A Novel Mutation in the PSEN2 Gene (T430M) Associated With Variable Expression in a Family With Early-Onset Alzheimer Disease

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**Background:** Autosomal dominant early-onset Alzheimer disease is a heterogeneous condition that has been associated with mutations in 3 different genes: the amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) genes. Most cases are due to mutations in the PSEN1 gene, whereas mutations in the APP and PSEN2 genes are rare.

**Objective:** To describe a novel mutation in the PSEN2 gene associated with early-onset autosomal dominant Alzheimer disease.

**Patients and Methods:** The proband was a 49-year-old individual who displayed progressive dementia beginning at age 45 years. One of the parents and one of the grandparents had developed dementia at ages 64 years and 60 years, respectively, and 1 sibling had mild cognitive impairment. Some family members also had Tourette syndrome. Mutation analysis of the APP, PSEN1, PSEN2, and tau (TAU) genes was performed. Apolipoprotein E (APOE) was also genotyped.

**Results:** We found a missense mutation at codon 430 of the PSEN2 gene that predicts a threonine-to-methionine substitution. This mutation was detected in the affected individuals and in 1 cognitively healthy sibling. The mutation was absent in 260 control chromosomes. The normal amino acid was conserved in the human and mouse PSEN1 and mouse PSEN2 homologues. No influence of the APOE genotype was observed.

**Conclusions:** We have found a novel mutation in the PSEN2 gene in a family with early-onset Alzheimer disease. The variation in the age at onset confirms that PSEN2 mutations are associated with variable clinical expression.

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**METHODS**

**FAMILY DESCRIPTION**

The studied family originated from Barcelona, Spain. The proband was a 49-year-old subject (Figure, A, III-3) who visited our center because of a 4-year history of cognitive decline. The family complained of frequent oversights, problems remembering recent events, word-finding difficulty, and paranoid thinking about the neighbors. This subject also had difficulty performing home tasks such as cleaning and using the washing machine. The patient's medical record was unremarkable except for a history of facial motor tics. The family history revealed that 1 parent and 1 grandpar...
ent (I-2 and II-2, respectively) had died following a diagnosis of AD. The parent died at age 75 years, and cognitive symptoms had started at age 64 years; the grandparent had died at age 70 years with an onset at 60 years. One of the proband’s siblings (III-1) had memory problems but no functional impairment. Some family members also had a history of Tourette syndrome (Figure). The proband’s initial neurologic examination showed disorientation, comprehension deficits, and facial motortics. Neuropsychological evaluation performed with the Wechsler Adult Intelligence Scale, Mini-Mental State Examination, Rey-Osterrieth Complex Figure Test, Wechsler Memory Scale, Trail-Making Test, and Boston Naming Test revealed anomia, poor verbal fluency, memory loss, and impairment in abstract thinking. The Mini-Mental State Examination score was 11. A magnetic resonance imaging scan of the brain showed discrete global atrophy, and technetium Tc 99m–labeled hexylmethylpropylene amineoxine single-photon emission computed tomography revealed right frontotemporal hypoperfusion. A diagnosis of probable AD was made.

During the following years, the cognitive and behavioral disturbances progressively worsened, and myoclonus, grasping, and generalized epileptic seizures were added to the clinical picture. The patient died at age 56 years, and autopsy was denied. No brain tissue from any of the family members who had died was available for pathologic study. Members III-1, III-2, III-4, and III-5 were also evaluated. Neuropsychological assessment carried out with the same tests used with the proband revealed normal scores in all family members except III-1, who had deficits in memory function but preserved global cognitive measures and therefore met the criteria for mild cognitive impairment.

GENETIC ANALYSIS

After gaining written informed consent, a blood sample for genetic analysis was obtained from the proband and members II-2, III-1, III-2, III-3, III-4, and III-5. The DNA was isolated according to standard procedures. The coding regions of the PSEN1, PSEN2, and APP genes (exons 16 and 17) were amplified using specific primers, as described previously. The polymerase chain reaction products were analyzed through single-stranded conformational polymorphism and subsequent sequencing of the samples with abnormal mobility using a sequencing kit (ABI PRISM Dye Terminator Cycle Sequencing Ready Reaction Kit; PerkinElmer, Foster City, Calif) and an automatic sequencer (ABI PRISM model 377; PerkinElmer). The coding region of the tau gene (TAU) (exons 9, 10, 12, and 13) and the TAU promoter polymorphism were also analyzed. The APOE genotyping was performed through polymerase chain reaction amplification and HhaI restriction enzyme digestion.

RESULTS

Genetic analysis showed a C-to-T transition at the second position of codon 430, which predicted a threonine-to-methionine substitution (T430M) (Figure, B). This mutation was identified in the proband (III-3) and in affected individuals II-2 and III-1 but was absent in 130 unrelated individuals (50 healthy controls and 80 patients with AD), pointing out that it is not a common polymorphism. The mutation was also found in a cognitively healthy sibling older than the proband. No additional mutations were found in the PSEN1, APP, or TAU genes. The APOE genotype is indicated in the Table. We did not detect an evident influence of the TAU promoter polymorphism on age at onset in this family (data not shown). This novel T430M mutation is located in exon 12 near the C-terminal end of the presenilin 2 protein. The residue is conserved in the human and mouse PSEN1 and mouse PSEN2 homologues.

COMMENT

We report herein a novel mutation in the PSEN2 gene in a family with early-onset AD and Tourette syndrome. The presence of the mutation in 3 members with cognitive impairment, its absence in 260 chromosomes, and the evolutionary conservation of this residue suggests that the mutation is causative for dementia in this family. It was found in 2 members affected by AD and in 1 cognitively healthy relative older than the proband’s age at onset. We also observed a significant variation in the age at onset in this family, which ranged from 45 to 64 years. Although Tourette syndrome has been linked to several candidate regions, we did not observe cosegregation between AD and Tourette syndrome in this family.

Mutations in the PSEN2 gene appear to be a rare cause of autosomal dominant early-onset AD. The first mutation was detected in a large group of families with diverse cultural and ethnic backgrounds. Since then, only

A, Pedigree of the family with early-onset Alzheimer disease bearing the T430M mutation. Arrow indicates the proband. Sex has been omitted to respect family confidentiality. B, The DNA sequence of exon 12 of the presenilin 2 gene showing a C-to-T missense mutation (arrow) at the second position of codon 430, which predicts a threonine-to-methionine substitution.

Clinical Features and Genetic Results in the Affected Family Members Carrying the T430M Mutation

<table>
<thead>
<tr>
<th>Feature</th>
<th>II-2</th>
<th>III-1</th>
<th>III-3</th>
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<tr>
<td>Age at onset, y</td>
<td>64</td>
<td>57</td>
<td>45</td>
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<tr>
<td>Age at death, y</td>
<td>75</td>
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<td>56</td>
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<tr>
<td>Disease duration, y</td>
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<td>11</td>
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<tr>
<td>Presenilin 2 mutation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Apolipoprotein E genotype</td>
<td>43</td>
<td>33</td>
<td>33</td>
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</tbody>
</table>

Abbreviation: NA, not applicable.
a few additional mutations have been described. Some of these families show a wide range in age at onset, and cases of nonpenetrance have been found. However, this variability is also present in some families with the PSEN1 gene, and mutations with incomplete penetrance have been reported as well. In our family, there was an almost 20-year gap between the proband and parent in age at disease onset. Although a longer follow-up period is needed, the presence of a cognitively healthy mutation carrier could indicate the existence of incomplete penetrance. Nevertheless, we cannot rule out that this individual is at risk for AD. The variation in age at onset observed in this family confirms that PSEN2 mutations are associated with variable clinical expression. This fact has important consequences for genetic-testing and genetic-counseling programs; it may determine the type of information given to these families. The variability reflects the existence of other genetic or environmental modifying factors that influence the expression of clinical disease. Although we did not detect any influence of the APOE genotype or TAU promoter polymorphism on disease onset, the small number of affected family members in our study could limit this type of analysis, which stresses the need to discover which factors modify the clinical picture.

The T430M mutation is located in exon 12 of the PSEN2 gene, near the D439A mutation and the C-terminal end of the protein. The presenilin 2 protein is an integral transmembrane protein normally processed by proteolytic cleavage. Interestingly, the C-terminus is a critical region for endoproteolytic processing and possibly for the pathologic function of the protein. Thus, the T430M mutation could disrupt the endoproteolytic process and interfere with the normal function of the protein.

In conclusion, we have described a novel mutation in the PSEN2 gene located near the C-terminal end of the protein in a family with early-onset AD, confirming that PSEN2 mutations are associated with variable clinical expression. This has important implications for genetic testing and counseling of individuals at risk and potentially for the development of new strategies for delaying the onset of AD.

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