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A novel mutation in \textit{PSEN1} (p.T119I) in an Argentine family with early and late-onset Alzheimer’s disease

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Abstract

Mutations in \textit{PSEN1} are the most common cause of early-onset Alzheimer’s disease (AD). Here, we present an Argentine family with autosomal dominant early- and late-onset AD. The proband and six family members were available for genetic testing and clinical and neuropsychological assessments. Cerebrospinal fluid (CSF) biomarkers were analyzed in the proband and a cousin (mutation carrier), who also underwent positron emission tomography using F-18-2-fluoro-2-deoxy-D-glucose and Pittsburgh Compound B. Exon sequencing of \textit{PSEN1}, \textit{PSEN2} and \textit{APP} revealed a novel heterozygous variant in \textit{PSEN1} (c.356C>T; p.T119I). Median age of onset in the family was 56. However, the proband’s uncle showed initial symptoms at age 71. Although no DNA was available, he was an obligate carrier since his daughter (proband’s cousin) carried the mutation. Both the proband and his cousin exhibited biomarker evidence (CSF or imaging) of underlying Alzheimer’s pathology. Overall, our results support that the \textit{PSEN1} p.T119I variant is likely pathogenic.

\textbf{Key words:} Latin America/sequencing/biomarker/cognitive impairment/imaging/genetics

1. Introduction

Most cases of Alzheimer’s disease (AD) have no clear mode of inheritance and occur after the age of 65. By contrast, autosomal dominant AD (ADAD) is rare and usually presents between the 3\textsuperscript{rd} and 5\textsuperscript{th} decade of life. The most commonly mutated gene in ADAD is \textit{PSEN1} (MIM: 104311), followed by \textit{APP} (MIM: 104760) and \textit{PSEN2} (MIM: 600759) (Carmona et al., 2018). Even though mutations in these genes are generally regarded as causing early-onset AD, a wide variance in age of onset has been reported for some variants (Finckh et al., 2000; Lladó et al., 2010; Morris et al., 2012)
Here, we describe a novel p.T119I variant in \textit{PSEN1} in an Argentine family with early- and late-onset AD.

\section{Materials and Methods}

\subsection{Individuals}

An Argentine family of Italian descent was evaluated at the Memory and Aging Center-FLENI (Buenos Aires). The proband (Figure 1. Individual III.6) and six family members (Individuals III.10, IV.1, IV.2, IV.4, IV.5, IV.6) were available for clinical evaluation and genetic testing. Only individuals III.6 and III.10 completed neuropsychological evaluation. Individual III.5 consented to DNA analysis but later dropped out from the study. All family members gave their informed consent to participate. This investigation was approved by the Institutional Ethics Committee.

\subsection{DNA analysis}

Genomic DNA was obtained from peripheral blood leukocytes using the Wizard Genomic DNA Purification kit (Promega) according to manufacturer’s instructions. All coding exons -including exon-intron boundaries- of \textit{PSEN1}, \textit{PSEN2}, and \textit{APP} were PCR-amplified using the proband’s DNA (primer sequences available upon request). Amplicons were sequenced bi-directionally on a 3730xl DNA Analyzer (ThermoFisher Scientific). In the remaining family members, only the p.T119I variant in \textit{PSEN1} was screened by PCR amplification and sequencing of exon 5. Sequence strings were analyzed using Mutation Surveyor (Softgenetics) and FinchTV (Digital World Biology) softwares. Apolipoprotein E (\textit{APOE}) genotyping was performed as previously described (Hixson and Vernier, 1990)
2.3 Cerebrospinal fluid (CSF) biomarker analysis

CSF was obtained in the morning by lumbar puncture and collected in polypropylene tubes. Samples were centrifuged at 2000xg during 10 minutes. Supernatants were stored at -80°C until analysis. Amyloid-beta$_{1-42}$ (Aβ$_{1-42}$), total-tau (t-tau), and phosphorylated-tau at T181 (p-tau) were quantified using INNOTEST immunoassays (Fujirebio, Belgium) according to the manufacturer’s instructions.

2.4 Imaging biomarkers

Evaluation of brain amyloid deposition and cortical metabolism was performed by positron emission tomography (PET) using $^{11}$C-PiB and $^{18}$F-FDG, respectively. Fifty minutes after $^{11}$C-PiB intravenous injection, dynamic three-dimensional images were obtained during 20 minutes on a multi-slice PET/CT Discovery 690 equipment (General Electric). Thirty minutes later, $^{18}$F-FDG was injected and after a 30-minute repose, images were acquired in a similar fashion. Images from both PETs were analyzed qualitatively by two Nuclear Medicine specialists blinded to the clinical aspects, and quantitatively using proprietary normal control templates.

3. Results and Discussion

Proband III.6 was referred to our Memory Clinic by individual IV.4 after being evaluated in a different institution. Previous medical record included cognitive complaint at the age of 49, with a Mini-Mental Status Examination (MMSE) score of 28/30 and only mild impairment on a Verbal Logical Memory test. Three years later, the participant was evaluated by a psychiatrist because of depression associated with the death of individual IV.3 in a car accident. The participant also referred cognitive impairment which had started
to interfere with the job as a laboratory representative. At the age of 58, a new cognitive evaluation revealed abnormal scores in Serial Verbal Learning tests and Logical Memory “A” Trail test, as well as a Clinical Dementia Rating (CDR) score of 0.5. Thus, a diagnosis of dementia of Alzheimer’s Type was made. Currently, at age 72 the proband exhibits severe dementia (CDR: 3) and is institutionalized.

At initial consultation, individual IV.5 provided a self-drawn pedigree with collected information on dementia cases and ages of death for several family members. Given that the pedigree was highly suggestive of an autosomal dominant form of Alzheimer’s disease (AD), we sequenced coding exons of PSEN1, PSEN2 and APP in the proband’s DNA. We found a heterozygous C>T transition at position c.356 of PSEN1 (NM_000021.4). This variant predicts a threonine-to-isoleucine substitution at codon 119 (p.T119I), located in the first extracellular loop of the protein (HL-I loop). This variant is not reported in the ALZforum database (https://www.alzforum.org/mutations) nor in common variant databases such as gnomAD (http://gnomad.broadinstitute.org) or the ExomeVariant Server Database (http://evs.gs.washington.edu/EVS/). Additionally, in silico mutational analysis by PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) and SIFT (http://sift.jcvi.org/) predicted that the p.T119I variant is possibly damaging or damaging, respectively. Also, Combined Annotation Dependent Depletion (CADD) scores were: PHRED= 24 and Raw= 3.407454 (model GRCh38-v1.4), which places this variant as being in the top 1% most deleterious variants in the genome. CADD integrates several genome annotations and measures deleteriousness, a property that strongly correlates with pathogenicity (Kircher et al., 2014). Several other variants have been reported as pathogenic in the HL-I loop (Cruts and Van Broeckhoven, 1998; Hutton et al., 1996; La Bella et al., 2004; Poorkaj et al., 1998;
Reznik-Wolf et al., 1996; Zekanowski et al., 2003), underscoring the relevance of this domain in PSEN1 function.

Some family members (Figure 1. Symbols with asterisks) agreed to performing the initial medical consultation and genetic testing. Of note, one of the proband’s siblings (Individual III.5) carried the p.T119I variant but no neuropsychological data could be obtained since the participant decided to drop out from the study. Another affected sibling (III.7), with an age of onset of 58, did not accept to participate. As for the proband’s children, none of them carried the p.T119I variant (age ranges 43-54). Even though no neuropsychological assessment was performed, none of them reported cognitive complaints at the initial visit. Also, APOE genotyping for each participant is shown in Figure 1.

Individual III.10 (proband’s cousin) came to consultation at the age of 54. At that moment, the participant referred memory complaints and dysthymia and later returned to be enrolled in the “Dominantly Inherited Alzheimer Network” (DIAN) at our center. Cognitive testing revealed mild impairment in executive, attention and memory domains with a CDR score of 0.5. Genetic testing showed that the participant carried the p.T119I variant. Interestingly, individual II.5 (III.10’s parent) had been diagnosed with dementia of Alzheimer’s type at the age of 71 and died at age 79. Even though no DNA was available, individual II.5 was an obligate mutation carrier. A thorough analysis by Ryman et al (Ryman et al., 2014) showed that some ADAD mutations display standard deviations of over 10 years in age of onset. Data presented here adds to the evidence that ADAD mutations, commonly perceived as causing only early-onset AD, may also cause late-onset AD.
Lumbar puncture for cerebrospinal fluid (CSF) biomarker assessment was performed on individuals III.6 and III.10. III.6 exhibited only pathological Aβ_{1-42}, while III.10 showed elevated phospho-tau (Table 1). A previous report (Lanoiselée et al., 2017) has shown that CSF biomarker profiles for some PSEN1 mutations are not exactly compatible with an AD signature. In particular, another mutation occurring in the PSEN1 HL-I loop (p.Y115C) exhibited only pathological Aβ_{1-42} and p-tau.

Also, individual III.10 underwent positron emission tomography (PET) with Pittsburgh Compound B (PiB) and F-18-2-fluoro-2-deoxy-D-glucose (FDG). Amyloid deposition was evidenced bilaterally in the following regions: frontal, parietal, precuneus/posterior cingulate, lateral temporal and striatum (Figure 2A). Interestingly, high striatal PiB binding has been more frequently reported in ADAD cases than in sporadic AD (Villemagne et al., 2009), further supporting the likely pathogenic role of the PSEN1 p.T119I variant. Additionally, PET-FDG demonstrated mild bilateral hypometabolism in: parietal lobe, precuneus, anterior cingulate, dorsal frontal lobe, and lateral temporal lobe with left predominance (Figure 2B).

One caveat of our study is that we could not unequivocally confirm segregation of the variant with the disease. Nonetheless, according to the guidelines from the American College of Medical Genetics and Genomics (ACMG) (Richards et al., 2015), this novel PSEN1 p.T119I variant can be classified as “likely pathogenic” (supporting evidence: PM1, PM2, PP2, PP3). In addition, our data shows that this variant is associated with both early- and late-onset AD.
4. Acknowledgements

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5. Disclosure statement

Authors declare no conflicts of interests.

6. References


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7. Figure Legends

Figure 1. Family pedigree showing unaffected individuals (unfilled) and individuals with cognitive impairment (filled). The proband is denoted with an arrow. Sex has been omitted for confidentiality reasons. Asterisks (*) indicates individuals who agreed to performing initial interview and genetic testing. Also, only III.6 and III.10 underwent neuropsychological evaluation. Cognitive status of remaining relatives was reported in IV.5’s anamnesis.

Figure 2. Positron emission tomography (PET) scans of individual III.10 at age 58.

A. PiB-PET scan. Positive PiB signal can be observed in the following regions: frontal, parietal, precuneus/posterior cingulate, lateral temporal and striatum.

B. FDG-PET scan. Mild bilateral hypometabolism can be observed in: parietal lobe, precuneus, anterior cingulate, dorsal frontal lobe, and lateral temporal lobe with left predominance.
Table 1. CSF biomarkers levels (pg/mL) in variant carriers. Pathological values are shown in bold.

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<tr>
<th></th>
<th>Individual III.6</th>
<th>Individual III.10</th>
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<tbody>
<tr>
<td>Aβ₁₋₄₂</td>
<td>180.4</td>
<td>636.0</td>
</tr>
<tr>
<td>total-tau</td>
<td>205.9</td>
<td>306.9</td>
</tr>
<tr>
<td>p-tau</td>
<td>28.7</td>
<td>59.6</td>
</tr>
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AD signature: Aβ₁₋₄₂ <534 pg/mL; total-tau>343.9 pg/mL; p-tau> 42.4 pg/mL
Highlights

- A novel variant in \textit{PSEN1}, p.T119I, was found in an Argentine family.
- Patients showed ages of onset within a wide range (49 – 71 years).
- Mutation carriers exhibited biomarker evidence of underlying AD pathology.
- \textit{PSEN1} p.T119I variant is likely pathogenic.