# Early-onset Alzheimer disease: what are we missing?

Memory is the first brain function that starts to fade away when Alzheimer disease (AD) pathology affects the brain of a patient. Decline of additional cognitive functions, shortly follows. This progressive and irreversible disease, intrudes the life of millions of people worldwide. Despite the tremendous advances made in the field, AD remains incurable. Taking the large numbers of affected people and their numbers steadily increasing due to the aging populations, there is a pressing need to expand our knowledge on the pathophysiology of AD.

AD is mostly a disease that occurs later in life, after 65 years of age (late-onset AD, LOAD). LOAD is a complex disease with multiple risk factors, both genetic and environmental, that contribute to the disease onset. Of all AD patients, about 10% develops the disease earlier in life, before 65 years of age, with the majority of patients between 45-65 years. These early-onset AD (EOAD) patients have a positive family history of disease in 35-60% of cases, implying that at least one first-degree relative is affected. In 10-15% of these familial EOAD patients the disease is inherited from generation to generation in autosomal dominant manner. In those families the cause of disease is almost entirely genetic with children of an affected parent having 50% chance of being affected. In the early 90's, genetic research identified three causal genes for EOAD coding for the amyloid precursor protein (*APP*), presenilin 1 and 2 (*PSEN1*, *PSEN2*). A simple genetic alteration in one of these three genes is a sufficient cause for EOAD. Together, they explain only a small fraction of families with inherited EOAD.

Why remain so many EOAD families unexplained?

Providing answers to this question was the major aim of this review paper. Successful genetic studies need access to extended families with large numbers of affected and unaffected family members in several generations to participate. In most of the unexplained families, the small size their pedigree was the major limitation. Nowadays, this can be overcome by making use of advanced sequencing technologies enabling gene discovery with fewer patients to study.

Why continue the search for novel genes in EOAD families and patients when the majority of patients have LOAD?

LOAD and EOAD have similar clinical and pathological characteristics and studies on *APP*, *PSEN1* and *PSEN2* have already answered questions about the pathological changes that happen in the brain of AD patients, before the appearance of the clinical symptoms independent of the age at onset. In this review paper, we present the historical findings and the milestones in EOAD research. From the discovery of causal and risk genes, to the identification of diagnostic biomarkers, to the (not yet successful) attempts to translate the findings into disease therapies. We discuss strategies and study designs in both families with known causal mutations as well as in single unexplained patients. We critically revisit the genetics of EOAD and we suggest that continuation of the investigations will lead to a better understanding of AD at large.

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## Publication

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