Genetic factors for survival in amyotrophic lateral sclerosis: an integrated approach combining a systematic review, pairwise and network meta-analysis

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Abstract

Background: The time of survival in patients with amyotrophic lateral sclerosis (ALS) varies greatly, and the genetic factors that contribute to the survival of ALS are not well studied. There is a lack of a comprehensive study to elucidate the role of genetic factors in the survival of ALS.

Methods: The published studies were systematically searched and obtained from PubMed, EMBASE, and the Cochrane Library without any language restrictions from inception to Oct 27, 2021. A network meta-analysis for ALS causative/risk genes and a systematic review and pairwise meta-analysis for other genetic modifiers were conducted. The PROSPERO registration number: CRD42022311646.

Results: A total of 29,764 potentially relevant references were identified, and 71 papers were eligible for analysis based on pre-decided criteria, including 35 articles in network meta-analysis for 9 ALS causative/risk genes, 17 articles in pairwise meta-analysis for four genetic modifiers, and 19 articles described in the systematic review. Variants in three genes, including ATXN2 (HR: 3.6), C9orf72 (HR: 1.6), and FUS (HR:1.8), were associated with short survival of ALS, but such association was not identified in SOD1, TARDBP, TBK1, NEK1, UBQLN2, and CCNF. In addition, UNC13A rs12608932 CC genotype and ZNF521B rs2275294 C allele also caused a shorter survival of ALS; however, APOE ε4 allele and KIFAP3 rs1541160 did not be found to have any effect on the survival of ALS.

Conclusions: Our study summarized and contrasted evidence for prognostic genetic factors in ALS and would help to understand ALS pathogenesis and guide clinical trials and drug development.

Keywords: Amyotrophic lateral sclerosis, Genes, Variants, Modifier, Survival

Background

Amyotrophic lateral sclerosis (ALS) is one of the most devastating neurodegenerative diseases, characterized by degeneration of the upper and lower motor neurons.

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to be associated with a risk of ALS [4]. Some of them also were reported to have a disease modification effect, which means they are always linked to a difference in the clinical phenotype of ALS, often survival time. As we all know, aging, environmental and genetic factors play an essential role in the development of ALS. However, as a rare disease, we still don’t have an excellent strategy for preventing it from developing due to the limited knowledge of its etiology. Hence, more attention has been paid to the associated factors that affect the survival time. In our recent study, twenty-five non-genetic factors associated with ALS survival were identified, such as age at onset, onset site, the time between onset and diagnosis, et al. [5]. However, these non-genetic factors associated with ALS survival could be affected by confounding factors. Therefore, other unbiased methods exploring clinical outcomes are in the ascendant, such as the Mendelian Randomization study, which focuses on the actual causal effect on diseases or their phenotype by applying genetic variants. Till now, the genetic factors that contribute to the survival of ALS are not well studied and remain to be explored. Previous researches have reported that some potential loci may modify the survival of ALS, such as \textit{UNC13A} rs12608932 and \textit{CAMTA1} rs2412208 [6–8]. In addition, the causative ALS genes (\textit{C9orf72}, \textit{SOD1}, \textit{FIIS}, \textit{TARDBP}) might modify the disease course as well [9–13]. Yet, due to the limited sample size of patients with rare variants in ALS causative genes, the different genetic backgrounds, or other factors, there are inconsistencies in those results and a lack of a comprehensive review to elucidate the role of genetic factors in the survival of ALS. Consequently, our study tries to clarify the genetic factors that affect the survival of ALS by an integrated approach combining a network meta-analysis (NMA) on ALS causative/risk genes and a pairwise meta-analysis on other modified loci along with a systematic review.

\textbf{Methods}

Different genetic variants are considered as different interventions in this study, so we employed a NMA following the International Society for Pharmaepidemiology and Outcomes Research (ISPOR) guidelines [14] and reported it using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for NMA [15]. In addition, the report of the pairwise meta-analysis for other modified loci was followed by the recommendations of the PRISMA (2009) guidelines [16]. The protocol for this study was registered with PROSPERO, registration number: CRD42022311646.

\textbf{Search strategies and selection criteria}

The published studies were systematically searched and obtained from PubMed, EMBASE, and the Cochrane Library without any language restrictions, by using the term: “\{gene* OR geno* OR variant* OR mutation OR haplotype* OR polymorphism* OR SNP OR Allel*\} AND \{(prognosis* OR progress* OR survival OR outcome OR mortality OR death) AND ((amyotrophic lateral sclerosis) OR (motor neuron disease) OR (Lou Gehrig’s disease) OR (Gehrig Disease))\}”. Reference lists of full review articles were also reviewed to search for additional articles. All randomized clinical trials (RCTs), quasi-RCTs, and observational studies were eligible, but no RCTs were identified. The articles were updated to October 27, 2021. According to previous survival research in ALS, survival was defined as the time between the onset of symptoms and noninvasive ventilation (NIV) for more than 23 hours per day, or tracheostomy or death [5, 17, 18]. The inclusion criteria are as follows: (1) assessed the association between present or absence with different genetic loci and survival time from the onset in patients with ALS; (2) had reported a hazard ratio (HR) and 95% confidential intervals (CI) for patients with genetic mutations or Kaplan-Meier plots from which we can estimate the HR and 95% CI; (3) abstract, reviews, letters without original study, secondary studies and studies that HR or 95% CI was unavailable in papers, excluded from the analysis; and (4) full papers published in English.

\textbf{Data collection}

First author’s name, year of publication or online, patients’ nation, number of patients, type of disease, diagnosis criteria, age at onset and gender distribution of patients, median survival time, and HR with their 95% CI were extracted. When HR was unavailable directly from the articles, the Kaplan-Meier curve was evaluated by Engauge Digitizer version 12.1, and HRs and 95% CI were estimated using Richard Steven’s excel workbook [19]. Data from multi-arm studies were extracted following the tutorial by B. S. Woods [20]. Extracted data from included studies by two independent reviewers to reduce bias and a third one verified the data to avoid repeat inclusion.

\textbf{Appraisal of methodological quality}

Only observational studies were included for analysis in this study, and their quality was appraised with the Newcastle-Ottawa Scale (NOS) [21]. As for publication bias, the assessment was conducted only when at least ten studies were available for the same factor by Begg’s test [22]. In addition, to overcome overestimation and mask funnel plot asymmetry induced by some multi-arm studies, we plotted data points corresponding to the study-specific basic parameters (different known ALS gene mutation comparisons with a common comparator). In each study, we used the control group (absence with
known ALS gene mutation) as the common comparator, if this was unavailable, we used the same comparator (always, group with \textit{SOD1} mutation) against the remaining groups.

Synthesis of included studies
HR was used for each dichotomous outcome, and traditional pairwise meta-analyses were performed for studies, which directly compared different groups. And from known ALS causative/risk genes variants, outcome data were pooled using NMA models through the R 4.1.1 software. A network relationship diagram was drawn, among which parameters such as each node and line thickness respectively represent a certain gene’s variants and the researches sizes were considered from the included studies. The model fit was assessed using three criteria based on the deviance and node-based residuals. We evaluated the inconsistency, which means the difference between the pooled direct and indirect evidence of a particular comparison, using inconsistency factors based on a modified back-calculation approach [23]. In addition, we performed the rankogram plots to show the probability of each genetic mutation [24]. The remaining modification loci were pooled analyzed under meta-analysis by random-effect model if analyzed in more than two studies (>3 studies); otherwise they were conducted for systematic review if analyzed in less than three studies (<3 studies) (including SMN2 deletion, SMN1 and SMN2 copy numbers, \textit{CX3CR1} V249I, \textit{CX3CR1} T280M, haplotype in \textit{CX3CR1}, \textit{ABCC8} rs4148646, \textit{KCNJ11} rs5219, \textit{LXR}\textit{s} rs2279238, \textit{LXR}s rs7120118, \textit{LXR}s rs35463555, \textit{LXR}s rs2695121, \textit{PRG}\textit{N} rs9897526, \textit{PRG}\textit{N} rs34424835, haplotype in \textit{PRG}\textit{N}, \textit{HTR2B} rs10199752, \textit{STMN2} CA repeat, \textit{BDFN} C270T, \textit{C7} gene rs3792646, \textit{PON1} rs854560, \textit{PON1} rs6626, \textit{NIPA1} polyalanine repeat expansions, \textit{SLC11A2} rs407135, \textit{CAMTA1} rs2412208, \textit{GSTM1} rs1695, \textit{CNTF}, \textit{HLA-DRA} or \textit{HLA-DRB5} rs9268856, rs4623951, \textit{EPHA4} rs6436254, and \textit{ID}\textit{E} rs139550538). All computations were conducted on R (V4.1.1) package “\textit{gemtc},” "\textit{rjags},” and STATA/MP 16.0.

Results

Literature results
We identified 29,764 potentially relevant references from PubMed, EMBASE, and Cochrane Library and three additional records from reference lists (Fig. 1). Of these records, only 71 articles met the inclusion criteria. Finally, we included 35 articles using network meta-analysis for variants in nine ALS causative/risk genes (Additional file 1: Table S1) [9–13, 25–54], 17 articles using pairwise meta-analysis for four modification loci in ALS-related genes (Additional file 1: Table S2) [6–8, 55–68], and 19 articles using systematic review according to pre-decided criteria (Additional file 1: Table S3) [7, 69–87]. The characteristics of the 71 included trials are summarized in Additional file 1: Table S1-S3 and the quality of 52 articles conducted by network meta-analysis and pairwise meta-analysis was shown in Additional file 1: Table S4.

Variants in nine ALS causative/risk genes by NMA
A total of 35 articles including 37 trials with nine known ALS causative/risk genes were involved in this network meta-analysis, which is shown in Fig. 2. \textit{C9orf72} was the most frequently investigated regimen with 40 comparisons (Additional file 1: Table S1). It was found that ALS patients carrying \textit{C9orf72} repeat expansion would have a poor prognosis compared to those without known ALS causative/risk genes variants and the HR was 1.6 (95%CI:1.4–1.9). In addition, patients with other two genes variants, \textit{ATXN2} and \textit{FUS}, presented a short survival time compared to those without known ALS causative genes variants (HR:3.6 or 1.8, respectively). However, \textit{SOD1}, \textit{TARDBP}, \textit{TBK1}, \textit{NEK1}, \textit{UBQLN2}, and \textit{CCNF} did not affect the survival of ALS. The detailed features for the risk genes variants, outcome data, and \textit{SOD1} polyQ were identified. The detailed results are illustrated in Fig. 3.

The rankogram plots are shown in Fig. 3. According to the surface under the cumulative ranking curve (SUCRA), \textit{ATXN2} polyQ repeats (≥31) had the largest probability of being the worst genetic variants (SUCRA = 86.3%, data not shown). \textit{TBK1}(70.0%), \textit{FUS} (69.5%), \textit{CCNF} (67.7%), and \textit{C9orf72} (63.4%) had a similar probability of being the worst. The result of pairwise comparison among these genes is shown in Fig. 3.

Furthermore, there is no significant difference between direct and indirect meta-analysis (Additional file 1: Fig. S1) and the heterogeneity between studies is also acceptable (Additional file 1: Fig. S2-S12), indicating the results of NMA are reliable. As for publication bias, we did not find significant funnel plot asymmetry in studies reporting \textit{C9orf72} expansion in patients with ALS compared to those without ALS-related mutation (Additional file 1: Fig. S13).

Four modification loci in ALS-related genes by pairwise meta-analysis
Four modification loci in ALS-related genes, \textit{APOE} e4 allele, \textit{KIFAP3} rs1541160, \textit{UNC13A} rs12608932, and \textit{ZNF512B} rs2275294, were available for pairwise meta-analysis (Additional file 1: Table S2). In this study, \textit{UNC13A} rs12608932 CC (recessive model) and
ZNF512B rs2275294 CC+CT (dominant model) could accelerate the death of ALS patients (HR 1.18 and 1.97, respectively, Fig. 4). However, APOE ε4 allele, KIFAP3 rs1541160 CC or CT (additive model) did not show any modificatory effect on ALS survival (Fig. 4). And no obvious heterogeneity was found.

Other loci in ALS-related genes by systematic review

The other loci in ALS-related genes, which were not suitable for pool analysis, were reviewed systematically and shown in Additional file 1: Table S3. We found the minor allele carriers of CX3CR1 V249I, KCNJ11 rs5219, LXRα rs2695121, PRGN rs34424835, HTR2B rs10199752, PON1 rs662, SLC11A2 rs407135, CAMTA1 s2412208, and IDE rs139550538 might have shorter survival than that without minor allele carriers, but ABCC8 rs4148646 GG, KCNJ11 rs5219 TT, HTR2B rs10199752 AA, and C7 gene rs3792646 AA might be related to more prolonged survival. Additionally, SMN1 and SMN2 copy numbers, and the remaining genes on display did not show any modificatory effect on ALS survival. However, there were not enough articles for meta-analysis.

Discussion

Genetic factors play a pivotal role in the pathogenesis and phenotypic modification of ALS. How the genetic factors affected the survival of ALS was largely unknown yet, especially for variants in the ALS causative genes, in consideration of the limited sample with genetic mutation. This study is the first systematic analysis for the effect of comprehensive genetic factors on the survival of ALS. Using NMA and pairwise meta-analysis, we found three genes, including ATXN2 polyQ, C9orf72 repeats, and FUS variants, and two genetic modifiers, ZNF521B rs2275294 C allele and UNC13A rs12608932 CC genotype, were associated with short survival of ALS.

This current study provided robust evidence that genetic factors affected the survival of ALS. For NMA, among the nine ALS causative/risk genes involved, we found C9orf72, ATXN2, and FUS were associated with
much shorter survival. Ataxin 2 is a protein-coding gene and the N-terminal region of this protein contains a polyglutamine tract of 14-31 residues that can be expanded in the pathogenic state to 32-200 residues. The long trinucleotide repeats expansions (≥36) in ATXN2 have been known to be related to spinocerebellar ataxia type 2 (SCA2) [108], but the intermediate length expansions (27-33 repeats) were also discovered to increase susceptibility to ALS [88], not only in FALS but also in SALS [109]. Meanwhile, another study also reported that ATXN2 polyQ may render C9orf72 repeat expansion carriers more susceptible to ALS [110]. It was also associated with a more severe phenotype and a worse prognosis of ALS, causing a significantly shorter survival (1.2 vs. 4.2 years) [26]. In this study, we found it had the most significant probability of becoming the genetic background with the worst prognosis for ALS (HR=3.6). Ataxin-2 plays a critical role in the normal physiological functions of cells, including RNA processing, receptor endocytosis, the formation of stress granules, and induction of aberrant TDP-43 cleavage [93]. In ALS, it altered protein homeostasis and RNA metabolism, leading to neurotoxicity [1, 94]. Motor neurons in this condition may degenerate faster than those without ATXN2 polyQ expansion or with other genetic variants. Therefore, several gene therapies targeted for ATXN2 used in cell or ALS animal models to prevent or delay its progression were reported [111].

Thanks to advances in the next-generation technology, C9orf72 GGGGCC (G4C2) hexanucleotide repeat expansion was identified as the most common mutation in Europe ALS and the second most common mutation in Asia ALS [95]. Hence, whether the clinical studies are based on genetics and biomarkers, or the basic research based on pathogenies mechanisms or therapeutics, C9orf72 was the most studied gene in the ALS research field in the last ten years. Although healthy individuals can have from 2 to 25 G4C2 repeats, ALS or FTD patients harbor hundreds to even thousands of these repeats [112, 113]. Furthermore, it is involved with RNA foci-mediated toxicity, dipeptide repeat protein (DPR)-mediated toxicity and/or loss-of-function due to reduced levels of C9orf72 protein [96]. Here, after synthesizing a total of 40 comparisons, we found C9orf72 expansion was also associated with shorter survival (HR:1.6, 95%CI [1.4, 1.9]). In addition, cases with C9orf72 expansion may have a more rapid rate of cognitive decline and a higher risk of developing FTD [114], which were predictors for poor

![Diagram](image-url)

**Fig. 2** Network of analyzed comparisons. Each circle corresponds to a regimen included in the analysis. “none” means that there were no known ALS genetic variants, and the others mean that there were corresponding genetic variants shown in the circle. Each line represents comparisons between regimens, with the thickness corresponding to the number of within-trial comparisons.
Table 1  The characteristics of genes included in network meta-analysis

| Gene     | Full name          | Location | Category in ALS | Proportion of patients with ALS | Common mutations in ALS | Possible pathogenesis                                                                 | Phenotype              | Total HR (95% CI) |
|----------|--------------------|----------|-----------------|---------------------------------|-------------------------|--------------------------------------------------------------------------------------|------------------------|------------------|
| ATXN2    | Ataxin 2           | 12q24.12 | Clinical modifier | <1% in northern European ancestry [88, 89], about 2% in French/French Canadian [90], about 2.5% in Italian [91], < 1% in Turkish [92] and in Chinese [93]. | CAG repeat size ≥ 31 | neurotoxicity caused by prion-like self-assembly and propagation of mutant or misfold protein [1, 94] | Mainly spinal onset | 3.6 (1.1, 12)   |
| C9orf72  | C9orf72-SMCR8 complex subunit | 9p21.2 | Definitive ALS gene | FALS 33.7%, SALS 5.1% in European, FALS 23%, SALS 0.3% in Asian [95]. | GGGGCC hexanucleotide repeat expansion usually > 30, even > 1000 | RNA foci-mediated toxicity; dipeptide repeat protein (DRP)-mediated toxicity, and/or reduced levels of C9orf72 protein [96] | Mainly spinal onset, always with FTD | 1.6 (1.4, 1.9) |
| SOD1     | Superoxide dismutase 1 | 21q22.11 | Definitive ALS gene | FALS 14.8%, SALS 1.2% in European, FALS 300%, SALS 1.5% in Asian [95]. | A4V, I113T, G41A, A4T, G37R, D90A, D101N, E100G, A140A, D76Y, E21G, H46R, I149T, L106V, L144F, et al | autophagy, mitophagy, and neuroinflammation by mutant or misfold protein aggregates due to decreased SOD1 enzymatic activity [1, 97] | Mainly spinal onset | 0.85 (0.70, 1.0) |
| FUS      | Fused in sarcoma    | 16p11.2  | Definitive ALS gene | FALS 2.8%, SALS 0.3% in European, FALS 64%, SALS 0.9% in Asian [95]. | P525L, R495X, R521H, R521C, G504WfsX12, et al | a toxic gain-of-function due to FUS aggregation and/or a loss-of-function resulting from cytoplasmic mis-localization of FUS and subsequent loss of nuclear function [1, 98] | Mainly spinal onset, early-onset | 1.8 (1.1, 2.9) |
| TARDBP   | TAR DNA binding protein | 1p36.22 | Definitive ALS gene | FALS 4.2%, SALS 0.8% in European, FALS 15%, SALS 0.2% in Asian [95]. | A382T, A382T, G295Q, G348C, M337V, et al | neurotoxicity and motor neuron caused by degeneration dysregulation of transposable elements due to TDP-43 loss-of-function [1, 99] | Mainly spinal onset | 0.77 (0.61, 1.0) |
| TBK1     | TANK binding kinase 1 | 12q14.2  | Definitive ALS gene | About 2.8% of ALS patients [100] | T79del, G272_L331del, 690-713del, et al | autophagy, mitophagy, and neuroinflammation due to decrease Tbk1’s kinase activity [101] | Mainly spinal onset | 2.4 (0.39, 14.0) |
| NEX1     | NIMA related kinase 1 | 4q33     | definitive ALS gene | About 3% of ALS patients [102] | M545T, R261H, et al | impaired function for DNA damage repair [103] | NA | 1.2 (0.49, 2.9) |
| UBIQLN2  | Ubiquilin 2         | Xp11.21  | Definitive ALS gene | rare [104] | P497H, P506S, T487T, T487T, et al | autophagy, mitophagy, and neuroinflammation by protein blocked protein degradation [105] | Mainly presence with FTD | 0.98 (0.40, 2.5) |
### Table 1 (continued)

| Gene | Full name | Location | Category in ALSod | Proportion of patients with ALS | Common mutations in ALS | Possible pathogenesis | Phenotype | Total HR (95% CI)<sup>a</sup> |
|------|-----------|----------|-------------------|---------------------------------|-------------------------|----------------------|----------|--------------------------|
| CCNF | Cyclin F  | 16p13.3  | Strong evidence   | rare [106]                      | A74T, E528Q, E624K et al | neurotoxicity and motor neuron degeneration by defective protein degradation systems and the pathological accumulation of a protein involved in RNA processing and metabolism [107] | NA       | 2.9 (0.19, 45.0)          |

<sup>a</sup> Total HR (95%CI) were calculated in this study

ALSod: Amyotrophic Lateral Sclerosis online Database [4]. NA not Available
prognosis for ALS as well [5]. So far, gene therapy targeting C9orf72 has been carried out in preclinical studies [115, 116], and these methods are promising approaches for future in vivo studies.

SOD1, FUS, and TARDBP, the other three common ALS causative genes, usually present as missense variants. When all the reported mutation sites were analyzed together, we found only FUS would shorten the survival time of ALS. However, we could not ignore that different variants on these genes have different effects on ALS survival. Based on previous genetic studies, we summarized the characteristics of several common variants in these genes in Additional file 1: Table S5 [117–119]. The most significant heterogeneity may exist in SOD1 with more than 150 ALS-associated SOD1 variants described. SOD1 was believed to cause ALS through toxic gain of function caused by aggregation of misfolded SOD1 [1, 97]. Variants with different influences on survival are usually located in different domains and are more likely to have a strikingly different effect on protein structure and function. For example, SOD1 A4V and SOD1 P525L associated, with the shorter and significantly longer duration, respectively, were identified not only in Caucasians but also in Asians. Our recent cohort study has yielded similar results [13]. Thus, the results obtained in the current study may be due to a mixture of different variants in SOD1. There, it does not mean that SOD1 variants do not affect the survival of ALS, for individuals, specific variants should be identified. Further, we found a similar but slight difference from a meta-analysis of published FUS-ALS cases [119]. It was found to have a different duration from onset to the severe event among FUS P521L, FUS P552L, frameshift/truncation, and the remaining variants in FUS [119]. However, there did not seem to be a mutation in FUS reported that would prolong the survival of ALS (Additional file 1: Table S5) [11–13, 119]. Taken together, it appears that genetic testing of FUS is indicated in patients with shorter disease duration. TARDBP gene encoded TDP-43, a DNA-/RNA-binding protein normally localized to the nucleus [120], which is also the most widespread and pathologic hallmark in the ALS/FTD spectrum [94]. Although TARDBP did not get a definitive positive result in this study, it seems tempting to suggest that TARDBP-ALS cases might have a better prognosis because the HR was 0.77 and 95% CI was 0.61 to 1. Moreover, there was no shortage of reports of TARDBP-ALS cases that have survived for decades [12]. Similarly, there are differences in the impact of different variants on the survival of ALS.

However, we did not find TBK1, NEK1, UBQLN2, and CCNF were associated with survival of ALS either. Maybe there were too few studies or limited patients with variants in these genes to reach the significant difference. The features for these genes were also shown in Table 1. It must be emphasized that those genes included in NMA have been regarded as ALS risk genes with strong evidence or above, but some of the variants in them might not be of demonstrated pathogenetic significance. For instance, most pathogenic variants identified in TBK1 are concentrated within the kinase and the coiled-coiled domains [121], which usually were loss-of-function types, while for some missense variants (such as p.K291E, p.L306I, p.H322Y, p.T3221I, p.R444Q, and p.A535T) may need more functional studies to research their pathogenicity [122]. And NEK1 missense variants confer risk of developing ALS is also a matter of debate [123], the similar condition exists in other genes as well. While repeat expansions in genes are more susceptible to reaching the statistical significance threshold. This limit due to our methods may have an impact on the results.

In addition, four genetic factors were studied by pairwise meta-analysis. Consistent with most previous studies [6, 8, 59, 60, 124], UNC13A rs12608932 CC was a predictor of poor survival in ALS. The rs12608932 in UNC13A is associated with ALS/FTD susceptibility [125] and may indicate poorer cognitive functioning, higher rates of behavioral impairment, and higher rates of FTD [60]. A previous meta-analysis for a single factor has already shown this effect [126]. Therefore, this genotype may function as a prognostic indicator and could be used to define patient endophenotypes in clinical trials. Although the mechanisms by which the CC genotype of rs12608932 in UNC13A significantly decreased the survival time of ALS patients was not entirely clear, the very recent studies found UNC13A variants exacerbate the effects of reduced TDP-43 function and TDP-43 can repress a cryptic exon-splicing event in UNC13A [127, 128]. Hence, it may provide a promising therapeutic target for TDP-43 proteopathies. We also detected that the ZNFS21B rs2275294 C allele indicates a poor prognosis of ALS, meanwhile a meta-analysis suggested that the ZNFS12B rs2275294 polymorphism is also associated
Fig. 3 (See legend on previous page.)
Fig. 4 Forest plots of HR for modification loci included in pairwise meta-analysis. **a** Forest plot of HR for *APOE* ε4. **b** Forest plot of HR for *KIFAP3* rs1541160 CC. **c** Forest plot of HR for *KIFAP3* rs1541160 CT. **d** Forest plot of HR for *UNC13A* rs12608932 CC. **e** Forest plot of HR for *ZNFS12B* rs2275294 CC+TT. HR, hazard ratio; CI, confidence interval.
with ALS risk [129]. The ZNF512B gene encodes a protein of 893 amino acids, which is expressed in the brain and spinal cord. Upregulation of ZNF512B activates TGF-β/Smad signaling, while downregulation inhibits this pathway and rs2275294C may reduce this neuroprotective TGF-β/Smad signaling [130]. Several other genes (such as EPHA4, CAMTA1, and HFE) may be associated with the prognosis of ALS, however, they cannot be performed by meta-analysis due to the limited studies.

It is controversial whether APOE polymorphism can change the course of ALS [56, 57]. However, APOE ε4 allele does not modify the clinical course of ALS as well under meta-analysis, so does KIFAP3 rs1541160. As for the remaining genetic factors, although SMN genes have been reported to be associated with ALS survival [69, 131], This conclusion was not supported based on the results of a recent and large study including new and all previously reported results on SMN1 and SMN2 copy number variation in ALS [87]. The genetic mechanisms of SMN1 and SMN2 are implicated in motor neuron death in spinal muscular atrophy, but SMN expression levels in the physiological range may not modify the progression of ALS [87]. Additionally, a very recent large GWAS also looked at the role of some genetic factors mentioned above on modifying ALS survival and found the effect of common genetic risk factors for ALS susceptibility on disease progression was limited [132], suggesting the influence of a single SNP or gene on ALS survival cannot be magnified.

Although we find some potential genetic factors that affected the survival of ALS, these findings should be interpreted with caution, given some limitations. First and foremost, different variants in the same gene might have different effects on survival, it may result in information missing when a gene was analyzed as a whole factor. What is more, as we discussed above, whether some of the variants in these genes are ALS-associated mutations remains in doubt. Therefore, the results were not absolutely correct. Besides, some studies did not report the HR directly, when we get HR from the survival curve, there may be some slight gap with the accurate results. Some differences in follow-up time, the included population, and the definition of outcomes may lead to publication bias and the non-genetic factors related to ALS survival may also play a role [5]. Moreover, the lack of commonality of prognostic factors investigated in different Cox PH models is also a limitation, and some studies are single-factor analyses and did not adjust for confounding factors. In addition, the small number of prospective studies was also a limitation. For example, ZNF521B rs2275294 were reported in only three articles, the results should be explained with caution. Therefore, more high-quality prospective studies are warranted.

Finally, the rules of the review methodology of its restriction to articles published in English, and the low specificity of the search strategy, increase the risk of missing relevant studies.

Conclusions
The present meta-analysis summarized and contrasted evidence for genetic prognostic factors in patients with ALS and will help to understand ALS genetics. Genetic prognostic factors deserve attention and careful consideration as the field moves forward to combat and prevent this devastating disease.

Abbreviations
ALS: Amyotrophic lateral sclerosis; CI: Confidence intervals; DPR: Dipeptide repeat protein; FALS: Familial amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; GWAS: Genome-Wide Association Study; HR: Hazard ratio; ISPOR: International Society for Pharmacoepidemiology and Outcomes Research; NIV: Noninvasive ventilation; NMA: Network meta-analysis; NOS: Newcastle-Ottawa Scale; PH: Proportional hazard; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT: Randomized clinical trial; SALS: Sporadic amyotrophic lateral sclerosis; SCA2: Spinocerebellar ataxia type 2; SNP: Single nucleotide polymorphism; SUCRA: Surface under the cumulative ranking curve.

Supplementary Information
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Additional file 1: Table S1. Characteristics of the articles included in network meta-analysis for variants in ALS causative genes. Table S2. Characteristics of the articles included in pairwise meta-analysis for other modification loci. Table S3. Characteristics of the articles included in systematic review for other modification loci. Table S4. The quality of articles included in network meta-analysis and pairwise meta-analysis by NOS. Table S5. The feathers for different variants in SOD1, FUS, TARDBP. Figure S1. Forest plot for inconsistency test in network meta-analysis. Figure S2-S12. Heterogeneity analysis in network meta-analysis. Figure S13, publication bias for studies reporting C9orf72 expansion in patients with ALS compared to those without ALS-related mutation.

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Authors’ contributions
WMS and YPC conceived and designed the study. WMS, YPC, XJG, and ZJ selected the articles and extracted and cross-checked the data. WMS, YPC, XJG, and QQD contributed to the statistical analysis. WMS and YPC wrote the first draft of the manuscript. WMS, XJG, YPC, and HFS revised and discussed the final edition. The authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article and its supplementary information files. Effect size and study details
were extracted from the original papers, which are available in the public domain.

**Declarations**

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

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**References**

1. Brown RH, Al-Chalabi A. Amyotrophic Lateral Sclerosis. N Engl J Med. 2017;377(2):162–72.
2. Zarei S, Carr K, Reiley L, Diaz K, Guerra O, Altamirano PF, et al. A comprehensive review of amyotrophic lateral sclerosis. Surg Neurol Int. 2015;6(1):171.
3. Byrne S, Walsh C, Lynch C, Bede P, Elamin M, Shatunov A, et al. Rate of familial amyotrophic lateral sclerosis: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2011;82(6):623–7.
4. Abel O, Powell JF, Andersen PM, Al-Chalabi A. ALSod: A user-friendly online bioinformatics tool for amyotrophic lateral sclerosis genetics. Hum Mutat. 2012;33(9):1345–51.
5. Su WM, Cheng YF, Jiang Z, Duan QQ, Yang TM, Shang HF, et al. Predictors of survival in patients with amyotrophic lateral sclerosis: a large meta-analysis. EBioMedicine. 2021;74:103732.
6. Diekstra FP, van Vuyl PW, van Rhenen W, Koppers M, Pasterkamp RJ, van Es MA, et al. UNC13A is a modifier of survival in amyotrophic lateral sclerosis. Neurobiol Aging. 2012;33(3):633–8.
7. Fogg I, Lin K, Tilocca C, Rooney J, Geller L, Diekstra FP, et al. Association of a Locus in the CAMTA1 Gene With Survival in Patients With Sporadic Amyotrophic Lateral Sclerosis. JAMA Neurolo. 2016;73(7):812–20.
8. Chio A, Mora G, Restagno G, Brunetti M, Ossola I, Barberis M, et al. UNC13A influences survival in Italian amyotrophic lateral sclerosis patients: a population-based study. Neurobiol Aging. 2013;34(1):357–e351–5.
9. Sabatelli M, Conforti FL, Zollino M, Mora G, Monsurro MR, Volanti P, et al. C9ORF72 hexanucleotide repeat expansions in the Italian sporadic ALS population. Neurobiol Aging. 2012;33(3):1848.e1815–20.
10. Miltenberger-Milteny G, Conceição VA, Gromich M, Pronoto-Laborinho AC, Pinto S, Andersen PM, et al. C9orf72 mutation association with accelerated decline of respiratory function and decreased survival in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2019;90(1):118–20.
11. Hübers A, Just W, Rosenbohm A, Müller K, Marroquin N, Goebel I, et al. De novo FUS mutations are the most frequent genetic cause in early-onset German ALS patients. Neurobiol Aging. 2015;36(11):3117–e3111–6.
12. Garcia P, Valdmanis P, Millecamps S, Lionnet C, Blasco H, Mouzat K, et al. Phenotype and genotype analysis in amyotrophic lateral sclerosis with TARDBP gene mutations. Neurology. 2012;78(19):1519–26.
13. Chen YP, Yu SH, Wei QQ, Cao B, Gu XJ, Chen XP, et al. Role of genetics in amyotrophic lateral sclerosis: a large cohort study in Chinese mainland population. J Med Genet. 2021. https://doi.org/10.1136/jmedgenet-2021-107965.
14. Jansen JP, Trikalinos T, Cappelleri JC, Daw J, Andes S, Eldefrouk Y, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. Value Health. 2014;17(2):157–73.
15. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777–84.
16. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
17. Cudkowicz ME, van den Berg LH, Shemet JM, Mitsumoto H, Mora JS, Ludolph A, et al. Dexamipipexole versus placebo for patients with amyotrophic lateral sclerosis (EMPOWER): a randomised, double-blind, phase 3 trial. Lancet Neurol. 2013;12(11):1059–67.
18. Miller RG, Mitchell JD, Moore DH. Rifuzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Cochrane Database Syst Rev. 2012;3:CD001447.
19. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16.
20. Woods BS, Hawkins N, Scott DA. Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: a tutorial. BMC Med Res Methodol. 2010;10:54.
21. Strang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603–5.
22. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088–101.
23. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Stat Med. 2010;29(7-8):932–44.
24. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011;64(2):163–71.
25. Borghero G, Pugliatti M, Marroso F, Marroso MG, Murr M, Floris G, et al. ATXN2 is a modifier of phenotype in ALS patients of Sardinian ancestry. Neurobiol Aging. 2015;36(10):2096.e2901–5.
26. Chio A, Calvo A, Moglia C, Caniosa A, Brunetti M, Barberis M, et al. ATXN2 polyQ intermediate repeats are a modifier of ALS survival. Neurology. 2015;84(3):251–8.
27. Byrne S, Elamin M, Bede P, Shatunov A, Walsh C, Corr B, et al. Cognitive and clinical characteristics of patients with amyotrophic lateral sclerosis carrying a C9orf72 repeat expansion: a population-based cohort study. Lancet Neuro. 2012;11(3):252–40.
28. Ratti A, Corrado L, Castelletti B, Del Bo R, Fogg I, Cereda C, et al. C9ORF72 repeat expansion in a large Italian ALS cohort: evidence of a founder effect. Neurobiol Aging. 2012;33(10):2528.e2527–14.
29. van Rhenen W, van Blitterswijk M, Huisman MH, Vlamin L, van Doormaal PT, Seelen M, et al. Hexanucleotide repeat expansions in C9ORF72 in the spectrum of motor neuron diseases. Neurology. 2012;79(9):878–82.
30. Milleccamps S, Boillée S, Le Ber I, Selhnan D, Teysou D, Giraudneau M, et al. Phenotype difference between ALS patients with expanded repeats in C9orf72 and patients with mutations in other ALS-related genes. J Med Genet. 2012;49(4):258–63.
31. Debray S, Race V, Crabbé V, Herdewyn S, Teysou D, Giraudneau M, et al. Frequency of C9orf72 repeat expansions in amyotrophic lateral sclerosis: a Belgian cohort study. Neurobiol Aging. 2013;34(12):2890.e2897–12.
32. García-Redondo A, Doki-Icardo R, Rojas-García R, Esteban-Pérez J, Cordero-Vázquez P, Muñoz-Blanco JL, et al. Analysis of the C9orf72 gene in patients with amyotrophic lateral sclerosis in Spain and different populations worldwide. Hum Mutat. 2013;34(1):79–82.
33. Irwin DJ, McMillan CT, Brettschneider J, Libon DJ, Powers J, Rascovsky K, et al. Cognitive decline and reduced survival in C9orf72 expansion frontotemporal degeneration and amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2013;84(2):163–9.
34. Van Laere K, Vanhee A, Verschueren J, De Coster L, Driessen A, DuPont P, et al. Value of 18fluorodeoxyglucose-postonmission tomography
in amyotrophic lateral sclerosis: a prospective study. JAMA Neurol. 2014;71(5):553–61.

35. Calvo A, Canosa A, Bertuzzo D, Cugnasco P, Solero L, Clerico M, et al. Influence of cigarette smoking on ALS outcome: a population-based study. J Neurol Neurosurg Psychiatry. 2016;87(11):1229–33.

36. Umoh ME, Fournier C, Li Y, Polak M, Shaw L, Landers JE, et al. Comparative analysis of C9orf72 and sporadic disease in an ALS clinic population. Neurology. 2016;87(10):1024–30.

37. Gendron TF, Daugherty LM, Heckman MG, Diehl NN, Wu J, Miller TM, et al. Phosphorylated neurofilament heavy chain: A biomarker of survival for C9orf72-associated amyotrophic lateral sclerosis. Ann Neurol. 2017;81(2):139–46.

38. Reniers W, Schooten M, Claeyss KG, Tilkin P, D’Hondt A, Van Reijen D, et al. Prognostic value of clinical and electrodiagnostic parameters at time of diagnosis in patients with amyotrophic lateral sclerosis. Amyotrophic Lateral Scler Frontotemporal Degener. 2017;18(5–6):341–50.

39. Cammack AJ, Atassi N, Hyman T, van den Berg LH, Harms M, Baloh RH, et al. Prospective natural history study of C9orf72 ALS clinical characteristics and biomarkers. Neurology. 2019;93(17):e1605–17.

40. Rooney J, Murray D, Campion A, Moloney H, Tattersall R, Doherty M, et al. The C9orf72 expansion is associated with accelerated respiratory function decline in a large Amyotrophic Lateral Sclerosis cohort. HRB Open Res. 2019;2:23.

41. Trojci F, Siciliano M, Femiano C, Santangelo G, Lunetta C, Calvo A, et al. Comparative Analysis of C9orf72 and Sporadic Disease in a Large Multicenter ALS Population: The Effect of Male Sex on Survival of C9orf72 Positive Patients. Front Neurol. 2019;13:485.

42. Benatar M, Zhang L, Wang L, Grant V, Statland J, Barohn R, et al. Validation of serum neurofilaments as prognostic and potential pharmacodynamic biomarkers for ALS. Neurology. 2020;95(1):e59–69.

43. De Schaepdryver M, Lunetta C, Tafarrini C, Mosca L, Chio A, Van Damme P, et al. Neurofilament light chain and Creative protein explored as predictors of survival in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2020;91(4):436–7.

44. Klappe U, Chamoun S, Shen Q, Finn A, Evertsson B, Zetterberg H, et al. Cardiac troponin T is elevated and increases longitudinally in ALS patients. Amyotrophic Lateral Scler Frontotemporal Degener. 2022;23(1):2–15.

45. Puentes F, Lombardi V, Lu CH, Yildiz O, Fratta P, Isaacs A, et al. Genetic architecture of ALS in Sardinia. Neurobiol Aging. 2020;95(1):128–36.

46. Vidal-Taboada JM, Lopez-Lopez A, Salvado M, Lorenzo L, Garcia C, Mahy N, et al. UNC13A confers risk for sporadic ALS and influences survival in a Spanish cohort. J Neurol. 2015;262(10):2285–92.

47. Tan HHG, Westeneng HJ, van der Burgh HK, van Es MA, Bakker LA, van Veenhuizen K, et al. The Distinct Traits of the UNC13A1 Polymorphism in Amyotrophic Lateral Sclerosis. Ann Neurol. 2020;88(4):796–806.

48. Tetsuka S, Morita M, Iida A, Ikegawa S, Nakano I. ZNF512B gene serves as a prognostic factor in patients with amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2012;13:122.

49. Yu CJ, Wang L, Mao SL, Zhang Y, Song LL, Cai LY, et al. The clinical assessment of amyotrophic lateral sclerosis patients’ prognosis by ZNF512 B gene, neck flexor muscle power score and body mass index (BMI). BMC Neurol. 2018;18(1):211.

50. Jiang H, Yang B, Wang F, Li K, Zhu Y, Liu B, et al. Association of Single Nucleotide Polymorphism at rs2775294 in the ZNF512B Gene with Prognosis in Amyotrophic Lateral Sclerosis. Neuromolecular Med. 2021;23(2):242–56.

51. Landers JE, Melki J, Meiningher V, Glass JD, van den Berg LH, van Es MA, et al. Reduced expression of the Kinesin-Associated Protein 3 (KIFAP3) gene increases survival in sporadic amyotrophic lateral sclerosis. Proc Natl Acad Sci U S A. 2009;106(22):9004–9.

52. Traynor BJ, Nalls M, Lai SL, Gibbs RJ, Schymick JC, Atepalli S, et al. Kinesin-associated protein 3 (KIFAP3) has no effect on survival in a population-based cohort of ALS patients. Proc Natl Acad Sci U S A. 2010;107(27):12335–8.

53. Orsetti V, Pegoraro E, Cima V, D’Asecurio C, Palmieri A, Querin G, et al. Genetic variation in KIFAP3 is associated with an upper motor neuron-predominant phenotype in amyotrophic lateral sclerosis. Neurodegener DIS. 2011;8(6):491–5.

54. van Doormaal PT, Ticozzi N, Geller C, Ratti A, Tamari F, Chio A, et al. Analysis of the KIFAP3 gene in amyotrophic lateral sclerosis: a multicenter survival study. Neurobiol Aging. 2014;35(10):2420.e2413–24.

55. Czell D, Sapp PC, Neuwirth C, Weber M, Andersen PM, Brown RH. Further analysis of KIFAP3 gene in ALS patients from Switzerland and Sweden. Amyotrophic Lateral Scler Frontotemporal Degener. 2017;18(3–4):302–14.

56. Gamez J, Barcelo MJ, Muñoz X, Carmona F, Cusco I, Baiget M, et al. Survival and respiratory decline are not related to homozygous SMN2 deletions in ALS patients. Neurology. 2002;59(9):1456–60.

57. Lopez-Lopez A, Gamez J, Syriani E, Morales M, Salvado M, Rodriguez MJ, et al. CX3CR1 is a modifying gene of survival and progression in amyotrophic lateral sclerosis. PLoS One. 2014;9(5):e95628.

58. Calvo A, Moglia C, Canosa A, Cammarosano S, Ilardi A, Bertuzzo D, et al. Common polymorphisms of chemokine (C-X-C motif) RANTES receptor 1 gene modify amyotrophic lateral sclerosis outcome: A population-based study. Muscle Nerve. 2018;57(2):212–6.

59. Vidal-Taboada JM, Pugliese M, Salvado M, Gámez J, Mahy N, Rodríguez ML. KATAP (Channel Expression and Genetic Polymorphisms Associated with Progression and Survival in Amyotrophic Lateral Sclerosis. Mol Neurobiol. 2018;55(10):7962–72.

60. Mouzat K, Molinari N, Kantar J, Polge A, Corgia P, Couratier P, et al. Liver X Receptor Genes Variants Modulate ALS Phenotype. Mol Neurobiol. 2018;55(3):1599–65.

61. Sleegers K, Brouwers M, Maurer-Stroh S, van Es MA, Van Damme P, van Vught PW, et al. Progranulin genetic variability contributes to amyotrophic lateral sclerosis. Neurology. 2008;71(4):253–9.

62. El Oussini H, Bayer H, Scicli-Zahirovic J, Vercruysse P, Sinneringer J, Dingir Grosch S, et al. Serotonin 2B receptor slows disease progression and
76. Theunissen F, Anderton RS, Magalhaes FL, Flynn LL, Winter SJ, James I, et al. Novel ST2M2 Variant Linked to Amyotrophic Lateral Sclerosis Risk and Clinical Phenotype. Front Aging Neurosci. 2021;13:658226.

77. Xu L, Tian D, Li J, Chen L, Tang L, Fan D. The Analysis of Two BONF Polymorphisms G196A/C270T in Chinese Sporadic Amyotrophic Lateral Sclerosis. Front Aging Neurosci. 2017;9:135.

78. He J, Fu J, Fan D. The complement C7 variant rs3792646 is associated with amyotrophic lateral sclerosis in a Han Chinese population. Neurobiol Aging. 2018;103:e101–7.

79. Diekstra FP, Beleza-Meireles A, Leigh NP, Shaw CE, Al-Chalabi A. Interaction between PON1 and population density in amyotrophic lateral sclerosis. NeuroReport. 2009;20(2):186–90.

80. Verde F, Tiloca C, Morelli C, Doretti A, Polletti B, Maderna L, et al. PON1 is a disease modifier gene in amyotrophic lateral sclerosis: association of the Q192R polymorphism with bulbar onset and reduced survival. Neurosci Lett. 2019;697:40–4.

81. Blauw HM, van Rheenen W, Koppers M, Van Damme P, Waibel S, Lemmens R, et al. NIPA1 polyalanine repeat expansions are associated with amyotrophic sclerosis. Hum Mol Genet. 2012;21(11):2497–502.

82. Blasco H, Vouc'h P, Nadjar Y, Bribouttou B, Gordon PH, Guertard YO, et al. Association between divergent metal transport 1 encoding gene (SLC11A2) and disease duration in amyotrophic lateral sclerosis. J Neurol Sci. 2011;303(1-2):124–7.

83. de Sousa Barros JB, de Faria SK, da Cruz Pereira Bento D, Prado Assunção LD, da Silva Santos R, da Silva Reis AA. Influence of GSTP1 rs1695 polymorphism on survival in male patients' amyotrophic lateral sclerosis: a genetic association study in Brazilian population. Mol Biol Rep. 2022;49(2):1655–9.

84. Al-Chalabi A, Scheffler MD, Smith BN, Parton MJ, Cudkowicz ME, Andersen PM, et al. Ciliary neurotrophic factor genotype does not influence clinical phenotype in amyotrophic lateral sclerosis. Ann Neurol. 2003;54(1):130–4.

85. Van Vught PW, Van Wijk J, Bradley TE, Plasmans D, Jakobs ME, Veldink JH, et al. Ciliary neurotrophic factor null alleles are not a risk factor for Charcot-Marie-Tooth disease, hereditary neuropathy with pressure palsies and amyotrophic lateral sclerosis. Neuromuscul Disord. 2007;17(11-12):964–7.

86. Yang X, Zheng J, Tian S, Chen Y, An R, Zhao Q, et al. HLA-DRA/HLA-DRB5 polymorphism affects risk of sporadic ALS and survival in a southwest Chinese cohort. J Neurol Sci. 2017;373:124–8.

87. Moisee M, Zwamborn RAJ, van Vugt J, van der Spek R, van Rheenen W, Lee T, et al. A potential loss-of-function mutation induces DNA damage accumulation in ALS-patient derived motoneurons. Stem Cell Res. 2020;17(2):15230–41.

88. Pan C, Jiao B, Xiao T, Hou L, Zhang W, Li X, et al. Mutations of CCNF gene is rare in patients with amyotrophic lateral sclerosis and frontotemporal dementia from Manchuria China. Amyotroph Later Scler Frontotemporal Degener. 2017;18(3-4):265–8.

89. Williams KL, Topp S, Yang S, Smith B, Fifita JA, Warraich ST, et al. CCNF mutations in amyotrophic lateral sclerosis and frontotemporal dementia. Nat Commun. 2016;7:11253.

90. Vandersteen VM, Reeveren JB, Bekris LM, Bird TD, Yuan W, Elman LB, et al. TARDBP mutations in amyotrophic lateral sclerosis with TDP-43 neuropathology: a genetic and histopathological analysis. Lancet Neurol. 2008;7(5):499–509.

91. Cui R, Tuo M, Li P, Zhou C. Association between TBK1 mutations and risk of amyotrophic lateral sclerosis/frontotemporal dementia spectrum: a meta-analysis. Neurol Sci. 2018;39(5):811–20.

92. Oakes JA, Davies MC, Collins MO. TBK1: a new player in ALS linking autophagy and neuroinflammation. Mol Brain. 2017;10(1):5.

93. Yao L, He X, Cui B, Zhao F, Zhou C. NEK1 mutations and the risk of amyotrophic lateral sclerosis (ALS): a meta-analysis. Neurol Sci. 2021;42(4):1277–85.

94. Higelin J, Catanese A, Semelink-Sedlacek LL, Oostuwe S, Lust AK, Bausinger J, et al. NEK1 loss-of-function mutation induces DNA damage accumulation in ALS- patient-derived motoneurons. Stem Cell Res. 2018;30:150–62.

95. McLaughlin RL, Kenn K, Vajda A, Byrne S, Bradley DG, Hardiman O. UBQLN2 mutations are not a frequent cause of amyotrophic lateral sclerosis in Ireland. Neurobiol Aging. 2014;35(1):269–76.

96. Freibaum BD, Taylor JP. The Role of Dipeptide Repeats in C9orf72-Related ALS-FTD. Front Mol Neurosci. 2017;10:35.

97. Ektkari Bidhendi E, Bergh J, Zetterstrom P, Forsberg K, Pakkenberg B, Andersen PM, et al. Mutant superoxide dismutase aggregates from human spinal cord transmit amyotrophic lateral sclerosis. Acta Neuropl. 2018;136(6):939–53.

98. Sharma A, Lysakhchenko AK, Lu L, Nasrabaday SE, Elmahle M, Mendelsohn M, et al. ALS-associated mutant FUS induces selective motor neuron degeneration through toxic gain of function. Nat Commun. 2016;7:10465.

99. Van Deerlin VM, Leverenz JB, Bekris LM, Bird TD, Yuan W, Elman LB, et al. TARDBP mutations in amyotrophic lateral sclerosis with TDP-43 neuropathology: a genetic and histopathological analysis. Lancet Neurol. 2008;7(5):499–509.
117. Bali T, Self W, Liu J, Siddique T, Wang LH, Bird TD, et al. Defining SOD1 ALS natural history to guide therapeutic clinical trial design. J Neurol Neurosurg Psychiatry. 2017;88(2):99–105.

118. Anisato T, Okubo R, Arata H, Abe K, Fukada K, Sakoda S, et al. Clinical and pathological studies of familial amyotrophic lateral sclerosis (FALS) with SOD1 H46R mutation in large Japanese families. Acta Neuropathol. 2003;106(6):561–8.

119. Naumann M, Peikert K, Günther R, van der Kooy AJ, Aronica E, Hübers A, et al. Phenotypes and malignancy risk of different FUS mutations in genetic amyotrophic lateral sclerosis. Ann Clin Transl Neurol. 2019;6(12):2384–94.

120. Polymenidou M, Lagier-Tourenne C, Hutt KR, Huelga SC, Moran J, Liang TV, et al. Long pre-mRNA depletion and RNA missplicing contribute to neuronal vulnerability from loss of TDP-43. Nat Neurosci. 2011;14(4):459–68.

121. Freischmidt A, Wieland T, Richter B, Ruf W, Schaeffer V, Müller K, et al. Haploinsufficiency of TBK1 causes familial ALS and fronto-temporal dementia. Nat Neurosci. 2015;18(3):631–6.

122. Chia R, Chio A, Traynor BJ. Novel genes associated with amyotrophic lateral sclerosis: diagnostic and clinical implications. Lancet Neurol. 2012;11(9):847–62.

123. Calvo A, Restagno G, Brunetti M, Ossola I, Majounie E, Renton AE, et al. UNC13A influences survival in an Italian population-based series. Eur J Neurol. 2012;19:262.

124. Diekstra FP, Van Deerlin VM, van Swieten JC, Al-Chalabi A, Ludolph AC, Weishaupt JH, et al. C9orf72 and UNC13A are shared risk loci for amyotrophic lateral sclerosis and frontotemporal dementia: a genome-wide meta-analysis. Ann Neurol. 2014;76(1):120–33.

125. Yang B, Jiang H, Wang F, Li S, Wu C, Bao J, et al. UNC13A variant rs12608932 is associated with increased risk of amyotrophic lateral sclerosis and reduced patient survival: a meta-analysis. Neurology. 2017;91(22):1126–32.

126. Brown AL, Wilkins OG, Keuss MJ, Hill SE, Zanovello M, Lee WC, et al. TDP-43 loss and ALS-risk SNPs drive mis-splicing and depletion of UNC13A. Nature. 2022;603:131–7.

127. McManus MC, Prudencio M, Koike Y, Vatsavayai SC, Kim G, Harbinski F, et al. TDP-43 represses cryptic exon inclusion in the FTD-ALS gene UNC13A. Nature. 2022;603:124–30.

128. Ning P, Yang X, Zhao Q, Huang H, An R, et al. Meta-analysis of the association between ZNF512B polymorphism rs2275294 and risk of amyotrophic lateral sclerosis. Neurobiol Dis. 2020;134:104635.

129. Schober A, Peterziel H, von Bartheld CS, Simon H, Krieglstein K, Unsicker K. GDNF applied to the MPTP-lesioned nigrostriatal system requires TGF-beta for its neuroprotective action. Neurobiol Dis. 2007;25:378–91.

130. Veldink JH, van den Berg LH, Cobben JM, Stulp RP, De Jong JM, Vogels OJ, et al. Homozygous deletion of the survival motor neuron 2 gene is a prognostic factor in sporadic ALS. Neurology. 2001;56(6):749–52.

131. van Rheenen W, van der Spek RAA, Bakker MK, van Vught J, Hop PJ, Zwamborn RAJ, et al. Common and rare variant association analyses in amyotrophic lateral sclerosis identify 15 risk loci with distinct genetic architectures and neuron-specific biology. Nat Genet. 2021;53(12):1636–48.