Novel genes associated with amyotrophic lateral sclerosis: diagnostic and clinical implications

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Summary

Background The disease course of amyotrophic lateral sclerosis (ALS) is rapid and, because its pathophysiology is unclear, few effective treatments are available. Genetic research aims to understand the underlying mechanisms of ALS and identify potential therapeutic targets. The first gene associated with ALS was SOD1, identified in 1993 and, by early 2014, more than 20 genes had been identified as causative of, or highly associated with, ALS. These genetic discoveries have identified key disease pathways that are therapeutically testable and could potentially lead to the development of better treatments for people with ALS.

Recent developments Since 2014, seven additional genes have been associated with ALS (MATR3, CHCHD10, TBK1, TUBA4A, NEK1, C2orf2, and CCNF), all of which were identified by genome-wide association studies, whole genome studies, or exome sequencing technologies. Each of the seven novel genes code for proteins associated with one or more molecular pathways known to be involved in ALS. These pathways include dysfunction in global protein homoeostasis resulting from abnormal protein aggregation or a defect in the protein clearance pathway, mitochondrial dysfunction, altered RNA metabolism, impaired cytoskeletal integrity, altered axonal transport dynamics, and DNA damage accumulation due to defective DNA repair. Because these novel genes share common disease pathways with other genes implicated in ALS, therapeutics targeting these pathways could be useful for a broad group of patients stratified by genotype. However, the effects of these novel genes have not yet been investigated in animal models, which will be a key step to translating these findings into clinical practice.

Where next? The identification of these seven novel genes has been important in unravelling the molecular mechanisms underlying ALS. However, our understanding of what causes ALS is not complete, and further genetic research will provide additional detail about its causes. Increased genetic knowledge will also identify potential therapeutic targets and could lead to the development of individualised medicine for patients with ALS. These developments will have a direct effect on clinical practice when genome sequencing becomes a routine and integral part of disease diagnosis and management.

Introduction

Typically, the disease course of amyotrophic lateral sclerosis (ALS) is rapid, and most patients die within 3–5 years of symptom onset as a result of respiratory failure.1 Although the disease is considered a rare type of motor neuron neurodegeneration, the number of patients with ALS is rapidly increasing because of population ageing. Most patients are aged between 50 and 75 years at diagnosis and, by 2040, an estimated 400,000 patients will be diagnosed with ALS worldwide.2 Approximately 10% of patients with ALS have a family history of disease, whereas the remainder of cases are classified as sporadic.1 The pathophysiology of ALS—familial or sporadic—is unclear, thus few effective treatments are available. Riluzole and edaravone are the current treatments effective treatments are available. Genetic research aims to understand the underlying mechanisms of ALS to analyse the disease process at the cellular level. By 2014, 22 genes were implicated in ALS, and mutations in these genes account for about two-thirds of all familial cases and approximately 10% of cases of sporadic ALS.3 Since 2014, seven novel genes associated with ALS—MATR3, CHCHD10, TBK1, TUBA4A, NEK1, C2orf2, and CCNF—have been identified. The rapid identification of multiple novel genes associated with ALS reflects improvements in sequencing technologies and, more importantly, provides an opportunity to better understand the disease (figure 1). Such advances are key to the development of disease-modifying treatments.

In this Rapid Review, we summarise the novel genetic discoveries associated with ALS in chronological order. We focus on the technologies and experimental design used to identify these genes, and have cross-checked genetic variants against the Exome Aggregation Consortium (ExAC) public database, which catalogue more than 7 million variants in the protein coding region of the genome identified in more than 60,000 mostly healthy individuals (ie, those without severe paediatric diseases). Genetic screening is becoming more accessible and common in clinical practice, thus understanding how a variant might cause disease within the context of the larger population could help in making reasonable inference about pathogenicity, especially when family history of disease is unknown. We also discuss the importance of these genes for the development of new therapies.
Novel ALS genes

Frequency data for these seven novel genes identified since 2014 are scarce because few studies have done large-scale screening of independent patient cohorts. The frequency data available for these genes are likely to be inflated, and we hypothesise that the frequency of mutations in these genes in the population will be lower when additional data is obtained. We estimated that for ALS—assuming full penetrance, no founder mutation effect, and disease prevalence of six cases per 100 000 individuals—

\[
\text{a variant observed more than five times per 121 000 alleles in the ExAC database (corresponding to an allele frequency of 0.0033%) is unlikely to cause ALS because it is too common.}
\]

However, absence of mutations in a gene in the ExAC database does not necessarily infer pathogenicity because rare genetic variants that are unique to one individual or a single family are remarkably common in the human population (about 3–4 million single nucleotide polymorphisms per individual).7

**MATR3**

In 2014, four mutations (p.S85C, p.F115C, p.P154S, and p.T622A) in MATR3 were identified by exome sequencing in four families of European descent with either ALS alone or with a combination of ALS and dementia.12 Since 2014, 11 additional variants have been described, predominantly occurring in patients with sporadic ALS.13-15 In the ExAC database, three variants (p.E664A, p.N787S, and c.48+1G>T) had a reported allele frequency of 0.03–0.05%, p.F115C was reported once, but none of the other variants were listed. Overall, the contribution of MATR3 to the development of ALS or ALS and frontotemporal dementia is relatively rare, with no significant correlation observed between phenotype and genotype.
In patients with ALS with MATR3 mutations, upper and lower motor neurons are affected and survival duration ranges from 2–12 years. The concomitant clinical presentation of ALS and myopathic features in individuals with the p.S85C mutation is important because these patients are initially diagnosed with vocal cord and pharyngeal dysfunction with asymmetric distal myopathy, but the presentation of pyramidal tract signs and progressive respiratory failure at end-stage disease usually warrants re-diagnosis. By contrast to TDP43 and FUS, whereby mutations cause relocalisation of the mutant protein from the nucleus to cytoplasm, studies have shown that the subcellular localisation of mutant MATR3 is generally unaffected. Furthermore, MATR3-positive inclusions were occasionally observed in histopathological sections from patients with MATR3 mutations, and in one individual with C9orf72 expansion.

MATR3 is a 125 kDa nuclear protein with RNA and DNA binding domains that appears to primarily regulate gene expression. Transgenic mice overexpressing human MATR3 protein develop hindlimb paralysis and muscle atrophy, indicating that neuromuscular function is sensitive to MATR3 levels. The protein forms a complex with two other ALS-associated RNA-binding proteins, TDP43 and FUS, in a RNA-dependent manner and the p.S85C mutation enhances this interaction. Thus, overlap might occur in the upstream regulatory proteins or downstream effector targets among ALS-RNA binding proteins. Elucidation of this potentially shared set of proteins might identify molecules suitable for therapeutic intervention.

**CHCHD10**

CHCHD10 was first linked to ALS in a study of a large French family who had a complex phenotype of ALS, ataxia, mitochondrial myopathy, parkinsonism, and sensorineural hearing loss. Exome sequencing identified a p.S59L mutation within CHCHD10. Subsequently, 20 additional missense variants, clustered in exon 2—which encodes an internal hydrophobic helical segment important for mitochondrial membrane binding—have been reported in a broad range of neurodegenerative disorders, including ALS and frontotemporal dementia, frontotemporal lobar degeneration, parkinsonism, Alzheimer’s disease, autosomal dominant mitochondrial myopathy, adult-onset spinal muscular atrophy, and Charcot-Marie-Tooth type 2. The pathogenicity of p.S59L, p.R15L, and p.G66V has been validated in family studies, whereby the mutations were shown to segregate with ALS. Additionally, the mutations were absent in the ExAC database. However, mutations in CHCHD10 appear to be a relatively rare cause of ALS, but might be more frequent among patients diagnosed with frontotemporal dementia.

CHCHD10 is a 14 kDa nuclear-encoded, mitochondrial protein localised to the mitochondrial intermembrane space. The protein is important for the maintenance of mitochondrial dynamics and cellular bioenergetics. Patient fibroblasts expressing mutant CHCHD10 protein (p.S59L) have a fragmented mitochondrial network and disrupted mitochondrial cristae. These effects are similar to abnormalities in mitochondrial dynamics induced by mutations in TDP43. CHCHD10 also interacts with TDP43, which promotes retention of TDP43 in the nucleus, but this localisation is disrupted in the presence of CHCHD10 mutations, causing an accumulation of TDP43 in the cytoplasm and synaptic damage. Further study is necessary to investigate the mechanistic association between these proteins and their involvement in mitochondrial dysfunction and TDP43 proteinopathy. This insight could identify therapeutic targets susceptible to manipulation by small molecules, to rescue the observed cellular defects involved in ALS.

**TUBA4A**

TUBA4A was implicated as a novel gene for familial ALS on the basis of exome sequencing data obtained from a large cohort of European and American patients with ALS and controls. This finding was replicated in an independent Belgian cohort, but not in Asian patients with ALS. All variants were absent or had very low frequency in the ExAC database and had adequate segregation data, with the exception of p.K430N. The overall frequency of TUBA4A mutations suggests it is a rare cause of ALS. Little information is available about the clinical presentation, prognosis, or neuropathological evaluation of patients with TUBA4A variants, and although patients often present with typical features of ALS, some also present with features of frontotemporal dementia.

The main cytoskeletal scaffold in cells is comprised of microtubules, composed of polymerised α-tubulin and β-tubulin subunits. In primary motor neurons, expression of missense mutation TUBA4A interferes with tubulin dimerisation, resulting in a weakened microtubule network. Mutations have been found to cluster in the protein domain responsible for the interaction with other tubulin subunits and the axonal transport proteins dynein and kinesin. This finding highlights the crucial role of cytoskeletal and axonal transport defects in the pathogenesis of ALS. Therapeutic approaches enhancing cytoskeletal integrity might be crucial for halting progression or reversing the disease course.

**TBK1**

A whole exome sequencing study revealed that TBK1 was implicated in ALS. Enrichment of nonsynonymous variants in patients with ALS compared with healthy controls was found across the entire coding region. This finding was validated by another whole exome sequencing study, which reported segregation of the pathogenic variants within affected families. Mutations in TBK1 are found in about 1% of patients with familial...
ALS and in approximately 1% of patients with sporadic ALS. The clinical phenotypes associated with TBK1 mutations are heterogeneous, with variable age of onset, differing progression, and irregular length of survival time. Extrapyramidal symptoms, ataxia, and psychiatric symptoms have also been reported in some patients with TBK1 mutations. Neuropathological examination of CNS tissue from patients with a TBK1 mutation showed SQSTM1/p62 and TDP43-positive inclusions, which are indicative of abnormal TDP43 protein aggregation and defective protein clearance pathways. Since these inclusions are also observed in other patients with ALS without TBK1 mutations, this suggests that a common disease mechanism might exist, and a broad treatment approach to restore defective proteostasis might also benefit patients with TBK1 mutations.

TBK1 is a homodimeric multidomain protein with a kinase domain, a ubiquitin-like domain, and two coiled-coil domains. The protein acts as an interaction platform for multiple proteins and regulates the activities of downstream protein targets involved in key cellular processes that have been implicated in ALS, including neuroinflammation, ubiquitin-proteasome systems, and autophagy pathways involving other genes also associated with ALS—ie, OPTN, SQSTM1/p62, VCP, and UBQLN2. Most pathogenic variants identified in TBK1 are concentrated within the kinase and the coiled-coiled domains, suggesting that these mutations might operate by altering these downstream regulatory pathways. We identified some variants (p.K291E, p.A535T) in the ExAC database that had a frequency higher than our estimated threshold of 0.0033%, p.A535T in the ExAC database, with an overall mutation frequency that ranged between 0.6 and 3.3% in white populations. Clinically, these patients presented with either typical ALS, ALS with frontotemporal dementia, or frontotemporal dementia alone.

CCNF

CCNF was identified as a causative gene for ALS on the basis of exome sequence analysis of a large family of European descent who had ALS, frontotemporal dementia, or both diseases, with an autosomal dominant pattern of inheritance. The authors reported additional, potentially pathogenic variants in CCNF in familial cases (all absent or less than the 0.0033% threshold in the ExAC database), with an overall mutation frequency that ranged between 0.6 and 3.3% in white populations. Clinically, these patients presented with either typical ALS, ALS with frontotemporal dementia, or frontotemporal dementia alone.

CCNF is the substrate-recognition component of the Skp1-cullin-F-box E3 ubiquitin-ligase complex, which is responsible for tagging proteins with ubiquitin and marking them for degradation via the ubiquitin-proteasome system. Neuronal cells overexpressing mutant CCNF show an increase in ubiquitin-tagged proteins, which include TDP43. This increase suggests that these variants affect the proteosomal degradation pathway by either aberrantly tagging all proteins with ubiquitin or failing to transfer ubiquitin-tagged proteins to the proteasome complex for removal. This finding indicates that mutations in CCNF might lead to abnormal proteostasis, which might be exacerbated by TDP43 proteinopathy. Therefore, therapies that enhance protein clearance or reduce ubiquitination might be viable approaches to treatment.

Role of genetics in therapy development

With the exception of riluzole, which was shown to prolong survival for 2–3 months, and edavarone, which was shown to decrease the rate of patient immobility, currently no treatments are available for ALS that can effectively stop or reverse the disease progression. Diagnosis of ALS is only possible through assessment of clinical symptoms after a substantial number of motor neurons have died. Thus, for a drug to be effective, early or presymptomatic diagnosis would be necessary to prevent further motor neuron degeneration and to preserve the function of remaining motor neurons. However, this presents a challenge because no reliable molecular biomarkers have been identified for presymptomatic diagnosis or for patient stratification in clinical trials. The genetic landscape of ALS is slowly evolving in response to novel genetic discoveries, helping to identify pathogenic cellular pathways (figure 2, table), and to provide both potential biomarkers and targets for drug discovery.

Pathogenicity in some cases is likely to be driven by the acquisition of a toxic function through genetic
the efficacy observed in experimental models can be achieved in human beings.

Similar biomarker development and antisense oligonucleotide studies targeting C9orf72 are in development. Although it remains unclear which toxic species drive pathogenicity, a single dose of antisense oligonucleotide that specifically targets the expanded allele was sufficient to alleviate behavioural symptoms in transgenic C9orf72 mice and reduce the number of RNA foci and dipeptide repeat proteins. Patients with C9orf72 expansion also showed increased toxic RNA accumulation in tissues and circulating dipeptide repeat proteins in blood and cerebrospinal fluid, suggesting that C9orf72 could be a candidate biomarker of disease diagnosis, treatment efficacy evaluation, and prognosis.

Genetic discoveries have been directly applied in clinical settings to alleviate disease—eg, riboflavin therapy for Brown-Vialetto-Van Laere syndrome, which is an inherited variant of ALS. The syndrome is a rare progressive neurodegenerative disorder that typically manifests as childhood ALS in combination with sensorineural deafness. Brown-Vialetto-Van Laere syndrome is caused by mutations in two riboflavin transporter genes (SLC52A2 and SLC52A3) that result in a reduction of plasma flavin and acylcarnitine concentrations. Patients treated with high-dose oral riboflavin had marked motor improvements and an overall alleviation of clinical symptoms.

TBK1 is a key regulatory molecule upstream of OPTN, SQSTM1/p62, and IFR3 in the autophagy and neuroinflammatory pathways that are implicated in ALS. Manipulation of TBK1 might potentially compensate for defects caused by other ALS-associated proteins in these pathways—eg, VCP and UBLQNL2. NEK1 and C21orf2 are known to interact at the protein level and, in addition to TUBA4A, PFN1, NEFH, and PRPH, they represent the building blocks of the cellular scaffold. Administration of small molecules that enhance cytoskeletal integrity could represent a viable therapy for stopping progression or reversing the disease course in patients with these mutations.

**Conclusions and future directions**

ALS research has been largely driven by advances in our understanding of the genetics underlying the disease. This, in turn, has been fuelled by technological developments in next generation sequencing. Since 2014, seven novel genes—MATR3, CHCHD10, TBK1, TUBA4A, NEK1, C21orf2, and CCNF—associated with ALS have been identified using these techniques. However, the precise disease mechanisms attributed to these genes are unclear, and further elucidation from in-vivo and in-vitro functional studies is required. The collective identification of these novel genes is important within the context of other established genes that are associated with ALS to enable investigation of the disease process at the cellular level (figure 2).
<table>
<thead>
<tr>
<th>Gene</th>
<th>Loci</th>
<th>Genetic effect</th>
<th>Familial amyotrophic lateral sclerosis (%)</th>
<th>Sporadic amyotrophic lateral sclerosis (%)</th>
<th>Implicated amyotrophic lateral sclerosis pathway</th>
<th>Disease features†</th>
<th>Other associated allelic disorders</th>
<th>DNA, RNA, and proteins found to interact with target gene¹</th>
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*(Table continues on next page)*
The considerable advances in genetic identification seen in the past decade are likely to continue as whole genome sequencing becomes more accessible. Such progress will facilitate the analysis of larger cohorts leading to a better understanding of the molecular defects that cause motor neuron degeneration. In particular, these techniques will help to identify rare polymorphisms in the non-coding intergenic regions of the genome and structural variants, such as repeat expansions, copy number variants, and indels that might contribute to ALS. The availability of well phenotyped cohorts and efforts in large-scale genomic sequencing are essential to improve our understanding of ALS pathophysiology, and thus, to identify therapeutic targets.
Increased knowledge about the genetic profiles that protect or confer disease risk in patients with ALS will change the way clinical trials are done and how therapy is prescribed to patients. The most important change will be the stratification of patient and control cohorts by genotype, which will increase the success rate of clinical trials. Because ALS is a genetically heterogeneous and complex disease, a personalised medicine approach is emerging, whereby treatment is tailored to the specific mutation that causes disease in an individual patient. Thus, genetic screening for known variants or mutations will be integral to diagnosis, treatment, and prevention of ALS. Many advances have been achieved in the past 5 years, such as the application of gene silencing for SOD1 and C9orf72, the development of viable biomarkers for the diagnosis of patients with ALS who have mutations in those genes, and the evaluation of the efficacy of potential treatments. More breakthroughs are expected to occur in the future when more genes are identified through these large-scale genetic studies.

Contributors
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References