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Review Article

Molecular genetics of early-onset Alzheimer's disease revisited

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Abstract As the discovery of the Alzheimer's disease (AD) genes, *APP*, *PSEN1*, and *PSEN2*, in families with autosomal dominant early-onset AD (EOAD), gene discovery in familial EOAD came more or less to a standstill. Only 5% of EOAD patients are carrying a pathogenic mutation in one of the AD genes or a apolipoprotein E (*APOE*) risk allele ε4, most of EOAD patients remain unexplained. Here, we aimed at summarizing the current knowledge of EOAD genetics and its role in ongoing approaches to understand the biology of AD and disease symptomatology as well as developing new therapeutics. Next, we explored the possible molecular mechanisms that might underlie the missing genetic etiology of EOAD and discussed how the use of massive parallel sequencing technologies triggered novel gene discoveries. To conclude, we commented on the relevance of reinvestigating EOAD patients as a means to explore potential new avenues for translational research and therapeutic discoveries.
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1. Dementia and Alzheimer's disease

The term dementia is used to define a heterogeneous group of progressive and degenerative brain pathologies, clinically characterized by deterioration in memory, learning, orientation, language, comprehension, and judgment. AD (OMIM# 104300), in its typical clinical presentation with progressive loss of memory and disturbance of additional cognitive functions namely word-finding, spatial cognition, reasoning, judgment, and problem solving [1], is the leading cause of dementia in the elderly. Of all dementia patients, 50% to 75% present with AD, which affects between 23 and 35 million people worldwide [2]. Age is the most prominent biological risk factor [3], and the age of 65 years is often used to classify AD patients in early-onset (EOAD) and late-onset (LOAD) groups. Of all AD patients, around 10% are diagnosed with EOAD [4], and they present with their first symptoms between 30 and 65 years with most of the EOAD patients being diagnosed between 45 and 60 years. Besides the typical clinical presentation with memory impairment, atypical clinical presentation with focal cortical symptoms, for example, visual dysfunction, apraxia, dyscalculia, fluent and non-fluent aphasia, executive dysfunction, has also been reported. This atypical presentation is more frequently reported in EOAD patients compared to LOAD, who mostly present with typical memory phenotype [5]. Additionally, a nonmemory phenotype is seen in roughly 25% of EOAD patients in whom visual or apraxic and language phenotypes are more frequent [5].

The neuropathologic hallmarks of AD brains are extracellular accumulation of diffuse and neuritic amyloid plaques, composed of amyloid-β (Aβ) peptide, and frequently surrounded by dystrophic neurites and the intraneuronal accumulation of neurofibrillary tangles (NFTs) composed of hyperphosphorylated protein tau (p-tau) [6,7]. These pathologic features are accompanied by gliosis and the loss of neurons and synapses [7]. Although, some studies reported a larger neuropathologic burden [8] or a more widespread pathology extending outside the medial temporal lobe in younger patients [5], overall the

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pathologic features of EOAD and LOAD patients are largely similar, indicating that at the end-stage of disease, it is difficult to distinguish the two AD age groups by any other criterion than onset age.

The main incentive for this review was the recent renewed interest in EOAD genetic studies due to the availability of high-throughput, genome-sequencing and exome-sequencing technologies, and bioinformatic tools, permitting new attempts to unravel the missing genetic etiology of EOAD. The expectations are that these new genetic approaches will uncover new molecular pathways or new molecular components of already known pathways. Furthermore, the availability of new genetic markers will help refining the different genetic signatures of clinical AD, allowing a more accurate stratification of patient cohorts, preclinical and clinical, for medical research, and for clinical trials. In the long term, the ability to identify different underlying molecular pathologies of clinical AD patients or at risk individuals will pave the way for personalized medicine and health care.

2. The genetic etiology of EOAD

In contrast to LOAD which is a complex disorder with a heterogeneous etiology and an heritability of 70 to 80% [9,10], EOAD is an almost entirely genetically determined disease with a heritability ranging between 92% to 100% [9]. Between 35 to 60% of EOAD patients have at least one affected first-degree relative [11–13], and in 10% to 15% of those familial EOAD patients, the mode of inheritance is autosomal dominant transmission [11,13]. Genetic analysis of exceptionally large and informative monogenic pedigrees was the basis for the identification of high-penetrant mutations in the three EOAD genes, coding for the amyloid precursor protein (*APP*) and the presenilins 1 and 2 (*PSEN1* and *PSEN2*).

2.1. Identification of causal EOAD genes in extended pedigrees

Down syndrome (DS), caused by chromosome 21 (partial) trisomy, played a pivotal role in the early attempts to identify genes for inherited EOAD. DS patients were shown to present with a comparable brain pathology of amyloid plaques and tau tangles as AD patients [14]. The strong homology between the amyloid β (Aβ) protein peptides, isolated from vessels [15] and from plaques [16] from DS and AD brains, was a first indication that both diseases shared a common genetic mechanism associated with chromosome 21 [15,17]. Whole-genome-linkage (WGL) studies in AD families provided supporting evidence for a genetic defect located on chromosome 21q [18–20]. Cloning of the gene coding for the amyloid β precursor protein (APP) [21], from which the amyloid β peptides are produced, and its mapping to chromosome 21q21.2–21q21.3 [22,23], encouraged a series of genetic studies aiming at identifying mutations in AD patients and families. Initial genetic studies in large families with autosomal dominant AD were negative [24,25] but could be explained by the observation of a high degree of genetic heterogeneity in familial AD indicating that genes other than *APP* had to be involved [26].

A segregation study in extended multigenerational families with autosomal dominant cerebral hemorrhage with amyloidosis Dutch type (HCHWA-D), conclusively linked *APP* to the disease [27]. HCHWA-D brain pathology consists mainly of vascular amyloid depositions of the same Aβ observed in AD brains [28]. Sequencing identified a mutation affecting the Aβ sequence in patients with HCHWA-D [29] and segregated with disease [30]. The discovery of a *APP* mutation linked to vascular Aβ pathology in HCHWA-D encouraged new mutation studies of *APP* in AD families. A first mutation was identified confirming a direct role for *APP* in AD pathogenesis in some AD families [31].

Segregation studies in EOAD pedigrees, negative for *APP* mutations, led to the identification of a new locus for EOAD on chromosome 14q24.3 [32–35]. Genetic mapping and gene cloning followed by mutation screening of candidate genes [36–38] identified presenilin 1 (*PSEN1*) as an EOAD gene with at that time unknown functions [39]. Based on protein homology, a second presenilin protein was identified and mapped to chromosome 1q31–q42 [40,41], in the region that was linked to AD in a series of families known as descendants of Volga-Germans [42,43] and was named presenilin 2 (*PSEN2*).

2.2. Genetic and phenotypic heterogeneity in EOAD

To date, 52 pathogenic mutations in *APP* have been reported in 119 probands of autosomal dominant families (http://www.molgen.vib-ua.be/ADMutations) [44]. Most of the *APP* mutations are nonsynonymous within or flanking the Aβ sequence (Fig. 1A). However, 25 genomic duplications of variable size containing *APP* have been identified co-segregating with AD in as many autosomal dominant families, as reported in http://www.molgen.vib-ua.be/ADMutations [44] and reviewed in [45], mimicking partial trisomy 21. Furthermore, a recessive one amino acid deletion (p.E693Δ) [46] and a recessive missense mutation with dominant negative effect on amyloidogenesis (p.A673V) [47,48] were described (Table 1). Missense mutations are identified at least 4-folds more frequently than *APP* genomic duplications in AD patients. Disease onset of *APP* mutation carriers ranged between 45 and 60 years [49,50]. In contrast to the missense mutations, showing a near-complete disease penetrance, *APP* genomic duplications display reduced penetrance and higher variability in onset age [45]. Besides the pathogenic mutations, a rare protective variant p.A673T in *APP* was reported that was enriched in the Icelandic population [51]. At the same amino acid position, the p.A673V variant showed

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