Molecular diagnosis of autosomal dominant early onset Alzheimer’s disease: an update

G Raux, L Guyant-Maréchal, C Martin, J Bou, C Penet, A Brice, D Hannequin, T Frebourg, D Campion

Background: Autosomal dominant early onset Alzheimer’s disease (ADEOAD) is genetically heterogeneous. Mutations of the amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) genes have been identified.

Objective: To further clarify the respective contribution of these genes to ADEOAD.

Methods: 31 novel families were investigated. They were ascertained using stringent criteria (the occurrence of probable or definite cases of Alzheimer’s disease with onset before 60 years of age in three generations). All cases fulfilled the NINCDS-ADRDA criteria for probable or definite Alzheimer’s disease. The entire coding regions of PSEN1 and PSEN2 genes and exons 16 and 17 of APP gene were sequenced from genomic DNA.

Results: PSEN1 mutations, including eight previously unreported mutations, were detected in 24 of the 31 families, and APP mutations were found in five families. In this sample, the mean ages of disease onset in PSEN1 and APP mutation carriers were 41.7 and 51.2 years, respectively.

Conclusions: Combining these data with previously published data, yielding 65 ADEOAD families, 66% of the cases were attributable to PSEN1 mutations and 16% to APP mutations, while 18% remained unexplained.

Ten years after the discovery of the presenilin 1 (PSEN1) gene,1 which is involved in autosomal dominant early onset Alzheimer’s disease (ADEOAD), there is an increasing requirement for presymptomatic testing in affected families. ADEOAD is genetically heterogeneous and mutations of the amyloid precursor protein (APP) and presenilin 2 (PSEN2) have also been identified in ADEOAD patients. However, there is no consensus about the relative contribution of PSEN1 mutations to ADEOAD. Accurate determination of the relative contribution of PSEN1, PSEN2, and APP mutations to ADEOAD is important to ensure efficient genetic counselling in affected families.

In a previous report, mutational analysis of these three genes in 34 ADEOAD families led us to conclude that 71% of cases in these families were attributable to mutations within the PSEN1 and APP genes.2 However, other groups have recently reported lower estimates on smaller samples.3–5 To further clarify the respective contribution of these genes to ADEOAD, we analysed 31 novel families ascertained using the stringent criteria we have previously defined (that is, the occurrence of probable or definite Alzheimer’s disease cases with onset before 60 years of age in three generations).2 All cases fulfilled the NINCDS-ADRDA criteria for probable or definite Alzheimer’s disease. Clinical and molecular investigations were carried out after informed consent of participating family members was obtained.

The entire coding regions of PSEN1 and PSEN2 were sequenced, either from reverse transcriptase polymerase chain reaction (RT-PCR), undertaken on mRNA extracted from lymphoblastoid cell lines as previously described,6 or from genomic DNA, and exons 16 and 17 of APP were sequenced from genomic DNA.7 APOE genotypes were also determined. The results are summarised in table 1. PSEN1 mutations, including eight previously unreported mutations, were detected in 24 of the 31 families, and APP mutations were found in five. In this sample, the mean ages of Alzheimer’s disease onset in PSEN1 and APP mutation carriers were 41.7 and 51.2 years, respectively. We detected no PSEN2 mutations in the two remaining families without mutation within PSEN1 or APP. In these families without detectable mutations within PSEN1, PSEN2, or APP exons 16 and 17, we completed the analysis by sequencing exons 1–5 of APP and exons 1–5, 7, and 9–14 of MAPT (microtubule associated protein tau) from genomic DNA, as the clinical presentation of Alzheimer’s disease and frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) may overlap. This complementary analysis revealed no additional mutations.

Among the eight novel PSEN1 mutations, four affected residues that had already been shown to be mutated in ADEOAD patients. The four other novel PSEN1 mutations concerned residues that are conserved between PSEN1 and PSEN2 genes and which are also conserved in evolution. For two of these eight novel PSEN1 mutations, cosegregation with the disease could clearly be demonstrated in two families with multiple affected living members. Three PSEN1 mutations (P264L, E280G, and F386S) were associated with an atypical presentation including spastic paraparesis.8,9,10 However, the novel F386S mutation appears to be also associated with this phenotype. The E318G variation, which had been described either as a non-pathogenic polymorphism10,11 or as a mutation with reduced penetrance,10,11 was present in three families. In these three families, DNA was only available from the proband, thus precluding any cosegregation analysis. In family ALZ-231, in which the Q120N mutation cosegregates with the disease, one patient also bore the R35G substitution already described by Rogaeva et al.12 Absence of cosegregation of the R35G substitution with the disease within this family shows that this substitution is a non-causative rare variant. Finally, 78% of the affected subjects had an APOE 3-3 genotype and none had the APOE 4-4 genotype.

Abbreviations: ADEOAD, autosomal dominant early onset Alzheimer’s disease; NINCDS-ADRDA, National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease and Related Disorders Association
These results, which are in accordance with those published by Janssen et al.,10 are attributable to 
PSEN1 mutations, while 18% remain unexplained. These results, which are in accordance with those published by Janssen et al.10 should be helpful for geneticists undertaking molecular diagnosis or genetic counselling for ADEOAD families.

**ELECTRONIC DATABASE INFORMATION**

The URL for data presented herein as follows:

- Alzheimer Disease Mutations Database: http://www.molgen.ua.ac.be/ADMutations/

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Competing interests: none declared

Additional data including pedigree structures are available from the corresponding author upon request.

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Table 1 Detection of PSEN1 and APP mutations among 29 families with autosomal dominant early onset Alzheimer’s disease

<table>
<thead>
<tr>
<th>Family</th>
<th>AOO (years)</th>
<th>Affected subjects (n)</th>
<th>APP</th>
<th>PSEN1</th>
</tr>
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</table>
| ALZ 184 | 53 to 58 | 3 | WT | c.315T→A; F105S
| ALZ 157 | 30 to 33 | 4 | WT | c.347C→A; T116N
| ANG 008 | 49 to 54 | 4 | WT | c.347C→T; T116A
| ALZ 231 | 43 to 48 | 4 | WT | c.360A→C; Q120N
| ROU 001 | 34 to 35 | 3 | WT | c.428T→A; I143N
| ALZ 173 | 45 to 50 | 5 | WT | c.459C→G; L153V
| ALZ 148 | 34 to 40 | 5 | WT | c.459C→G; L153V
| ALZ 180 | 39 to 44 | 4 | WT | c.459C→G; L153V
| ALZ 156 | 36 to 42 | 4 | WT | c.529T→C; F177L
| ALZ 219 | 32 to 34 | 5 | WT | c.617G→A; G206N
| RIK 001 | 30 to 35 | 15 | WT | c.617G→A; G206N
| ALZ 178 | 37 to 45 | 5 | WT | c.640C→T; H214Y
| ALZ 163 | 37 to 46 | 5 | WT | c.698T→A; V717I
| ALZ 202 | 38 to 40 | 3 | WT | c.791C→T; F264L
| ALZ 183 | 47 to 51 | 4 | WT | c.839A→G; E280Q
| ALZ 179 | 52 to 58 | 3 | WT | c.953G→A; E318G
| LBF 063 | 43 to 47 | 4 | WT | c.1157T→C; F386S
| KER 061 | 49 to 59 | 3 | WT | c.1157T→C; F386S
| POI 060 | 37 to 58 | 5 | WT | c.1157T→C; F386S
| ALZ 174 | 42 to 43 | 5 | WT | c.1171G→T; V391F
| ALZ 154 | 39 to 47 | 5 | WT | c.1174G→A; V391F
| ALZ 147 | 41 to 48 | 6 | WT | c.1174G→A; V391F
| ALZ 161 | 38 to 42 | 3 | V127I
| ALZ 191 | 35 to 41 | 3 | c.2084C→T; T116A
| ALZ 196 | 50 to 60 | 3 | c.2092G→A; V717I
| ALZ 166 | 42 to 56 | 4 | WT | c.2092G→A; V717I
| ALZ 170 | 48 to 57 | 6 | WT | c.2092G→A; V717I
| ALZ 221 | 40 to 54 | 3 | c.2092G→A; V717I

*Novel mutations at codons previously reported mutant in Alzheimer’s disease.
†Segregation with Alzheimer’s disease demonstrated.

**REFERENCES**


Received 29 March 2005
Revised version received 28 June 2005
Accepted for publication 2 July 2005

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