No Association between the SORD Gene and Amyotrophic Lateral Sclerosis in a Chinese Cohort

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Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder. Recently a juvenile ALS patient was reported carrying the c.757delG mutation of the sorbitol dehydrogenase (SORD) gene, which was also a related mutation of Charcot-Marie-Tooth disease (CMT) and distal hereditary motor neuropathy (dHMN). ALS shares pathogenesis and overlapping genes with CMT and dHMN. We used whole-exome sequencing technology to screen the full-length SORD gene in 601 Chinese sporadic ALS patients and 174 controls without a history of neurological diseases. No SORD pathogenic variants were identified in the ALS patients. Our current results did not find an association between SORD and ALS in Chinese patients, and further studies will be required.

Keywords: amyotrophic lateral sclerosis; Chinese population; SORD gene; whole-exome sequencing

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by rapidly progressing muscle weakness and death due to respiratory failure within two to four years of symptom onset [1]. Approximately 10% of ALS cases are classified as familial ALS (FALS), while 90% of those who do not have affected relatives are considered sporadic ALS cases (SALS) [2]. There are more than 20 genes known to cause ALS, including SOD1, C9orf72, TARDBP, FUS, OPTN, DCTN1, KIF5A, TBK1, and SQSTM1 [3]. The mutation in these genes may be found in 50–70% of FALS patients but only in 10% of patients with SALS [4]. Genetic factors are vital to the pathogenesis and development of treatments for ALS. Therefore, we need to learn more about the mutations associated with SALS.

Recently, a homozygous c.757delG mutation of the sorbitol dehydrogenase (SORD) gene was identified in a 24-year-old juvenile ALS (JALS) patient [5]. However, whether this JALS patient had familial or sporadic ALS was unclear, as he was adopted by his parents. No additional pathogenic variants of JALS or CMT/dHMN were discovered by next-generation sequencing of two panels of genes associated with (J)ALS and peripheral neuropathies. The SORD gene on chromosome 15q21.1 encodes the sorbitol dehydrogenase enzyme, which is involved in the two-step polyol pathway, converting glucose into sorbitol and subsequently into fructose [6]. Defects in the SORD gene would lead to a high risk of intracellular sorbitol accumulation. Sorbitol is not only an osmotic stressor but also an oxidative stressor through its sorbitol dehydrogenase reaction [7], playing a role in the pathogenesis of axonal neuropathy and diabetic peripheral neuropathy.

Since biallelic mutations of the SORD gene were first reported as the most common causes for hereditary neuropathies [8], SORD prevalent mutation c.757delG
(p.Ala253Glnfs*27) has been considered one of the most frequent causes of axonal neuropathy, including autosomal recessive axonal Charcot-Marie-Tooth neuropathy (CMT2) and distal hereditary motor neuropathy (dHMN) [9–17]. ALS shows high overlap in terms of clinical presentation, targets, and mechanisms of damage with CMT2 and dHMN [18]. Many of the genes involved in CMT2 and dHMN are also associated with ALS, such as the Kinesin family member 5A (KIF5A) gene, Dynactin subunit 1 (DCTN1) gene, GlycyltRNA synthetase (GARS) gene, Neurofilament heavy (NEFH) gene, and Senataxin (SETX) gene [19]. Therefore, it is significant to analyze their overlapping genes. In addition, the SORD gene was also proposed as a biomarker candidate gene for another neurodegenerative disease, Alzheimer’s disease (AD), since it is commonly dysregulated between AD blood and brain tissues [20]. Those data imply that SORD mutation might be a possible cause of ALS. Therefore, in this study, we sought to investigate the occurrence of SORD gene mutations in ALS patients and explore the relationship between SORD mutations and ALS clinical phenotypes.

2. Materials and Methods

2.1. Subjects

The study included 601 Chinese SALS patients registered with the Neurology Department of Peking University Third Hospital from January 2007 to December 2012 and 174 neurologically normal controls. Patients in the case-cohort study were diagnosed with definite, probable, or laboratory-supported probable ALS according to the El Escorial revised criteria [21] by a neurologist specializing in ALS. In this cohort, none of the patients had any symptoms of dementia, and all of them had normal scores on the Edinburgh Cognitive and Behavioral ALS Screen (ECAS) scale [22]. The study was approved by the ethics committee of Peking University Third Hospital. Written informed consent was obtained from all participants. We screened SOD1, TARDBP, FUS, C9orf72, OPTN, DCTN1, KIF5A, TBK1, and SQSTM1 genes for all patients before our research.

2.2. Mutation Analyses

Genomic DNA samples were extracted from whole blood using standard protocols (Qiagen, Valencia, CA, USA). All 601 SALS patients and 174 controls underwent whole-exome sequencing (WES). We screened the variants by using the Short Genetic Variations Database (dbSNP) (https://www.ncbi.nlm.nih.gov/snp (accessed on 2 October 2022)), the 1000 Genomes Project (1000G) database (http://www.1000genomes.org/ (accessed on 2 October 2022)), gnomAD v2.11 (http://gnomad-sg.org/ (accessed on 2 October 2022)), the China Metabolic Analytics Project (ChinaMAP, www.mBiobank.com (accessed on 2 October 2022)), and the online Chinese Millionome Database (CMDB, https://db.cngb.org/cmdb/ (accessed on 2 October 2022)). The minor allele frequency of the variants was restricted to less than 0.1%. Variants found by WES were further validated by Sanger sequencing and interpreted according to the American College of Medical Genetics and Genomics (ACMG) standards and guidelines [23]. The potential impact of variants was conducted with SIFT (http://sift.jcvi.org (accessed on 2 October 2022)), PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/ (accessed on 2 October 2022)), MutationTaster software (http://www.mutationtaster.org (accessed on 2 October 2022)), and Combined Annotation Dependent Depletion (CADD, https://cadd.gs.washington.edu/ (accessed on 2 October 2022)), described in our previous studies [10,24].

3. Results

This study recruited 601 SALS patients and 174 neurologically normal control individuals. Among them, 225 patients were females, and 376 patients were males; the mean age of onset was 50.61 ± 11.85. Generally, 15.1% of patients were bulbar-onset ALS, whereas 84.9% were spinal-onset ALS; 78.3% of patients were Classic ALS, 8.9% were Bulbar ALS, 7.5% were Flail Arm Syndrome, and 5.3% were Flail leg Syndrome.
The mutation analysis of the SORD gene in this study is listed in Table 1. We identified seven nonsynonymous variants in ten SALS patients; among them, five were missense variants (p.Ser82Thr, p.Cys140Ser, p.Ala233Thr, p.Lys243Arg, p.Glu249Lys), one was frameshift variant (p.Ala253Glnfs*27), and the other one was a splice site variant (c.545-6G > C). At the same time, we found another missense variant (p.Val83Leu) and one splice site variant (c.908 + 1G > C) in the two controls. All of the variants were heterozygous. Variants found in SALS patients weren’t found in controls and the other way around. The variant c.908 + 1G > C, identified in controls in this study, was reported as compound heterozygous mutation c.908 + 1G > C/c.404A > G in a Chinese dHMN patient [9]. Different from the homozygous c.757delG (p.Ala253Glnfs*27) mutation previously reported in an ALS patient, we found four SALS patients carrying the heterozygous polymorphism c.757delG (p.Ala253Glnfs*27, rs55901542), but no homozygous or compound heterozygous mutation was found in our subjects. According to the GnomAD v3 database, the heterozygous c.757delG allele count was 623 with an allele frequency of about 0.0043, while the homozygous c.757delG allele count of the SORD gene was 1 with an allele frequency of about 0.000007.

Table 1. Descriptions of the nonsynonymous variant of SORD.

| cDNA     | Amino Acid Change | Type       | Exon | dbsNP     | 1000 Genomes | GnomAD East Asian | ChinaMap | SALS        | Controls |
|----------|-------------------|------------|------|-----------|--------------|-------------------|----------|-------------|----------|
| c.244T > A | p.Ser82Thr       | Heterozygous | 3    | /         | /            | /                 | 1/601    | 0/174       |
| c.247G > T | p.Val83Leu       | Heterozygous | 3    | /         | /            | /                 | 0/601    | 1/174       |
| c.418T > A | p.Cys140Ser      | Heterozygous | 4    | rs569483540 | 0.0001087    | 0.00377786        | 1/601    | 0/174       |
| c.545-6G > C | /, splicing      | Heterozygous | intron 5–6 | /         | /            | /                 | 1/601    | 0/174       |
| c.697G > A | p.Ala233Thr      | Heterozygous | 7    | rs376874432 | /            | /                 | 1/601    | 0/174       |
| c.728A > G | p.Lys243Arg      | Heterozygous | 7    | /         | /            | /                 | 1/601    | 0/174       |
| c.745G > A | p.Glu249Lys      | Heterozygous | 7    | rs776518780 | 0.000236116   | 1/601    | 1/174       |
| c.757delG | p.Ala253Glnfs*27 | Heterozygous | 7    | rs55901542 | 0.0002928    | 0.00316936       | 4/601    | 0/174       |
| c.908 + 1G > C | /, splicing      | Heterozygous | intron 8–9 | /         | /            | /                 | 0/601    | 1/174       |

Abbreviations: dbsNP, The Single Nucleotide Polymorphism Database; gnomAD, Genome Aggregation Database; SALS, sporadic amyotrophic lateral sclerosis.

Results predicted by in silico tools of nonsynonymous variants of SORD were listed in Table 2. The locations and distributions of SORD variants in our study are presented in Figure 1B. For the missense variants detected in ALS patients, variant (c.244T > A, p.Ser82Thr) was located in the Zinc binding domain, and variant (c.728A > G, p.Lys243Arg) was located in the tetramer interface domain. The splicing variant c.545-6G > C was located at the intron 5. Human Splicing Finder 3.1 (Genomni SAS, Marseille, France) predicted this splicing variant as benign. All of the variants were classified as variants of uncertain significance (VUS) according to the standards and guidelines of the ACMG. The clinical characteristics of the SALS patients with SORD variants are listed in Table 3.

Table 2. Results predicted by in silico tools of nonsynonymous variants of SORD.

| cDNA      | Variant | Type        | SIFT       | PolyPhen-2 | MutationTaster | CADD   | Evidence ACMG     | SALS        | Controls |
|-----------|---------|-------------|------------|------------|----------------|--------|-------------------|-------------|----------|
| c.244T > A | p.Ser82Thr | Heterozygous | Tolerated   | Benign     | Polymorphism   | 4.909  | PM2, BP4          | Uncertain significance | 1/601    | 0/174       |
| c.247G > T | p.Val83Leu | Heterozygous | Deleterious | Probably damaging | Disease-causing | 5.800  | PM2, PP3          | Uncertain significance | 0/601    | 1/174       |
| c.418T > A | p.Cys140Ser | Heterozygous | Deleterious | Probably damaging | Disease-causing | 25.4   | PP3               | Uncertain significance | 1/601    | 0/174       |
Table 2. Cont.

| cDNA Variant Type | SIFT | PolyPhen-2 | MutationTaster | CADD | Evidence ACMG | SALS Controls |
|-------------------|------|------------|----------------|------|---------------|-------------|
| c.545-6G > C /, splicing | Heterozygous | / | / | 3.039 | PM2 | Uncertain significance | 1/601 | 0/174 |
| c.697G > A p.Ala233Thr | Heterozygous | Tolerated | Benign | Disease-causing | 18.12 | PM2, BP4 | Uncertain significance | 1/601 | 0/174 |
| c.728A > G p.Lys243Arg | Heterozygous | Tolerated | Benign | Polymorphism | 20.2 | PM2, BP4 | Uncertain significance | 1/601 | 0/174 |
| c.745G > A p.Glu249Lys | Heterozygous | Deleterious | Probably damaging | Disease-causing | 26.4 | PM2, PP3 | Uncertain significance | 1/601 | 0/174 |
| c.757delG p.Ala253Glnfs*27 | Heterozygous | / | / | / | PVS1 | Uncertain significance | 4/601 | 0/174 |
| c.908 + 1G > C /, splicing | Heterozygous | / | / | 10.218 | PVS1, PM2 | Uncertain significance | 0/601 | 1/174 |

Abbreviations: CADD, Combined Annotation Dependent Depletion; ACMG, American College of Medical Genetics and Genomics; SALS, sporadic amyotrophic lateral sclerosis.

Figure 1. Schematic graph of the SORD protein and published variants. (A, B) The SORD gene structure; (C) overview of the SORD-related neuropathy. Variants identified in our ALS cohort are marked in black; variants identified in CMT2 are marked in blue; variants identified in dHMN are marked in green; variants identified in CMT intermediate are marked in orange; variants identified in both CMT2 and dHMN are marked in red. † means co-occurrence of SORD c.757delG variant. ‡ means homozygous variant and identified in the CMT intermediate as well.
Table 3. Clinical features of the SALS patients with SORD variants.

| cDNA Variant | ID   | Sex | Age of Onset (Years) | Site of Onset | Disease Duration (Months) | Clinical Phenotype |
|--------------|------|-----|----------------------|---------------|--------------------------|--------------------|
| c.244T > A   | p.Ser82Thr | 9113 | Female | 50 | Right hand | 46 | Classic ALS |
| c.545-6G > C | /, splicing | 8371 | Male | 58 | Right leg | 42 | Classic ALS |
| c.728A > G   | p.Lys243Arg | 7160 | Female | 56 | Right hand | 48 | Classic ALS |
| c.757delG    | p.Ala253Glnfs*27 | 7158 | Male | 53 | Left hand | 36 | Classic ALS |
|              |       | 8366 | Male | 55 | Left leg | 15 | Classic ALS |
|              |       | 8386 | Female | 37 | Right leg | 54 | Classic ALS |
|              |       | 8180 | Male | 56 | Left hand | 60 | Classic ALS |

4. Discussion

This is the first study assessing the possible association between the SORD gene and ALS. We performed a case-control analysis to determine if SORD mutations are associated with ALS in Chinese individuals, and we found no correlation between the SORD gene and ALS patients of Chinese descent.

The previously reported French juvenile ALS patient [5] carrying c.757delG homozygous mutation developed lower limb weakness at the age of 21 years old, with a relatively fast course and rapid upper limb involvement. This SORD variant is the only variant associated with ALS so far, which is characterized as a homozygous state. Inconsistent with this JALS patient, no c.757delG homozygous mutations nor compound heterozygous mutations were identified in our SALS patients. We only found four SALS patients carrying the heterozygous polymorphism c.757delG (p.Ala253Glnfs*27). Most of these four patients showed an older age at onset and had longer disease duration than this JALS patient. The identification of four heterozygous carriers of this variant, which is relatively common across populations, is not enough to establish a causative role for ALS in these individuals. We hypothesize that the absence of SORD mutations in our SALS cohort may be due to the small number of JALS patients (with an onset before the age of 25): 4.8% (29/601). To confirm the possible contribution of SORD variants to ALS, more research is required in certain ALS groups, such as the JALS cohort.

The SORD is an important enzyme that converts sorbitol to fructose in the polyol pathway. SORD deficiency leads to increased levels of tissue and blood sorbitol, cellular osmolarity and oxidative stress, and decreased NADPH levels at the same time [7]. Mutations in SORD have been described as the most frequent cause of recessive inherited neuropathies in many studies. Some researchers analyzed the mutation of SORD in CMT and dHMN patients. Our team also explored the frequency of SORD mutations in CMT and dHMN patients in the previous study. We screened a cohort of 485 unrelated Chinese patients and identified five dHMN patients carrying the SORD variant, with the frequency of SORD variants being 1% (5/485) in all hereditary neuropathy patients and 6.4% (5/78) in patients with unclarified CMT2 and dHMN [10]. However, the frequency of SORD variants in the ALS cohort in our study was 1.7% (10/601), and the frequency in the control cohort was 1.1% (2/174), much lower than that in previous CMT and dHMN studies, which means that the prevalence of SORD variants in Chinese ALS patients was lower than that in CMT and dHMN patients. Meanwhile, we did not find an association between ALS and SORD in the current study. We speculate that the absence of SORD mutations in Chinese SALS patients or other factors could lead to the lack of an association in our cohort.

We have summarized all reported variants of SORD-related neuropathy so far in Table 4. We found that the modes of inheritance of SORD-related neuropathy were mainly divided into one kind of homozygous mutation and two kinds of compound heterozygous mutations, of which the homozygous mutation was c.757delG (p.Ala253Glnfs*27), and the compound heterozygous mutations were c.757delG (p.Ala253Glnfs*27) with another SORD mutations, and c.908 + 1G>C/c.404A > G (p.His135Arg). The phenotypes of patients with SORD mutations were that most patients developed their first symptom in adolescence.
The schematic graph of the SORD protein and all published variants of SORD-related neuropathy is shown in Figure 1. There were no significant differences in the regions and domains of variation for different SORD-related diseases.

Table 4. Summary of clinical features of patients with SORD neuropathy.

| Inherited Type | cDNA Change | Amino Acid Change | Count | Phenotype | Sex | Age at Onset (Years) | References |
|----------------|-------------|-------------------|-------|-----------|-----|----------------------|------------|
| Homozygous | c.757del | p.Ala253Glnfs*27 | 14 | dHMN | 9 male, 5 female | 12–40 | Cortese et al. [15] |
| | | | 20 | CMT2 | 13 male, 7 female | 10–40 | Cortese et al. [15] |
| | | | 3 | CMT intermediate | male | 12–25 | Cortese et al. [15] |
| | | | 1 | dHMN | male | 26 | Aliqumani et al. [25] |
| | | | 2 | dHMN | female | 4, 14 | Wu et al. [26] |
| | | | 2 | CMT2 | male, female | 17, 16 | Yuan et al. [11] |
| | | | 2 | CMT2 | male | 5, 16 | Lin et al. [27] |
| | | | 2 | dHMN | male, female | 10, 12 | Lin et al. [27] |
| | | | 1 | dHMN | male | 10 | Laššuthová et al. [14] |
| | | | 1 | CMT intermediate | male | 13 | Laššuthová et al. [14] |
| | | | 9 | CMT2 | male, female | 0–40 | Laššuthová et al. [14] |
| | | | 3 | dHMN | male | 9, 10, 15 | Dong et al. [9] |
| | | | 2 | dHMN | female | 21–30 | Liu et al. [10] |
| | | | 1 | dHMN | female | 17, 6 | Liu et al. [10] |
| Compound heterogeneous | c.757del | | 1 | CMT2 | male | 15 | Cortese et al. [15] |
| | | | 1 | CMT intermediate | male | 13 | Cortese et al. [15] |
| | | | 2 | CMT2 | male, female | 10, 20 | Cortese et al. [15] |
| | | | 1 | dHMN | female | 10–20 | Laššuthová et al. [14] |
| | | | 5 | CMT2 | male, 2 female | 0–51 | Laššuthová et al. [14] |
| | | | 1 | dHMN | female | 2–10 | Frasquet et al. [28] |
| | | | 1 | unclear | female | unclear | Frasquet et al. [28] |
| | | | 1 | CMT2 | male | 2 | Cortese et al. [15] |
| | | | 1 | CMT2 | male | 15 | Cortese et al. [15] |
| | | | 1 | dHMN | male | 18 | Cortese et al. [15] |
| | | | 1 | CMT2 | male | 15 | Cortese et al. [15] |
| | | | 1 | CMT2 | male | 15 | Yuan et al. [11] |
| | | | 1 | CMT2 | male | 49 | Laššuthová et al. [14] |
| | | | 1 | CMT intermediate | male | 10–20 | Laššuthová et al. [14] |
| | | | 1 | CMT2 | male | 20–25 | Laššuthová et al. [14] |
| | | | 1 | dHMN | male | 16 | Liu et al. [10] |
| | | | 1 | dHMN | male | 15 | Liu et al. [10] |
| | | | 1 | dHMN | male | 16 | Liu et al. [10] |

5. Conclusions

In conclusion, our study did not find any pathogenic SORD variants in the SALS cohort due to the limited sample size. Further studies with more participants or in specific
ALS populations, such as the JALS cohort, are needed to validate the potential contribution of SORD variants to ALS.

Author Contributions: Designed the protocol of the study, collected the original data, analyzed the results, and wrote the original manuscript, M.Y.; performed the genetic testing and helped with the study design and manuscript revision, J.H.; helped to revise the manuscript, L.T. and Y.C.; conceived the study and reviewed and edited the manuscript, X.L. and D.F. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional ethics committee of Peking University Third Hospital (PUTH) (IRB00006761). Written informed consent was obtained from all participants in advance to study enrolment.

Informed Consent Statement: Written informed consent was obtained from all participants in advance to study enrolment.

Data Availability Statement: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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References
1. van Es, M.A.; Hardiman, O.; Chio, A.; Al-Chalabi, A.; Pasterkamp, R.J.; Veldink, J.H.; van den Berg, L.H. Amyotrophic lateral sclerosis. Lancet 2017, 390, 2084–2098. [CrossRef]
2. Hardiman, O.; Al-Chalabi, A.; Chio, A.; Corr, E.M.; Logroscino, G.; Robberecht, W.; Shaw, P.J.; Simmons, Z.; van den Berg, L.H. Amyotrophic lateral sclerosis. Nat. Rev. Dis. Prim. 2017, 3, 17071. [CrossRef] [PubMed]
3. Brown, R.H.; Al-Chalabi, A. Amyotrophic Lateral Sclerosis. N. Engl. J. Med. 2017, 377, 162–172. [CrossRef]
4. Tohnai, G.; Nakamura, R.; Atsuta, N.; Nakatochi, M.; Hayashi, N.; Ito, D.; Watanabe, H.; Watanabe, H.; Katsuno, M.; Izumi, Y.; et al. Mutation screening of the DNAJC7 gene in Japanese patients with sporadic amyotrophic lateral sclerosis. Neurobiol. Aging 2022, 113, 131–136. [CrossRef] [PubMed]
5. Bernard, E.; Pegat, A.; Vallet, A.E.; Leblanc, P.; Lumbroso, S.; Mouzat, K.; Latour, P. Juvenile amyotrophic lateral sclerosis associated with biallelic c.757delG mutation of sorbitol dehydrogenase gene. Amyotroph. Lateral Scler. Front. Degener. 2021, 23, 473–475. [CrossRef]
6. Gabbay, K.H. The sorbitol pathway and the complications of diabetes. N. Engl. J. Med. 1973, 288, 831–836. [CrossRef]
7. Dewey, C.M.; Cenik, B.; Sephton, C.F.; Dries, D.R.; Mayer, P.; Good, S.K.; Johnson, B.A.; Herz, J.; Yu, G. TDP-43 is directed to stress granules by sorbitol, a novel physiological osmotic and oxidative stressor. Mol. Cell Biol. 2011, 31, 1098–1108. [CrossRef]
8. Cortese, A.; Zhu, Y.; Rebelo, A.P.; Negri, S.; Courel, S.; Abreu, L.; Bacon, C.J.; Bai, Y.; Bis-Brewer, D.M.; Bugiardini, E.; et al. Biallelic mutations in SORD cause a common and potentially treatable hereditary neuropathy with implications for diabetes. Nat. Genet. 2020, 52, 473–481. [CrossRef]
9. Dong, H.L.; Li, J.Q.; Liu, G.L.; Yu, H.; Wu, Z.Y. Biallelic SORD pathogenic variants cause Chinese patients with distal hereditary motor neuropathy. NPJ Genom. Med. 2021, 6, 1. [CrossRef]
10. Liu, X.; He, J.; Yilahumu, M.; Duan, X.; Fan, D. Clinical and Genetic Features of Biallelic Mutations in SORD in a Series of Chinese Patients with Charcot-Marie-Tooth and Distal Hereditary Motor Neuropathy. Front. Neurol. 2021, 12, 733926. [CrossRef]
11. Yuan, R.Y.; Ye, Z.L.; Zhang, X.R.; Xu, L.Q.; He, J. Evaluation of SORD mutations as a novel cause of Charcot-Marie-Tooth disease. Ann. Clin. Transl. Neurol. 2021, 8, 266–270. [CrossRef] [PubMed]
12. Record, C.; Pipis, M.; Rossor, A.; Laura, M.; Skorupinska, M.; Cortese, A.; Reilly, M. SORD-related CMT: Expanding the phenotype. J. Peripher. Nerv. Syst. 2021, 26, 340–341.
13. Rebelo, A.; Cortese, A.; Zuchner, S.; Huang, J.Y. Detection of increased sorbitol levels by ultra performance liquid chromatography-tandem mass spectrometry in CMT PATIENTS with SORD mutations. J. Peripher. Nerv. Syst. 2021, 26, 130.
14. Laššuthová, P.; Mazanec, R.; Staněk, D.; Sedláčková, L.; Plevová, B.; Haberlová, J.; Seeman, P. Biallelic variants in the SORD gene are one of the most common causes of hereditary neuropathy among Czech patients. Sci. Rep. 2021, 11, 8443. [CrossRef] [PubMed]

15. Cortese, A.; Dohrn, M.; Stojkovic, T.; Schenone, A.; Kennerson, M.; Sevilla, T.; Manganelli, F.; Zhang, R.; Houlden, H.; Hermann, D.; et al. Genotype and phenotype spectrum of SORD neuropathy. J. Peripher. Nerv. Syst. 2021, 26, 431.

16. Armírola-Ricurte, C.; De Vriendt, E.; Canayán, A.; Asenov, O.; Parman, Y.; Chamova, T.; Tournev, I.; Battaglou, E.; Jordanova, A. Screening of SORD mutations in a CMT cohort expands the clinical spectrum of SORD-related neuropathy. J. Peripher. Nerv. Syst. 2021, 26, 426.

17. Carneiro, D.; Matos, A.; Freixo, J.; Oliveira, J.; Costa, C.; Fineza, I.; Ribeiro, J.A. Sensorymotor neuropathy with dysautonomia associated to SORD gene mutations. Eur. J. Neurol. 2021, 28, 541.

18. Fischer, L.R.; Glass, J.D. Axonal degeneration in motor neuron disease. Neurodegener. Dis. 2007, 4, 431–442. [CrossRef]

19. Gentile, F.; Scarlino, S.; Falzone, Y.M.; Lunetta, C.; Tremolizzo, L.; Quattrini, A.; Riva, N. The Peripheral Nervous System in Amyotrophic Lateral Sclerosis: Opportunities for Translational Research. Front. Neurosci. 2019, 13, 601. [CrossRef]

20. Rahman, M.R.; Islam, T.; Shahjaman, M.; Quinn, J.M.W.; Holsinger, D.; Moni, M.A. Identification of common molecular biomarker signatures in blood and brain of Alzheimer’s disease. bioRxiv 2018. [CrossRef]

21. Brooks, B.R.; Miller, R.G.; Swash, M.; Munsat, T.L.; World Federation of Neurology Research Group on Motor Neuron, D. El Escorial revisited: Revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph. Lateral Scler. Other Mot. Neuron Disord. 2000, 1, 293–299. [CrossRef] [PubMed]

22. Abrahams, S.; Newton, J.; Niven, E.; Foley, J.; Bak, T.H. Screening for cognition and behaviour changes in ALS. Amyotroph. Lateral Scler. Other Mot. Neuron Disord. 2014, 15, 9–14. [CrossRef] [PubMed]

23. Lek, M.; Karczewski, K.J.; Minikel, E.V.; Samocha, K.E.; Banks, E.; Fennell, T.; O’Donnell-Luria, A.H.; Ware, J.S.; Hill, A.J.; Cummings, B.B.; et al. Analysis of protein-coding genetic variation in 60,706 humans. Nature 2016, 536, 285–291. [CrossRef] [PubMed]

24. Yilihamu, M.; He, J.; Liu, X.; Tian, J.; Fan, D. GLT8D1 may not be significant in Chinese sporadic amyotrophic lateral sclerosis patients. Neurobiol. Aging 2021, 102, 224.e1–224.e3. [CrossRef]

25. Alluqmani, M.; Basit, S. Association of SORD mutation with autosomal recessive asymmetric distal hereditary motor neuropathy. BMC Med. Genom. 2022, 15, 88. [CrossRef]

26. Wu, C.; Xiang, H.; Chen, R.; Zheng, Y.; Zhu, M.; Chen, S.; Yu, Y.; Peng, Y.; Yu, Y.; Deng, J.; et al. Genetic spectrum in a cohort of patients with distal hereditary motor neuropathy. Ann. Clin. Transl. Neurol. 2022, 9, 633–643. [CrossRef]

27. Lin, Z.; Li, X.; Huang, S.; Zhao, H.; Liu, L.; Cao, W.; Liu, X.; Tang, B.; Zhang, R. Genetic and clinical features of sorbitol dehydrogenase gene-related Charcot-Marie-Tooth disease in Chinese population. Chin. J. Neurol. 2020, 12, 882–887.

28. Frasquet, M.; Rojas-Garcia, R.; Argente-Escrig, H.; Vazquez-Costa, J.F.; Muelas, N.; Vilchez, J.J.; Sivera, R.; Millet, E.; Barreiro, M.; Diaz-Manera, J.; et al. Distal hereditary motor neuropathies: Mutation spectrum and genotype-phenotype correlation. Eur J. Neurol. 2021, 28, 1334–1343. [CrossRef]