Molecular genetics of Alzheimer’s disease: Presenilin 1 gene analysis in a cohort of patients from the Poznañ region

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Abstract. Alzheimer’s disease (AD) is a progressive neurodegenerative disorder characterized by memory loss and personality changes. Pathological hallmarks of AD are: deposition of amyloid plaques and neurofibrillary tangles in the brain, accompanied by neuronal and synaptic loss. The genetic background of AD is heterogeneous and strongly depends on the form of the disease. In most of the families with early-onset AD (EOAD) (10% of the total population of patients), the disease segregates as an autosomal dominant fully penetrant trait. To date, some missense mutations in three genes encoding the amyloid precursor protein, presenilin 1 (PS1) and 2 (PS2) have been found to cause familial EOAD. We screened for mutations in the presenilin genes in a sample of 55 patients with familial or sporadic form of EOAD from the Poznan region. We found 4 missense mutations in the PS1 gene: A246E in exon 7, P267L in exon 8, E318G in exon 9, and L424R in exon 12 among 5 unrelated patients. The frequency of PS1 mutations was 11% (5 of 55) in the whole sample of the patients with EOAD or 50% (3 of 6) if the analysis was restricted to familial cases with a positive history of dementia in the patient’s family.

Key words: Alzheimer’s disease, dementia, molecular diagnosis, mutation, presenilin-1 gene.
Alzheimer’s disease (AD) is characterized by deposition of β-amyloid (Aβ) in senile plaques in the extracellular compartment of the brain and cerebral blood vessels. Moreover, intracellular neurofibrillary tangles formed from abnormally phosphorylated cytoskeletal protein tau are observed. The “amyloid cascade hypothesis” postulates that a dysregulation of metabolism of Aβ is the first and central event in the pathogenesis of the devastating neurodegenerative disorder. Aβ is produced from amyloid precursor protein (APP) by the sequential action of β and γ-secretases in amyloidogenic pathway of APP processing. The postulated hypothesis has gained a strong support by the findings of pathogenic mutations in three genes: APP, presenilin-1 (PS1), and presenilin-2 (PS2) responsible for early-onset dominant inherited AD. All the mutations lead to increased Aβ production. Recently, a direct link between the mutations and APP metabolism has been established. It has been discovered that presenilins are a part of the catalytic centre of the multiprotein γ-secretase complex (ESLER, WOLFE 2001).

We performed screening for mutations in presenilin 1 and presenilin 2 genes in a cohort of 55 patients with familial or sporadic forms of early-onset AD (EOAD) from the Poznań region. Ages of patients ranged from 31 years to 65 years. The diagnosis based on NINCDS-ADRDA work group guidelines according to MCKHANN et al. (1984), was made by clinical evaluation and exclusion of other cases of dementia, in the majority of cases including CT scan. Genomic DNA was extracted from blood samples with the use of a QIAGEN Blood Kit. Screening for mutations was carried out by SSCP analysis of PCR products according to the method described earlier by KOWALSKA et al. (1998).

Table 1. Mutations identified in the presenilin 1 gene

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at onset</th>
<th>Mutation</th>
<th>Amino-acid substitution</th>
<th>Localization</th>
<th>Domain of PS1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pedigree W.T.</td>
<td>50</td>
<td>A246E</td>
<td>Ala → Glu</td>
<td>Exon 7</td>
<td>TM-VI</td>
</tr>
<tr>
<td>2. Pedigree H.A.</td>
<td>59</td>
<td>P267L</td>
<td>Pro → Leu</td>
<td>Exon 8</td>
<td>HL-VI</td>
</tr>
<tr>
<td>3. SAD Z.G.</td>
<td>58</td>
<td>E318G</td>
<td>Glu → Gly</td>
<td>Exon 9</td>
<td>HL-VI</td>
</tr>
<tr>
<td>4. SAD/FTD J.L.</td>
<td>59</td>
<td>E318G</td>
<td>Glu → Gly</td>
<td>Exon 9</td>
<td>HL-VI</td>
</tr>
<tr>
<td>5. Pedigree J.P.</td>
<td>31</td>
<td>L424R</td>
<td>Leu → Arg</td>
<td>Exon 12</td>
<td>TM-VII</td>
</tr>
</tbody>
</table>

The results of our analysis have been summarized in Table 1. We identified the following missense mutations: A246E in exon 7, P267L in exon 8, and L424R in exon 12 of the PS1 gene in three familial cases. The E318G mutation in exon 9 was found in two unrelated patients with the sporadic form of EOAD. The patient with a C to A transversion, responsible for the mutation 246Ala → Glu, had the age of onset 50 years. The 63-year-old patient with an age of onset for AD of 59 years had a C to T transition, causing the mutation 267Pro → Leu. The earliest
age of onset, 31 years, of AD was determined by a T to G transversion, responsible for the mutation 424Leu → Arg. It has been suggested previously that the age of onset for AD could be determined by the nature of the mutation and its position in the gene (VAN BROECKHOVEN 1995). Indeed, families from other ethnic groups with the same PS1 mutations have a very similar disease onset (CAMPION et al. 1999). All the mutations found by us occurred in functional domains of presenilin 1 molecule: a transmembrane domain VI (246E) and VII (L424R), and a hydrophilic loop VI (P267L, E318G) (Figure 1). Although it was demonstrated that the mutations influence the presenilin 1 function, a role of the A to G transition causing the 318Glu → Gly substitution remains still unclear in AD pathology. The E318G mutation was first described in an EOAD case without a known family history (SANDBRINK et al. 1996) and has been also found in familial EOAD cases, although co-segregation with AD could not be demonstrated (CRUTS et al. 1998). Later, it was suggested that the mutation did not necessarily cause EOAD and could be considered as rare DNA polymorphism (MATTILA et al. 1998, DERMAUT et al. 1999). Recent studies show that the frequency of the E318G mutation is increased in FAD patients (HELISALMI et al. 2000, TADDEI et al. 2002), suggesting its potential role as a genetic risk factor contributing to the pathogenesis of familial AD. We did not find any mutations in other analysed 47 sporadic cases of AD. To contribute to our knowledge on the distribution of the E318G variation in the general Polish population and among AD patients, the screening of the normal population (control) will be performed. In this study, the frequency of PS1 mutations was estimated at 11% (5 of 55) in a whole sample of the patients with EOAD, or 50% (3 of 6) if the analysis was restricted to familial
cases with a positive history of dementia in the patient’s family. These data indicate that there should exist additional genetic factors contributing to AD.

REFERENCES


