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Early-Onset Autosomal Dominant Alzheimer Disease: Prevalence, Genetic Heterogeneity, and Mutation Spectrum

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Summary

To determine the prevalence of early-onset Alzheimer disease (EOAD) and of autosomal dominant forms of EOAD (ADEOAD), we performed a population-based study in the city of Rouen (426,710 residents). EOAD was defined as onset of disease at age <61 years, and ADEOAD was defined as the occurrence of at least three EOAD cases in three generations. Using these stringent criteria, we calculated that the EOAD and ADEOAD prevalences per 100,000 persons at risk were 41.2 and 5.3, respectively. We then performed a mutational analysis of the genes for amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*) in 34 families with ADEOAD ascertained in France. In 19 (56%) of these families, we identified 16 distinct *PSEN1* missense mutations, including 4 (Thr147Ile, Trp165Cys, Leu173Trp, and Ser390Ile) not reported elsewhere. *APP* mutations, including a novel mutation located at codon 715, were identified in 5 (15%) of the families. In the 10 remaining ADEOAD families and in 9 additional autosomal dominant Alzheimer disease families that did not fulfill the strict criteria for ADEOAD, no *PSEN1, PSEN2,* or *APP* mutation was identified. These results show that (1) *PSEN1* and *APP* mutations account for 71% of ADEOAD families and (2) nonpenetrance at age <61 years is probably infrequent for *PSEN1* or *APP* mutations.

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Introduction

Mutations of the presenilin 1 gene (*PSEN1*), located on chromosome 14, and of the amyloid precursor protein gene (*APP*), located on chromosome 21, have been identified in families with autosomal dominant forms of early-onset Alzheimer disease (ADEOAD; MIM 104311 and MIM 104760). To date, >50 different missense mutations of *PSEN1* have been described in ~100 families (for a recent review, see Rohan de Silva and Patel 1997; for additional references, see Aoki et al. 1997; Crook et al. 1997; Forsell et al. 1997; Fox et al. 1997; Gomez-Isla et al. 1997; Kwok et al. 1997; Lendon et al. 1997*a* and 1997*b*; Yasuda et al. 1997; Aldudo et al. 1998; Axelman et al. 1998; Harvey et al. 1998; Poorkaj et al. 1998; Wisniewski et al. 1998). In addition, an in-frame deletion of exon 9, associated with a missense mutation at the junction point (Perez-Tur et al. 1995*b*; Crook et al. 1998), and a deletion affecting the intron 4 splice-donor consensus sequence and resulting in a premature stop codon (Tysoe et al. 1998) have also been reported. *APP* mutations are less frequent: seven different missense mutations located in exons 16 and 17 of *APP* have been reported (reviewed in Lendon et al. 1997*a*) in 23 families with AD or related phenotypes. Although both intra- and interpedigree variability in age at onset (AAO) exists, a close examination of the published data shows that, except for four *PSEN1* mutations (Ala79Val [Cruts et al. 1998], Ile143Phe [Rossor et al. 1996], His163Tyr [Axelman et al. 1998], and His163Arg [Poorkaj et al. 1998]), *PSEN1* and *APP* mutations are fully penetrant at the beginning of the 7th decade of life. The case of two mutations occurring at codon 143 of *PSEN1* is of particular interest, since a nonconservative change (Ile143Thr) causes AD with an average AAO of 35 years (Cruts et al. 1995), whereas a semiconservative change at the same residue (Ile143Phe) causes AD with an average AAO of 55 years (Rossor et al. 1996) and has also been detected in an asymptomatic carrier 68 years of

age. The Glu to Gly substitution occurring at codon 318 of *PSEN1* (Sandbrink et al. 1996) was initially considered an incompletely penetrant mutation (Forsell et al. 1997) but is probably a noncausative polymorphism (Mattila et al. 1998; Dermaut et al. 1999).

Mutations of a third gene, *PSEN2*, located on chromosome 1, have also been identified in some autosomal dominant AD cases (ADAD; MIM 600759). *PSEN2* mutations are excessively rare, having been described only in the Volga-German isolate, where a founder effect exists, and in one Italian family (reviewed in Lendon et al. 1997*a*). However, the pattern of AAO associated with *PSEN2* mutations is noteworthy and is reminiscent of that associated with "atypical" *PSEN1* mutations, with AAO of 45–88 years in Met239Val carriers and 40–75 years in Asn141Ile carriers.

The relative contribution of *PSEN1* and *APP* mutations to ADEOAD is the subject of considerable controversy: Hutton and Hardy (1997) have found that, in a series of 19 families with ADEOAD, all pedigrees could be explained by *PSEN1* or *APP* mutations, whereas Cruts et al. (1998) have reported only two *PSEN1* mutations, one each in 2 (18%) of 11 kindreds with ADEOAD that were sampled.

The purpose of this study was (1) to provide, in a population-based study, a nonbiased estimate of the prevalence of ADEOAD, (2) to establish, in a large family study, the respective contribution of *PSEN1, PSEN2,* and *APP* mutations in the etiology of these autosomal dominant forms, and (3) to examine the extent to which *PSEN1, PSEN2,* and *APP* mutations are involved in other forms of familial aggregations of AD.

Subjects and Methods

Prevalence Study

Since 1991, in the city of Rouen and its suburbs (with 426,710 residents, as of March 1, 1991), all general practitioners, neurologists, and psychiatrists were asked to refer to the Department of Neurology of the University Hospital all known patients with dementia, the onset of which occurred at age <61 years. Patients residing in nursing homes or in the local psychiatric hospital were considered eligible for inclusion in the study only if they had been residents of Rouen prior to their institutionalization. For each patient, a standardized clinical evaluation including neurological examination, computed-tomography scan imaging, and neuropsychological and laboratory tests were performed (described in detail in Campion et al. 1995*c*). Patients fulfilling the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorder Association for probable AD (McKhann et al. 1984) were included in this study. The AAO for AD was defined as the age at which cognitive impairment began to have a significant impact on social functioning.

For each patient, detailed information concerning sibs, parents, grandparents, uncles, and aunts was obtained from the next of kin and was confirmed by at least a second informant. Whenever possible, medical records and hospital charts were consulted. This information was used to categorize our families: families with ADEOAD were defined by the occurrence of AD cases *with onset at age <61 years* in three generations. Alternatively, families with ADAD were defined by the presence of *both early- and late-onset cases* in three generations. Accordingly, patients belonging to these two types of families were referred to as "ADEOAD" and "ADAD," respectively.

Information concerning index patients and their families has been updated regularly during the past 7 years. When the last follow-up was completed in the second trimester of 1998, prevalences for EOAD and ADEOAD were calculated by dividing the number of relevant patients alive on June 1, 1998, by the appropriate denominators determined on the basis of data from the last (1991) census.

Mutational Analysis

Mutational analysis was performed both in the families with ADEOAD and ADAD identified during the prevalence study and in additional families with ADEOAD and ADAD referred to our laboratory by several French hospitals. All but three of these additional families fulfilled the inclusion criteria described above. These three families (CAE 10, ROU118, and ALZ25) were nevertheless considered families with ADEOAD, for the following reasons: in families CAE 10 and ROU118, only two subjects (the proband and one parent) were affected, but, in both kindreds, one grandparent (related to the affected parent) died at age <40 and could therefore be considered an asymptomatic carrier. Thus, within these two families, the pattern observed was related to a censoring effect. In the third family (ALZ25), the proband and his father had the disease, and the paternal grandparents were dead and unaffected by age 75 years. The AAO of the affected subjects (35 and 37 years in the proband and the parent, respectively) led us to speculate that the presentation of this family could be explained either by a de novo mutation or by an exclusion of paternity and to consider this pedigree as a family with ADEOAD.

We analyzed *PSEN1* and *APP* (exons 16 and 17) in a total of 43 families (34 ADEOAD and 9 ADAD). When a mutation was found in the proband, additional pedigree members were also genotyped to establish the cosegregation between the mutation and the disease. In some families, however, this analysis was not possible,

Table 1

No. of EOAD and ADEOAD Cases and Prevalences of EOAD and ADEOAD, by Sex

Sex	No. of			Prevalence of[a]	
	Individuals at Risk[b]	EOAD Patients	ADEOAD Patients	EOAD	ADEOAD
Male	46,068	11	2	23.9	4.3
Female	48,525	28	3	57.7	6.2
Overall	94,593	39	5	41.2	5.3

[a] Per 100,000 inhabitants.
[b] Age 41–60 years.

since no affected relative was still alive. When no mutation was found within *PSEN1* or *APP,* we analyzed *PSEN2*.

PSEN1 and *PSEN2* sequence analysis was performed on cDNA obtained by reverse transcription–PCR after extraction of mRNA from lymphoblastoid cell lines, as described elsewhere (Campion et al. 1995*b*). For each gene, the complete open reading frame was amplified and submitted to gel electrophoresis, to detect a change affecting the length of the transcript, and was then completely sequenced (see Campion et al. 1995*b;* Sherrington et al. 1996; Dumanchin et al. 1998). Sequence analysis of exons 16 and 17 of *APP* was performed on genomic DNA, as described by Campion et al. (1996). In families with no *APP, PSEN1,* or *PSEN2* mutation, we also sequenced exons 7, 8, and 18 of *APP,* using primers described by Fidani et al. (1992). All sequence analyses were performed by use of the PRISM Ampli*Taq*FS Ready Reaction Dye Primer sequencing kit (Applied Biosystems, Perkin Elmer Cetus) and an Applied Biosystems model 373A or 377 automated sequencer. For each subject included in either the population study or the mutational analysis, *APOE* genotype was determined by PCR digestion, according to the method of Hixson and Vernier (1990).

Results

On June 1, 1998, 39 patients with EOAD (with AAO <61 years) were living in the town of Rouen; 15 had isolated cases, and 24 had familial cases defined by the presence of at least one secondary case among sibs, parents, grandparents, uncles, or aunts. Of the patients with familial cases, five were from families with ADEOAD. Although they were ascertained independently, three of these patients were in fact members of the same very

Table 2

Kindreds with ADEOAD with *PSEN1* Mutations

Family	No. of		AAO (range [years])	Codon Change	Amino Acid Change	*APOE* Genotype[a]
	Affected Subjects	Generations				
SAL 508	3	3	53–58	GTG→CTG	Val82Leu	ϵ3/ϵ3
ALZ 25	2	2	35–37	TAT→CAT	Tyr115His	ϵ3/ϵ4
ALZ 76	3	3	36–47	TAT→CAT	Tyr115His	ϵ3/ϵ3
ALZ 57	4	3	42–53	GAA→GAC	Glu120Asp	ϵ3/ϵ3
CAE 010	2	2	48–50	ATG→ACG	Met139Thr	ϵ3/ϵ3
ALZ 204	6	3	38–47	ATG→CTG	Met146Leu[b]	ϵ3/ϵ3
ALZ 047	4	3	37–46	ACT→ATT	Thr147Ile[b,c]	ϵ3/ϵ3
SAL 001	4	3	42–47	CAT→CGT	His163Arg[b]	ϵ3/ϵ3
ROU 118	2	2	24–29	TTG→TGG	Leu173Trp[c]	ϵ2/ϵ4
ALZ 064	3	3	37–47	TGG→TGC	Trp165Cys[c]	ϵ3/ϵ3
ALZ 043	4	3	45–57	GCC→ACC	Ala231Thr	ϵ3/ϵ3
ALZ 079	5	3	38–45	ATG→ACG	Met233Thr[b]	ϵ3/ϵ3
SAL 510	5	3	29–39	CTG→CCG	Leu235Pro[b]	ϵ2/ϵ3
SAL 511	6	3	45–56	CCG→CTG	Pro264Leu[b]	ϵ3/ϵ4
SAL 506	4	3	46–52	CCG→CTG	Pro264Leu[b]	ϵ3/ϵ4
SAL 1633	4	3	51–55	CCG→CTG	Pro264Leu	ϵ3/ϵ3
ALZ 059	3	3	42–50	GAA→GGA	Glu318Gly[d]	ϵ3/ϵ3
ALZ 107	4	3	39–40	AGT→ATT	Ser390Ile[c]	ϵ3/ϵ3
FAD RO1[e]	38	5	39–52	CTG→GTG	Leu392Val[b]	ϵ3/ϵ3
ROU 011	14	4	40–60	TGT→TAT	Cys410Tyr[b]	ϵ2/ϵ3

Note.—Several kindreds with *PSEN1* mutation have been reported elsewhere (Campion et al. 1995*b*).
[a] Of the index case.
[b] Cosegregation between the mutation and AD could be demonstrated.
[c] New mutation not reported elsewhere.
[d] Noncausative polymorphism (Mattila et al. 1998; Dermaut et al. 1999).
[e] Family included in the population study.

Table 3

***APP* and *PSEN2* Analysis in Kindreds with ADEOAD with No *PSEN1* Mutation**

Family	No. of Affected Subjects	No. of Generations	AAO (range [years])	*APP*[a]	*PSEN2*[a,b]	*APOE* Genotype[c]
ALZ 074	4	3	41–60	Val715Met [d,e]	NA	ε3/ε3
FAD R03	6	3	50–60	Val717Ile[e]	NA	ε3/ε3
FAD R04[f]	5	3	53–55	Val717Ile[e]	NA	ε3/ε3
JUB 001	9	4	38–51	Val717Ile[e]	NA	ε3/ε3
ALZ 066	4	3	53–60	Val717Ile	NA	ε3/ε3
ALZ 009	5	3	50–57	WT[e]	WT	ε3/ε4
ALZ 013	10	4	45–56	WT	WT	ε3/ε3
ALZ 028	4	3	45–48	WT	WT	ε3/ε4
ALZ 036	3	3	52–60	WT	WT	ε3/ε4
ALZ 060	3	3	37–58	WT	WT	ε3/ε3
ALZ 061	3	3	40–59	WT	WT	ε3/ε3
ALZ 063	3	3	45–51	WT	WT	ε3/ε4
ALZ 383[f]	3	3	51–60	WT	WT	ε3/ε4
TOU 035	4	3	50–60	WT	WT	ε3/ε3

NOTE.—Several kindreds with *APP* mutation have been reported elsewhere (Campion et al. 1996).

[a] WT = wild type.
[b] NA = not analyzed.
[c] Of the index case.
[d] New mutation not reported elsewhere.
[e] Cosegregation between the mutation and AD could be demonstrated.
[f] Family included in the population study.

large pedigree (Campion et al. 1995*a*). Two patients with familial cases had ADAD. Finally, 17 patients had a familial history of AD that did not correspond with either ADEOAD or ADAD. Global prevalences (per 100,000 inhabitants at risk) for EOAD and ADEOAD were estimated as 41.2 and 5.3, respectively. Sex-specific prevalences for EOAD and ADEOAD are shown in table 1.

Mutational analysis of *PSEN1, APP,* and *PSEN2* was then performed in 34 French families with ADEOAD. Characteristics of the pedigrees with ADEOAD and details of the mutations detected are shown in tables 2 and 3. Sixteen different *PSEN1* mutations (not including the polymorphism Glu318Gly) and two different *APP* mutations were found in a total of 20 and 5 families, respectively. Four *PSEN1* mutations (Thr147Ile, Trp165Cys, Leu173Trp, and Ser390Ile) had not been reported elsewhere. The mutation Leu173Trp is, to our knowledge, the *PSEN1* mutation associated with the youngest AAO (24 years) so far reported for an ADEOAD case. Neuropathological confirmation of the diagnosis was obtained for one patient from this kindred. The common Pro264Leu *PSEN1* mutation was associated, in family SAL 1633, with a particular phenotype including spastic paresis, which had so far been associated only with a deletion of exon 9 (Crook et al. 1998) and a missense mutation at codon 278 (Kwok et al. 1997). Finally, a novel *APP* mutation, which introduces a Val to Met substitution near the γ-secretase cleavage site, was detected at codon 715 (Ancolio et al. 1999). In 13 families (see tables 2 and 3) DNA from relatives was available, allowing us to test the cosegregation of the mutation found in the index patient with the disease. All affected subjects for which DNA was available were mutation carriers. No asymptomatic subject ⩾60 years of age was a mutation carrier. If we assume that the *PSEN1* Glu318Gly substitution found in pedigree ALZ 059 (table 2) is a noncausative polymorphism (Mattila et al. 1998; Dermaut et al. 1999), no

Table 4

Families with ADAD Screened for *APP, PSEN1,* or *PSEN2* Mutations

Family[a]	No. of Affected Subjects	AAO (range [years])	*APOE* Genotype[b]
ROU 047[c]	3	60–65	ε3/ε3
ALZ 053	6	59–79	ε3/ε3
ALZ 049	6	60–65	ε3/ε3
ALZ 062	4	47–66	ε3/ε3
ALZ 091	4	60–74	ε3/ε3
ROU 099[c]	4	57–65	ε3/ε4
ALZ 342	5	60–77	ε3/ε4
ALZ 338	4	59–66	ε3/ε4
ALZ 005	5	60–72	ε3/ε4

NOTE.—All *APP, PSEN1,* and *PSEN2* were wild type.

[a] Three generations were studied per family.
[b] Of the index case.
[c] Family included in the population study.

Table 5

Estimation of Prevalence (per 100,000 Inhabitants) of EOAD in Three Other Studies

Study	No. of Individuals at Risk (range [years])	Cases	Prevalence
Schoenberg et al. (1985)	4,422 (40–59)	2[a]	45.2
Kokmen et al. (1989)[b]	7,422 (45–59)	2	26.9
Sulkava et al. (1985)	5,466 (30–59)	1[c]	18.2

[a] "Severe dementia" of uncertain etiology.
[b] Register of cases.
[c] "Primary degenerative dementia" expected to correspond to AD in >80% of cases.

PSEN1, PSEN2, or *APP* pathological mutation was detected in a total of 10 pedigrees with ADEOAD (tables 2 and 3). In these 10 families, we sequenced not only exons 16 and 17 of *APP* but also exons 7, 8, and 18, since they correspond to important functional regions—the Kunitz inhibitor domain and the reinternalization domain, respectively—and this screening remained negative. Nine families with ADAD were also screened for *APP* and presenilin mutations. As indicated in table 4, we identified no mutation in these families.

APOE genotyping revealed that, among the 17 patients with non-ADEOAD or ADAD familial cases identified during the prevalence study, 5 (29%) were homozygous, and 10 (59%) were heterozygous, for the *ϵ4* allele. In contrast, no index patient with ADEOAD or ADAD who was included in the mutational study carried the *APOE ϵ4/ϵ4* genotype (tables 2–4). The frequency of the *APOE ϵ4* allele among these index patients was .15 and thus did not differ from that observed in the general French population.

Discussion

To assess the prevalence of ADEOAD, we conducted a population-based study of presenile AD cases. The strength of our study lies in (1) the neurological examination of index cases allowing accurate diagnoses, (2) the use of a structured family-history questionnaire with multiple informants for checking of information about relatives, (3) the outlining of stringent criteria for ADEOAD or ADAD, and (4) the length of our follow-up period. Since ascertainment was done on the basis of detection, by physicians, of eligible cases, it could be argued that some patients may have been missed because they did not come to medical attention. This hypothesis is very unlikely, however, because EOAD is a debilitating illness that affects subjects who are still active and has a large impact on everyday life. In France, to obtain appropriate social assistance, affected individuals must visit a physician. Most of the epidemiological studies on AD have measured prevalence of the disease in elderly populations and have thus ascertained patients with AD with AAO >60—or even >65 years. Only three other studies have estimated the prevalence of EOAD (table 5). The prevalence of EOAD reported in this study is at the upper boundary of those in other reports.

Although our patients were referred irrespective of their family history, we found that a large proportion (24 [62%] of 39) of patients with EOAD indeed had a positive family history. This proportion is similar to that reported by Van Duijn et al. (1994) in another population-based study, in which patients with EOAD (with AAO <65 years) from four regions of the Netherlands were ascertained. In that study, 61% of index patients had at least one affected first-degree relative.

In the present study, only five patients (belonging to three families) fulfilled the rigid criteria for ADEOAD. This low proportion (13%) of ADEOAD cases among EOAD cases is comparable to—albeit slightly less than—that estimated in our previous study, which relied on patients with EOAD ascertained through consecutive admission to several French hospitals (Campion et al. 1995*a* and 1995*b*).

Sequencing analysis revealed that ADEOAD in 24 (71%) of 34 French families studied was attributable to *PSEN1* or *APP* mutations. Evidence for cosegregation with the disease was not available in all families (tables 2 and 3), but the pathological nature of most *PSEN1* mutations has now been established. Nevertheless, we cannot exclude the fact that some mutations are nonpathogenic. The high proportion of *PSEN1* and *APP* mutations described in the present study sharply contrasts with that reported by Cruts et al. (1998). The low percentage (18%) of families with ADEOAD with *PSEN1* or *APP* mutations reported by those authors might be explained by their inclusion criteria (i.e., at least three patients with dementia in two generations), which could not differentiate between families with ADEOAD and other types of familial aggregation. Probably some multiplex families with EOAD have been misclassified by Cruts et al. as autosomal dominant. This latter hypothesis is supported by the high prevalence (31%) of *APOE ϵ4/ϵ4* genotypes among their "autosomal dominant" probands, whereas in the present sample no index patient with ADEOAD included in the mutational analysis had the *APOE ϵ4/ϵ4* genotype (see tables 2 and 3). It is now well established that the *ϵ4* allele is a potent risk factor for EOAD (Van Duijn et al. 1994; Perez-Tur et al. 1995*a*) and that the presence of one *ϵ4* allele in an affected proband sharply increases the cumulative incidence of AD in first-degree relatives. This increased risk is obvious when the proband is homozygous for the *ϵ4* allele (Farrer et al. 1995; Martinez et al. 1998), and these data are confirmed by the proportion (29%) of *APOE ϵ4/ϵ4* genotypes, among our

familial cases, that did not correspond to either ADEOAD or ADAD cases.

The absence of *APP, PSEN1,* or *PSEN2* mutation in 10 families with ADEOAD might be explained either by a mutation located outside the regions that we analyzed or by the involvement of another gene. Interestingly, in the nine families with ADAD, no *APP* or *PSEN1* mutation was detected (table 4).

We conclude that (1) *PSEN1* and *APP* mutations are involved in the majority of ADEOAD cases and (2) that nonpenetrance of *PSEN1* and *APP* mutations by age 60 years is infrequent. These findings are important for genetic counseling and for the strategy of molecular analyses.

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Electronic-Database Information

Accession numbers and URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for *PSEN1* [MIM 104311], *PSEN2* [MIM 600759], and APP [MIM 104760])

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