which suggested that ALS may be familial in nearly 10% of cases (1–2). The application of molecular genetic techniques to ALS, marked by the report in 1993 of linkage of the superoxide dismutase 1 (*SOD1*) gene in familial ALS, 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 pathological correlates continues to provide key insights into the causes of ALS and inform therapy development (4).

This review examines genetic correlates of classical 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

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frontotemporal dementia and parkinsonian features. Technological developments that have facilitated recent 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 ALS gene discovery

Advances in molecular genetic technology and capacity for handling extensive data sets generated by large scale DNA sequencing have had significant impact on 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 relatively 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 of the tremendous amount of sequence data produced. Whole exome or whole genome sequencing produce essentially complete data on all protein-coding genes or on the entire genetic sequence, respectively, allowing identification of wide range of potential DNA variants potentially associated with ALS (6–8).

Clinical spectrum of ALS 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 classical 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 frontotemporal dementia (FTD), which may develop with, prior to, 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). While familial ALS 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).

Genetic susceptibility to ALS

ALS clinical registry data and more recent meta-analysis based on prospective population based registries suggest that up to 10% of ALS patients have a family history of ALS in a first- or second-degree relative, generally classified as familial ALS (FALS) (8, 13). The remaining 90% of patients with no evident family history of ALS are designated as sporadic ALS (SALS), a potentially misleading designation for several reasons. First, persons with ALS associated with a causative gene variant may lack a family history of ALS as a result of reduced penetrance or small family size. In addition, family history may be incomplete or inaccurate owing to incomplete family history, incorrect diagnoses in ancestors, or death from other causes prior to onset of ALS in relatives genetically at risk (14).

Several studies have investigated the risk of developing ALS in relatives of ALS patients in efforts to quantitate genetic contributions to ALS susceptibility. An investigation in Sweden of the relative risk of ALS in siblings and children of ALS probands that did not exclude FALS probands found a relative risk of 9.7 (95% CI = 7.2–12.8), and two other studies, one in UK that considered only SALS patients, and a US study that included FALS and SALS patients, reported an approximately 1% risk of ALS among first degree relatives of an ALS patient (15–17). Further, estimates of the heritability of ALS, a measure of the extent of phenotypic variability that is attributable to genetic variation, provide additional evidence that genetic factors play a significant role in sporadic as well as familial ALS. In a study of identical twins that included twins with or without a history of ALS in other relatives heritability was estimated to be about 76% (95% CI=60–86%) for twins with a family history of ALS, and approximately 61% (95% CI=38–78%) for twins with no other family history of ALS (18).

Recently it has been suggested that genetic contributions to ALS may represent the inheritance of risk variants of multiple genes, acting interdependently to cause ALS (19). The hypothesis that ALS may be oligogenic implies that at least two pathogenic ALS gene variants are required to initiate disease. Several studies have shown that a subset of FALS and SALS patients carry at least one known ALS-linked gene variant in conjunction with a second potentially pathogenic variant and offer support for the oligogenic concept of ALS genetics, but these data have been questioned on the basis that the second gene variant may represent a benign variant, potential cohort selection bias and small sample size, and further validation was recommended (6, 8). Regardless of the extent to which an oligogenic mechanism is proven in ALS pathogenesis, available data suggest that genetic risk for ALS probably represents combined effects of multiple genes that establish a person’s overall genetic susceptibility, acting in conjunction with environmental and random effects leading to disease onset (8, 12).

Familial inheritance patterns in ALS

Inheritance of most forms of familial ALS is autosomal dominant although autosomal recessive and X-linked dominant familial ALS also occur. Different modes of inheritance

may be associated with the same gene depending on the specific sequence variant involved, as noted below (12). In practice there has been some agreement that ALS is considered familial if at least one first- or second-degree relative is reported to have ALS (20). However, the presentation of ALS and FTD in first degree relatives in some families, and observed co-occurrence of ALS with FTD in some ALS patients, was considered in a recently proposed algorithm for the diagnosis of familial ALS (Table 1) (14). Within that framework, a seemingly sporadic ALS patient with a family history of FTD in a first-degree relative would be considered to have possible familial ALS (14). Validity of this concept is supported by the discovery that an abnormal expansion of a hexanucleotide repeat (GGGGCC) in chromosome 9 open reading frame 72 *(C9ORF72)*, a gene of unknown function further discussed below, is the most common gene variant linked to ALS and is also commonly associated with ALS-FTD and pure FTD (21–22). While there remains no formally agreed upon definition of familial ALS in the literature, the proposed working definition based on a history of ALS in a first degree or second degree relative, or potentially in the case of a history of FTD in a first-degree relative seems adequately supported (Table 1).

Gene variants linked to ALS pathogenesis

A growing number gene variants associated with Mendelian inheritance of ALS have been reported (Table 2). In outbred populations approximately 60–70% of FALS is accounted for by known ALS-linked genes (8). However, reports of families in which linkage to known loci has been excluded indicate further genetic heterogeneity (23–25). With some geographic variation, the *C9ORF72* hexanucleotide repeat expansion accounts for approximately 40% of FALS in North America and Europe, while *SOD1* variants linked to disease are found in about 12%, transactive response DNA binding protein 43 (*TARDPB)* and fused in sarcoma (*FUS)* gene variants account for a few percent each, and other less common or rare gene variants are found in the remainder (8). As mentioned, these figures may vary depending upon the population being considered; for example, sequence variants such as the *C9ORF72* hexanucleotide repeat expansion in ALS patients in Finland, and *TARDBP* in ALS patients in Sardinia are significantly more frequent as causes of FALS than in the US or other parts of Europe, and *SOD1* variants are rare among ALS patients in the Netherlands (22, 26–27).

Although associations between the foregoing gene variants and FALS are well established each is also found infrequently in SALS patients. The possibility of incomplete information regarding the family history may be the basis for some of these observations, but documented nonpenetrance is established for the *C9ORF72* repeat expansion and for some *SOD1*, *TARDBP*, and *FUS* variants (28–33). De novo occurrence of sequence variants associated with ALS appears to be uncommon, but has been documented in a single report of a *SOD1* variant, and in multiple reports on *FUS* variants (34–36). The main message from these observations is that absence of a family history of ALS may not rule out the presence of a gene variant associated with FALS, although the likelihood is modest, approximately ~7% in the case of the *C9ORF72* repeat expansion, 1–2% for *SOD1* variants and ~1% for *TARDBP*, *FUS*, and *VCP* variants (8).

Four ALS causative genes linked to over 50% of FALS patients are discussed briefly below in order based on relative frequency of association with ALS. These genes are also the most the most likely to be involved in SALS patients found to carry a recognized ALS-linked gene variant.

Chromosome 9 open reading frame 72 *(C9ORF72)*

A GGGGCC hexanucleotide repeat in the first intron of a gene that encodes a protein of unknown function on chromosome 9, *C9ORF72*, is the most common gene variant associated with FALS, found in 40% of FALS and about 6–8% of SALS patients, with ethnic variation as noted above (37). “C9FTD/ALS” phenotypes include classical ALS (infrequently PMA or PLS), ALS/FTD, and FTD, as well as dopa non-responsive parkinsonian and Huntington disease phenotypes (38–41). FTD or less severe frontotemporal cognitive impairment in C9FTD/ALS patients with ALS may arise with, prior to or after onset of motor signs in up to 50% of patients (42). Inheritance is autosomal dominant with incomplete penetrance; median age of onset is 58 years, ranging from the 4th through 9th decades (37). Genetic anticipation, the onset of C9FTD/ALSALS at earlier age in affected offspring than in affected parents, was suggested by some reports but is not confirmed (38, 43–44). Normal repeat length is 2–10 G_4C_2 units; expansions larger than 20 units are reported with c9FTD/ALS but minimum repeat length linked to disease is not established (21–22, 44). Molecular pathogenesis of C9FTD/ALS may include haploinsufficiency of *C9ORF72* proteins and neurotoxicity from RNA-based gain of function mechanisms, although data increasingly support the latter as the primary component (45–46). Support for the diagnosis of C9FTD/ALS can be obtained at autopsy owing to the presence in brain of distinctive neuronal inclusions reactive for p62, ubiquitin and dipeptide repeat protein species bidirectionally transcribed from the repeat expansion, referred to as C9RAN proteins (47–48). These changes occur on a background of ubiqutin- and TDP-43-positive inclusions in neurons and glia of affected brain regions, similar to that in sporadic ALS (49–51). DNA testing for the repeat expansion is generally based on a polymerase chain reaction (PCR) screening test which does not reliably quantitate repeat number beyond about 50 repeats (21–22). Southern blot, the ‘gold-standard’ for confirmation of the presence of abnormal *C9ORF72* repeat expansions, is technically demanding and may not allow precise determination of repeat length in patients with relatively long repeats but should be performed if PCR screening is ambiguous regarding the presence or absence of an abnormal repeat expansion (21, 44). An additional issue is that repeat length varies across and within tissues and estimates of repeat length in blood may not reflect repeat length in brain (52).

Superoxide dismutase 1 *(SOD1)*

Sequence variants in the Cu/Zn superoxide dismutase gene (*SOD1*) on chromosome 21q12.1, were the first causative gene variants identified in ALS (3). Native *SOD1* protein catalyzes reduction of superoxide to hydrogen peroxide; molecular pathogenesis of SOD1 ALS is not established but several lines of evidence point to a toxic gain-of-function mechanism (12). Disease-linked variants are mainly point mutations and account for a approximately 12% of patients with FALS and 1–2% of SALS, with ethnic variation in prevalence (3, 8). Over 160 pathogenic *SOD1* variants are known, with significant

geographic variation reported for some variants (12). Inheritance with all but one of these is autosomal dominant. The *SOD1* D91A variant, found mainly in ALS patients in Sweden and Finland, is associated with a relatively slowly progressive motor with autosomal recessive inheritance (53). Phenotypes of *SOD1* ALS include classical ALS and PMA, often with asymmetrical lower limb onset; when upper motor neuron signs are found lower motor neuron signs tend to predominate (54). Age of onset in most reported patients with *SOD1* ALS is approximately 47 years with greater variability in disease duration than for age of onset (54–55). However, age at onset and severity may vary significantly depending upon the variant involved, and within families for some variants such as *SOD1* I114T, and penetrance may be < 100% (30, 55–57). Frontotemporal cognitive impairment is rare in *SOD1* ALS (12). Pathological hallmarks of *SOD1* ALS in post mortem brain and spinal cord include intracellular neuronal and astrocytic protein aggregates marked by ubiquinated neuronal and astrocytic inclusions reactive for SOD1 in motor and non-motor systems (54). DNA testing for *SOD1* variants is available through clinical laboratories to establish a genetic diagnosis of *SOD1* ALS (58).

Transactive response DNA binding protein 43 (*TARDBP*)

Identification of *TARDBP* variants in ALS patients followed the discovery in 2006 that neuronal cytoplasmic inclusions immunoreactive for ubiquitin, a pathological hallmark in the large majority of cases of FALS and SALS, are also immunoreactive for TDP-43 (59). Recognition at that time that about half of patients with pathologically proven frontotemporal lobar degeneration (FTLD, the pathological basis for the clinical syndrome FTD) have similar TDP-43 immunoreactive inclusions established a pathological link between ALS and FTD, and led to the concept that ALS, ALS-FTD and FTD represent a clinical and pathological spectrum referred to as TDP-43 proteinopathies (60). Gene variants in *TARDBP*, which encodes the 43-kD TAR DNA-binding protein 43 (TDP-43), are found in approximately 4% of FALS and 1% of SALS, with some regional variation. (8, 29, 32). TDP-43 regulates gene expression and RNA splicing (60). Available evidence suggests that dysregulation of gene expression, including RNA splicing, attributed to pathogenic *TARDPB* variants, in conjunction with a toxic gain-of-function of mutant TDP-43 protein, contribute to neurodegeneration but the causal mechanism is not established (61). More than 30 sequence variants have been associated with *TARDBP* ALS, most in the C-terminal glycine-rich domain; inheritance in all is autosomal dominant (60). Clinical phenotypes linked to pathogenic *TARDPB* variants include classical ALS and rarely Parkinson disease or FTD (62–66). Upper limb onset is reported to be more common in *TARDBP* ALS and survival somewhat longer than in SALS generally, but in clinical practice these differences have limited utility in identifying patients with *TARDBP* ALS (64). Pathology of *TARDPB* ALS is similar to most cases of SALS pathology, demonstrating neuronal cytoplasmic inclusions immunoreactive for TDP-43 throughout the brain, but particularly in motor cortex, spinal cord, basal ganglia and thalamus (60). DNA testing for ALS-linked *TARDPB* variants is available through clinical laboratories (58).

Fused in sarcoma (*FUS*)

Variants in the gene fused in sarcoma (*FUS*) are linked to autosomal dominant ALS in about 4% of FALS and 1% of SALS patients (8, 33, 67–68). FUS appears to regulate DNA and

RNA metabolism and be involved in RNA transcription, splicing and processing; gene sequence variants that alter these functions may contribute to neurodegeneration but the molecular pathogenesis of *FUS* related neurodegeneration is not fully defined (69). Pathogenic *FUS* variants include point mutations and other structural defects, and are notable for several reports confirming de novo mutations associated with ALS (35–36, 70–73). Inheritance is autosomal dominant aside from a single family with apparent autosomal recessive inheritance (68). ALS phenotypes include adult-onset ALS, ALS/FTD, and juvenile ALS, and rarely as pure FTD (69). A single family with a *FUS* "ALS-plus" syndrome with ocular, autonomic and cerebellar features also has been reported (74). Disease progression in juvenile *FUS* ALS tends to be rapid, without development of FTD (75–76). Pathological hallmarks of adult-onset *FUS* ALS in post mortem brain and spinal cord include abnormal protein aggregates immunoreactive for FUS, mainly in the cytoplasm but also in nuclei of neurons and glia (33, 77). Juvenile onset *FUS* ALS demonstrates distinctive pathology marked by neuronal basophilic inclusions immunoreactive for FUS protein; similar pathology has been reported in adult-onset *FUS* FTD but rarely for *FUS* ALS (75–76, 78–79). DNA testing to identify *FUS* variants is available through clinical laboratories (58).

Other ALS risk genes and insights from ALS genetics on the pathogenesis of ALS

The list of additional genes with sequence variants associated with ALS and related phenotypes continues to grow, aided by technological advances in large scale genetic screening in FALS and SALS patients, particularly whole exome analysis in recent studies (Table 2) (6–7). Although most of these genes contribute to a relatively small proportion of FALS and/or SALS, they and more common FALS genes have offered insights regarding ALS pathogenesis. Shared functional characteristics of protein products of these genes and related post mortem pathology have directed attention to specific molecular pathways in ALS pathogenesis, and in turn has supported development of molecular models of ALS pathogenesis and development of new therapeutic strategies (61, 80–81).

Pathogenic *TARDPB* and *FUS* variants found in ALS and recognized functional and structural similarities between TDP-43 and FUS protein focused attention on potentially disordered RNA processing and splicing in ALS generally (33, 62–63, 68). Relevance of defective RNA processing to ALS pathogenesis was more recently reinforced by the discovery of pathogenic *MATR3* and *nhRNPA1* variants in ALS patients, as both genes appear to have a role in normal RNA processing (82–83). Although the specific function of C9ORF72 protein is not established, molecular and pathological evidence in C9FTD/ALS offers further support for the concept that disordered RNA processing contributes to ALS (45–46, 84–87).

The discovery that mutations in the ubiquilin-2 gene (*UBQLN2*, which encodes ubiquilin-2) are a rare cause X-linked dominant ALS and ALS/FTD in males, with reduced penetrance in females, reinforced the concept that disruption of protein degradation pathways may be important in ALS (88). Abnormal protein aggregates in affected brain regions in the majority of cases of FALS and SALS patients are immunoreactive at post mortem for ubiquilin-2, and functional analysis suggests that *UBQLN2* mutations resulting in ALS and

ALS/FTD are pathogenic owing to disruption of autophagic protein degradation (81, 88). Relevance of autophagy in ALS is further supported by associations between sequence variants in the genes encoding valosin containing protein (*VCP*), optineurin (*OPTN*) and TANK-Binding Kinase 1 (*TBK1*) in ALS (89–92). Protein products of these genes are involved in normal protein autophagy (89).

Genes pathogenically associated with ALS and FTD have also been linked to conditions involving other organ systems such as bone and muscle, giving rise to the designation "multisystem proteinopathy" as a group of genetic disorders demonstrating a wide phenotypic spectrum. In addition to *VCP* and *OPTN*, sequestosome 1/P62 (*SQSTM1/p62*), heterogeneous ribonucleoprotein A2B1 and A1 (*HNRNPA2B1* and *HNRNPA1*) are genes in this category that have been linked to Paget disease of bone, inclusion body myopathy and ALS (83, 91, 93). Disease-linked variants in these genes are uncommon in ALS but they have implicated toxic conformational changes in RNA-binding proteins with prion-like domains, such as TDP-43 and FUS, in neurodegeneration (83, 94).

ALS-susceptibility genes associated with lower risk and potential disease modifying genes

Beyond genes noted above, an expanding number of additional genes has been implicated in the pathogenesis of ALS, based on varied levels of supporting data, and in some cases uncertainty whether reported variants represent modifiers of clinical disease rather than direct causative factors (Table 3) (4, 6–7). These variants tend to be uncommon, with limited data supporting linkage with ALS; more detailed discussion is beyond the scope of this review but further information is available in recent reviews (4, 6–7). Further studies are needed to clarify the level of ALS risk associated with these genes and, in some cases confirm that the reported variant is associated with ALS rather than being a benign variant (6).

Epigenetics of ALS

Epigenetic factors may influence gene expression and disease states through dynamic cellular and physiological processes that activate and deactivate parts of the genome. DNA methylation is a well studied example shown to be involved in neurodegeneration, and could potentially play a role in phenotypic expression of FALS as well as SALS(95). Genomic DNA methylation patterns in ALS examined for alterations that could represent disease-specific epigenetic alterations in ALS have suggested that such changes may influence gene expression, but this requires confirmation(96–97). More recent studies focusing on ALS associated with the *C9ORF72* repeat expansion offer evidence that in this form of FALS histone methylation appears reduce expression of the mutant allele, and DNA methylation may be associated with less severe clinical phenotype in the form of longer survival and reduced mutation-specific pathology in affected brain regions (98–100). More studies are needed to confirm these results and investigate the potential role of epigenetic factors in other forms of FALS and in SALS. Analysis of epigenetic factors could refine genetic testing in ALS if detection and interpretation of epigenetic characteristics becomes a routine component of a patient's genetic risk profile.

ALS gene testing in clinical practice

Clinical Vignette

A 59-year-old woman with a confirmed diagnosis of ALS has mild bulbar features but is mainly disabled by upper limb and less pronounced lower extremity weakness. Symptoms began 14 months earlier and upper and lower motor neuron signs are now present. There is mild pseudobulbar affect but no features suggestive of neuropsychiatric dysfunction; mild depression responded well to antidepressant medication. The patient questions whether her children are at risk for ALS.

There is no known family history of ALS. Her father died at 76 of a myocardial infarction with no history of neurological disorders. Her mother died of complications of dementia at age 63, characterized as “Alzheimer disease” with a clinical course of approximately 4 years, becoming mute and bedridden toward the end of her disease course with significant weight loss. The patient’s only sibling is an older brother who is well. A maternal aunt developed dementia and died at approximately age 70 but no details otherwise are available; the aunt had a son thought to be alive but the patient has no information otherwise. The maternal grandparents are believed to have lived past age 70 without neurological problems.

The family history illustrates issues that can arise in evaluating the possibility that ALS in a given patient may be associated with an ALS risk gene. The family history is said to be negative with regard to ALS, but the dementia in the patient’s mother had a shorter clinical course than is typical for Alzheimer disease, raising the possibility that the patient’s mother may actually have had frontotemporal dementia, perhaps even accompanied by undiagnosed motor neuron disease. Dementia in the maternal aunt could reflect a familial predisposition to dementia, but limited information prevents meaningful conclusions. Family history may be clarified by review of family medical records or autopsy reports, but these may be unavailable.

If no further family history becomes available a case can be made to discuss with the patient the possibility that her disorder could be associated with a *C9ORF72* repeat expansion, particularly given that frontotemporal dementia is recognized phenotype of the *C9ORF72* repeat expansion. Dementia is also reported in association with other ALS linked genes including *FUS* and *TDP-43*, although these are less common. Dementia linked to *SOD1* variants, the second most common ALS linked gene after *C9ORF72*, is rare. Confirmation of frontotemporal dementia in the patient’s mother or the aunt would meet criteria for possible FALS according to criteria suggested by Byrne et al. (Table 1). A more common situation is the question of whether to offer DNA testing if further investigation suggests that neither the patient’s mother nor the aunt are likely to have had FTD in the patient thought to have SALS.

Considerations in the clinical application of DNA testing in ALS

A challenge for the clinician upon establishing that a patient has ALS is the question of whether to offer the patient DNA testing to investigate the possibility that the patient carries an ALS-linked gene variant. While confirmation that the patient carries a sequence variant associated with ALS offers no proven gene-specific treatment options, research in this area

may provide the patient with options for participation in future research trials involving gene targeted therapy. Anti-sense oligonucleotide and small molecule therapy has undergone early stage testing and similar experimental treatment approaches are anticipated to become available in human studies in coming years (86, 101–104).

Clinical features of ALS in general do not provide a reliable basis for separating of FALS from SALS in individual patients given the extent of phenotypic overlap(12). Clinical characteristics that may offer some insight as to the potential for involvement of one or another specific genes in FALS are discussed above. Family history provides critical information when available, and criteria noted in Table 1 offer a reasonable basis for clinical decision making, recognizing that fully validated criteria are not available(14, 20). In a patient lacking a family history of ALS the relevance of a family history of dementia in a first- or second-degree relative may be uncertain, as genetic risk applies primarily for FTD and it may be difficult to specifically confirm whether or not the cognitive disorder in the relative in question was FTD as opposed to dementia on some other basis(14). A further confound is that an amnestic syndrome diagnosable as Alzheimer disease is reported infrequently in patients with a *C9ORF72* repeat expansion(105).

The foregoing discussion regarding DNA testing refers to patients with suspected FALS, but in view of data suggesting that approximately 10% of SALS patients may carry a major ALS susceptibility gene variant, there are grounds to make people with SALS aware of this possibility in order to allow the patient to make an informed decision regarding DNA testing(8). Although there may be exceptions depending upon the experience and training of the clinician, in most situations ALS patients seeking further information regarding the rationale for DNA testing and review of test results should be referred to a genetic counselor (106).

An additional issue once the decision to order DNA testing has been made is which test or tests to order. Clinical tests for ALS-linked genes are available, including *C9ORF72*, *SOD1*, *FUS* and *TARDBP*, variants of which are found in over 50% of FALS patients (8). Although DNA tests can involve screening for several genes ordered as a group, a case can be made to consider sequential testing based on published frequency data for individual genes, in which case the *C9ORF72* repeat expansion is most frequent, followed by *SOD1* and then *FUS* and *TARDPB* variants. Clinical DNA test options are anticipated to increase as new ALS genes are identified. Further, as the cost of whole exome and whole genome testing declines it is likely that these methods may supplant test panels composed of a limited number of disease-linked genes. The likelihood that genetic susceptibility to ALS is polygenic and increasing knowledge of gene variants that modify clinical phenotype will also motivate the use of next-generation screening techniques, in order to support more efficient and cost effective evaluation of the genetic risk profile of individual patients.

Conclusions

Although genetic mechanisms in ALS pathogenesis appear to play a major role in the development of ALS in a minority of patients, studies suggest that genetic factors at some level are important components of disease risk in the majority of ALS patients (8). However,

identification of gene variants associated with ALS, regardless of the prevalence or magnitude of associated risk, has informed concepts of the pathogenesis of ALS, aided the identification of therapeutic targets, facilitated research to develop new ALS biomarkers, and supported the establishment of clinical diagnostic tests for ALS-linked genes. It has been suggested that a deeper understanding of the genetic landscape of ALS is key to recognition of environmental risk factors in ALS given the likelihood that sensitivity to environmental risks is influenced by a person's genetic background (107).

New treatment strategies aimed at blocking expression of ALS gene mutations have successfully completed early phase safety testing in the case *SOD1* anti-sense oligonucleotide therapy, and efforts are underway to introduce small molecule and gene therapy targeting expression of the *C9ORF72* repeat expansion (86, 102–104). Results of studies applying increasingly powerful next generation sequencing methodology to the discovery of new ALS risk genes, and work to identify and characterize epigenetic factors contributing to ALS pathogenesis are anticipated. These efforts are likely to contribute significantly to ALS therapy development and continue to move ALS into the realm of individualized medicine.

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Key Points

ALS is genetically heterogeneous with over 50 potential causative or disease modifying genes identified, but *C9ORF72*, *SOD1*, *TARDPB* and *FUS* presently account for >50% of ALS-linked gene variants found in ALS patients and variants in other genes are relatively 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 in individual patients owing to phenotypic overlap; family history, including history of frontotemporal dementia, aids in recognizing that a patient may have familial ALS.

ALS-linked gene variants can be presently be identified in be identified in ~60–70% of patients with familial ALS, a proportion likely to grow, and a pathogenic ALS gene variant may be found in an increasing minority of patients with sporadic ALS.

Table 1

Criteria for the diagnosis of familial amyotrophic lateral sclerosis.

Classification/Level of Certainty	Family History
Definite	≥ 2 First- or second-degree relatives with ALS
	≥ 1 Relative with ALS and gene-positive cosegregation
Probable	1 First- or second-degree relative with ALS
Possible	Distant relative (third degree or beyond) with ALS
	Sporadic ALS patient with no family history but positive for a FALS gene
	≥ 1 First- or second-degree relative with confirmed frontotemporal dementia
Definitions: First-degree relatives: parents, children and siblings; second-degree relatives: grandparent, aunts/uncles. Adapted from Byrne, et al. (14).	

Table 2

Genes linked to ALS pathogenesis

Gene	Protein	Function	Inheritance	Phenotype(s)	%FALS[2]	%SALS[2]
ALS2[1] (108)	Alsin	Rho guanine nucleotide exchange factor	AR	Juvenile ALS, Juvenile PLS, HSP		
ANG; ALS9 (109–110)	Angiogenin	Ribonuclease; angiogenesis	AD/Sporadic	ALS, PD		
ATXN2; ALS13 (111–112)	Ataxin-2	RNA processing	Not established	ALS, SCA2, parkinsonism		
CHCHD10 (113–114)	Coiled-coil-helix-coiled-coil-helix domain containing 10	Mitochondrial protein	AD	FTD, cerebellar ataxia, myopathy		
CHMP2B; ALS17 (115)	Chromatin modifying protein 2B	Recycling/degradation of cell surface receptors	AD	ALS, ALS-FTD, FTD		
C9ORF72 (21–22, 116–117)	Chromosome 9 open reading frame 72	Unknown	AD	ALS, ALS-FTD, FTD, parkinsonism (rare), Psychosis	40	7
DAO (118)	D-amino-acid oxidase	Peroxisomal enzyme; potential role in glutamatergic neurotransmission	AD	ALS		
DCTN1 (119–121)	Dynactin	Axonal transport	AD	PMA, FTD, HMN VIIB, Perry Syndrome		
FIG4; ALS11 (122)	SAC1 lipid phosphatase domain containing (S. cerevisiae)	Polyphosphoinositide phosphatase	AD, AR	ALS, PLS, CMT4J, Yunis-Varon Syndrome		
FUS; ALS6 (33, 68)	Fused in sarcoma	RNA-binding protein, DNA repair, exon splicing	AD	ALS, Juvenile ALS, FTD	4	1
HNRNPA1; ALS20 (83)	Heterogenous nuclear ribonucleoprotein A1	mRNA processing, transport and metabolism	AD	ALS, FTD, IBMPFD		
HNRNPA2B1 (83)	Heterogenous nuclear ribonucleoprotein A2B1	mRNA processing, transport and metabolism	AD	ALS, FTD, IBMPFD		
MATR3; ALS21 (82)	Matrin 3	Nuclear matrix protein, may stablilize mRNA species	AD	ALS, distal myopathy 2, ALS plus myopathy		
OPTN; ALS12 (123)	Optineurin	Membrane and vesicle trafficking, transcription activation	AD, AR	ALS, Progressive open angle glaucoma	<1	<1
PFN1; ALS18 (124)	Profilin 1	Actin binding protein, actin polymerization	AD	ALS	<1	<1
SETX; ALS4 (125)	Senataxin	RNA/DNA helicase	AD	Onset < age 25 years; SETX mutation causes Spinocerebellar ataxia 1/ataxia-ocular apraxia 2		
SIGMAR1; ALS16 (126–128)	Sigma non-opioid intracellular receptor 1	Endoplasmic reticulum chaperone protein; proteosome inhibition, mitochondrial stress	AR	ALS, FTD		
SOD1; ALS1 (3, 54–55)	Superoxide dismutase 1	Oxidative stress	AD, AR, de novo	ALS, FTD (rare), PMA	12	2
SPG11 (129–130)	Spatacsin	DNA damage repair	AR	Juvenile ALS, HSP (SPG11)		

Gene	Protein	Function	Inheritance	Phenotype(s)	%FALS[2]	%SALS[2]
SQSTM1 (131–132)	Sequestosome 1	Scaffold protein, NFKB signaling	AD	ALS, FTD	1	<1
TARDBP; ALS10 (62–64)	TAR DNA binding protein 43	Transcriptional repressor, splicing regulation	AD, AR, de novo	ALS, FTD, PD	4	1
TBK1 (89–90)	TANK-Binding Kinase 1	Mediates growth factor activation of NFKB	AD	ALS		
TUBA4A; ALS22 (133)	Tubulin Alpha 1	Structural component of cytoskeleton; GTP binding	AD	Spinal onset ALS, ALS-FTD, FTD		
UBQLN2; ALS15 (81, 88)	Ubiquilin 2	Ubiquitination, protein degradation	XLD	ALS, FTD	<1	<1
VAPB; ALS8 (134)	Vesicle-associated membrane associated-protein B	Vesicular trafficking	AD	ALS, PMA		
VCP; ALS14 (91)	Valosin-containing protein	ATP-binding protein, vesicle transport and fusion	AD	ALS, ALS-FTD, FTD, IBMPFD	1	1

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CMT, Charcot-Marie-Tooth; FTD, frontotemporal dementia; HSP, hereditary spastic paraplegia; IBMPFD, Inclusion body myopathy with early-onset Paget disease and frontotemporal dementia; PMA, progressive muscular atrophy; PLS, primary lateral sclerosis; SPG, spastic paraplegia; XLD, X-linked dominant

[1]The Human Genome Organization (HUGO) Nomenclature Committee has approved numerical designations for 22 ALS-linked genes or genetic loci to date, ALS1 through ALS22. These designations are not used as a primary numbering system here given that numbers have not been assigned for multiple ALS genes and the gene is not identified for three numerically designated forms. ALS3, ALS5 and ALS7 represent ALS-linked gene loci on chromosomes 18q21, 15q15.1-q21.1 and 20p13. Causative genes are not yet established for these loci.

[2]Percentages of FALS and SALS cases are shown where data seem sufficient to support an estimate. Frequency estimates are not listed where data on the frequencies of disease-associated variants are limited, and in most such instances frequency may be low or rare.

Table 3

Genes associated with potential causative or disease modifying effects in ALS

Gene	Protein	Function
APOE(135)	Apolipoprotein E	Lipoprotein metabolism, immune regulation
ARHGEF28 (136–137)	Rho guanine nucleotide exchange factor (GEF) 28	Regulates integrin and growth factor signaling pathways
CHGB(138)	Chromogranin B	Neuroendocrine secretory granule protein
CHRNA3 (139)	Neuronal acetylcholine receptor subunit alpha-3	Nicotinic acetylcholine receptor subunit
CHRNA4 (140)	Neuronal acetylcholine receptor subunit alpha-4	Nicotinic acetylcholine receptor subunit
CHRNB4 (139)	Neuronal acetylcholine receptor subunit beta-4	Nicotinic acetylcholine receptor subunit
CX3CR1(141)	CX3C chemokine receptor 1	Chemokine receptor
DPP6 (142–144)	Dipeptidyl-peptidase 6	Alters expression/properties of voltage-gated K+ channels
DPYSL3(145)	Dihydropyrimidinase-Like 3	Class 3 semaphorin signaling, cytoskeletal remodeling
ELP3(146)	Elongator acetyltransferase complex subunit 3	Transcript elongation
EPHA3 (147)	EPH receptor A3	Neighboring cell signaling, axonal segregation during development
EPHA4(147)	EPH receptor A4	Neighboring cell signaling, repair after nerve injury, angiogenesis
ERBB4; ALS19 (148)	V-erb-B2 avian erythroblastic leukemia viral oncogene homolog 4	Tyrosine protein kinase involved in cell signaling; potential effects on anti-apoptosis and gene expression
ERLIN2 (149)	Endoplasmic reticulum lipid raft-associated protein 2	Endoplasmic reticulum-associated degradation of IP3 receptors
EWSR1 (150)	EWS RNA-binding protein 1	Gene expression, cell signaling, RNA processing and transport
GRN(151–152)	Progranulin	Regulation of cell growth
FGGY(143)	FGGY carbohydrate kinase domain containing	Phosphorylation of carbohydrates
HFE(153–154)	Hemochromatosis	Iron absorption
ITPR2 (155)	Inositol 1,4,5-trisphosphate receptor	Mobilization of intracellular Ca2+ stores
KIFAP3 (156)	Kinesin-associated protein 3	Small G-protein
MAOB(157)	Monoamine oxidase B	Mitochondrial metabolism of neuroactive and vasoactive amines
MAPT(158)	Microtubule-associated protein tau	Supports microtubule assembly and stability
NEFH(159–160)	Neurofilament heavy polypeptide	Intracellular axonal and dendritic transport, axonal structure
PON1, 2,3(161)	Paraoxonase	Hydrolysis of organophosphates
PPARGC1A(162)	Peroxisome proliferator-activated receptor gamma, coactivator 1 alpha	Transcriptional coactivator, regulates genes involved in energy metabolism
PRPH (163)	Peripherin	Cytoskeletal protein
SMN1(164)	Survival of motor neuron 1	mRNA processing
SPAST (165–167)	Spastin	Microtubule function
SS18L1 (168–169)	Synovial sarcoma translocation gene on chromosome 18-like 1	Neuronal chromatin-remodeling, neurite outgrowth
TAF15 (94)	TATA box binding protein (TBP)-associated factor	RNA polymerase II gene transcription
TMEM106B(170–171)	Transmembrane protein 106B	Lysosomal trafficking, dendrite morphogenesis and maintenance

Gene	Protein	Function
TREM2(172)	Triggering receptor expressed on myeloid cells 2	Immune system regulation
UNC13A(173–174)	Unc-13 homolog A	Synaptic neurotransmitter release
VEGF(175)	Vascular endothelial growth factor	Vasculogenesis and angiogenesis factor
ZNF512B(176–177)	Zinc finger protein 512B	Regulation of transcription