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# Novel Aspects on Motor Neuron Disease: The Recent Genetic Studies on ALS

Junling Wang

## Abstract

At present, with the advanced affordable genetic testing, the rate of discovering amyotrophic lateral sclerosis (ALS)-related genes rapidly increases. These genetic findings provide new insights into therapies that target genetic subset of ALS. However, the research on the genetic and environmental causes of ALS is still in the early stage. In this chapter, we review the current understanding of ALS-related genes and summarize the worldwide ALS distribution feature by the frequency of occurrence in different regions. We summarize the advances in genetic testing and counseling for ALS. Based on the increase in genetic testing, we believe that the ALS patients and families would be benefited from our studies in the near future.

**Keywords:** ALS, genetic frequency features, GWAS, genetic testing, genetic counseling, genetic therapy

## 1. Introduction

Amyotrophic lateral sclerosis (ALS) is an adult onset and generally fatal neurodegenerative disease characterized by progressive weakness and atrophy of voluntary skeletal muscles due to dysfunction and death of upper and lower motor neurons. Onset typically occurs between 60 and 69 years of age, with wide-range severity. About 90% of cases are sporadic amyotrophic lateral sclerosis (SALS), while familial amyotrophic lateral sclerosis (FALS) accounts for the remaining 10% cases [1]. The pathogenesis of ALS remains obscure, but genetic mutations have been accounted for several impaired cellular and molecular mechanisms and, thus, provide clues for potential therapeutic strategies.

The superoxide dismutase 1 (*SOD1*), identified in 1993, was the first gene discovered to be associated with ALS. Subsequently, several gene mutations that have been identified to cause ALS. Till 2018, more than 180 genes have been identified as causative genes or related genes of ALS. Many of these genes are related to metabolism, trafficking of RNA, and chromatin, including *C9orf72*, *TDP43*, *FUS*, *TAF15*, *ELP3*, *ANG*, *hnRNPA1*, and *hnRNPA2B1* [2]. Some genes are involved in conformational instability and aggregation of proteins, such as *SOD1*, *VCP*, *OPTN*, and *UBQLN2*; others are related to axonal and cytoskeletal biology, such as *PFN1*, *DCTN1*, *TUBA4A*, and *EPHA4* [2].

In most cases, FALS is inherited in the dominant pattern and the penetrance is associated with age. It has been observed that the differences of age onset and disease progression within and between ALS families are significant. In addition, some ALS

is recessive inherited, such as *OPTN*, *SPG11*, *FUS*, and *SOD1* (definite, Asp90Ala homozygous mutation), and *UBQLN2 associated ALS* is X-linked dominant inherited. Besides causative genes, multiple genetic variants interact simultaneously to increase ALS susceptibility. Considering oligogenic manner of ALS described by some researchers, many ALS patients may not appear to be familial in a conventional Mendelian manner. Therefore, the oligogenic manner may underlie the apparently sporadic form of the disease [3].

Some ALS caused by specific genetic mutations exhibit unique clinical characteristics. For example, ALS associated with *SPG11* and *ALS3* has clinical features of early onset and slow progression. *SPG11* mutations were identified in autosomal recessive juvenile ALS [4], and the patients with *ALS3* mutations have an early onset of approximately 45 years and the average disease duration about 5 years.

Recently, progress in gene discovery and technology has both complicated and empowered the process of genetic testing options, which may help neurological clinicians and ALS patients to understand the pathogenesis of ALS, and then provide genetic counseling for family members, allow accurate risk assessment, and open the door for genotype-specific treatments. As the genetic basis of the remainder of FALS, and potentially SALS, is unraveled, genetic testing and counseling will become increasingly vital and should be incorporated into the routine management of ALS [4–6].

## 2. Recent advances in ALS gene map

### 2.1 *SOD1*

The superoxide dismutase 1 (*SOD1*), located in 21q22, was discovered in 1993. Up to date, more than 180 mutations have been described to be associated with ALS, while most of these mutations are missense mutations. Its mutation probability accounts for 20% of FALS cases and 1–2% of SALS cases [1, 2, 7, 8].

### 2.2 *C9orf72*

The *C9orf72*, located in 9p21.2, was discovered in 2011. The protein encoded by *C9orf72* is mainly related to autophagy, endosomal transport, and immune function. According to statistics, about 40–50% of FALS and 10% of SALS carried the *C9orf72* expanded alleles. The pathogenic alleles of *C9orf72* may have hundreds or even thousands of the GGGGCC hexanucleotide repeats. A large number of clinical investigations have shown that about 700–1600 GGGGCC hexanucleotide repeats are inserted into the intron located between the two untranslated optional exons 1a and 1b of the *C9orf72* gene [1–3, 9, 10].

### 2.3 *FUS*

The FUS RNA-binding protein (*FUS*) gene, discovered in 2009, was mapped in 16p11.2.

Mutations in *FUS* are observed in 4% of FALS and 1% of SALS. At present, more than 79 mutations have been described, predominantly in the 3' region encoding an arginine/glycine-rich region and a NLS domain (nuclear localization signal). FUS protein, essentially localized in the nucleus, regulates RNA processing, splicing, and mRNA trafficking. Mutant FUS localized to cytoplasmic stress granules (SGs) and interacted with the stress granule protein PABP in an RNA-dependent manner resulting in mislocalization of the wildtype protein to stress granules [7–9, 11].

## 2.4 *CCNF*

*CCNF*, located in 16p13.3, encoding the cyclin F, was first reported in 2016. The mutation of *CCNF* accounts for approximately 4% of FALS and 2% of SALS [7].

*CCNF* protein is a kind of kithe cell cyclin, involved in the regular of cell cycle transitions by activating cyclin-dependent protein kinases. Furthermore, it is the substrate recognition component of the Skp1-cullin-F-box E3 ubiquitin ligase complex. The neurons of the over-expressed mutant *CCNF* showed an increase in protein-labeled proteins, including TDP43. It indicates that mutated-*CCNF* protein interfere the proteasome degradation pathway by using traversing protein abnormalities to mark all proteins or inhibiting transferring transprotein-labeled proteins to proteasome complexes. This finding suggests that the *CCNF* mutation may cause abnormal protein homeostasis, which may be exacerbated by TDP43 protein disease.

Therefore, enhancing protein removal or reducing ubiquitin may be a feasible treatment [1, 3].

## 2.5 *TIA1*

The *TIA1* gene, located in 2p13.3, encodes an RNA-binding protein involved in splicing regulation and translational repression. The mutations in *TIA1* were identified in 2.2% of FALS and 0.4% of SALS [7]. *TIA1* protein is a key component of SGs, cytoplasmic foci sequester untranslated mRNAs upon different types of cellular stress, and the low complexity domain (LCD) region of *TIA1* plays a central role in promoting SGs assembly. A heterozygous founder mutation (E384K) in the LCD was first reported in Swedish/Finnish patients as the cause of Welander distal myopathy (WDM). Recently, a mutation (p.P362L) in *TIA1* affecting a highly conserved residue in the LCD was identified as one cause of ALS/ALS-FTD [12].

## 2.6 *TBK1*

The TANK-binding kinase 1 (*TBK1*) gene, located in 12q14.2, was discovered in 2015 [7]. The protein encoded by this gene is similar to the  $\text{I}\kappa\text{B}$  kinase and can mediate NF $\kappa\text{B}$  activation in response to certain growth factors. The *TBK1* mutations were found in approximately 1% of FALS and 1% of SALS. The clinical phenotypes associated with the *TBK1* mutation are heterogeneous, with different ages at onset, different progressions, and irregular survival times.

Some patients also reported with extrapyramidal, ataxia, or psychosis. Neuropathological examination of central nervous system (CNS) tissues from patients with *TBK1* mutations revealed that SQSTM1/p62- and TDP-43-positive inclusion bodies which can indicate abnormalities in TDP-43 protein aggregation and protein clearance pathways [1, 2, 4, 5].

## 2.7 *TARDBP*

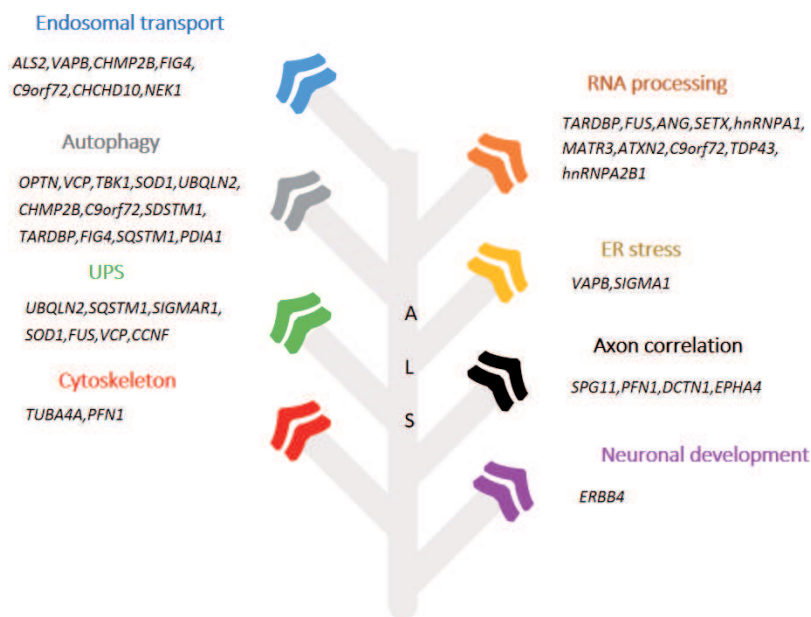
The *TARDBP* (trans-activation element DNA-binding protein), located in 1p36.22, was discovered in 2008 [5].

The *TARDBP* gene mutation was found in 5% of FALS cases and 1% in SALS cases. Till now, more than 50 different mutations have been identified [9]. Except for D169G, a majority of these mutations are located in the 3' region encoding a glycine-rich domain in its product, TDP-43. ALS patients carrying *TARDBP* gene mutations normally exhibit a classical ALS phenotype and rare dementia, they also have earlier disease onset, with upper limb onset being more common and compatible with a longer life. Most of TDP-43 is expressed in nucleus, involved in RNA

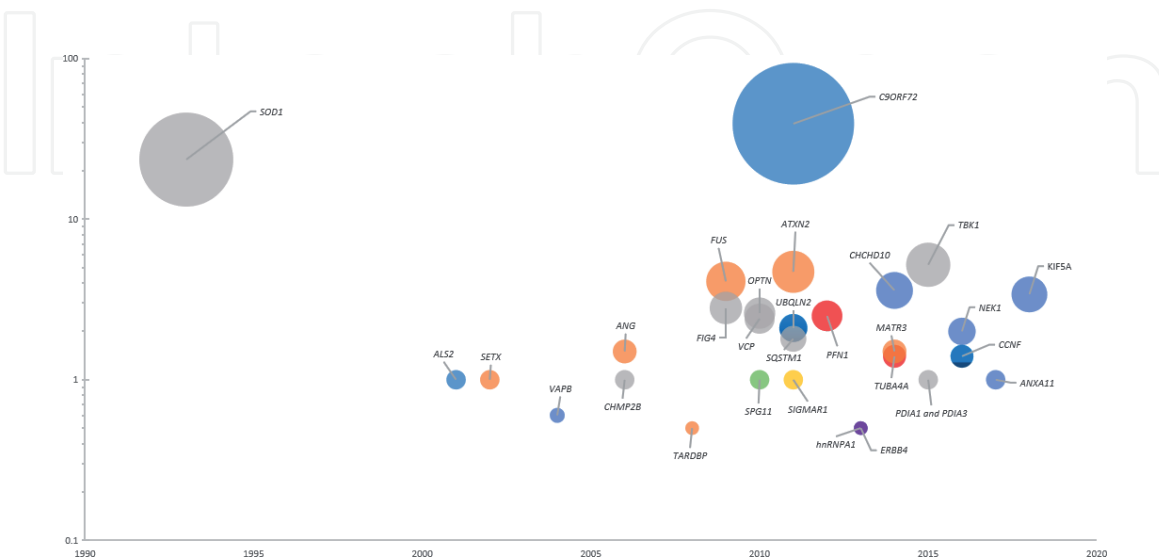
metabolism in many ways—transcriptional regulation, splicing, mRNA stabilization (including its own transcripts), and microRNA processing. TDP43 also regulates axonal transport and neuronal plasticity. In ALS, TDP-43 is often observed in cytoplasm. The pathogenesis of TDP-43 mainly includes cytoplasm construction of high phosphorylation TDP-43 and clearance of nuclear TDP-43 [1, 2, 7, 8].

## 2.8 Pathogenesis of ALS-related genes

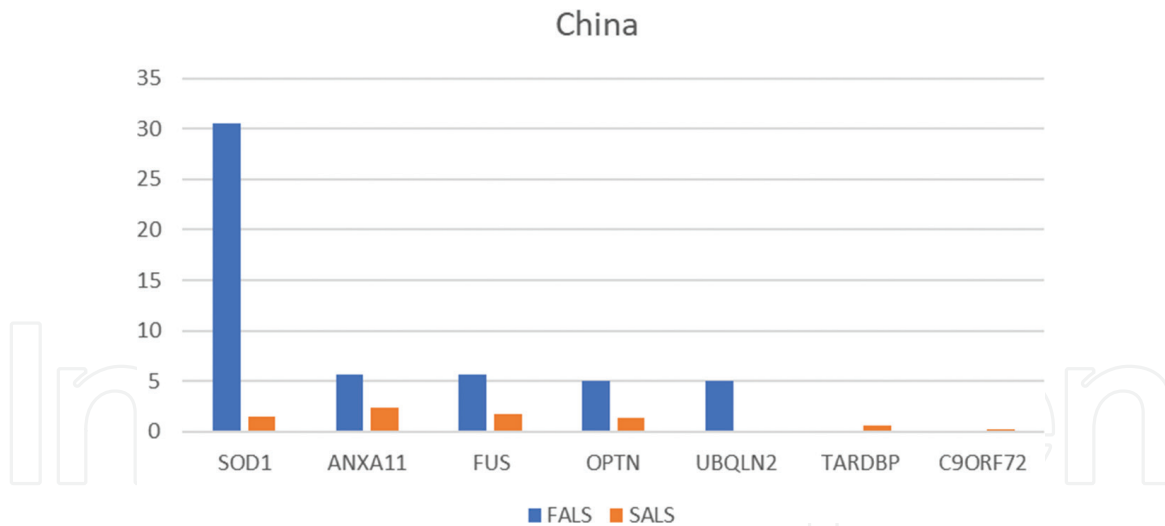
The cellular processes, including RNA processing, protein degradation pathways, ubiquitin-proteasome system (UPS), autophagy, and so on, are all reported related to ALS pathogenesis [1–3, 7–22]. Sorted by the various processes, we summarize the causative genes and genes might increase susceptibility of ALS which impact physiological activities mentioned above (**Figure 1**).



**Figure 1.** Dysfunction cellular processes and related genes contributed to the pathogenesis of ALS.



**Figure 2.** The worldwide frequency of ALS-related genes. The x-axis is the time when genes discovered. The y-axis is the logarithms of the mutation frequency of genes in ALS. The mutation frequency of C9orf 72, CHCHD10, CCNF, KIF5A, and ANXA11 are only within FALS. Where gene frequency was not available (ALS2, SETX, SIGMAR1, and PDIA1), one “circle size” equivalent to 1% is given for illustrative purposes.



**Figure 3.** ALS mutation genes frequency among FALS and SALS in Mainland China. The y-axis means the percentage of different mutation genes.

## 2.9 Advances on gene discovery and frequency

We describe the worldwide ALS distribution feature by frequency of occurrence in different regions (**Figure 2**) [1–3, 7–9, 11, 14, 23, 24]. We summarize ALS mutation genes frequency according to the researches in Mainland China (**Figure 3**).

## 3. GWAS on ALS

Recently, the studies on ALS have shown the development trend of the blowout with the technology improving, however, no longer limited by technical condition, the number of newly discovered ALS-related gene did not meet expectation. It indicates a shift in the genetic pathway that multiple genetic variants and environmental factors may interact simultaneously to increase ALS susceptibility. On the basis of the fact that sporadic form apparently accounts for high rate of ALS and the hypothesis that ALS may not appear to be familial in a conventional Mendelian manner, a new research method, genome-wide association study (GWAS), is applied to the research of ALS.

Since GWAS was applied to complex diseases, remarkable achievements have been made in certain fields. It is also hoped that in this way, we will be able to find the risk factors of ALS [25–27].

### 3.1 SNPs and GWAS

The International HapMap Project, which began in 2002, mapped the single-nucleotide polymorphisms (SNPs) haplotypes of the human genome from four major populations in the world and promoted the development of GWAS. At the same time, the rapid development of high-density and high-throughput genotyping technology, which can detect hundreds of thousands of SNPs in a single reaction, makes it possible to systematically screen mutations associated with complex diseases throughout the genome. Unlike previous candidate gene studies, GWAS does not need to build any assumptions based on disease pathophysiology prior to the study and can relatively be an unbiased screen for almost all common mutations in the genome. At present, some risk factors of complex diseases, such as age-related macular degeneration, diabetes mellitus, breast cancer, and so on, have been initially identified by GWAS.

### 3.2 ALS GWAS boot

Schymiek et al. firstly reported GWAS in SALS in February 2007 [28]. A total of 276 patients and 271 controls with white American ancestry were recruited in this research. They used a chip to detect 555,352 SNPs and found 34 of the most relevant SNPs by association analysis. For negative results, they elucidated that SALS might contain a group of diseases with similar clinical manifestations like FALS, each of which is determined by different mutation sites, and that different diseases and mutation sites may interfere with GWAS's shooting out of susceptible genes. Among the 34 SNPs, there was an overexpression of genes associated with cytoskeletal actin regulation. For example, the *KIAA1721* gene of rs11099864 and the *FMN2* gene of rs1037666 had a homologous region that played an important role in the regulation of cytoskeletal actin. The most closely related rs4363506 of 34 SNPs was located in the *DOCK1* gene, which plays an important role in nerve growth. Although no disease-susceptible gene was found, the study identified possible SNPs and published all the results, which facilitated subsequent large-scale SALS GWAS studies.

Recently, a series of ALS GWAS studies have been published and found several potential risk genes [29–32]. However, the results of these studies are different with the same ideas and methods. The biological process of some candidate genes is unclear, and the evidence needs to be supplemented.

## 4. Genetic testing

Gene testing helps ALS patients and families enhance their understanding on the condition and information requested in genotype-specific treatments. Although ALS patients desire access to genetic testing, genetic advances have been slow to reach the clinical care of the ALS patient. In recent years, the landscape of genetic testing and genetic counseling for ALS has been rapidly transformed with the identification of novel genes and the advent of next-generation sequencing technology.

### 4.1 Genetic testing options

As with all clinical testing, genetic risk assessment, including family history and pedigree analysis, and pretest counseling, helping patients anticipate the possible impact of genetic testing on themselves and their family members, are necessary for patients before genetic testing.

Currently available genetic testing options for ALS include Sanger sequencing for traditional simple mutations, assays for the *C9orf 72* repeat expansion, next-generation sequencing panels, whole-exome sequencing, and whole-genome sequencing.

### 4.2 Post-test counseling

Regarding the positive result, specific mutation, genotype-phenotype correlations, family history, and inheritance pattern should be thoroughly analyzed. Meanwhile, implications and risks for family members, including offspring and siblings, and theories about why the disease occurs also should be reviewed and addressed. For the reported definite pathogenic mutations, clinicians should provide information and hope about the potential genetic therapies in the future.

### 4.3 Presymptomatic testing

To increase certainty, make health or lifestyle choices, and make decisions about family planning, the presymptomatic testing could be conducted. According to the guidelines for presymptomatic genetic testing in other neurodegenerative diseases such as Huntington disease and Alzheimer disease, ALS should be tailored as following: pretest genetic counseling, baseline neurologic and cognitive assessment, psychological evaluation, in-person disclosure, presence of support person, and posttest genetic counseling. Most of important, presymptomatic testing should be offered to adult first-degree relatives of ALS patients with established mutations after written informed consent obtained [4].

## 5. Gene therapy

With the exception of riluzole, an anti-glutamatergic agent which was shown to prolong survival for 2–3 months by blocking the presynaptic release of glutamate, and edaravone, an antioxidant which was shown to decrease the rate of patient immobility, no effective treatment is currently available for ALS that can stop or reverse the disease progression.

Gene therapy is a promising therapeutic approach for ALS since it can be used to deliver “gene drugs,” encoding for blocking the novel gene expression, antiapoptotic proteins, and for neurotrophic factors, to the motor neurons crossing the blood-brain barrier specifically to prevent further motor neuron degeneration and to preserve the function of remaining motor neurons.

Here, we are to illustrate some examples of each therapeutic strategy for describing the present status and advance of gene therapy treatment.

### 5.1 SOD1

The neurotoxicity of mutant SOD1 is related to the dose of the toxic protein through multiple pathological mechanisms. A potential therapeutic approach to SOD1-related ALS is to block the expression of the toxic SOD1 that could cause motor neuron degeneration [33]. This therapy option which is more worthy of attention is that it possibly avoids and decreases potential influence in downstream pathological cascades. Recently, the studies mostly focus on antisense oligonucleotides and RNA interference which are both to block gene expression through enhancing the degradation of RNA.

#### 5.1.1 Antisense oligonucleotides in models and human

In animal models of SOD1-associated ALS, antisense oligonucleotide treatment significantly delayed disease onset, improved neuromuscular function, and prolonged survival.

The first clinical trial of antisense oligonucleotide treatment in human beings had favorable safety outcomes, and now the clinical trial to assess the safety, tolerability, and pharmacokinetics of a second generation SOD1 antisense oligonucleotide is in progress (ClinicalTrials.gov, NCT02623699) [34].

#### 5.1.2 Short hairpin RNA (shRNA) treatment in mutant SOD1 ALS models

According to literature, in SOD1<sup>G93A</sup> mice, reduction of human SOD1 expression can significantly slow ALS progression and extend survival by using a single



peripheral injection of an adeno-associated virus serotype 9 (AAV9) encoding shRNA [35].

While, in a recent study reported, SOD1 expression in the motor cortex of P70 *SOD1<sup>G93A</sup>* models was selectively silenced by delivery of AAV9-SOD1-shRNA. As a result, not only the ALS progression was slowed and the survival was extended significantly, but also the survival of spinal motor neurons was significantly enhanced [36].

### *5.1.3 miRNA treatment in mutant SOD1 ALS models and healthy nonhuman primates*

In a study, scientists reported a new method that systemically delivered drug based on an artificial microRNA. In the *SOD1<sup>G93A</sup>* mice, this drug delayed ALS onset, prolonged the survival, and significantly preserved muscle strength and motor and respiratory functions. Notably, the research of this drug has been conducted in nonhuman primates, and the result showed that *SOD1* expression in lower motor neurons was safely blocked [37].

## **5.2 C9orf72**

Similar therapeutic approach targeting C9orf72 for ALS is also in development. The toxicity of mutated C9orf72 is imparted by the formation of nucleolar RNA foci that sequester important RNA-binding proteins and by the generation of toxic dipeptide repeat (DPR) proteins.

The C9orf72 hexanucleotide repeat expansion (HRE) of GGGGCC DNA and RNA enables the formation of complex structures including G-quadruplexes. Because the Guanosine-rich DNA and RNA sequences are prone to formation of G-quadruplexes, a stable four-stranded structure present within ribosomal DNA sequences, transcription start sites, the promoter and untranslated regions of mRNA, human telomeric DNA sequences. It may play an important role in various cellular processes such as telomere maintenance, ribosome biogenesis, gene replication, transcription, and translation. Therefore, both C9orf72 HRE DNA and RNA may contribute to the pathogenesis of ALS/FTD disease through a mechanism associated with their structure polymorphism. Presently, based on the above mechanism, two strategies including antisense-mediated interventions and small-molecule-based approach have been developed to interfere with neurodegenerative diseases associated with G-quadruplexes [38].

### *5.2.1 Antisense oligonucleotides in mutant C9orf72 ALS models*

A recent study reported that the RNA foci and DPR proteins were reduced significantly in mutant C9orf72 ALS mice by a single-dose injection of antisense oligonucleotides to reduce C9orf72 RNA repeats, and after 6 months of treatment, the motor function was also preserved [39].

### *5.2.2 Small-molecule ligands targeting the G-quadruplex structure in mutant C9orf72 cells*

The small-molecule ligands, such as porphyrin, acridine, pentacridium, telomestatin, naphthalene diamide, and bisquinolium, directly target and bind to the G-quadruplex structure and selectively modulated the function of the G-quadruplex. For example, TMPyP4, a cationic porphyrin, can bind and disrupt the secondary structures of C9orf72 HRE and even damage its interactions with hnRNPA1 and ASF/SF2 proteins [40].

Similarly, some studies also showed that three small-molecule ligands can bind G-quadruplex and decreased RNA foci and RNA translation in both cultured cells and patient-derived neurons [41].

### 5.3 Others

TBK1 is a key regulatory molecule upstream of OPTN, SQSTM1/p62, and IRF3 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—for example, VCP and UBQLN2. 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 [4–6].

## 6. Conclusion

Nearly a decade ago, the only way to test ALS-related gene was SOD1 sequencing, whereas clinicians now have a wide availability of testing options already. Whole-exome sequencing is current standard in most related searches. However, the factors such as high rate of incomplete penetrance in ALS, few large pedigrees, and short survival of patients lead to the discovery of ALS-related genes worse than expected and the identification of susceptible mutations limited.

Although many known ALS-related genes' structural characteristics and roles have been discovered, which have highlighted critical processes, pathways, and intracellular localizations of dysregulation, there are still many reported variants with uncertain significance. Further functional studies are needed to clarify the pathogenesis of these genes. Till now, more people believe that ALS is the result of interaction between multiple genes that each increases the susceptibility of the disease, but does not initiate the pathogenesis alone. So, we need to do more research on oligogenic ALS cases. Most importantly, with the improvement of understanding of ALS genetics, we will have more opportunities to develop meaningful therapies.

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