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Mutation analysis of KIF5A in Chinese amyotrophic lateral sclerosis patients

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is an age-related fatal neurodegenerative orphan disorder that is characterized by progressive injury of both the upper and lower motor neurons. Recently, loss-of-function mutations predominately disrupting the C-terminal amino acid sequence of KIF5A via aberrant exon 27 splicing have been reported in European ALS cohorts. However, the contributions of *KIF5A* mutations in Asian patients with ALS remain unclear. *KIF5A* sequences, including exons 26 and 27, were analyzed in a large Chinese ALS cohort comprising 33 unrelated familial ALS probands, 645 sporadic ALS (SALS) patients, 15 ALS patients presenting with concomitant frontotemporal dementia, 400 in-house controls, and 12,951 East Asian individuals from the Exome Aggregation Consortium and Genome Aggregation Database databases. As a result, the previously reported canonical splicing site mutation c.2993-1G>A was found in 1 SALS patient, while no mutations were detected in familial ALS case or ALS patients presenting with concomitant frontotemporal dementia. The frequency of *KIF5A* mutations accounts for 0.16% (1/645) of Chinese SALS patients, implying that it is an uncommon genetic determinant of ALS in Chinese patients.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is an age-related fatal neurodegenerative orphan disorder that causes injury to both the upper and lower motor neurons. ALS patients ultimately succumb to respiratory failure, with a median survival of 3–5 years from initial symptom onset. Approximately 10% of ALS patients have positive family histories (familial ALS [FALS]) with disease-causing mutations, whereas the genetic causes of the remaining 90% of cases—that is, sporadic ALS (SALS)—are largely unknown, and there exists no known cure for ALS(Brown and Al-Chalabi, 2017; Hardiman et al., 2017). Riluzole was the first medication approved by American Food and Drug Association in 1995 to extend patient survival (Miller et al., 2012). Last year, the Food and Drug Association approved a new drug called edaravone for ALS treatment, which has brought great encouragement to patients worldwide (Traynor, 2017; Writing and Edaravone, 2017).

Recent research achievements have brought advancement in understanding genetic events promoting ALS. Exome sequencing and rare variant analysis have identified enrichment of abnormal splicing at exon 27 of *KIF5A* (NM_004984.2) in FALS cases, implicating *KIF5A* as a novel ALS gene (Brenner et al., 2018). More recently, multiple centers in Europe and North America have carried out a large-scale genome-wide association study and exome-wide rare variant burden analysis, confirming that *KIF5A* is a novel ALS gene (Nicolas et al., 2018). Interestingly, all mutation sites founded in both studies predominately disrupted the C-terminal amino acid sequence by skipping exon 27 (Fig. 1A). However, ALS

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patients in the 2 above mentioned studies did not include Asian populations. Importantly, different genetic architecture is typically seen between Asian and European ALS populations (Zou et al., 2017). Our previous studies have shown that mutations in superoxide dismutase-1 gene are the most common cause of ALS in China (Liu et al., 2016). In contrast, the hexanucleotide repeat expansion in the *C9orf72* gene that is the most frequent mutation in European ALS patients is very rare in the Chinese population (Liu et al., 2013; Zou et al., 2013). Considering the distinct genetic architectures of different worldwide populations, caution should be taken in generalizing new pathogenic genes for ALS, such as *KIF5A*. Thus, the aim of the present study is to investigate the contribution of *KIF5A* mutations in the C-terminal hot spot, including exon 26 and exon 27, to Chinese ALS populations.

2. Material and methods

2.1. Study population

Over 1000 Chinese participants, including 33 unrelated FALS probands, 645 SALS patients, 15 ALS patients presenting with concomitant frontotemporal dementia, and 400 neurologically normal control subjects, were enrolled in the present study. Patient demographic features are presented in Table 1. All patients registered at the ALS clinic of the Neurology Department of Peking Union Medical College Hospital from January 2016 to April 2018 were of Han descent and from mainland China. ALS cases were diagnosed according to revised El Escorial criteria (Brooks et al., 2000). Patients were diagnosed with frontotemporal dementia according to established clinical criteria (Neary et al., 1998; Rascovsky et al., 2011). All subjects provided written informed consent for the genetic research, and the Peking Union Medical College Hospital ethics committee approved the study.

Table 1
Demographic of the patients included in the study

Variable	FALS	SALS	ALS-FTD
n	33	645	15
Mean onset age (y)	48.7 ± 11.1	51.3 ± 11.2	62.6 ± 9.0
Male, n	17	372	11

Key: ALS, amyotrophic lateral sclerosis; FALS, familial amyotrophic lateral sclerosis; FTD, frontotemporal dementia; SALS, sporadic amyotrophic lateral sclerosis.

2.2. Mutation screening

Peripheral venous blood samples were collected from patients and healthy controls. Genomic DNA was extracted using MagNA Pure LC DNA Isolation Kit I (Cat. No. 03003990001; Roche, Basel, Switzerland) according to manufacturer instructions. All participants were screened for *KIF5A* exon 26 to exon 27 sequences using polymerase chain reaction. This region was chosen because all pathogenic *KIF5A* mutations identified in ALS patients to date were located at splicing-related sites of exons 26 and 27. Forward (5′-AGGGCTGAGCAGCTCTATCA-3′) and reverse primers (5′-AGAAGCCACAGATGGGATTG-3′) were designed using Primer 3 online software (http://bioinfo.ut.ee/primer3-0.4.0/). Amplification products were directly sequenced in both directions using an ABI 3730 automated DNA sequencing system (Applied Biosystems, Foster City, CA, USA). Sample DNA sequences were aligned to a reference human genome (UCSC hg19) using the CodonCode Aligner tool. Each mutation was verified through repeated amplification and sequencing. Patients carrying *KIF5A* mutations were screened for

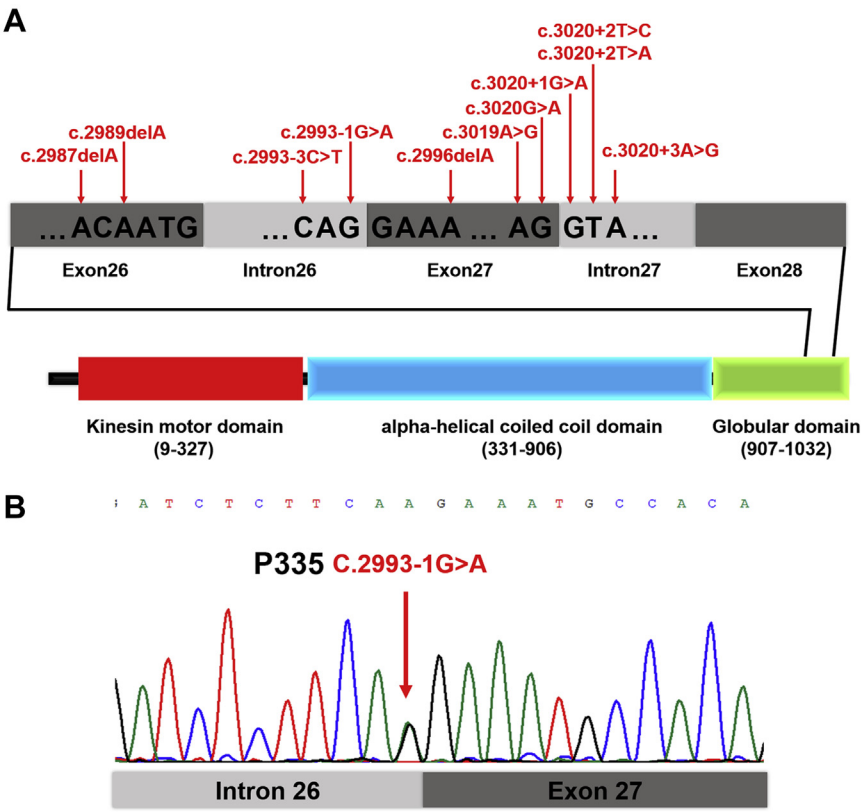

Fig. 1. ALS-associated mutations identified in KIF5A. (A) Localizations of mutations in *KIF5A* reported in prior studies. (B) DNA sequencing of a SALS patient P335 from our cohort reveals a splicing site mutation c.2993-1G>A in boundary of intron 26 and exon 27. Abbreviations: ALS, amyotrophic lateral sclerosis; SALS, sporadic amyotrophic lateral sclerosis.

other ALS-related mutations including *SOD1, ALS2, SETX, FUS, VAPB, ANG, TARDBP, FIG4, OPTN, VCP, UBQLN2, SIGMAR1, CHMP2B, PFN1, ATXN2, AR, DCTN1, NEFH, PRPH, DAO, TFG, TAF15, GRN, CHCHD10, TBK1, GLE1, CCNF, ANXA11, and TIA1*). *C9orf72* expansion was also examined using repeat-primed polymerase chain reaction.

2.3. Bioinformatic analysis

The frequency of variants in the general population was evaluated using 2 large population sequencing databases: Exome Aggregation Consortium (ExAC) and Genome Aggregation Database (gnomAD). In silico prediction of splice site mutations was conducted with Human Splicing Finder 3.1 software.

3. Results

3.1. Mutation analysis

KIF5A sequence analysis identified the canonical splice site mutation c.2993-1G>A in a SALS patient P335, which was absent from our 400 healthy control subjects. This mutation was also absent from East Asians included in the ExAC and gnomAD (Table 2). This single-nucleotide variant resided at the junction of exon 27 and intron 26 and was reported in a previous study (Fig. 1B) (Brenner et al., 2018; Nicolas et al., 2018). Human Splicing Funder 3.1 predicted that the c.2993-1G>A mutation alters the wild-type acceptor site and most likely affects splicing. In addition, screening other ALS-related genes uncovered that the same patient also carried p.E1173K (c.3517G>A, rs41309046) in *ALS2*, p.E1267K (c.3799G>A, rs146083590) in *DCTN1,* and p.S2054N (c.6161G>A, rs200778360) in *SETX* (Table 2). These 3 missense mutations all have a >0.1% allele frequency in East Asian populations in the ExAC and gnomAD.

3.2. Clinical information

Patient P335 harboring the exon 27 splice-altering mutation c.2993-1G>A was a Han male from mainland China. He presented with clinically observable fasciculations in his right upper limbs without obvious loss of muscle strength at 46 years of age. Three months later, proximal right arm weakness incepted and the patient exhibited difficulty in elevating this arm above his head. A year later, his right lower limb manifested loss of strength, but he could still walk without any help. Fifteen months after symptom onset, he was accompanied by family on a visit to our outpatient clinic. A neurological examination revealed that muscle strength of his right arm and right leg were IV^{-} and IV, respectively; left limb muscle strength was V. Bilateral biceps, triceps, knee and ankle jerk reflexes were all hyperactive. Bilateral Babinski, Chaddock, palmomental, and Hoffmann signs were all positive. Muscle atrophy was not obvious in any limb. Needle electromyography testing showed diffuse neurogenic involvement in the sternocleidomastoid and all 4 limbs. His cognitive function was normal and he had a negative family history for ALS, cognitive impairment or Charcot-Marie-Tooth/hereditary spastic paraplegia–like features. During subsequent follow-up, the patient gradually developed weakness in the left arm and leg. Now, the patient has been alive for 56 months since symptom onset and can walk a short distance, slowly, with the help of his family members.

4. Discussion

KIF5A is a microtubule-based motor protein belonging to the kinesin superfamily, which plays an important role in intracellular transport (Hirokawa et al., 2009). Previous studies have shown that *KIF5A* missense mutations in the N-terminal motor domain are associated with hereditary spastic paraplegia and Charcot-Marie-Tooth disease type 2 (Liu et al., 2014b). Recently, mutations affecting splicing exon 27 located in C-terminal of *KIF5A* that can cause FALS have been discovered using whole-exome sequencing in 426 European FALS patients (Brenner et al., 2018). Subsequently, a large-scale genome-wide association study and an independent rare variant burden analysis were conducted, finding ALS-associated mutations located at a hot spot region covering the stretch of exon 26 to exon 27 that confer a loss-of-function phenotype (Nicolas et al., 2018). The 2 studies, taken together, demonstrate *KIF5A* as a novel ALS susceptibility gene. Notably, Asian populations were not included in these 2 studies. The present study is the first interrogating ALS-associated *KIF5A* mutations in over 1000 Chinese mainland participants. We identified the canonical splice site mutation c.2993-1G>A in only 1 SALS patient. *KIF5A* mutation accounted for 0.16% (1/645) of Chinese SALS patients. We did not detect any disease-causing *KIF5A* mutations in FALS patients and ALS patients presenting with concomitant frontotemporal dementia from our cohort.

Interestingly, the patient carrying the c.2993-1G>A mutation also carried 3 different missense mutations in ALS-associated genes: *ALS2* (c.3517G>A, p.E1173K), *DCTN1* (c.3799G>A, p.E1267K), and *SETX* (c.6161G>A, p.S2054N). ALS incidence ranges from 0.31/100,000 in the Chinese Hong Kong population to 2–3/100,000 in Europeans (Chio et al., 2013; Fong et al., 1996). However, all 3 distinct ALS gene mutation sites have much higher allele frequencies in healthy East Asian populations (Table 2) than incidence of ALS. The American College of Medical Genetics and Genomics/Association for Molecular Pathology 2015 guideline for interpretation of sequence variants clearly states that “allele frequency is greater than expected for disorder” is strong evidence for benign variants (Richards et al., 2015). Thus, we consider all 3 missense variations as benign single-nucleotide polymorphisms rather than pathogenic mutations.

In terms of the relationship between genotype and phenotype, Nicolas et al. reported that ALS patients harboring *KIF5A* loss-of-function mutations present younger age of onset and longer survival (Nicolas et al., 2018). However, Brenner et al. found that clinical presentations of patients with *KIF5A* splice site mutations are similar to classical ALS syndrome comprising adult onset, rapid progression and early death (Brenner et al., 2018). The onset age of patient P335 in our cohort was 46 years, which is consistent with the mean age at onset in Chinese ALS patients (52.4 ± 12.1 years) (Liu et al., 2014a). At present, the patient is still able to walk slowly with help 56 months since first clinical presentation, suggesting slow disease development. Notably, survival times are substantially

Table 2
Description of mutations identified in the P335 SALS patient

Gene	Mutation	cDNA	dbSNP 150	ExAC (East Asian)	gnomAD (East Asian)
KIF5A (NM_004984)	-	c.2993–1G>A	-	-	-
ALS2 (NM_020919)	p.E1173K	c.3517G>A	rs41309046	2.6%	2.6%
DCTN1 (NM_004082)	p.E1267K	c.3799G>A	rs146083590	0.15%	0.21%
SETX (NM_015046)	p.S2054N	c.6161G>A	rs200778360	0.16%	0.17%

Key: dbSNP, database of single-nucleotide polymorphism; ExAC, exome aggregation consortium; gnomAD, genome aggregation database; SALS, sporadic amyotrophic lateral sclerosis.

different in patients with the same mutation site but different base changes, such as c. 3020+2T>A and c. 3020+2T>C, ranging from 34 to 124 months (Brenner et al., 2018; Nicolas et al., 2018). The above mentioned manifestations mentioned indicate that there may exist no fixed relationship between ALS-related *KIF5A* mutation and clinical phenotype. Further study is required to confirm any link between *KIF5A* genotype and phenotype.

Including mutation c.2993-1G>A identified in our study, 10 total pathogenic variants of the *KIF5A* gene are associated with ALS, all of which are found in the region surrounding exons 26 and 27 (Fig. 1A). Our analysis presents a *KIF5A* mutation frequency of 0.16% in Chinese SALS patients, implying that it is unlikely to be a common genetic cause for this population. Nevertheless, the identification of ALS-associated mutations in *KIF5A* deepens our understanding of ALS disease progression and provides a new direction for finding possible therapeutic targets in the future.

Disclosure statement

The authors have no actual or potential conflicts of interest.

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References

Brenner, D., Yilmaz, R., Muller, K., Grehl, T., Petri, S., Meyer, T., Grosskreutz, J., Weydt, P., Ruf, W., Neuwirth, C., Weber, M., Pinto, S., Claeys, K.G., Schrank, B., Jordan, B., Knehr, A., Gunther, K., Hubers, A., Zeller, D., , German ALS network MND-NET, Kubisch, C., Jablonka, S., Sendtner, M., Klopstock, T., de Carvalho, M., Sperfeld, A., Borck, G., Volk, A.E., Dorst, J., Weis, J., Otto, M., Schuster, J., Del Tredici, K., Braak, H., Danzer, K.M., Freischmidt, A., Meitinger, T., Strom, T.M., Ludolph, A.C., Andersen, P.M., Weishaupt, J.H., 2018. Hot-spot KIF5A mutations cause familial ALS. Brain 141, 688–697.

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

Brown, R.H., Al-Chalabi, A., 2017. Amyotrophic lateral sclerosis. N. Engl. J. Med. 377, 162–172.

Chio, A., Logroscino, G., Traynor, B.J., Collins, J., Simeone, J.C., Goldstein, L.A., White, L.A., 2013. Global epidemiology of amyotrophic lateral sclerosis: a systematic review of the published literature. Neuroepidemiology 41, 118–130.

Fong, K.Y., Yu, Y.L., Chan, Y.W., Kay, R., Chan, J., Yang, Z., Kwan, M.C., Leung, K.P., Li, P.C., Lam, T.H., Cheung, R.T., 1996. Motor neuron disease in Hong Kong Chinese: epidemiology and clinical picture. Neuroepidemiology 15, 239–245.

Hardiman, O., Al-Chalabi, A., Chio, A., Corr, E.M., Logroscino, G., Robberecht, W., Shaw, P.J., Simmons, Z., van den Berg, L.H., 2017. Amyotrophic lateral sclerosis. Nat. Rev. Dis. Primers 3, 17071.

Hirokawa, N., Noda, Y., Tanaka, Y., Niwa, S., 2009. Kinesin superfamily motor proteins and intracellular transport. Nat. Rev. Mol. Cell Biol. 10, 682–696.

Liu, R., Tang, L., Cai, B., Liu, X., Ye, S., Ma, Y., Zhang, H., Fan, D., 2013. C9orf72 repeat expansions are not detected in Chinese patients with familial ALS. Amyotroph. Lateral Scler. Frontotemporal Degener. 14, 630–631.

Liu, M.S., Cui, L.Y., Fan, D.S., Chinese ALS Association, 2014a. Age at onset of amyotrophic lateral sclerosis in China. Acta Neurol. Scand. 129, 163–167.

Liu, Y.T., Laura, M., Hersheson, J., Horga, A., Jaunmuktane, Z., Brandner, S., Pittman, A., Hughes, D., Polke, J.M., Sweeney, M.G., Proukakis, C., Janssen, J.C., Auer-Grumbach, M., Zuchner, S., Shields, K.G., Reilly, M.M., Houlden, H., 2014b. Extended phenotypic spectrum of KIF5A mutations: from spastic paraplegia to axonal neuropathy. Neurology 83, 612–619.

Liu, Q., Liu, F., Cui, B., Lu, C.X., Guo, X.N., Wang, R.R., Liu, M.S., Li, X.G., Cui, L.Y., Zhang, X., 2016. Mutation spectrum of Chinese patients with familial and sporadic amyotrophic lateral sclerosis. J. Neurol. Neurosurg. Psychiatry 87, 1272–1274.

Miller, R.G., Mitchell, J.D., Moore, D.H., 2012. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Cochrane Database Syst. Rev. 3, CD001447.

Neary, D., Snowden, J.S., Gustafson, L., Passant, U., Stuss, D., Black, S., Freedman, M., Kertesz, A., Robert, P.H., Albert, M., Boone, K., Miller, B.L., Cummings, J., Benson, D.F., 1998. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 51, 1546–1554.

Nicolas, A., Kenna, K.P., Renton, A.E., Ticozzi, N., Faghri, F., Chia, R., Dominov, J.A., Kenna, B.J., Nalls, M.A., Keagle, P., Rivera, A.M., van Rheenen, W., Murphy, N.A., van Vugt, J., Geiger, J.T., Van der Spek, R.A., Pliner, H.A., Shankaracharya, Smith, B.N., Marangi, G., Topp, S.D., Abramzon, Y., Gkazi, A.S., Eicher, J.D., Kenna, A., ITALSGEN Consortium, Mora, G., Calvo, A., Mazzini, L., Riva, N., Mandrioli, J., Caponnetto, C., Battistini, S., Volanti, P., La Bella, V., Conforti, F.L., Borghero, G., Messina, S., Simone, I.L., Trojsi, F., Salvi, F., Logullo, F.O., D'Alfonso, S., Corrado, L., Capasso, M., Ferrucci, L., Genomic Translation for ALS Care (GTAC) Consortium, Moreno, C.A.M., Kamalakaran, S., Goldstein, D.B., ALS Sequencing Consortium, Gitler, A.D., Harris, T., Myers, R.M., , NYGC ALS Consortium, Phatnani, H., Musunuri, R.L., Evani, U.S., Abhyankar, A., Zody, M.C., Answer ALS Foundation, Kaye, J., Finkbeiner, S., Wyman, S.K., LeNail, A., Lima, L., Fraenkel, E., Svendsen, C.N., Thompson, L.M., Van Eyk, J.E., Berry, J.D., Miller, T.M., Kolb, S.J., Cudkowicz, M., Baxi, E., Clinical Research in ALS and Related Disorders for Therapeutic Development (CReATe) Consortium, Benatar, M., Taylor, J.P., Rampersaud, E., Wu, G., Wuu, J., SLAGEN Consortium, Lauria, G., Verde, F., Fogh, I., Tiloca, C., Comi, G.P., Soraru, G., Cereda, C., French, ALS Consortium, Corcia, P., Laaksovirta, H., Myllykangas, L., Jansson, L., Valori, M., Ealing, J., Hamdalla, H., Rollinson, S., Pickering-Brown, S., Orrell, R.W., Sidle, K.C., Malaspina, A., Hardy, J., Singleton, A.B., Johnson, J.O., Arepalli, S., Sapp, P.C., McKenna-Yasek, D., Polak, M., Asress, S., Al-Sarraj, S., King, A., Troakes, C., Vance, C., de Belleroche, J., Baas, F., Ten Asbroek, A., Munoz-Blanco, J.L., Hernandez, D.G., Ding, J., Gibbs, J.R., Scholz, S.W., Floeter, M.K., Campbell, R.H., Landi, F., Bowser, R., Pulst, S.M., Ravits, J.M., MacGowan, D.J.L., Kirby, J., Pioro, E.P., Pamphlett, R., Broach, J., Gerhard, G., Dunckley, T.L., Brady, C.B., Kowall, N.W., Troncoso, J.C., Le Ber, I., Mouzat, K., Lumbroso, S., Heiman-Patterson, T.D., Kamel, F., Van Den Bosch, L., Baloh, R.H., Strom, T.M., Meitinger, T., Shatunov, A., Van Eijk, K.R., de Carvalho, M., Kooyman, M., Middelkoop, B., Moisse, M., McLaughlin, R.L., Van Es, M.A., Weber, M., Boylan, K.B., Van Blitterswijk, M., Rademakers, R., Morrison, K.E., Basak, A.N., Mora, J.S., Drory, V.E., Shaw, P.J., Turner, M.R., Talbot, K., Hardiman, O., Williams, K.L., Fifita, J.A., Nicholson, G.A., Blair, I.P., Rouleau, G.A., Esteban-Perez, J., Garcia-Redondo, A., Al-Chalabi, A., Project MinE ALS Sequencing Consortium, Rogaeva, E., Zinman, L., Ostrow, L.W., Maragakis, N.J., Rothstein, J.D., Simmons, Z., Cooper-Knock, J., Brice, A., Goutman, S.A., Feldman, E.L., Gibson, S.B., Taroni, F., Ratti, A., Gellera, C., Van Damme, P., Robberecht, W., Fratta, P., Sabatelli, M., Lunetta, C., Ludolph, A.C., Andersen, P.M., Weishaupt, J.H., Camu, W., Trojanowski, J.Q., Van Deerlin, V.M., Brown Jr., R.H., van den Berg, L.H., Veldink, J.H., Harms, M.B., Glass, J.D., Stone, D.J., Tienari, P., Silani, V., Chio, A., Shaw, C.E., Traynor, B.J., Landers, J.E., 2018. Genome-wide analyses identify KIF5A as a novel ALS gene. Neuron 97, 1268–1283.e6.

Rascovsky, K., Hodges, J.R., Knopman, D., Mendez, M.F., Kramer, J.H., Neuhaus, J., van Swieten, J.C., Seelaar, H., Dopper, E.G., Onyike, C.U., Hillis, A.E., Josephs, K.A., Boeve, B.F., Kertesz, A., Seeley, W.W., Rankin, K.P., Johnson, J.K., Gorno-Tempini, M.L., Rosen, H., Prioleau-Latham, C.E., Lee, A., Kipps, C.M., Lillo, P., Piguet, O., Rohrer, J.D., Rossor, M.N., Warren, J.D., Fox, N.C., Galasko, D., Salmon, D.P., Black, S.E., Mesulam, M., Weintraub, S., Dickerson, B.C., Diehl-Schmid, J., Pasquier, F., Deramecourt, V., Lebert, F., Pijnenburg, Y., Chow, T.W., Manes, F., Grafman, J., Cappa, S.F., Freedman, M., Grossman, M., Miller, B.L., 2011. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 134 (Pt 9), 2456–2477.

Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W.W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K., Rehm, H.L., ACMG Laboratory Quality Assurance Committee, 2015. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the american College of medical genetics and Genomics and the association for molecular pathology. Genet. Med. 17, 405–424.

Traynor, K., 2017. FDA approves edaravone for amyotrophic lateral sclerosis. Am. J. Health Syst. Pharm. 74, 868.

Writing, G., Edaravone, A.L.S.S.G., 2017. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 16, 505–512.

Zou, Z.Y., Li, X.G., Liu, M.S., Cui, L.Y., 2013. Screening for C9orf72 repeat expansions in Chinese amyotrophic lateral sclerosis patients. Neurobiol. Aging 34, 1710.e5–1710.e6.

Zou, Z.Y., Zhou, Z.R., Che, C.H., Liu, C.Y., He, R.L., Huang, H.P., 2017. Genetic epidemiology of amyotrophic lateral sclerosis: a systematic review and meta-analysis. J. Neurol. Neurosurg. Psychiatry 88, 540–549.