Clinical research

Identification of novel missense mutations (c.1156T>C and c.785T>C) in the *PSEN1* gene in Chinese families with early-onset Alzheimer's disease

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Abstract

Introduction: Mutations in the presenilin 1 (*PSEN1*) gene are associated with the inherited form of early-onset Alzheimer's disease (AD). Currently, more than 200 *PSEN1* mutations have been identified.
Material and methods: Two Chinese families with early-onset Alzheimer's disease were enrolled in this study. Their clinical and radiological profiles were analyzed, and their genomic DNA was extracted from peripheral blood and amplified for sequencing. The sequences of all exons and intron/exon boundaries in the *PSEN1* gene were analyzed. The potential pathogenicity of the identified mutations was predicted using the SIFT and PolyPhen-2 bioinformatics software tools.
Results: In the first family, a novel heterozygous missense mutation (c.1156T>A) was identified in exon 11 of the *PSEN1* gene. This nucleotide substitution led to an amino acid change from phenylalanine to leucine at codon 386 (p.F386L), and was predicted to be 'deleterious' by SIFT and 'probably damaging' by PolyPhen-2. This mutation was not consistent across all family members with the disease. In the second family, a novel heterozygous missense mutation (c.785T>C) was identified in exon 8 of the *PSEN1* gene, which also caused an amino acid change (p.L262S). This mutation was also predicted to be 'deleterious' by SIFT and 'probably damaging' by PolyPhen-2.
Conclusions: We identified two novel heterozygous missense mutations (c.1156T>C and c.785T>C) in the *PSEN1* gene in separate Chinese families with early-onset Alzheimer's disease. This study provides new *PSEN1* gene mutation profiles, which help to elucidate the pathogenesis of early-onset Alzheimer's disease.

Key words: early-onset Alzheimer's disease, presenilin 1, *PSEN1,* mutation, DNA sequencing, Chinese.

Introduction

Alzheimer's disease is a degenerative and progressive disorder of the brain, and is the most common neurological condition that leads to dementia. Typically, Alzheimer's disease can be classified into two forms: early-onset Alzheimer's disease (onset before the age of 65 years) affects approximately 95% of patients, and late-onset Alzheimer's disease (onset at or after the age of 65 years) affects only a small proportion

of the patients (< 5%) [1]. Early-onset Alzheimer's disease can sporadically develop or be inherited; the latter subset is considered to be an autosomal dominant disease, and linkage studies have confirmed that it is associated with mutations in the genes encoding the β-amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*) [2]. As previously reported, the proportion of families linked to the mutations of the three genes has been estimated at 78% for *PSEN1*, 18% for *APP*, and 4% for *PSEN2* [3]. Currently, more than 200 mutations in the *PSEN1* gene have been documented in the Alzheimer Research Forum Database (http://www.alzforum.org/mutation) and Alzheimer Disease & Frontotemporal Dementia Mutation Database (http://www.molgen.ua.ac.be/admutations).

The *PSEN1* gene, located on chromosomes 14q24.3, consists of 13 exons that encode for a 467-amino-acid protein that is extensively expressed in neural tissue that includes the cortex, cerebellum and hippocampus [4, 5]. The PSEN1 protein contains 9 transmembrane domains and is a catalytic subunit of γ-secretase, an enzyme that performs an initial endopeptidase cleavage of the substrates (e.g. β-amyloid precursor protein) followed by a continuous carboxypeptidase-like cleavage. These cleavage effects are widely involved in a variety of physiological functions, including myelin repair, vascular regulation and the immune response. Mutations in the *PSEN1* gene may reduce the efficiency of this carboxypeptidase-like activity, leading to overproduction of the β-amyloid precursor protein. Additionally, *PSEN1* mutations also affect the endopeptidase activity, and to varying degrees, disturb the processing of substrates other than APP [6]. As reported, missense mutations in the *PSEN1* gene can lead to an increase in the proportion of Aβ42/Aβ40, which is a plausible explanation for the pathophysiology of early-onset Alzheimer's disease [7].

To date, little is known about the genetic alterations that lead to early-onset Alzheimer's disease in the Chinese population [5]. Some researchers have found that pathogenic mutations of autosomal dominant diseases usually exhibit remarkable genetic heterogeneity among different races and ethnicities [8, 9]. In the current study, we investigated the genetic defects of early-onset Alzheimer's disease in two Chinese families.

Material and methods

Subjects

This study was approved by the local Ethics Committee and written informed consent was obtained from each participant. The patients (probands) were recruited from the Department of Neurology at the First Hospital of Shanxi Medical University. The pedigree of each proband was established with the help of family members, and their clinical, radiological, and laboratory profiles were collected. The individual's cognitive function was assessed using the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), and the Activities of Daily Living Scale (ADL). The analyses also included 100 unaffected individuals of matched geographical ancestry as healthy control individuals.

Mutation screening

Peripheral blood samples were obtained from the proband and the family members. Genomic DNA was extracted from the peripheral blood (~300 µl) using the RelaxGene Blood DNA System (Tiangen Biotech Co., Ltd., Beijing, China). The purity and quantity of DNA were determined using a Nanodrop 2000 spectrophotometer and an Invitrogen Qubit 3.0 fluorometer (Thermo Fisher Scientific, Inc., Waltham, MA, USA). The hybrid selection of genomic DNA was performed using an Agilent SureSelect Human All Exon Kit v6 (Agilent Technologies, Inc., Santa Clara, CA, USA). DNA libraries were purified by magnetic beads (AMPure XP beads; Beckman Coulter, Inc., Brea, CA, USA). Coding regions and intron/exon boundaries were enriched, and sample quality control was conducted by an Agilent 2100 Bioanalyzer system (Agilent Technologies, Inc.). The extracted DNA was stored at –20°C and prepared later for the subsequent sequencing.

DNA samples were sequenced using the Illumina HiSeq X Ten platform (Illumina, Inc., San Diego, CA, USA). The results were analyzed and annotated using an in-house pipeline. Briefly, raw reads were preprocessed to remove reads with low quality or adaptors. Read alignment was performed using the Burrows-Wheeler Aligner tool (version 0.7.17) with default parameters against the human genome assembly hg19(GRCh37) as previously described [10]. The generated bam file was sorted by SAMtools. The genome Analysis Toolkit (GATK; http://software.broadinstitute.org/gatk) was used to detect single-nucleotide variants (SNVs) and indels (< 50 bp), and the copy number variations (CNVs) were detected using a CNV kit. Then, the Variant Effect Predictor was applied to annotate SNVs, indels and CNVs. For calculating the homozygous ratio with SNV data, the following rules were adopted: i) SNPs with a depth of < 20× were removed; ii) only SNPs with a variant allele frequency between 0.2 and 0.8 were considered to be heterozygous. Moreover, subsequent filtering was restricted to the genes linked to FAD.

The potential pathogenicity of the identified variations was predicted using the Sorting Intol-

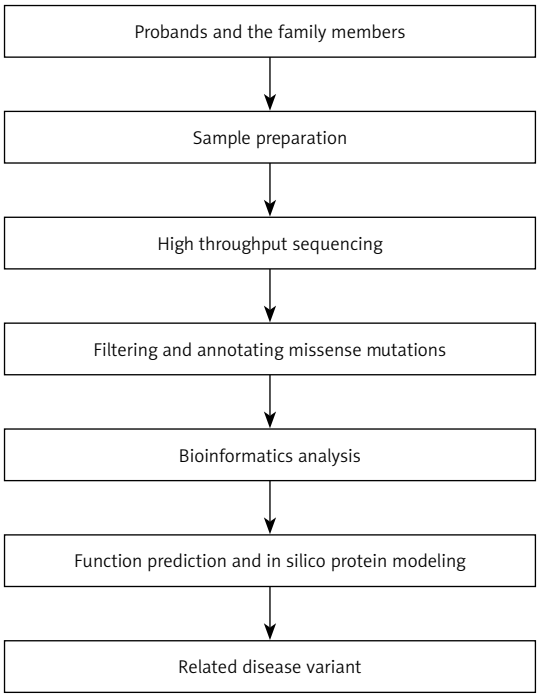

Figure 1. The flow chart illustrates the main steps of the working procedure from patient sample analysis to mutation identification, including genetic analysis and biological analysis

erant from Tolerant (SIFT) [11] and Polymorphism Phenotyping version 2 (PolyPhen-2) [12] bioinformatics software tools. Figure 1 illustrates the major steps.

Results

First family

The proband was a 47-year-old man with a 3-year history of memory deterioration. One year after onset, his relatives noted personality changes and the development of deficiencies in computing power and location orientation. He had a 10-year history of alcoholism; however, his other previous medical history was unremarkable. The neuropsychological assessment revealed that he had cognitive impairment (MMSE score: 6/30; MoCA score: 3/30; and ADL score: 41). Laboratory tests of the blood, including for vitamin B_{12}, folic acid, syphilis index, and thyroid function parameters, were all normal. Vascular ultrasound showed no abnormalities. Brain magnetic resonance imaging (MRI) revealed a reduced volume in the bilateral hippocampus (Figure 2 A) and positron emission tomography-computed tomography (PET/CT) showed temporoparietal hypoperfusion. The cerebrospinal fluid (CSF) biomarkers were as follows: the Aβ42/Aβ40 ratio was 0.03, the Aβ42 level was 295.56 pg/ml (normal range, > 550 pg/ml), the total tau level was 1540 pg/ml (normal range, < 452 g/ml), and the T181-phosphorylated tau level was 193 pg/ml (normal range, < 61 pg/ml). Based on this collective profile, a diagnosis of early-onset Alzheimer's disease was made.

The pedigree for this patient is shown in Figure 2 B. This patient's father and one of his brothers had dementia, and they exhibited similar clinical symptoms as the proband at the age of 50 years. Genetic sequencing revealed a novel heterozygous missense mutation (c.1156T>A) in exon 11 of the *PSEN1* gene (Figure 2 C). This nucleotide substitution leads to an amino acid change from phenylalanine to leucine at codon 386 (p.F386L). The mutation was not consistent in those with the disease in the family. The affected amino acid is located at the seventh transmembrane (TM7) domain of the PSEN1 protein and was predicted to be 'deleterious' by SIFT and 'probably damaging' by PolyPhen-2. No mutation of PSEN2, APP or other dementia causative genes was detected in the family. Exon 11 of PSEN1 was normal in the 100 healthy controls.

Second family

The proband was a 56-year-old man with a 5-year history of memory impairment and difficulty with communicating (especially in finding words). He had a 30-year history of alcoholism. The patient came to us 2 years after symptom onset, and a neuropsychological assessment showed cognitive impairment (MMSE score: 18/30; and MoCA score: 13/30). Oral donepezil hydrochloride was prescribed; however, after 1 year of treatment, he developed loss of orientation. A neuropsychological reassessment demonstrated that cognitive dysfunction was aggravated (MMSE score: 13/30; and MoCA score: 7/30). Laboratory tests and brain MRI were all normal. He was diagnosed with early-onset Alzheimer's disease.

The pedigree for this patients is shown in Figure 3 A. The patient's mother and uncle exhibited memory loss at the age of 72 years and 60 years, respectively. The other family members did not show dementia-like symptoms. We were unable to collect peripheral blood samples of these family members as they had died before this study took place. Nevertheless, we did obtain a DNA sample of the patient's 27-year-old son.

Sequence analysis revealed a novel heterozygous missense mutation (c.785T>C) in exon 8 of the *PSEN1* gene (Figure 3 B), which caused an amino acid change from leucine to serine at codon 262 (p.L262S). The affected amino acid is located at the sixth transmembrane (TM6) domain of the PSEN1 protein and was predicted to be 'deleterious' by SIFT and 'probably damaging' by PolyPhen-2. This mutation was predicted to be pathogenic and his son also carries the mutation. No mutation of PSEN2, APP or other dementia causative genes was detected in the family. Exon 8 of PSEN1 was normal in the 100 healthy controls.

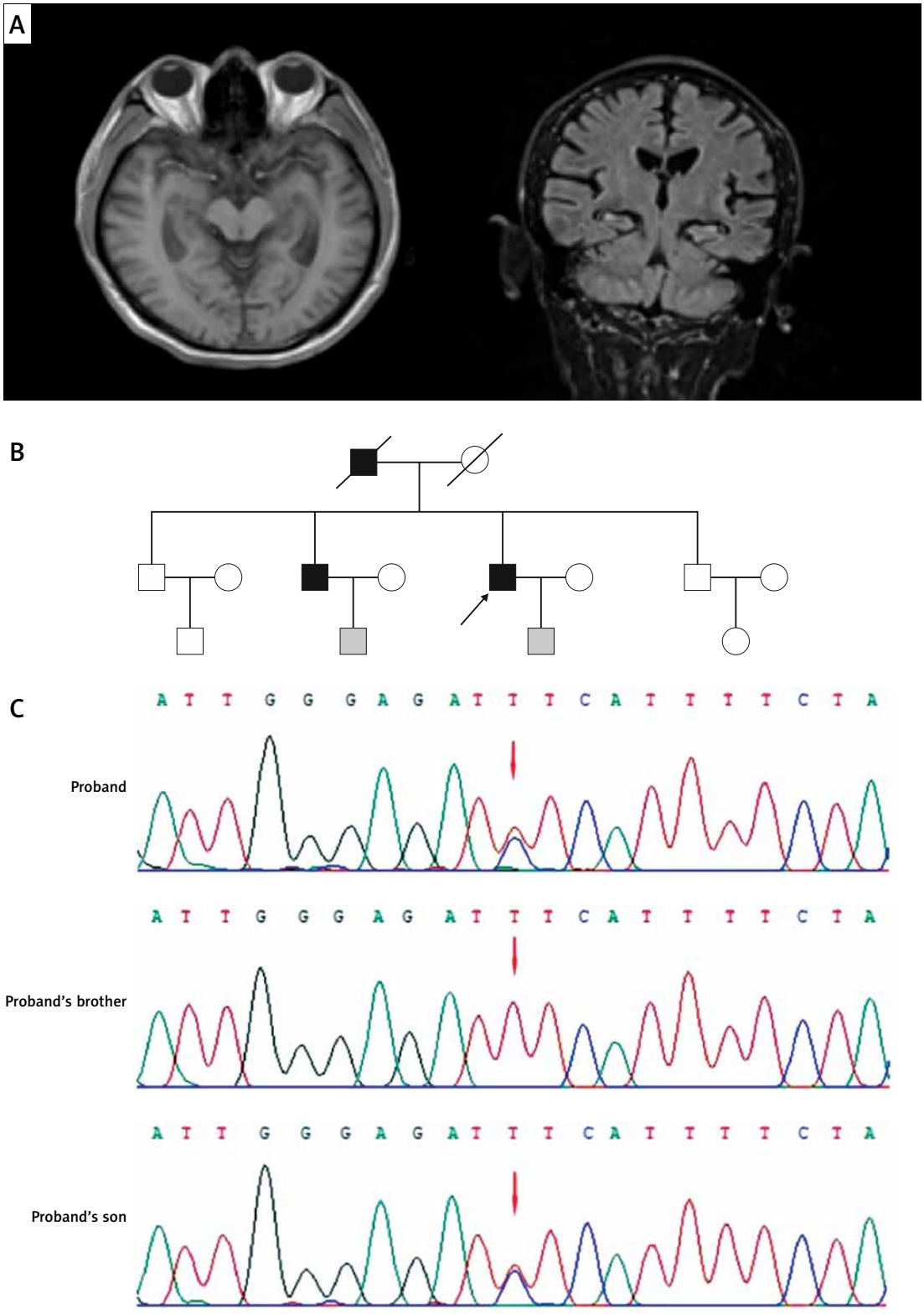

Figure 2. Neuroimaging, pedigree diagram and sequence chromatograms for the first family. **A** – Brain magnetic resonance imaging (MRI) revealed a reduced volume in the bilateral hippocampus without white matter demyelination and atrophy of cerebral cortex. **B** – In the family pedigree, the arrow designates the proband, and the circles indicate females and squares indicate males. Solid black symbols indicate the affected individuals, and solid gray symbols indicate asymptomatic mutation carriers. The proband's father and brother both carried the mutated gene disease and showed clinical symptoms. The proband and his brother's son both carried the mutated gene but showed no clinical symptoms. **C** – DNA sequencing revealed a novel heterozygous missense mutation (c.1156T>A) in exon 11 of the *PSEN1* gene. Arrows indicate the mutation sites. Blood samples were available from the son and brother of the proband with the mutation confirmed

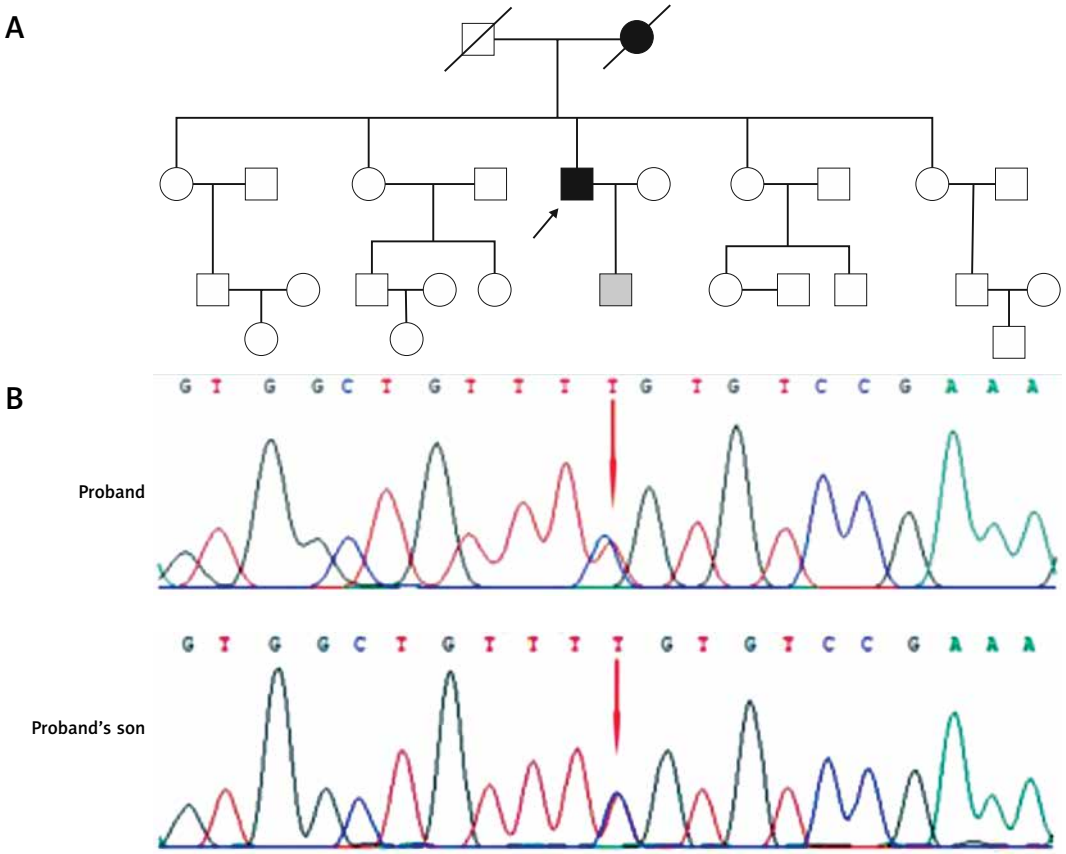

Figure 3. Pedigree diagram and sequence chromatograms for the second family. **A** – In the family pedigree, the arrow designates the proband, and the circles indicate females and squares indicate males. Solid black symbols indicate the affected individuals, and the solid gray symbol indicates the asymptomatic mutation carrier. The proband's son carried the mutated gene but showed no clinical symptoms. **B** – DNA sequencing revealed a novel heterozygous missense mutation (c.785T>C) in exon 8 of the *PSEN1* gene. Arrows indicate the mutation sites. Blood samples were available from the son of the proband with the mutation confirmed

Discussion

In the first Chinese family, typical clinical symptoms, abnormal neuroimaging scans and changes in CSF biomarkers strongly supported a diagnosis of early-onset Alzheimer's disease. DNA sequencing showed a heterozygous missense mutation (c.1156T>A) in exon 11 of the *PSEN1* gene, and was thought to be inherited from his father. This mutation has never been reported in literature or documented in the following public available databases: Alzheimer Research Forum (http://www.alzforum.org/mutation) and Alzheimer Disease & Frontotemporal Dementia Mutation Database (http://www.molgen.ua.ac.be/admutations). The affected amino acid (p.F386L) is located at the TM7 domain of the PSEN1 protein, which is considered to play an important role in protein-protein interactions. Both SIFT and PolyPhen-2 predicted that this mutation has pathogenicity. The position of amino acid 386 is a hot spot for mutations in the *PSEN1* gene, where another three mutations (p. F386L, p. F386S, p.F386I) have been reported previously in the literature [13–16]. Yagi *et al.* identified a mutation at nucleotide 1158 (c.1158C>A) in a Japanese family, which leads to an amino acid transition at p.F386L; in this family, four mutation carriers developed early amnesia, work difficulties, and even depressive symptoms at the age of 42–50 years [13]. Subsequently, an adjacent mutation (c.1157T>C) was identified in a French family, in which four carriers developed clinical spastic paraparesis at the age of 34–40 years [14]. Shea *et al.* identified a heterozygous novel missense mutation (c.1156T>A) in the *PSEN1* gene, changing phenylalanine into isoleucine at codon 386 (p.F386I). In this Chinese family, six mutation carriers developed symptoms that included memory and cognitive impairment at the age of 40–60 years, and one carrier exhibited atypical epilepsy [16].

In some experimental studies, *PSEN1* mutations were found to increase the Aβ42/Aβ40 ratio *in vitro*. In mutant cells, the secretion of Aβ42 was increased [17]. However, Sun *et al.* analyzed the effects of *PSEN1* mutations on the *in-vitro* production of Aβ42 and Aβ40 peptides by γ-secretase, and found no significant correlation between the Aβ42/Aβ40 ratio produced by a γ-secretase variant with a specific *PSEN1* mutation and the mean age at onset of patients carrying the muta-

Table I. Mutations in PSEN1 as reported in Chinese population

Mutation(s)	Nucleotide	Location (exon)	Age at onset [years]	Sex	Onset symptom	Pathogenicity	Ref
V97L	c.289G>T	4	58	Female	Amnesia	Pathogenicity	[27]
V103G	c.308T>G	4			No report	Uncertain	[28]
F105C	c.314T>G	4	45	Female	Amnesia	Uncertain	[29]
G111V	c.332G > T	4	54	Male	Amnesia	Pathogenicity	[30, 31]
A136G	c.407G>T	5			No report	Pathogenicity	[32, 33]
M139L	c.415 A > T	5	45	Female	Amnesia	Pathogenicity	[28, 34]
M139I	C.417G>A	5	38	Male	Amnesia	Pathogenicity	[5,35]
T147I	c.440C>T	5	35	Female	Amnesia	Uncertain	[5]
R157S	c.471G>T	5	60	Male	Amnesia	Uncertain	[5]
I167del	c.497_499delTTA	6	45	Female	Amnesia and spastic paraparesis	Pathogenicity	[29]
S169del	c.]507-509delATC	6	42	Female	Amnesia	Pathogenicity	[36]
L173W	c.518T>G	6	31	Male	Amnesia	Pathogenicity	[5]
F177S	c.530T>C	6	30	Male	Amnesia	Pathogenicity	[5, 37]
F177V	c.529T>G	6			No report	Uncertain	[28]
G206V	c.614A>G	7	30	Female	Amnesia	Uncertain	[38]
H214R	c.641A>G	7	41	Female	Amnesia	Uncertain	[38]
L226R	c.677T>G	7	60	Male	Amnesia	Uncertain	[39]
M233L	c.697A>C	7	40	Female	Epilepsy and amnesia	Pathogenicity	[40]
L248P	c.743T>C	7	42	Female	Amnesia	Uncertain	[29]
Y256N	c.766T>A	7	40	Female	Amnesia	Uncertain	[38]
R269H	c.806G>A	8	51	Male	Amnesia	Uncertain	[5]
K311R	c.932A>G	9	77	Male	Amnesia	Pathogenicity	[30]
R352C	c.1054C>T	10	56	Female	Amnesia	Pathogenicity	[40]
F386I	c.1156T>A	11	51	Male	Amnesia and spatial disorientation	Uncertain	[16]
F388L	c.1164C > G,	11	42	Female	Amnesia	Pathogenicity	[19]
V391G	c.1172T>G	11	22	Male	Extrapyramidal signs	Uncertain	[41]
A434T	c.1300G>A	12	38	Female	Hallucinations and delusions amnesia	Uncertain	[29]

tion [18]. Furthermore, overexpression of *PSEN1* caused by the F388L mutation significantly increased the secretion of Aβ42 and the Aβ42/Aβ40 ratio compared to the wild-type control, which may explain the development of early-onset Alzheimer's disease [19].

Additionally, we found a novel heterozygous missense mutation (c.785T>C) in exon 8 of the *PSEN1* gene, resulting in an amino acid substitution (p.L262S) at the conserved transmembrane domain TM-6. SIFT and PolyPhen-2 predicted that this variation may be a destructive mutation. In previous studies, two pathogenic mutations in the same location have been reported (L262F and L262V) [13, 19, 20]. In the family with the L262F mutation, the affected carriers developed short-term memory decline and difficulty with articulation at the age of 50 years [20]. The L262V mutation has been previously reported in two families: a family in Turkey, in which mutation carriers exhibited memory impairment at an onset age of about 50 years [21], and a family in France, in which the relevant clinical profiles were not described [14]. In our study, the age of onset and clinical symptoms were consistent with these previous reports. Therefore, we speculate that the early-onset Alzheimer's disease observed in the two Chinese families described in the current work was caused by these novel mutations. It should be noted that in the affected families, some elderly relatives remained asymptomatic, indicating that this inherited disease caused by *PSEN1* mutations may harbor an incomplete penetrance like some other autosomal dominant diseases [22]. Sun

et al. performed a functional study and found that the L262F mutation was associated with an increased Aβ42/Aβ40 ratio *in vitro* [18].

According to cumulative clinical evidence, early-onset Alzheimer's disease is characterized by an onset age of 65 years and early-onset memory impairment. Moreover, other cognitive deficits, such as language disorders, visual-spatial deficits, and behavioral disorders, are more common in early-onset Alzheimer's disease than the late-onset counterpart [23]. In addition, early-onset Alzheimer's disease may manifest with various unique features, such as spastic paralysis, early myoclonus, epilepsy, dysarthria, pseudobulbar disease, broader amyloid angiopathy and atypical amyloid plaques [24]. A systematic review showed differences in the clinical manifestation of *PSEN1* mutations before and after codon 200. While patients with a codon 200 amino-side *PSEN1* mutation had an earlier onset and were more susceptible to seizures and myoclonus, patients with a codon 200 carboxy-side mutation were more susceptible to visual space damage and spastic paraparesis [4]. However, while these results are compelling, various researchers have reported inconsistent findings overall [25]. In our study, no such clinical manifestations were noted, and a much longer follow-up is warranted.

With the rapid economic development, China's population aging problem has become increasingly serious and has attracted increasing attention. Studying the risk genes of AD has important strategic significance for in-depth understanding of the underlying mechanism of disease development and providing a strong theoretical basis for the development of anti-AD drugs. The identification of AD risk genes is mostly based on the Caucasian population, and the correlation between rare mutations and disease phenotypes may not be directly applicable to Chinese people. According to previous studies, the detection rate of PSENs in China is lower than that of the Caucasian population, and not all Caucasian susceptibility genes are present in Chinese AD [26]. We summarized the known PSEN1 mutations (Table I [27–41]) found in Chinese patients. Among them, Guo, J discovered that a novel mutation (Ser169del) in the *PSEN1* gene is related to an early-onset familial AD. Except for their early onset, the mutation produced a clinical phenotype similar to that of sporadic AD. There are two other mutations at codon 169 (Ser-169Pro [42] and Ser169Leu [43]) associated with an atypical phenotype, characterized by a very early onset (mean age of onset was 32), rapid progression (mean age of death was 38) and the presence of other phenotypes, such as seizures, generalized myoclonic jerks and so on. It shows that there are different clinical phenotypes with different amino acid transversions even at the same codon. At present, the reason for the heterogeneity of the mutant PSEN1 phenotype is not yet clear. There may be other unidentified genes and environmental factors involved, which requires further research. Several mutations in PSEN1, including N24S, V97L, G111V, M139L, L172W, and K311R, were also first identified in the Chinese population. The clinical phenotypes of the novel mutations reported by us are not significantly different from those of different amino acid transversions even at the same codon compared with previous reports.

Carrying out large-scale genetic analysis in China will help expand the understanding of AD risk genes in different ethnic groups. In summary, in order to better understand the pathogenesis of AD and formulate diagnostic and treatment strategies, it is necessary to establish a nationwide network and conduct systematic genetic analysis, which is currently lacking in China.

In conclusion, we identified two novel heterozygous missense mutations (c.1156T>C and c.785T>C) in the *PSEN1* gene in Chinese families with early-onset Alzheimer's disease. While the pathogenetic role of these mutations still needs further research, our findings provide new *PSEN1* gene mutation profiles and will help elucidate the pathogenesis of early-onset Alzheimer's disease.

Conflict of interest

The authors declare no conflict of interest.

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