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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

Yat-Fung Shea [a,*], Leung-Wing Chu [a,b], Angel On-Kei Chan [c], Joyce Ha [a], Yan Li [d], You-Qiang Song [e]

[a] *Department of Medicine, LKS Faculty of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong, Hong Kong Special Administrative Region*
[b] *Alzheimer's Disease Research Network, Strategic Research Theme on Aging, The University of Hong Kong, Pok Fu Lam, Hong Kong, Hong Kong Special Administrative Region*
[c] *Division of Clinical Biochemistry, Department of Pathology and Clinical Biochemistry, Queen Mary Hospital, Hong Kong, Hong Kong Special Administrative Region*
[d] *Center for Transport Phenomena, Energy Research Institute of Shandong Academy of Sciences, Jinan, People's Republic of China*
[e] *Department of Biochemistry, LKS Faculty of Medicine, The University of Hong Kong, Pok Fu Lam, Hong Kong, Hong Kong Special Administrative Region*

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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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* Corresponding author. Division of Geriatric Medicine, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, 102 Pok Fu Lam Road, Hong Kong, Hong Kong Special Administrative Region.
E-mail address: syf321@ha.org.hk (Y.-F. Shea).

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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.

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 FAD[4] 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&FTDMDB[3]; 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 AOO[7–94] (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: sociodemographic 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 ($n = 137$).