Early-onset familial Alzheimers disease (EOFAD; AD1, AD3, and AD4)

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Citation
Early-onset familial Alzheimers disease (EOFAD; AD1, AD3, and AD4) . Lansdale: HAYES, Inc.. 2010

Authors' objectives
Alzheimer disease (AD) is a progressive neurological disorder characterized by deficits in memory and cognition. Psychiatric disturbances (such as hallucinations or delusions), swallowing problems, incontinence, and seizures may also occur over the course of the disease. AD is the most common form of dementia, with approximately 1 in 10 individuals in the general population developing the disease at some point in his or her lifetime. Although the reference standard for diagnosis is the presence of specific pathological changes in brain tissue (amyloid plaques and neurofibrillary tangles), which cannot be detected until autopsy, patients may receive a diagnosis of either “probable” or “possible” AD based on clinical evaluation. Approximately 80% to 90% of patients with a clinical diagnosis of AD will have the diagnosis confirmed after autopsy. AD is typically classified based on age at onset, with early-onset disease beginning before 60 to 65 years of age. Approximately 60% of patients with early-onset AD have a family history of dementia, and 13% have a clearly autosomal dominant form of the disease. Three different subtypes of early-onset familial AD (EOFAD) have been described. Alzheimer disease type 1 (AD1) may result from sequence variants in the amyloid precursor protein gene (APP), which is located on chromosome 21 at band q21. While most APP gene variants occur in exons 16 or 17, AD1 may also result from large genomic duplications involving the APP locus. Alzheimer disease type 3 (AD3) is caused by variants in the presenlin 1 gene (PSEN1), which is located on chromosome 14 at band q24.3. Alzheimer disease type 4 (AD4) is caused by variants in the presenlin 2 gene (PSEN2) located on chromosome 1 at band q31 to q42. Among patients with EOFAD, it is estimated that the prevalence of sequence variants is 30% to 70% for PSEN1, 10% to 15% for APP, and < 5% for PSEN2. APP, PSEN1, and PSEN2 gene variants are inherited in an autosomal dominant manner, with a 50% recurrence risk for the first-degree relatives of variant-positive individuals. The clinical manifestations of all three subtypes of EOFAD are generally the same as those of the more common late-onset form of the disorder, and the penetrance is essentially complete (although age-dependent). However, atypical features, such as spastic paraparesis and myoclonus, may be present.

Project page URL
http://www.hayesinc.com

Indexing Status
Subject indexing assigned by CRD

MeSH
Age of Onset; Alzheimer Diseases

Language Published
English

Country of organisation
United States