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Brief communication

Identification of PSEN1 mutations p.M233L and p.R352C in Han Chinese families with early-onset familial Alzheimer's disease

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ABSTRACT

Early-onset familial Alzheimer's disease (EOFAD) is characterized by the onset of dementia symptoms before 65 years, positive family history, high genetic predisposition, and an autosomal dominant inheritance. We aimed to investigate mutations and to characterize phenotypes in Chinese EOFAD families. Detailed clinical assessments and genetic screening for mutations in the presenilin 1 (PSEN1), presenilin 2, amyloid precursor protein, and APOE genes were carried out in 4 EOFAD families. Two PSEN1 mutations (p.R352C and p.M233L) were identified in 2 EOFAD families, respectively. Mutation p.M233L was associated with prominent very early onset, rapidly progressive dementia, and neurologic symptoms, whereas p.R352C was associated with a progressive dementia, psychiatric syndrome, and chronic disease course. Both mutations are predicted to be pathogenic. Our results showed that mutations in PSEN1 gene might be common in Chinese EOFAD families.

1. Introduction

Early-onset familial Alzheimer's disease (EOFAD) is characterized by the onset of progressive dementia symptoms before 65 years, positive family history, and more aggressive course than late-onset sporadic AD. To date, more than 230 mutations have been identified in the amyloid precursor protein (*APP*), the presenilin 1 (*PSEN1*), and the presenilin 2 (*PSEN2*) genes (Bettens et al., 2010; Wu et al., 2012).

Hitherto, there are a few reports about the *PSEN1*, *PSEN2*, and *APP* gene mutations in Han Chinese families (Jiao et al., 2014; Niu et al., 2014; Peng et al., 2014). Further mutation profiling is needed. In this study, we screened mutations of the 3 AD causal genes in 4 Han Chinese EOAD families. Two *PSEN1* mutations (p.M233L and p.R352C) were identified in 2 of the 4 EOAD families. According to searches with available genetic database, p.R352C is a previously unidentified *PSEN1* mutation, and p.M233L has been reported in European patients. The 2 mutations are associated with cognitive impairment and quite different clinical spectrum.

2. Methods

This study enrolled 4 Han Chinese EOFAD families. Five patients with progressive memory loss and 7 individuals without obvious cognitive dysfunction disorder from these 4 families were clinically evaluated by Mini-Mental State Examination and Montreal Cognitive Assessment (MoCA). All patients and unaffected individuals were recruited from the outpatient psychiatry department of the First Affiliated Hospital of Kunming Medical University, Yunnan Province. Magnetic resonance image scan and

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blood testing were performed to exclude other causes of dementia. The study was approved by the Ethics Committee of Kunming Institute of Zoology, Chinese Academy of Sciences. Written informed consents were obtained from all patients or their guardians.

Pedigrees of the 4 Chinese families with EOFAD are listed in Fig. 1 and Supplementary Fig. 1. The detailed clinical features and sequencing methods are listed in the Supplementary Materials. The primer pairs and polymerase chain reaction conditions are listed in Supplementary Table 1. The APOE status was investigated following the detailed methods described in our previous study (Bi et al., 2014).

3. Results

We evaluate the clinical phenotype and the clinical assessments score for partial individuals of the 4 families (Table 1). Brain magnetic resonance image of the probands from the 4 families showed generalized-global cerebral atrophy (Supplementary Fig. 2).

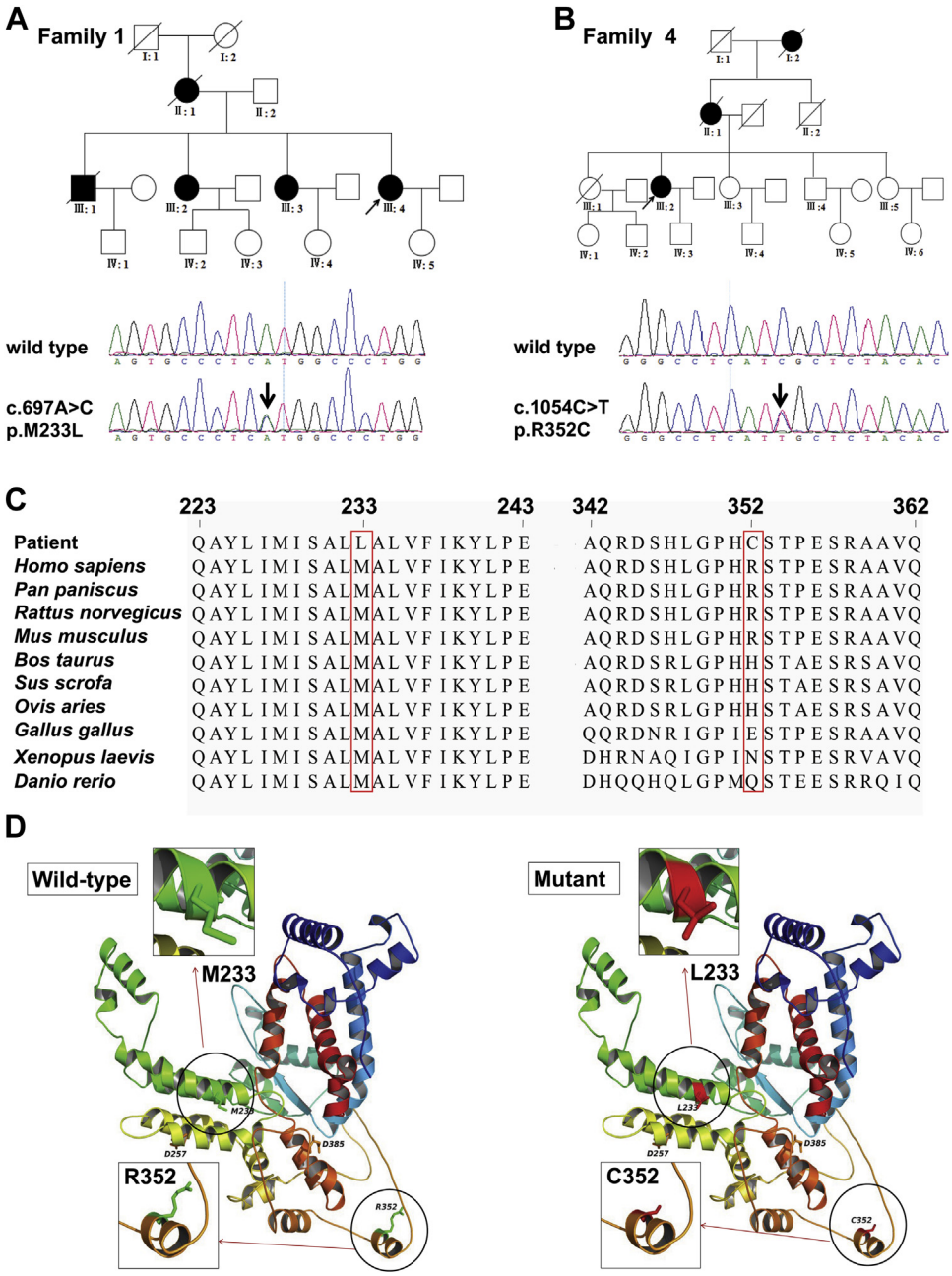

Fig. 1. Pedigrees of EOFAD families with *PSEN1* mutations, sequencing chromatogram, evolutionary conservation analysis, and homology modeling of the PSEN1 protein with and without p.M233L and p.R352C. (A) Family 1 with p.M233L (c.697A>C) mutation. (B) Family 4 with p.R352C (c.1054C>T) mutation. Probands are marked by arrow, black symbols denote affected members, white symbols denote unaffected members, square denotes man, and circle denotes women. (C) Protein sequences of *Homo sapiens* (NP_000012), *Pan paniscus* (XP_003824183), *Mus musculus* (NP_032969), *Rattus norvegicus* (NP_062036), *Bos taurus* (NP_777146), *Ovis aries* (XP_004010819), *Sus scrofa* (NP_001072135), *Gallus gallus* (NP_989494), *Xenopus laevis* (NP_001084023), and *Danio rerio* (NP_571099) were retrieved from GenBank. (D) Secondary structural elements were colored from blue (N-terminus) to red (C-terminus). The residues in codons 233 and 352 were highlighted. The wild-type and mutant residues were colored with green and red, respectively. The active sites D257 and D385 were colored with orange. Mutations p.M233L and p.R352C change the side chain of residues in the positions 233 and 352. Abbreviation: EOFAD, early-onset familial Alzheimer's disease.