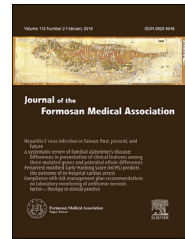




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REVIEW ARTICLE

A systematic review of familial Alzheimer's disease: Differences in presentation of clinical features among three mutated genes and potential ethnic differences



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There are great diversities of clinical phenotypes among the various familial Alzheimer's disease (FAD) families. We aimed to systematically review all the previously reported cases of FAD and to perform comparisons between Asian and white patients. In this regard, we collected individual-level data from 658 pedigrees. We found that patients with presenilin 1 (*PSEN1*) mutations had the earliest age of onset (AOO; 43.3 ± 8.6 years, $p < 0.001$) and were more commonly affected by seizures, spastic paraparesis, myoclonus, and cerebellar signs ($p < 0.001$, $p < 0.001$, $p = 0.003$, and $p = 0.002$, respectively). Patients with *PSEN2* mutations have a delayed AOO with longest disease duration and presented more frequently with disorientation ($p = 0.03$). Patients with amyloid precursor protein (*APP*) mutations presented more frequently with aggression ($p = 0.02$) and those with *APP* duplication presented more frequently with apraxia ($p = 0.03$). *PSEN1* mutations before codon 200 had an earlier AOO than those having mutations after codon 200 (41.4 ± 8.0 years vs. 44.7 ± 8.7 years, $p < 0.001$). Because 42.9% of the mutations reported are novel, the mutation spectrum and clinical

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features in Asian FAD families could be different from that of whites. Asian patients with *PSEN1* mutations presented more frequently with disorientation ($p = 0.02$) and personality change ($p = 0.01$) but less frequently with atypical clinical features. Asian patients with *APP* mutations presented less frequently with aphasia ($p = 0.02$). Thus, clinical features could be modified by underlying mutations, and Asian FAD patients may have different clinical features when compared with whites.

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Introduction

Alzheimer's disease (AD) usually has sporadic occurrence, with age of onset (AOO) in most cases being 65 years and older. Autosomal dominant familial AD (FAD) accounts for 0.5% of all AD cases and usually presents before the age of 65 years in individuals with a positive family history in at least three generations.¹ Approximately 50% of the FAD patients carry mutations in one of the three genes, namely, *presenilin 1* (*PSEN1*), *PSEN2*, and amyloid precursor protein (*APP*).¹ In these patients, > 230 mutations have been identified in one of these three genes.^{2,3} These mutations increase the production of amyloid beta 42, which results in the younger age of FAD onset.¹ Identification of FAD is of paramount importance as the family should be offered genetic counseling. In addition, identification of underlying mutations enhances our knowledge about the pathogenesis of AD and most importantly, the asymptomatic carriers of mutations can be ideal candidates for future clinical trials of disease-modifying treatment for AD.

Given the diversities of reported clinical phenotypes among the various FAD families with different mutations, it is important to perform a systematic review of the previously reported FAD families to study the variations in clinical phenotypes and genotypes and to increase the awareness of FAD to allow for accurate diagnosis of more FAD families. There has only been one comprehensive systematic review on AOO and disease course of FAD⁴ and two systematic reviews on *PSEN2* mutations.^{5,6} However, there has been no comprehensive systematic review on clinical characteristics of FAD patients having mutations in all three genes or any comparison between different ethnicities. There might be differences in clinical features between Asian and white FAD patients because of ethnic differences or differences in the location of mutations. Therefore, our objective is to systematically review all the reported cases of FAD worldwide and compare the clinical characteristics according to the mutated genes, position of mutations for *PSEN1*, and ethnicity (particularly between Asians and whites).

Methods

Data sources and study selection

We searched through Alzheimer's disease/Frontotemporal Dementia Mutation Database (AD&FTDMDb), the Alzheimer Research Forum Database (ALZFORUM), PubMed, and the

China Knowledge Resource Integrated Database KNS, between February 1, 1991, and January 31, 2015, using the following keywords: "early onset Alzheimer's disease," "autosomal dominant Alzheimer's disease," "familial Alzheimer's disease," "presenilin," "*PSEN1*," "*PSEN2*," and "*APP*". The articles retrieved were further screened to identify additional articles satisfying the inclusion criteria. The articles were evaluated individually according to the following inclusion criteria: (1) reporting the clinical features of autosomal dominant FAD in humans carrying *PSEN1*, *PSEN2*, and *APP* mutations or *APP* duplications, (2) describing those mutations with possible or proven pathogenicity as defined by the algorithm proposed by Guerreiro et al,⁷ ALZFORUM,² and AD&FTDMDb³; and (3) written in either English or Chinese. Studies describing nonpathogenic *PSEN1*, *PSEN2*, or *APP* mutations were excluded from this study.

Study selection and appraisal of the studies were performed independently by two authors (Y.-F.S. and L.-W.C.). Disagreement was resolved by consensus. To avoid potential double reporting, pedigrees for each mutation type were manually examined for possible duplicates and these were removed where identified. We have included an unreported pedigree with p.His163Arg missense mutation of *PSEN1* diagnosed in Hong Kong, including two affected family members: a female patient with AOO at 42 years and a male patient with AOO at 41 years. The combined dataset contains 658 pedigrees, 1890 individuals, of whom 790 were affected by FAD with known AOO⁷⁻⁹⁴ (please refer to supplementary materials online for a full list of references included). From each of the study, clinical features of the patients were extracted. Asymptomatic mutation carriers were not considered. The following information was extracted if available: socio-demographic characteristics (age, sex, and ethnicity), clinical features (AOO, age of death, disease duration, initial cognitive disturbances, initial neuropsychiatric symptoms, atypical manifestations, and neurological examination), types of mutation, apolipoprotein E (APOE) status, and initial Mini-Mental State Examination (MMSE) scores. AOO refers to the age of onset of progressive cognitive symptoms as determined by investigators rather than the age at which the individual received a clinical diagnosis of dementia or mild cognitive impairment. "Disease course in years" was calculated by the difference between the AOO and the known age at death. Clinical data from whites (including Europeans and non-African Americans, $n = 871$) were extracted and compared with those of Asians ($n = 137$).

Statistical analysis

Statistical analyses were performed using one-way analysis of variance or Kruskal–Wallis test for continuous variables and Chi-square test for categorical variables. A correlation analyses between the AOO and disease duration was performed by Spearman correlation. All analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). A p value ≤ 0.05 was considered statistically significant.

Results

Overall worldwide data

The characteristics of the patients included are summarized in Table 1. The number of patients suffering from mutations in *PSEN1* and *PSEN2* and in *APP* and *APP* duplication were 1444 (76.4%), 78 (4.1%), 287 (15.2%), and 81 (4.3%), respectively. Information on AOO, age of death, sex, APOE status, and presenting MMSE score was available in 790 (41.8%), 318 (16.8%), 558 (29.5%), 459 (24.3%), and 167 (8.8%) patients, respectively. The total number of mutations included in this review for *PSEN1*, *PSEN2*, and *APP* (including duplication) were 220, 19, and 28, respectively (see Table S1 in the supplementary material online for each of the mutations in our dataset).

Table 2 summarizes the AOO, sex distribution, presenting MMSE score, age of death, and disease duration for patients with mutations in *PSEN1* and *PSEN2* and in *APP* and *APP* duplications. Patients with *PSEN1* mutations had the lowest AOO and age of death (mean 43.3 ± 8.6 years and

50.5 ± 9.7 years, respectively; $p < 0.001$) and patients with *PSEN2* mutations had the oldest AOO and age of death (mean 58.1 ± 9.5 years and 71.8 ± 10.6 years, respectively; $p < 0.001$). Patients with *PSEN2* mutations had the longest disease duration [median 11 years, interquartile range (IQR) 10–15 years; $p = 0.03$]. There was a higher proportion of women with mutations in *APP*, compared with other gene mutations ($p = 0.018$). The AOO of disease did not correlate with the duration of disease before death ($p = \text{NS}$). The APOE status did not affect the age of presentation, age of death, or duration of clinical course of the disease irrespective of whether we included all the patients or calculated it according to individual mutated genes (i.e., *PSEN1*, *PSEN2*, and *APP* mutations and *APP* duplications; data not shown).

Table 3 summarizes the initial cognitive symptoms, neuropsychiatric symptoms, and atypical clinical features of patients with *PSEN1*, *PSEN2*, or *APP* mutations and *APP* duplication. The *PSEN2* mutations presented more commonly with disorientation ($p = 0.03$); *APP* mutations presented more commonly with aggression ($p = 0.02$); *APP* duplication presented more commonly with apraxia ($p = 0.03$). With regard to the atypical clinical features along the clinical course, patients with *PSEN1* mutations were more likely to be affected by atypical clinical features including seizures ($p < 0.001$), spastic paraparesis ($p < 0.001$), myoclonus ($p = 0.003$), and cerebellar features ($p = 0.002$).

Table 4 presents a comparison of clinical characteristics between patients with *PSEN1* mutations before and after codon 200. Patients with *PSEN1* mutations before codon 200 ($n = 227$) have an earlier AOO than those after codon 200 ($n = 337$; 41.4 ± 8.0 years vs. 44.7 ± 8.7 years, $p < 0.001$), but there was no difference in the total disease duration before death ($p = 0.15$). Patients with *PSEN1* mutations before codon 200 were more likely to be affected by seizures (36.9% vs. 23.1%, $p = 0.01$) and myoclonus (42.7% vs. 21.6%, $p < 0.001$) along their clinical course than those with mutations after codon 200. Patients with *PSEN1* mutations after codon 200 were more likely to be affected by visuo-spatial impairment (8.0% vs. 2.0%, $p = 0.02$) and spastic paraparesis (33.7% vs. 7.8%, $p < 0.001$).

Asian (Chinese, Japanese, and Korean) FAD and ethnic differences

Table 5 summarizes the reported FAD cases in Chinese families. There were a total of 18 Chinese families with 47 patients affected by FAD (mean age 44 ± 6.6 years; $n = 41$). As much as 56% of the Chinese families harbored novel mutations. Table 6 summarizes the reported FAD cases in Asian families. There were a total of 77 Asian families with 137 patients affected by FAD (mean age 45.0 ± 7.9 years; $n = 123$). As much as 42.9% of the Asian families harbored novel mutations. The median duration of disease was 11 years (IQR 8–13 years) and *PSEN1* was the most frequent mutation (71.5%). Asian patients with *PSEN1* mutations had the earliest mean AOO (44 ± 7.7 years, $p = 0.008$) and longest duration of disease (median 12 years; IQR 9–14 years, $p = 0.046$; Table S3 in the supplementary material online). We estimated the prevalence of

Table 1 Summary of basic characteristics of patients included.

Baseline characteristics	Findings
Total No. of pedigrees included	658
Total No. of patients	1890
Total No. of publications	262
Information on clinical features available	469
Age of onset (y)	45.6 ± 9.4 ($N = 790$)
No. of female patients	318 (57.0) ($N = 558$)
MMSE at presentation	16 ± 7.3 ($N = 167$)
Age of death (y)	53.6 ± 10.9 ($N = 318$)
Disease duration (y)	9.2 ± 4.7 ($N = 336$)
Apolipoprotein E status ($N = 459$)	
$\epsilon 2\epsilon 2$	0
$\epsilon 2\epsilon 3$	22 (4.8)
$\epsilon 2\epsilon 4$	12 (2.6)
$\epsilon 3\epsilon 3$	311 (67.8)
$\epsilon 3\epsilon 4$	102 (22.2)
$\epsilon 4\epsilon 4$	12 (2.6)

Data are presented as %, n (%) or mean $\pm$ SD, unless otherwise indicated.

MMSE = Mini-Mental State Examination; SD = standard deviation.

Table 2 Comparison of clinical characteristics of patients suffering from familial Alzheimer's disease with mutations in *PSEN1*, *PSEN2*, and *APP*.

Genotypes	<i>PSEN1</i> mutations	<i>PSEN2</i> mutations	<i>APP</i> mutations	<i>APP</i> duplication	<i>p</i>
Mean age of onset (y)	43.3 ± 8.6 (<i>N</i> = 564)	58.1 ± 9.5 (<i>N</i> = 65)	47.6 ± 7.1 (<i>N</i> = 119)	51.5 ± 5.3 (<i>N</i> = 42)	<0.001 *
Female	57.7	54.5	65	35	0.018 **
Mean MMSE score at presentation	16 ± 7.3 (<i>N</i> = 120)	18 ± 7.4 (<i>N</i> = 11)	14 ± 7.0 (<i>N</i> = 22)	12 ± 6.0 (<i>N</i> = 14)	NS *
Mean age of death (y)	50.5 ± 9.7 (<i>N</i> = 226)	71.8 ± 10.6 (<i>N</i> = 17)	58 ± 8.4 (<i>N</i> = 48)	60.4 ± 6.2 (<i>N</i> = 27)	<0.001 *
Median years of clinical course before death (IQR)	8 (5–11) (<i>N</i> = 239)	11 (10–15) (<i>N</i> = 17)	8 (6–14) (<i>N</i> = 52)	8 (5–13) (<i>N</i> = 28)	0.03 ***

Data are presented as or mean ± SD unless otherwise indicated.

APP = amyloid precursor protein; IQR = interquartile range; MMSE = Mini-Mental State Examination; NS = not significant; *PSEN* = presenilin.

* One-way analysis of variance.

** Chi-square test (*PSEN1* vs. *PSEN2* vs. *APP* vs. *APP* duplication).

*** Kruskal–Wallis test.

Table 3 Initial presenting cognitive symptoms and atypical clinical features in FAD patients.

Initial presenting symptoms	Overall	<i>PSEN1</i>	<i>PSEN2</i>	<i>APP</i>	<i>APP</i> duplications	<i>p</i> *
Amnesia	379 (84)	271 (84.2)	29 (87.9)	67 (81.7)	12 (85.7)	NS
Agnosia	28 (6.2)	18 (5.9)	2 (6.0)	5 (6.1)	3 (21.4)	NS
Apraxia	76 (16.9)	47 (14.6)	8 (24.2)	15 (18.3)	6 (42.8)	0.03
Aphasia	130 (28.1)	102 (30.6)	7 (21.2)	17 (20.7)	4 (28.6)	NS
Dyscalculia	54 (12)	37 (11.5)	4 (12.1)	13 (15.9)	0	NS
Disorientation	102 (22.7)	61 (19.0)	12 (36.3)	24 (29.3)	5 (35.7)	0.03
Apathy	58 (12.9)	40 (12.5)	7 (21.2)	10 (12.2)	1 (7.1)	NS
Depression	63 (14.0)	44 (13.7)	9 (27.2)	10 (12.2)	0	NS
Aggression	20 (4.4)	9 (2.8)	3 (9.0)	8 (9.8)	0	0.02
Auditory hallucination	15 (3.3)	14 (4.3)	0	1 (1.2)	0	NS
Visual hallucination	19 (4.2)	15 (4.6)	3 (9.0)	1 (1.2)	0	NS
Visuospatial impairment	28 (6.2)	17 (5.3)	0	7 (8.5)	3 (21.4)	NS
Delusion	22 (5.1)	12 (3.7)	4 (12.1)	5 (6.1)	1 (7.1)	NS
Personality change	40 (8.9)	33 (10.3)	2 (6.1)	5 (6.1)	0	NS
Atypical clinical features						
Parkinsonism	61 (13.3)	44 (13.4)	3 (9.1)	13 (15.9)	1 (7.1)	NS
Seizures	135 (28.0)	101 (29.4)	5 (15.2)	13 (15.9)	16 (66.7)	<0.001
Spastic paraparesis	77 (16.3)	76 (22.1)	1 (3.0)	0	0	<0.001
Myoclonus	126 (26.8)	107 (31.3)	3 (9.1)	14 (17.1)	2 (14.3)	0.003
Cerebellar sign	41 (9.1)	40 (12.5)	0	1 (1.2)	0	0.002

Data are presented as *n* (%).

APP = amyloid precursor protein; FAD = familial Alzheimer's disease; NS = not significant; *PSEN* = presenilin.

* Chi-square test.

FAD based on the reported cases and population census data from Asian countries.^{95–97} The estimated prevalence of FAD in China was 0.003 cases/100,000 population. The estimated prevalence of FAD was 0.06 cases/100,000 population in Japan and 0.02 cases/100,000 population in South Korea.

Clinical data from Asian FAD patients (including Chinese, Japanese, and Korean patients) were compared with whites (Europeans and non-African Americans) and summarized in [Tables S2 and S3](#) in the supplementary material online. When compared with whites, Asian FAD patients had a longer disease duration (median 11 years vs. 8 years,

p = 0.03). Those with *PSEN1* mutations more frequently presented with disorientation (31.8% vs. 17.8%, *p* = 0.02) and personality change (25.8% vs. 6.3%, *p* = 0.01) but less frequently had dysexecutive syndrome (1.5% vs. 11.5%, *p* = 0.01), seizures (16.7% vs. 31.9%, *p* = 0.02), spastic paraparesis (13.6% vs. 27.3%, *p* = 0.02), myoclonus (10.6% vs. 37.0%, *p* < 0.001), and cerebellar features (0% vs. 17.3%, *p* < 0.001) along the clinical course; those with *APP* mutations presented less frequently with aphasia (4.3% vs. 28.1%, *p* = 0.02). There was no difference in the distribution of mutations (i.e., before or after codon 200) between Asians and whites with *PSEN1* mutations (*p* = 0.98). We

Table 4 Comparison of clinical features between *PSEN1* mutations before or after codon 200.

Clinical features	Before codon 200	After codon 200	<i>p</i> *
Visuospatial impairment	3 (2) (<i>N</i> = 148)	14 (8) (<i>N</i> = 173)	0.02
Seizures	58 (36.9) (<i>N</i> = 157)	43 (23.1) (<i>N</i> = 186)	0.01
Spastic paraparesis	12 (7.8) (<i>N</i> = 154)	64 (33.7) (<i>N</i> = 190)	<0.001
Myoclonus	67 (42.7) (<i>N</i> = 157)	40 (21.6) (<i>N</i> = 185)	<0.001

* Chi-square test.

were only able to perform a comparison between Asian and white FAD patients with p.Val717Ile *APP* and p.His163Arg *PSEN1* mutations, which showed no difference in clinical characteristics (data not shown).

Discussion

To the best of our knowledge, we have performed the most comprehensive review of all the reported articles on FAD patients published in the past 24 years. Such a review is important because from the clinical point of view, accurate description of the FAD cases is important for allowing early detection of FAD and performing a good genetic counseling. Most of the literatures on the FAD cases were in the form of isolated case reports or case series and it is difficult for clinicians to grasp certain basic fundamental clinical characteristics including AOO, disease duration, initial clinical manifestations, or development of atypical clinical features along the clinical course. From the scientific point of view, these monogenic mutations offer us a great opportunity to link the genotypic changes with the pathophysiological and clinical manifestations to enhance our knowledge of AD.

The mean AOO and disease duration in all FAD patients were similar to the findings in another systematic review and meta-analysis (mean AOO 45.6 ± 9.4 years vs. 46.3 years; mean disease duration 9.2 ± 4.7 years vs. 9.7 ± 5.1 years).⁴ Our findings of mean AOO for patients with *PSEN1* and *APP* mutations were similar to the published systematic review and meta-analysis (*PSEN1*: 43.3 ± 8.6 years vs. 43.8 years; *APP*: 47.6 ± 7.1 years vs. 49.7 years).⁴ Our findings of mean AOO for patients with *PSEN2* mutations were similar to the other systematic review (58.1 ± 9.5 years vs. 55.3 years).⁵ All these findings signify that our studied patients were representative of the general FAD patients. We have confirmed in our systematic review that patients with *PSEN1* mutations have the earliest AOO, whereas patients with *PSEN2* mutations have the oldest AOO and longest disease duration.

With regard to the clinical features, up to 16% of the FAD patients did not present with memory problem. Some cognitive symptoms are gene specific. For example, we found that *APP* duplications more commonly presented with apraxia; *PSEN2* mutations more commonly presented with disorientation; and *APP* mutations more commonly presented with aggression. In addition, patients with *PSEN1* mutations are likely to experience atypical clinical features along their clinical course (including seizures, spastic paraparesis, myoclonus, and cerebellar signs). Clinicians should be aware about these associations during the clinical consultation. Such observations may also reflect the relationship between the underlying genes mutated and clinical manifestations. Mutation position in *PSEN1* can also result in differences in clinical manifestations: patients with mutations before codon 200 are more likely to suffer from seizures and myoclonus along the clinical course, whereas the reverse is true for visuospatial impairment and spastic paraparesis. It has been found previously that cases with mutations between codon 1 and 200 showed, in the frontal cortex, many diffuse plaques, few cored plaques, and mild or moderate amyloid angiopathy. While cases with mutations occurring after codon 200 also showed many diffuse plaques, the number and size of cored plaques were

Table 5 Summary of reported familial Alzheimer's disease in Chinese families.

Genotypes	Overall	<i>PSEN1</i> mutations	<i>PSEN2</i> mutations	<i>APP</i> mutations	<i>p</i>
Affected patients	47 (100)	29 (61.7)	2 (4.3)	16 (34.0)	—
No. of families	18 (100)	12 (66.7)	1 (5.6)	5 (27.8)	—
Mean age of onset (y)	44 ± 6.6 (<i>N</i> = 41)	44 ± 6.2 (<i>N</i> = 24)	46 ± 4.2	45 ± 8.8 (<i>N</i> = 16)	NS*
Female	34 (81.0) (<i>N</i> = 42)	19 (79.2) (<i>N</i> = 24)	2 (100) (<i>N</i> = 2)	13 (81.3) (<i>N</i> = 16)	NS**
Median MMSE at presentation (IQR)	15 (10–18) (<i>N</i> = 16)	12 (4–19) (<i>N</i> = 11)	17.5 (17–18) (<i>N</i> = 2)	14 (13–18) (<i>N</i> = 3)	NS***
Median years of clinical course before death (IQR)	10.5 (7.3–14.3) (<i>N</i> = 12)	10.5 (8.5–11.8) (<i>N</i> = 4)	10.5 (9–12) (<i>N</i> = 2)	11 (5.8–15.3) (<i>N</i> = 6)	NS***

Data are presented as *n* (%) unless otherwise indicated.

APP = amyloid precursor protein; IQR = interquartile range; MMSE = Mini-Mental State Examination; NS = not significant; *PSEN* = presenilin.

* Independent sample *t* test (*PSEN1* vs. *APP*).

** Chi-square test.

*** Mann–Whitney test (*PSEN1* vs. *APP*).

Table 6 Clinical spectrum among different genotypes of FAD in Asian (Chinese, Korean, and Japanese) families.

Genotypes	Overall	<i>PSEN1</i> mutations	<i>PSEN2</i> mutations	<i>APP</i> mutations ^a	<i>p</i>
No. of patients	137 (100)	98 (71.5)	2 (1.5)	37 (27.0)	—
No. of families	77 (100)	56 (72.7)	1 (1.3)	20 (26.0)	—
Mean age of onset (y)	45 ± 7.9 (<i>N</i> = 123)	44 ± 7.7 (<i>N</i> = 87)	46 ± 4.2	49 ± 7.6 (<i>N</i> = 34)	0.008 *
Female	73 (68.2) (<i>N</i> = 107)	47 (63.5)	2 (100)	24 (77.4)	NS **
Mean MMSE at presentation	15 ± 7.5 (<i>N</i> = 45)	15 ± 8.2 (<i>N</i> = 32)	18 ± 0.7	14 ± 6.0 (<i>N</i> = 11)	NS *
Mean years of clinical course before death	11 (8–13) (<i>N</i> = 34)	12 (9–14) (<i>N</i> = 21)	11 (9–12)	7 (5–15) (<i>N</i> = 11)	0.046 ***

Data are presented as *n* (%).

APP = amyloid precursor Protein; FAD = familial Alzheimer's disease; MMSE = Mini-Mental State Examination; NS = not significant; *PSEN* = presenilin.

^a Including two families with two patients with *APP* duplication.

* Independent sample *t* test (*PSEN1* vs. *APP*).

** Chi-square test (*PSEN1* vs. *APP*).

*** Mann–Whitney test (*PSEN1* vs. *APP*).

increased and these were often clustered around blood vessels severely affected by amyloid angiopathy.⁹⁸ The differences in clinical manifestations might be related to these underlying differences in pathological changes.

To our knowledge, the presented review was the first systematic review on Asian FAD. Asians account for only 11.7% of all FAD families in this review. In 2010, the number of individuals with dementia in Asia was estimated to be 15.94 million and 60% of them were diagnosed with AD. Based on estimates, there should be around 47,820 patients with FAD.⁹⁹ Based on these estimations, we believe that many Asian FAD patients remain under-recognized due to the lack of awareness. The comparison of clinical features between Asian and white FAD patients with *PSEN1* and *APP* mutations indicated that there might be differences in clinical characteristics between these patients. Thus, these differences in clinical features must also be considered when encountering potential Asian FAD patients. In addition, 42.9% of Asian families harbor new mutations. Diagnosing more FAD in Asians can potentially detect more novel mutations, which can facilitate our understanding of pathophysiology of AD. Asymptomatic FAD carriers can serve as good candidates for disease-modifying treatment trial. The Dominantly Inherited Alzheimer Network has been established since 2008 in Western countries.¹⁰⁰ By increasing the awareness of FAD in Asian countries, perhaps FAD families in Asia can form a similar network to facilitate research on imaging, cerebrospinal fluid biomarkers, and disease-modifying drug trials in FAD asymptomatic carriers so that definitive treatment for sporadic AD will one day be made possible.

There were limitations in this review. Approximately 42% of the included FAD patients had analyzable clinical details. The reason is that most of the articles mainly focused on the biological effects of the mutations while reporting less on the phenotypic information. In addition, novel mutations are more likely to be published compared with known mutations; therefore, our review may not be comprehensive due to publication bias. There were significant

heterogeneity of the purposes and methods among different studies and case reports; additionally, the clinical data were heterogeneous in quality; hence, there were significant selection bias during the comparison of clinical features of patients. In addition, there were significant differences in the number of Asian and white FAD patients, together with the missing clinical information, and thus, our results should be interpreted with caution and treated as a preliminary finding only. However, these results should be confirmed in future studies with more reported Asian FAD patients and once a large clinical database has been set up. It was not possible to ascertain whether specific manifestations were not reported because they were not available in the clinical history or because there was no information regarding their presence. Therefore, we considered each symptom or sign as present or absent only if their presence or absence were clearly stated, which may affect our results. We have included in our review the mutations considered as “possibly pathogenic” according to Guerreiro et al⁷ as we wanted to perform an exhaustive review on all the available FAD patients. However, we might have included noncausative or rare normal variants as well. The disease duration was unable to reflect the “true” quality of life experienced by the FAD patients.

Conclusion

In conclusion, certain clinical characteristics are gene specific: *PSEN1* mutations have the earliest AOO and were more frequently affected by atypical clinical features along the clinical course; *PSEN2* mutations have a delayed AOO with the longest disease duration and presented more frequently with disorientation; *APP* mutations presented more frequently with aggression and *APP* duplication presented more frequently with apraxia. Because 42.9% of the mutations reported are novel, the mutation spectrum and clinical features in Asian FAD families could be different from whites patients.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jfma.2015.08.004>.

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