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Review

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Genetic dissection of Alzheimer disease, a heterogeneous disorder

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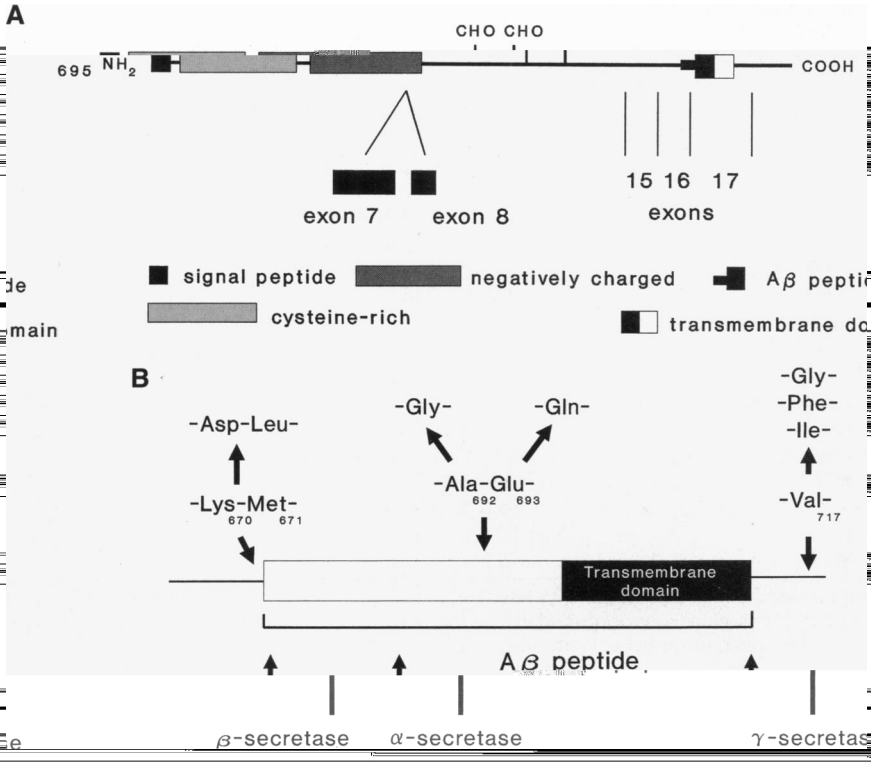

FIG. 1. *APP* gene structure. (*A*) The APP_{695} splice variant is shown along with the location

AD patients (29, 31, 37, 38). (The term sporadic is used here to indicate AD subjects with no family history of AD and does not necessarily imply a nongenetic etiology.) Subsequently, two other point mutations at codon 717 were identified, each in a single family (39, 40). One results in Phe-717 (39), and the other results in Gly-717 (40). A double mutation has been identified in a Swedish pedigree at codons 670 and 671 resulting in Asn-Leu in place of the normal Lys-Met (41). These mutations are in exon 16 of the *APP* gene and preceding the beginning of the Aβ sequence. Another pathogenic *APP* mutation has been identified in a Dutch family with both cerebral hemorrhage disease and presenile dementia (42). This mutation, also in the Aβ region, is at codon 692 and results in a Gly → Ala replacement. The disease in this family is a variant of both HCHWA-D disease and AD. Exhaustive screening of other early-onset AD, late-onset FAD, and sporadic AD patients and a large number of controls has been performed for each of these mutations (29, 37, 38, 43), and all are only rarely observed in dementia pedigrees and have never been seen in controls. Thus,

cleavage, referred to as α-secretase, has not been identified. Initially, the α-secre-

Table 1. Early-onset FAD kindreds

Family	Age of onset, years	Ref(s)
Chromosome 14 kindreds		
Finnish kindred	36 ± 3 (n = 6; 32–39)	64
L	42 ± 4.6 (n = 16; 30–48)	63
LH/603	48 ± 6.5 (n = 18; 37–68)	63, 65
Tor1.1	43	65
FAD1	52 ± 6.23 (n = 25)	19, 65
FAD2	48.7 ± 5.3 (n = 12)	19, 65
FAD3/SNW	52 ± 2.5 (n = 7; 48–56)	63, 65

normal processing and the production of intact Aβ was thought to be a disease process. Subsequent work in a variety of systems has now shown that normal cells can produce intact Aβ (51–53). Moreover, the detection of Aβ in normal cerebral spinal fluid (51, 52) demonstrates that Aβ is produced in the absence of disease. The

causes of dementia such as multiinfarct dis-

come common and confound the diagnosis of AD.

Despite the difficulties outlined above, the *APOE* gene at 19q13.2 has been shown

APOE gene encodes apoE and is part of an apolipoprotein gene cluster that spans ≈40 kb and contains in addition to *APOE*, *APOCII*, *APOCI*, and an *APOCI* pseudo-

While most of the populations studied have been late-onset, one report of an early-onset population-based group (onset ≤ 65 years; sample mean = 57 years) and extensively clinically and neuropathologically characterized, no interaction between the Gln-693 mutation, in which 31 affected subjects were genotyped for *APOE*

peptides (128). *In vitro* experiments demonstrate that apoE binds to Aβ in an isoform-specific fashion (129), with apoE-ε4 binding more rapidly to Aβ com-

the ε4 allele is a risk factor for developing AD. However, 50–60% of all AD patients

tributing to late-onset AD remain to be

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