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Clinical characterization of an *APP* mutation (V717I) in five Han Chinese families with early-onset Alzheimer's disease

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ABSTRACT

The missense mutation V717I in amyloid precursor protein (*APP*) gene has been reported in many early-onset familial Alzheimer's disease (EOFAD) families. However, no detailed clinical picture regarding this mutation has ever been described for Chinese EOFAD. We investigate the age at onset (AAO), initial clinical features and non-cognitive neurological symptoms in 34 affected subjects from five Han Chinese EOFAD families with the *APP*V717I mutation to characterize the clinical phenotype. The AAO was 54.7 ± 4.9 years ($n = 34$), with the *APOE* ε4 allele correlating with a decreased AAO. Prominent early affective symptoms, executive dysfunction and disorientation at onset were exhibited in 26 (76.5%), 18 (52.9%) and 16 (47%) cases, respectively. Spastic paraparesis and cerebellar ataxia occurred frequently in 13 (38.2%) and 12 (35.3%) cases, respectively, during the late stages of disease. The specific clinical phenotype of the *APP*V717I mutation for Chinese families is characterized by prominent early affective symptoms, executive dysfunction and disorientation as well as frequent late spastic paraparesis and cerebellar ataxia as compared to Western reports. We conclude that ethnic differences, environment or additional unknown factors may challenge the homogeneity of EOFAD with identical *APP* mutations.

1. Introduction

Alzheimer's disease (AD) is the most common type of dementia. It is estimated that China has the largest number of AD patients in the world [1]. Approximately up to 5% of all AD is early-onset familial Alzheimer's disease (EOFAD), which is characterized by a relatively young age of dementia onset (before 65 years) and a positive family history for dementia [2]. Three causative genes are most commonly associated with EOFAD: amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*) [3–5]. Currently, more than 230 known mutations in these three genes are responsible for about 50% of individuals with EOFAD [6].

Missense mutations in the *APP* gene, located at chromosome 21q21, account for nearly 15–20% of EOFAD [6]. Until now, 39 different *APP* gene mutations have been identified worldwide [7]. One of these, the "London" *APP*V717I mutation, a missense mutation at position 717 in exon 17 of *APP*, was the first identified in EOFAD. Since Goate et al. [3] described two families carrying the *APP*V717I mutation, 36 other families with the mutation have subsequently been reported in the world [7]. Correspondingly, the clinical phenotype associated with the *APP*V717I mutation has been described in a number of European, American and Japanese families [8–14]. Clinically, EOFAD patients with known mutations show considerable phenotypic variability, which may provide further clues to improve our understanding and future treatment of AD. Thus, further phenotypic profiling of EOFAD mutations is needed. In contrast to the large amount of research on sporadic AD (SAD), there have been few systemic studies on EOFAD in China. As far as we know, only two novel *APP* mutations (M722K, by our team, and K724M), and one known *APP* mutation (V717I) have ever been identified in Chinese EOFAD families [15–17]. To date, there have been no detailed descriptions of the clinical phenotypes associated with those *APP* mutations, even the most common *APP*V717I mutation for Chinese EOFAD.

In this study, we investigate the age at onset (AAO), initial clinical features, and non-cognitive neurological symptoms in five unrelated Chinese Han EOFAD families with the *APP*V717I mutation in order to

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characterize the clinical phenotype. We also explore whether there is a difference regarding the above-mentioned features between Chinese and Western families carrying this mutation.

2. Subjects and methods

2.1. Subjects

This study included 34 affected subjects and 106 unaffected members from five EOFAD families with the *APP*V717I mutation. The five families were chosen from established Han Chinese EOFAD cohorts by our team based on genetic screening for mutations in *PSEN1*, *PSEN2* and *APP* genes. One hundred and twenty-five living subjects (19 affected subjects with EOFAD and 106 unaffected members) were recruited from the memory clinics of Xuan Wu Hospital of the Capital Medical University over a 9-year period (2006 to 2015) in China. At the same time, the 15 deceased affected subjects were also identified by available medical and death records and multiple family respondents' reports. Probable AD was clinically diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorder Association (NINCDS-ADRDA) criteria [18]. Diagnosis of mild cognitive impairment (MCI) was determined according to the Petersen criteria [19]. Diagnosis of EOFAD was made if at least two first-degree relatives suffered from probable AD in at least two generations with an age of onset before 65 years. Vascular dementia, frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), Parkinson's disease dementia (PDD), and or dementia caused by traumatic brain injuries, tumor, infection or human immunodeficiency virus (HIV) and syphilis serology, thyroid dysfunction, low vitamin B12 level, alcohol and drug abuse etc. were excluded. The diagnosis of EOFAD patients was initially made by the junior neurologist or psychiatrist and finally reconfirmed by the dementia specialist. This study was approved by the ethics committee of Xuan Wu Hospital of the Capital Medical University. Written informed consent was obtained from every subject.

2.2. Clinical assessment

All 125 living subjects underwent a thorough clinical assessment involving general medical and neurologic examinations and laboratory tests including serum folate, HIV, vitamin B12, thyroid function, and syphilis serology. Moreover, we gathered demographic information (sex, AAO, disease duration, age at death, and education level) and clinical features for all 140 subjects. Clinical features comprised cognitive manifestations (memory, language ability, attention, visuospatial ability, and executive function), neuropsychiatric symptoms and non-cognitive neurological symptoms (spastic paraparesis, cerebellar ataxia, myoclonus, seizures, and extrapyramidal signs, etc).

2.3. Neuropsychological examination

Neuropsychological tests were conducted for the 120 living subjects (14 affected subjects and 106 unaffected members). A Chinese version of the Mini-Mental State Examination (MMSE) [20] was used to assess global cognitive function. The other neuropsychological test battery was as follows: immediate recall, delayed recall, tracking recall, and recognition of the Rey Auditory Verbal Learning Task (RAVLT)-World Health Organization (WHO) [21] (memory function); the Clock Drawing Test (CDT) [22] (visuospatial ability); the 30-item Chinese version of the Boston Naming Test (BNT) (language ability) [23]; Trail Making Test (TMT) part A [24] and Digit Span Forward Subtest of the Chinese version of the Wechsler Adult Intelligence Test (WAIS-RC) [25] (attention); and Trail Making Test (TMT) part B [24] and Digit Span Backward Subtest of the Chinese version of the WAIS-RC [25] (executive function). The Clinical Dementia Rating (CDR) [26] was used to evaluate cognitive dysfunction severity. The Neuropsychiatric Inventory (NPI) [27] was used to assess neuropsychiatric symptoms and the scoring of NPI was based on the information from the caregivers.

2.4. Magnetic resonance imaging (MRI)

The traditional non-enhancement MRI scans of the 75 living subjects (14 affected subjects and 61 unaffected members) were performed to investigate brain atrophy and white matter hyperintensities (WMHs) and to exclude other causes of dementia. MRI with coronal T1-weighted images was performed to visually examine the presence, distribution, and severity of atrophy in the hippocampus and medial temporal lobes. T2- and FLAIR-weighted sequences were used to evaluate the presence and distribution of WMHs.

2.5. Genetic study

For all 125 living subjects, peripheral blood samples were drawn into ethylene diamine tetraacetic acid (EDTA)-containing tubes for DNA sequencing. Genomic DNA was isolated from whole blood using the phenol extraction method [28]. Subsequently, all DNA samples were normalized to 50 ng/mL for polymerase chain reaction (PCR), which was performed on the exonic regions of *PSEN1* (NM_000021.3; NP_000012.1), *PSEN2* (NM_000447.2; NP_000438.2) and *APP* (NM_000484.3; NP_000475.1), as well as their corresponding flanking intronic sequences. The *PSEN1* (exons 3–12), *PSEN2* (exons 3–12), *APP* (exons 16–17) were amplified using primers designed according to the Gene Bank entries and previous studies [3,29] and are available on request. Each PCR product was sequenced using the same forward and reverse primers with BigDye v3.1 sequencing chemistry on an ABI 3730xl DNA analyzer (Applied Biosystems, USA). *APOE* genotypes were analyzed for 34 living subjects (19 affected subjects and 15 unaffected members) by PCR amplification and *Hha* I restriction enzyme digestion [30].

2.6. Statistical analysis

All data were expressed as the mean ± SEM. Comparisons of the mean values of AAO between the affected subjects with ε4 allele and the affected subjects without ε4 allele were performed using Student's *t*-test. SPSS version 18.0 was used for statistical analysis. Differences with p values of less than 0.05 were considered significant.

3. Results

3.1. Genetic analysis

The missense mutation of G to A (c.2149G>A) (Fig. 1) resulting in a valine to isoleucine substitution at codon position 717 in exon 17 of *APP* was identified in 19 affected subjects and 16 of 106 (15.1%) unaffected members in a total of 125 genotyped subjects. No coding mutations were identified in exons from the *PSEN1* and *PSEN2* genes.

The *APOE* genotypes and alleles in 19 affected subjects, 14 unaffected non-carriers and 1 unaffected carrier from 5 families were listed in Tables 1 and 5. The proportion of the *APOE* ε3/ε3 genotype was highest in these affected subjects at 63.2% (12 of 19), while *APOE* ε3/ε4 and *APOE* ε4/ε4 genotype appeared in 15.8% (3 of 19) and 21.0% (4 of 19) affected subjects, respectively. Additionally, of 14 unaffected non-carriers, 10 (71.4%) had *APOE* ε3/ε3 genotype and 4 (28.6%) had *APOE* ε4/ε3 genotype in absence of *APOE* ε4/ε4 genotype. However, the ε2/ε3 genotype was rare, and was only present in one unaffected carrier.

3.2. Demographic characteristics

Demographic data are shown in Table 1. In five Chinese families, the largest number of affected subjects observed in two families (family 2 and family 3) over five generations was 10, whereas the smallest

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