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Genetic screening in two Iranian families with early onset Alzheimer's disease identified a novel *PSEN1* mutation

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Abstract

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5. Conflict of interest

Authors declare they have nothing to report.

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A subset of early onset Alzheimer's disease (AD) is inherited as an autosomal dominant trait and is associated with mutations in the genes encoding β -amyloid precursor protein, presenilin 1, or presenilin 2. In this study, we identified two *PSEN1* mutations (one novel and one known) in two unrelated Iranian families with autosomal dominant AD. The disease progressed rapidly with a mean age at onset of 33 and 42 years and an age at death ranging from 43 to 48 years.

Keywords

PSEN1 mutation; early onset Alzheimer's disease; rapid disease progression

1. Introduction

Dementia is a major cause of disability and dependency among older people that is caused by a variety of diseases and/or injuries that affect cognitive function. Among these, Alzheimer's disease (AD) is the most common cause of dementia, accounting for ~ 60–80% of all reported dementia cases (Alzheimer's, 2016). Approximately 10% of all AD patients are classified as early-onset AD (EOAD) with clinical symptoms manifesting before the age of 65 years. A subset of EOAD is inherited as an autosomal dominant trait (ADAD) and is associated with mutations in the genes encoding β -amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), or presenilin 2 (*PSEN2*) (Tang et al., 2016). In this study, we clinically examined two Iranian families with ADAD, and performed a genetic screen for pathogenic mutations in *APP*, *PSEN1*, and *PSEN2* genes. Two *PSEN1* mutations (one known and one novel) were identified as likely disease-causing mutations.

2. Materials and Methods

2.1 Subjects

Two Iranian ADAD families with similar age at onset (AAO) were clinically examined (Fig. 1). In the first generation of Family 1 the father was cognitively healthy but now deceased, while the mother was affected by dementia with an estimated AAO of 37 years. She died at the age of 43 years after 6 years of progressive dementia. In the second generation there are four affected individuals, of which only one remains alive, and two unaffected siblings. The estimated onset of dementia in this generation ranges from 35 to 42 years (Fig. 1A). Family 2 is a three-generation family, in which the grandmother and two of her five children were diagnosed with AD. Among the fourteen descendants of the two affected individuals in generation II, nine individuals have been diagnosed with an early onset progressive dementia. Among the affected individuals, five individuals were reported to have an AAO that ranged from 33 to 45 years. Seven different participants, including four affected and three healthy individuals were available for examination (Fig. 1B). DNA samples from 87 ethnicity-matched control individuals were also available. DNA samples from all participants were isolated from whole blood using standard procedures. The local ethics committee at Shahid Beheshti University of Medical Sciences approved this study, and informed consent according to the Declaration of Helsinki was obtained from all participants.

2.2 Molecular analyses

We screened exons containing known pathogenic AD mutations by using primer pairs flanking coding exons of *APP* (exons 16 and 17), *PSEN1* (exons 4, 5, 6, 7, 8, 9, 11, and 12), and *PSEN2* (exons 4 and 5). Primer sequences are available upon request. Each PCR product was amplified with corresponding primers and sequenced as previously described (Kauwe et al., 2008; Ruiz-Martinez et al., 2017). The pathogenicity of the novel *PSEN1* missense mutation was predicted by several computational methods, including MutPred (<http://mutpred.mutdb.org/>), SNPs&GO (<http://snps-and-go.biocomp.unibo.it/snps-and-go/>), Mutation taster (<http://www.mutationtaster.org/>), and SIFT (<http://sift.jcvi.org/>). The “The Genome Aggregation Database” (gnomAD; <http://gnomad.broadinstitute.org/>) was also used to investigate its allele frequency.

3. Results

3.1 Patients’ clinical details

Family 1—In this family, recent episodic memory (unable to remember conversations, plans, appointments, and object places) and visuospatial perception, as patients couldn’t maintain orientation and got lost several times in familiar places, were the most affected symptoms in the early stages of the disease. Memories from the distant past were otherwise spared. As the disease progressed, other cognitive domains, such as working memory and executive function, were also affected and patients had problems expressing common words, which made their language progressively poorer. Behavioral changes, including depression, apathy, agitation, and aggression, and sleep disorders, such as insomnia and sundowning were commonly observed. On examination, two patients had moderately severe stage (Mini-Mental State Examination (MMSE): 8, 10; Functional Assessment Staging Test (FAST): 6b, 6c; and Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB): 14, 15) and two other patients had severe dementia (MMSE: 5, 7; FAST: 7a, 7c; and CDR-SOB: 16, 18) (Folstein et al., 1975; Morris, 1993; Sclan and Reisberg, 1992). All patients suffered from myoclonic jerks in advanced stages of disease. The disease progressed rapidly with three individuals dying within 6 years of symptom onset. Brain MRI performed in affected subject II-1 in the end stage of the disease revealed severe generalized cortical atrophy especially in frontal and temporal lobes (Fig. 1C).

Family 2—The only affected member available for examination was a 43-year-old man with a history of 5 years of progressive cognitive decline. The most prominent symptoms were problems in recent episodic memory, such as forgetting recent events, talks and dates. As the disease progressed, impairments in managing finances and job matters, paraphasic errors, and psychiatric presentations, including anxiety, irritability, and paranoid delusions, also occurred. On bedside cognitive testing the patient scored 8 out of 30 on the MMSE. He was in a moderately severe stage of disease (FAST: 6b and CDR-SOB: 12).

3.2 Molecular Analyses

Our sequencing analysis revealed that the affected individual from Family 1 carried a novel *PSEN1* mutation (c.424G>T, exon 5, Fig.1A) that resulted in p.Val142Phe amino-acid substitution. This mutation, which was found to be absent in the two available unaffected

individuals as well as in 87 ethnicity-matched neurologically normal individuals, is located in transmembrane domain 2 of *PSEN1* (data not shown). No other pathogenic variants in *APP*, *PSEN1*, and *PSEN2* were observed. The *PSEN1* Val142Phe mutation was not reported in the gnomAD or the Alzheimer Disease & Frontotemporal Dementia Mutation (<http://www.molgen.ua.ac.be/admutations/>) database. This novel variant is predicted to be pathogenic by several different computational methods, including MutPred (0.784), SNPs&Go (disease), Mutation Taster (disease-causing), and SIFT (deleterious). The wild type residue Val142 of *PSEN1* is highly conserved across different species (Fig. 1A) as well as in *PSEN2* (data not shown). We also identified a known *PSEN1* mutation (c.617G>A, exon 7, Fig. 1B) that resulted in p.Gly206Asp amino-acid substitution in all affected participants (n=5) from Family 2, while this mutation was absent in the three available healthy individuals, confirming its segregation with disease status.

4. Discussion

Here we report two novel Iranian families with ADAD due to *PSEN1* mutations. Both families presented with severe and rapid disease progression. Myoclonic seizures, which are usually reported in about 47% of the cases with *PSEN1* mutations with 23% of the patients presenting them in the advanced stages of the disease (Ryan et al., 2016), were also developed in all patients from Family 2. Although an *APP* mutation was previously reported in Iranian AD subjects (Noroozian et al., 2014), this study represents the first report of *PSEN1* genetic variability in the Iranian population. The identified *PSEN1* p.Gly206Asp mutation has been previously reported as a causal mutation in ADAD patients of various origins (Dobricic et al., 2012; Raux et al., 2005; Rogaeva et al., 2001). The AAO and disease duration in this family is similar to other families with Gly206Asp, Gly206Ser, and Gly206Val mutations (<http://www.molgen.ua.ac.be/ADMutations/>). The novel p.Val142Phe mutation was predicted to be pathogenic by various computational methods and was absent in public SNV databases and neurologically normal individuals of Iranian ancestry. Its pathogenicity is also supported by its location in the encoded protein, since several *PSEN1* pathogenic mutations occur near codon 142, including p.Asn135Asp, p.Met139Val/Ile/Thr, p.Ile143Thr/Phe, p.Met146Val/Leu/Ile, p.Thr147Ile, and p.Leu153Val, which are aligned on one helical face of transmembrane domain 2 (Hardy and Crook, 2001). Further, the AAO of 4 affected siblings in this family is similar to the AAO range (32y < mean onset age < 43y) of many known pathogenic mutations in the transmembrane domain 2.

In conclusion, we report the first *PSEN1* mutations described in the Iranian population: the *PSEN1* p.Gly206Asp, which is reported worldwide, and the novel *PSEN1* p.Val142Phe mutation, which is located in the transmembrane domain 2 like many other pathogenic *PSEN1* mutations. These findings are consistent with what has been previously described in patients with *PSEN1* mutations and expand the mutational spectrum of *PSEN1*-associated disease.

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Highlights

- First *PSEN1* mutational screening in the Iranian Population.
- Identification of novel and known *PSEN1* mutations in Iranian families with ADAD.
- This report expands the mutational spectrum of *PSEN1*-associated disease

Fig. 1. ADAD Families with *PSEN1* mutations

(A) Pedigree structure of Family 1 (left panel) and *Sanger* chromatograms showing the novel *PSEN1* p.Val142Phe mutation and its conservation in different species (right panel). (B) Pedigree structure of Family 2 (left panel) and *Sanger* chromatograms showing the known *PSEN1* p.Gly206Asp mutation (right panel). (C) Brain MRI image of patient II-1 (Family 1), in which severe hippocampal atrophy is observed (white arrows). * denotes individuals with available DNA sample. Hs: Homo sapiens; Pt: Pan troglodytes; Mm: Macaca mulatta; Cl: Canis lupus; Bt: Bos taurus; Mms: Mus musculus; Rn: Rattus norvegicus; Gg: Gallus gallus; Xt: Xenopus tropicalis; Dr: Danio rerio.