

# ANXA11 mutations prevail in Chinese ALS patients with and without cognitive dementia

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## Abstract

### Objective

To investigate the genetic contribution of *ANXA11*, a gene associated with amyotrophic lateral sclerosis (ALS), in Chinese ALS patients with and without cognitive dementia.

### Methods

Sequencing all the coding exons of *ANXA11* and intron-exon boundaries in 18 familial amyotrophic lateral sclerosis (FALS), 353 unrelated sporadic amyotrophic lateral sclerosis (SALS), and 12 Chinese patients with ALS-frontotemporal lobar dementia (ALS-FTD). The transcripts in peripheral blood generated from a splicing mutation were examined by reverse transcriptase PCR.

### Results

We identified 6 nonsynonymous heterozygous mutations (5 novel and 1 recurrent), 1 splice site mutation, and 1 deletion of 10 amino acids (not accounted in the mutant frequency) in 11 unrelated patients, accounting for a mutant frequency of 5.6% (1/18) in FALS, 2.3% (8/353) in SALS, and 8.3% (1/12) in ALS-FTD. The deletion of 10 amino acids was detected in 1 clinically undetermined male with an ALS family history who had atrophy in hand muscles and myotonic discharges revealed by EMG. The novel p. P36R mutation was identified in 1 FALS index, 1 patient with SALS, and 1 ALS-FTD. The splicing mutation (c.174-2A>G) caused in-frame skipping of the entire exon 6. The rest missense mutations including p.D40G, p.V128M, p.S229R, p.R302C and p.G491R were found in 6 unrelated patients with SALS.

### Conclusions

The *ANXA11* gene is one of the most frequently mutated genes in Chinese patients with SALS. A canonical splice site mutation leading to skipping of the entire exon 6 further supports the loss-of-function mechanism. In addition, the study findings further expand the *ANXA11* phenotype, first highlighting its pathogenic role in ALS-FTD.

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## Glossary

**ALS** = amyotrophic lateral sclerosis; **ExAC** = Exome Aggregation Consortium; **FALS** = familial amyotrophic lateral sclerosis; **FTD** = frontotemporal lobar dementia; **MAF** = minor allele frequency; **PUMCH** = Peking Union Medical College Hospital; **SALS** = sporadic amyotrophic lateral sclerosis.

Amyotrophic lateral sclerosis (ALS) is a fatal neurologic disease characterized by progressive paralysis and ultimately respiratory failure within 5 years of symptom onset.<sup>1</sup> Approximately 5%–10% of ALS cases exhibit familial amyotrophic lateral sclerosis (FALS) inheritance, and causative gene mutations can be found in 60% of patients with FALS. The remaining 90%–95% of ALS cases exhibit sporadic amyotrophic lateral sclerosis (SALS), and mutations in the same genes are responsible for 10% of patients with SALS.<sup>2</sup> To date, rare variants in more than 30 genes have been reported to cause or be associated with ALS.<sup>3</sup> Recently, mutations of *ANXA11* have been identified in patients with ALS of European ancestry, but pathogenicity of *ANXA11* in other ALS cohorts remained unproved.<sup>4</sup> In the current study, we investigated *ANXA11* mutations in Chinese ALS patients with or without cognitive decline.

## Methods

### Study population

A total of 383 Chinese patients with ALS were recruited at the ALS clinic of Neurology Department, Peking Union Medical College Hospital (PUMCH) from January 2016 to August 2017. Patients were diagnosed according to the established clinical criteria and standard protocol by specialists in ALS.<sup>5–7</sup>

### Mutation screening

Genomic DNA was extracted from peripheral blood leukocytes using a QIAamp DNA Blood Midi Kit (Qiagen, Valencia, CA) according to the manufacturer's instructions. All coding exons and at least 100 bp of flanking introns of *ANXA11* (NM\_145869) were amplified and put to Sanger Sequencing with published primer sequences<sup>4</sup> using an ABI 3730 automated DNA sequencing system (Applied Biosystems). Sequence alignment were performed against human genome (UCSC hg 19) using CodonCode Aligner. Each identified mutation was reamplified and resequenced from both ends with the same primer pairs. Rare variants (minor allele frequency [MAF] < 0.1%) with high conservation were further assessed for pathogenicity using online prediction software, SIFT (sift.bii.a-star.edu.sg), and PolyPhen-2 (genetics.bwh.harvard.edu/pph2/). Bioinformatics analysis software MutationTaster (mutationtaster.org), ESEfinder 3.0 (krainer01.cshl.edu/cgi-bin/tools/ESE3/esefinder.cgi?process=home), and Human Splicing Finder 3.0 (umd.be/HSF3/index.html) were applied to predict the effect of mutation on mRNA splicing.

The current cohort of patients had been screened for known ALS genes (*SOD1*, *ALS2*, *SETX*, *FUS*, *VAPB*, *ANG*, *TARDBP*, *FIG4*, *OPTN*, *VCP*, *UBQLN2*, *SIGMAR1*, *CHMP2B*, *PFN1*,

*C9ORF72*, *ATXN2*, *AR*, *DCTN1*, *NEFH*, *PRPH*, *DAO*, *TFG*, *TAF15*, and *GRN*) using a massive parallel sequencing gene panel by the Ion Torrent PGM system as described before<sup>8</sup> and Sanger sequencing of genes including *CHCHD10*, *TBK1*, *CCNF*, and *GLE1*. *C9orf72* expansion was also examined using repeat-primed PCR.

### Transcripts investigation of the splicing mutation

Total RNA was extracted using TRIzol (Invitrogen) from peripheral white blood cells. Then, 2.5 µg of RNA was used to perform reverse transcriptase PCR according to the Reverse Transcription System (Promega, Madison, WI) instructions. cDNA was amplified using the primer pair *ANXA11*-RT-F (5'-CCATGAGCTACCCTGGCTAT-3') and *ANXA11*-RT-R (5'-GACTCCCCAGGCAGTCAAT-3') located at *ANXA11* exon 4 and exon 8 (shown in figure 3), respectively. The PCR products were isolated on a 1.5% agarose gel. DNA fragments of interest were gel purified and sequenced.

### Standard protocol approvals, registrations, and patient consents

The study was approved by the Ethical Review Board of PUMCH. After an informed consent form was obtained from the participant or his family, the blood specimen of the participant was collected.

## Results

The current patient cohort included 18 FALS index patients and 365 unrelated patients with SALS. Twelve patients with SALS had concomitant frontotemporal lobar dementia (ALS-FTD). Of the 12 patients with ALS-FTD, 11 met the probable behavioral variant FTD (bvFTD) diagnosis following the Rascovsky criteria,<sup>7</sup> and the remaining one was diagnosed as semantic dementia. The demographic features of the current cohort are presented in table 1.

### Mutations in *AXAN11* and updated mutation spectrum of ALS causal genes in Chinese patients with ALS

In total, we identified 6 nonsynonymous heterozygous mutations (5 novel and 1 recurrent), 1 splice site mutation, and 1 deletion of 10 amino acids (not accounted in the mutant frequency) in 11 unrelated patients, accounting for a mutant frequency of 5.6% (1/18) in FALS, 2.3% (8/353) in SALS, and 8.3% (1/12) in ALS-FTD (figures 1 and 2 and figure e-1, links.lww.com/NXG/A57). These mutations were all absent in 384 healthy controls. No additional mutations were detected in other known ALS genes. A missense variant we identified

**Table 1** Demographics of the study population

Variable	FALS	SALS	ALS-FTD
<b>N</b>	18	353	12
<b>Mean onset age (y)</b>	44.71 ± 12.54	51.92 ± 11.56	58.60 ± 9.812
<b>Male, n (%)</b>	10 (55.6)	197 (55.8)	8 (66.7)
<b>Site of onset, bulbar (%)</b>	2 (11.1)	48 (13.6)	2 (16.7)

Abbreviations: ALS = amyotrophic lateral sclerosis; FALS = familial amyotrophic lateral sclerosis; FTD = frontotemporal lobe dementia; SALS = sporadic amyotrophic lateral sclerosis.

(c.119A>G, p.D40G) was already reported in European patients with ALS. Three novel mutations (c.174-2A>G, p.A58\_Q187del; c.382G>A, p.V128M; and c.687T>A, p.S229R) were identified, which had not been documented in online databases of human polymorphisms including dbSNP147, 1000 Genomes, and Exome Aggregation Consortium (ExAC). The remaining 3 coding variants (c.107C>G, p.P36R; c.904C>T, p.R302C; and c.1471G>A, p.G491R) had an allele frequency of less than 0.005% in the ExAC database and were predicted to be damaging by bioinformatics analysis. Of note, the p.P36R mutation was detected both in patients with ALS and in patients with ALS-FTD. Detailed information concerning the *ANXA11* mutations and mutation carriers identified in the current cohort are presented in table e-1 ([links.lww.com/NXG/A56](https://links.lww.com/NXG/A56)). In addition, a deletion mutation (c.1146\_1175del, p.L383\_V392del)

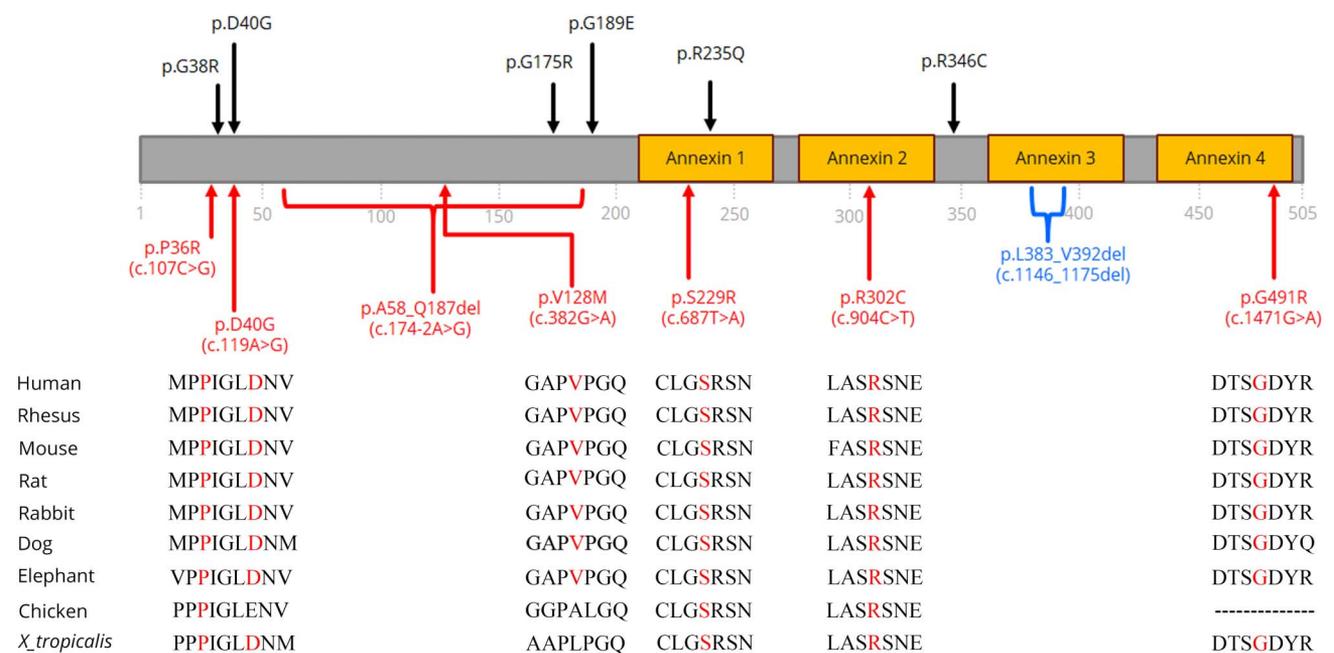
was also detected in 1 clinically undetermined male patient whose father was diagnosed as having ALS and deceased at the age of 70 years before DNA was obtainable. The son had mild atrophy in the left hand, which was noticed at the age of 31 years; myotonic discharges in bilateral limbs and thoracic paraspinal muscles were revealed by EMG (figure e-1).

### Effect of the c.174-2A>G variation on *ANXA11* mRNA splicing

The c.174-2A>G variation was predicted to affect splicing by multiple bioinformatics analysis. RNA extracted from the patient's peripheral blood showed the alternatively spliced transcript lacking the entire coding part of exon 6 (p.A58\_Q187del). Electrophoresis on a 1.5% agarose gel revealed 1 fragment encompassing exons 5–7 in the healthy control. Of interest, 3 distinct fragments were observed in the mutant patient. Sanger sequencing for those 3 fragments confirmed that an approximate 750-bp transcript was a normal spliced fragment encompassing exons 5–7, an approximate 250-bp transcript was an aberrant one resulting from exon 6 skipping, and an approximate 500-bp transcript was a heterodimer consisting a normal transcript and an abnormal transcript. Therefore, the c.174-2A>G mutation affects exon 6 causing 58–187 amino acid deletions. The schematic diagram of gel fractionation and sequence traces of reverse transcriptase PCR products are shown in figure 3.

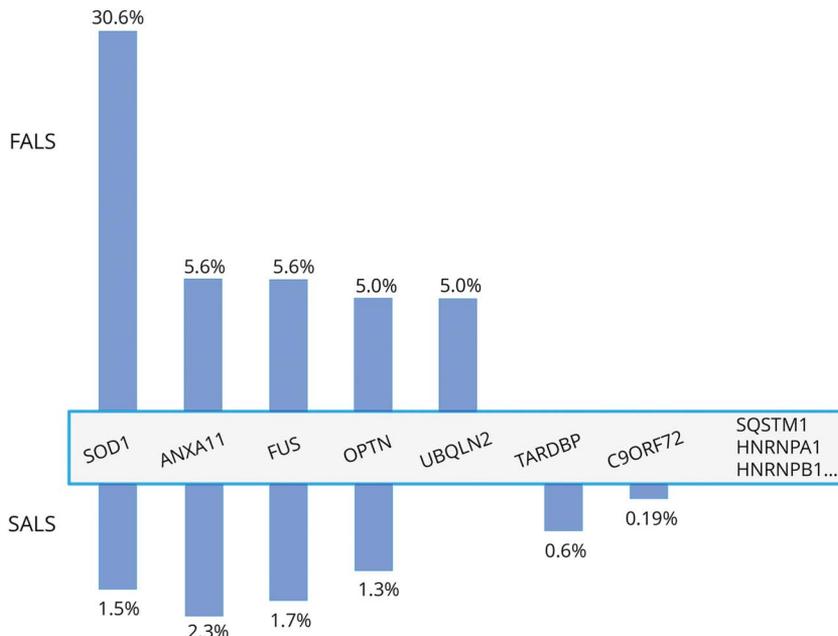
### Clinical characteristics of patients with the *ANXA11* mutation

All 10 patients (7 men and 3 women) carrying *ANXA11* variant came from Chinese mainland, and the age of symptom onset

**Figure 1** Mutations identified in *ANXA11* in ALS and ALS-FTD patients

Mutations found in the previous study and in the present study are marked in black and in red, respectively. A deletion mutation associated to a clinically undetermined patient is marked in blue. Conservation of amino acid across species is shown at the bottom. ALS = amyotrophic lateral sclerosis; FTD = frontotemporal lobe dementia.

**Figure 2** Updated mutation spectrum of FALS and SALS in Chinese populations



*SOD1* is the most common mutant gene in FALS, and *ANXA11* in SALS. FALS = familial amyotrophic lateral sclerosis; SALS = sporadic amyotrophic lateral sclerosis.

ranged from 37 to 71 years. Four patients initially exhibited dysarthria and dysphagia, and 6 patients exhibited limb weakness as the first symptom. Two patients (case 534, p.P36R, and case 395, p.P36R) died, survived 28 and 24 months, respectively. The rest of the patients are still alive, and 2 individuals (case 479, p.G491R, and case 545, p.A58\_Q187del) survived for over 5 years. All patients denied sarcoidosis. There was a patient (case 534, p.P36R) with a positive family history of ALS whose older brother had similar symptoms including dysarthria and dysphagia and died of respiratory failure 2 years after disease onset. The p.P36R mutation carrier (case 474) initially presented slurred speech at age 70 years. A few months later, his symptom quickly extended to his both legs with muscle weakness and atrophy. About a year and a half later, His family members reported that he became easily irritable, aggressive and inappropriate behaviors, such as laughing at inappropriate occasions. Over the subsequent 1 year, his both arms showed weakness. EMG demonstrated chronic and acute denervation changes in the cervical, thoracic, and lumbar segments. MRI showed bilateral temporal lobe atrophy and moderate frontal atrophy. 18F-fluorodeoxyglucose-PET imaging showed bilateral frontotemporal hypometabolism. His Mini-Mental State Examination score was 20/30, and the Montreal Cognitive Assessment (MoCA) test score was 15/30. He was diagnosed as having ALS with bvFTD. In addition, case 479 (p.G491R) was accompanied by cognitive impairment. The detailed clinical information is summarized in table e-1 ([links.lww.com/NXG/A56](http://links.lww.com/NXG/A56)).

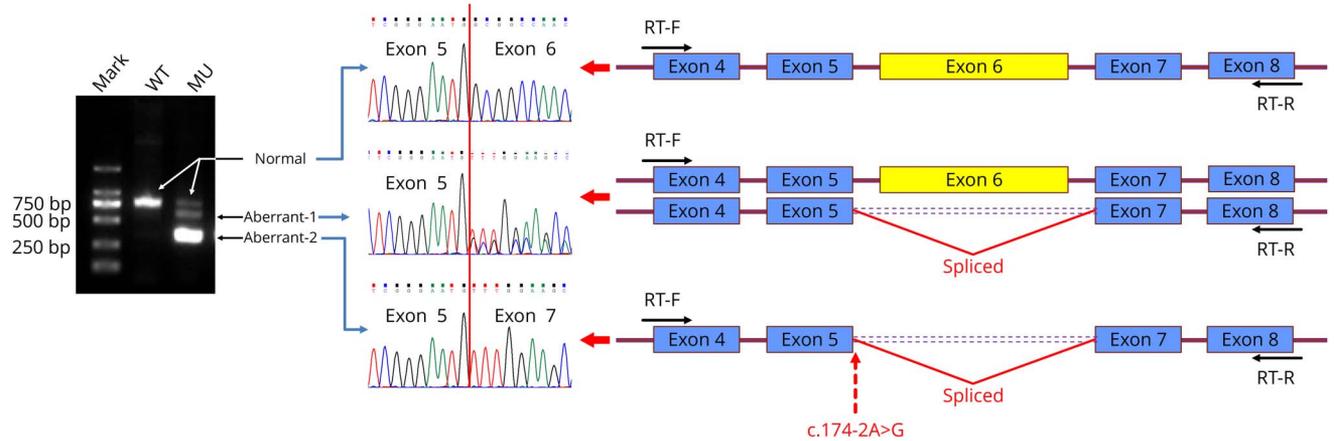
## Discussion

With evolving technologies for gene sequencing, a large number of ALS causal genes were found. In the past 3 years, 7

causative genes, including *MATR3*, *TUBA4A*, *CHCHD10*, *GLE1*, *TBK1*, *NEK1*, and *CCNF*<sup>3,9–16</sup>, were confirmed to be related to ALS. However, the frequency of mutations in these genes is very low in Chinese patients with ALS. Lately, 6 *ANXA11* heterozygous missense mutations were reported in European patients with ALS.<sup>4</sup> In the present study, we screened the *ANXA11* gene mutation in a large ALS and ALS-FTD cohort of Chinese mainland for the first time. We found 7 potentially pathogenic mutations in a total of 10 unrelated cases. The *ANXA11* mutation frequency in our current cohort is 2.6% (10/383), with 5.6% (1/18) in FALS, 2.3% (8/353) in SALS, and 8.3% (1/12) in ALS-FTD, which is higher than the frequency in a European cohort (1% in FALS and 1.7% in SALS).<sup>4</sup> A recent meta-analysis regarding Asian ALS populations revealed that the most frequent mutations were *SOD1* (SALS 1.5%, FALS 30.0%), followed by *FUS* (SALS 0.9%, FALS 6.4%), *C9orf72* (SALS 0.3%, FALS 2.3%), and *TARDBP* (SALS 0.2%, FALS 1.5%) mutations.<sup>17</sup> Moreover, we previously reported the prevalence of *FUS*, *SOD1*, and *OPTN* responsible for 1.7%, 1.5%, and 1.3% of Chinese patients with SALS respectively, whereas the mutation frequency in Chinese FALS was 30.6% for *SOD1* mutations, 5.6% for *FUS* mutations, and 5% for *OPTN* mutations.<sup>8</sup> Considering those studies together, among Chinese patients with ALS, *ANXA11* is the leading gene in SALS, and *SOD1* is the most frequent causal gene in FALS (figure 2), which indicate a different genetic architecture between Caucasians and Chinese. Therefore, the sequencing analysis of *SOD1*, *ANXA11*, and *FUS* is preferentially recommended in Chinese patients with ALS.

All variants identified except for p.D40G are first reported. The p.D40G mutation was previously reported in European

**Figure 3** Transcripts of the splicing mutation (c.174-2A>G) detected by reverse transcription PCR analysis



A 1.5% agarose gel fractionation of RT-PCR products of blood RNA shows the distinct fragments of cDNA obtained by specific primers. Lane WT represents a normal transcript in a healthy control. Lane MU represents an aberrant transcript in a patient carrying the c.174-2A>G mutation, which contains 3 different bands. Sequencing results show that the band located at 750 bp implies a normal transcript; the band located at 250 bp implies an aberrant transcript, which was caused by exon 6 skipping; and the band located at 500 bp is confirmed to be a result of formation of heterodimer consisting of 1 normal transcript and 1 aberrant transcript. ALS = amyotrophic lateral sclerosis; cDNA = complementary DNA; FTD = frontotemporal lobe dementia; RT-PCR = reverse transcription PCR.

patients with ALS and had a common European founder.<sup>4</sup> Among these mutations, p.P36R, p.R302C, and p.G491R had a very low allele frequency (<0.005%) in the ExAC database. Nevertheless, the pathogenicity of the 3 mutational sites is supported by the following evidences. First, the 3 mutations were absent from our healthy controls. Second, the 3 mutant positions are all highly conserved across species, implicating that those amino acids are of functional importance. Third, different *in silico* prediction algorithms, all demonstrated the 3 sites pathogenic. We should recognize that many definite pathogenic variants of disease-causing genes, such as cancer gene and cardiomyopathy gene, may have an allele frequency of less than 0.01% in the ExAC database.<sup>18</sup> In addition, the p.V128M variant was predicted to be benign by bioinformatics software, but it was not observed in population-based databases and our controls. No mutations of other ALS causal genes were discovered in the patient carrying p.V128M. The p.V128M mutation may play a detrimental role in ALS, and further functional experiment and additional cohorts screening will draw firm conclusions.

It is difficult to pinpoint dominant features of ANXA11-mutated patients. Patients carrying the same variant may have different clinical presentations. For instance, in contrast to our 1 patient (case 506) harboring the p.D40G variant initially presented left arm weakness at his 59 years, European p.D40G variant carriers exhibited late disease onset (average, 67 years) and mostly bulbar onset reported by the original article.<sup>4</sup> Similarly, the cognitive function varied among patients harboring the identical p.P36R variant, with normal cognitive ability and concomitant FTD observed in the present study. Moreover, we found that a splice site mutation c.174-2A>G (p.A58\_Q187del) and the living affected carrier (case 545) showed slow progression and >8 years disease duration, which

was different from other patients. These variable manifestations imply apparent clinical heterozygous among the specific ANXA11 mutation carriers. Case 660 is a p.S229R carrier of Han ethnicity, and she also harbors c.688C>T (p.R230C). The common single nucleotide polymorphism (rs1049550, C>T, p.R230C, MAF 0.44) in ANXA11 was associated with the increased risk of sarcoidosis.<sup>19</sup> Actually, the ANXA11 rs1049550 T allele is a protective factor for affecting sarcoidosis in the Chinese Han population.<sup>20</sup> It is notable that nobody had a family or personal history of sarcoidosis in our cohort. Of interest, the p.L383\_V392del mutation carrier (case 399) did not fulfill the diagnosis of ALS, although his father died of the disease. This may further suggest the varied phenotype caused by the ANXA11 mutation and would require long-term follow-up of the patient.

In the current study, 2 unrelated patients with ALS (case 534 and case 395) harboring the p.P36R mutation had no cognitive impairment. Case 534 has a positive family history. Unfortunately, unavailability of DNA samples from his family members precluded us from confirming whether the mutation segregates with the disease. The same genetic change was also detected in an individual (case 474) having ALS-FTD and had classic upper and lower motor nervous system damage combined with bilateral frontotemporal atrophy. To our knowledge, it is the first time for us to find the ANXA11 mutation in the patient with ALS-FTD, which provides further genetic support for ALS and FTD as a disease continuum. Indeed, the number of causal ALS-FTD genes increased rapidly in the past few years. Mutations in *C9orf72*, *TARDBP*, and *TBK1* are the major genetic causes in ALS-FTD, and TDP-43 inclusions as a common pathologic character are resulted from each of these variants.<sup>1,21-25</sup> Pathogenic mutations in other genes including *FUS*, *CHCHD10*, *CCNF*, *UBQLN2*, *SQSTM1*, and *VCP* have also

been found in patients with ALS-FTD.<sup>26</sup> However, the genetic etiology of quite a few patients with ALS-FTD remains unclear.

*ANXA11* is located on human chromosome 10q22.3 and encodes the 505 amino acid annexin A11 protein that belongs to a group of calcium-dependent phospholipid-binding proteins. Annexin A11 is a member of the annexin protein family. Four conserved annexin domains (annexin 1, annexin 2, annexin 3, and annexin 4) constitute its conserved C terminus.<sup>27</sup> Unlike other annexins, it has a unique long N-terminal domain containing the binding site of calyculin (residues 50–62).<sup>28</sup> Calyculin can mediate the ubiquitination and proteasomal degradation of many target proteins.<sup>29</sup> Functional data showed that p.D40G and p.G38R, which both located in proximity to the calyculin binding region, could result in abnormal binding of calyculin.<sup>4</sup> That may be the major cause of formation of annexin A11-positive inclusions in postmortem nervous tissue observed from *ANXA11* mutant carriers. Of note, the exon-skipping mutation c.174-2A>G (p.A58\_Q187del) resulting in 58–187 amino acid deletions directly impaired the functional domain, undoubtedly disrupted calyculin binding. Furthermore, the p. P36R mutation close to the residues 50–62 might affect normal calyculin binding as well, although there is no functional study to support this possibility. Combined with original article's experimental data,<sup>4</sup> 13 of the 23 *ANXA11* mutations (p.P36R, p.G38R, p.D40G, and p.A58\_Q187del) are around the binding site of calyculin. We speculate that this region is a hot spot of mutation and has significant biological functions. Those variants disrupt the normal physiologic function of annexin A11, suggesting that the pathogenesis of *ANXA11* mutations is mediated by a loss-of-function mechanism. However, the pathogenetic mechanism of the remaining *ANXA11* mutations is unclear, and further functional experiments are needed to shed light on this.

Our result showed that the *ANXA11* gene is one of the most frequently mutated genes, which runs just next to *SOD1* in Chinese patients with ALS. Patients in our cohort with *ANXA11* mutations showed varied disease characteristics, but no phenotype-genotype correlations were observed. A canonical splice site mutation leading to skipping of the entire exon 6 further supports the loss-of-function mechanism. In addition, our findings further expanded the *ANXA11* phenotype, first highlighting its pathogenic role in ALS-FTD.

### Author contributions

Kang Zhang, Qing Liu, Xue Zhang, and Liying Cui designed the experiments. Kang Zhang, Qing Liu, Keqiang Liu, Dongchao Shen, Hongfei Tai, Shi Shu, Hanhui Fu, Shuangwu Liu, and Zhili Wang performed the experiments. Qing Liu, Qingyun Ding, Xiaoguang Li, Mingsheng Liu, and Liying Cui recruited and evaluated the patients. Kang Zhang, Qing Liu, Keqiang Liu, Xue Zhang, and Liying Cui contributed to data analysis and manuscript preparation.

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### Disclosure

The authors report no disclosures. Full disclosure form information provided by the authors is available with the full text of this article at [Neurology.org/NG](http://Neurology.org/NG).

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