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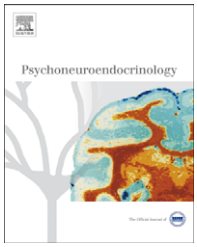

Genetic heterogeneity of Alzheimer's disease: Complexity and advances

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Summary
Most of what we know about the pathological process of Alzheimer's disease (AD) results from research on the amyloid cascade hypothesis. This hypothesis in turn is derived largely from the characterization of rare disease-causing mutations in three genes, which code for the amyloid precursor protein (APP), presenilin 1 (PS-1) and presenilin 2 (PS-2) and account for most cases of early-onset autosomal dominant familial AD.
These genetic findings also suggested that better understanding of the genetic components of AD, even in the late-onset sporadic forms of the disease, might help to identify central pathways of the AD process and lead to the rapid development of active molecules. Twin studies have reinforced the rationale of this approach, for they indicate that more than 50% of the late-onset AD risk may be attributable to genetic factors.
The 1993 discovery that the apolipoprotein E4 (ApoE4) allele is genetically associated with increased risk in both sporadic and familial late-onset Alzheimer's disease strongly supports the validity of this genetic approach. Further progress based on this major finding has nonetheless been disappointing and raises questions about it. First, despite intensive researches, the exact role of APOE in the pathophysiological process still remains unknown. Second, the APOE gene is the only gene so far recognized as a consistent genetic determinant of sporadic forms of AD, even though numerous studies have looked for such genes; these disappointing results suggest persistent methodological limitations. However, recent methodologies allowing new strategies may allow important breakthrough.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that occurs predominantly in later life. About 5% of people aged 65 or older have AD, and the prevalence rises steeply—to 19% after 75 years and to 30% after 85. The 85-and-older age group is one of the fastest growing population

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segments in industrialized countries. Because of this huge increase in the elderly population and the possibility that a large fraction of this elderly population may develop AD, it is essential to understand the causes of this disease so that effective preventive measures can be devised.

The main pathological features of AD are neurofibrillary tangle and senile plaque formation. This latest is caused by the progressive deposition of amyloid β protein (Aβ) in the brain, composed mainly of 39–43 amino acid peptides generated through proteolytic cleavage of the Aβ precursor protein (APP). Since the first report some 20 years ago of the genetic predisposition to AD, considerable efforts have gone into characterizing the genetic determinants involved. The underlying postulate of this research is that a better understanding of the genetic components of AD may help to identify central pathways of the AD process and lead to the rapid development of active molecules.

We will review successively the genetic determinants of the hereditary forms of AD and sporadic cases. Then we will analyze the APOE ε4 allele story. We will finally debate and challenge in some ways the recent advances and evolutions of your knowledge in the field of AD genetics: potential methodological limitations of the classical genetic strategy, promises and problems of the recent methodological high-throughput analyses.

2. Forms with autosomal dominant transmission

Since 1934, it has been known that some forms of AD are determined purely by genetics, that is, are inherited through autosomal dominant transmission (Lowenberg and Waggoner, 1934). Nonetheless, not until the 1980s were systematic methodological approaches finally available to characterize the genes involved. These forms are estimated to account for less than 1% of AD cases (Campion et al., 1999), and the genes carrying these pathogenic mutations: APP, presenilin (PS) 1 and 2 (Goate et al., 1991; Levy-Lahad et al., 1995; Sherrington et al., 1995), are becoming well documented. It is important to note, however, that these monogenic forms concern only early- or very early-onset forms of AD. We cannot rule out the possibility that some monogenic familial forms—but of later onset—have not been detected because of the possible censoring associated with deaths of some family members at a subclinical stage. It is thus probable that the number of monogenic familial forms is currently underestimated.

Twenty-three mutations of the APP gene have been already described; 19 of them unambiguously cause AD or other dementias associated with cerebral hemorrhages (http://www.alzforum.org/res/com/mut/app). These mutations are all found at or near secretase cleavage sites, which determine APP metabolism and therefore amyloid peptide production. Beyond these isolated mutations, duplication of the APP gene is reported to cause some autosomal dominant forms (Rovelet-Lecrux et al., 2006). This observation implies that substantial overexpression of this gene alone is sufficient to cause AD. Active research to characterize mutations or polymorphisms in the APP gene promoter is currently underway and indicates that genetic variations within this promoter may modify the risk of developing AD (Theuns et al., 2006).

One hundred and fifty-five mutations of the PS1 gene have been described (http://www.alzforum.org/res/com/mut/ps1). According to a broad consensus in the literature, PS1 participate in the catalytic core of the γ-secretase complex and its mutations induce a relative increase in the production of Aβ_{x-42} peptides (Wolfe et al., 1999).

Nine mutations of the PS2 gene have been described (http://www.alzforum.org/res/com/mut/ps2). Some PS2 mutations, like those of PS1, were functionally associated with an increase in the production of Aβ_{x-42} peptides. Nonetheless, *in vitro* studies showed that four of them did not modify of either Aβ_{x-40} or Aβ_{x-42} peptide production. Given that their segregation with AD was not clearly showed, these findings suggest that these mutations are simply rare polymorphisms rather than disease-causing mutations (Walker et al., 2005).

The causal links between mutations, the functions of the mutated genes, and disease development led to a pathophysiologic hypothesis that radically adjusted our understanding of AD: the hypothesis of the amyloid cascade. The systematic association of pathogenic mutations with modifications in the APP metabolism and more particularly with a relative overproduction of Aβ_{x-42} peptides indicates that this metabolism is at the heart of the disease process (at least in the monogenic forms of the disease). The relative overproduction of these neurotoxic peptides appears to lead first to neurofibrillary degeneration and then to neuronal death (Hardy, 1997).

Nonetheless, this hypothesis, often presented as dogma, has not yet been clearly demonstrated and other pathophysiologic mechanisms—not necessarily mutually exclusive—are still under study. These include, for example, alterations in cell trafficking (Naruse et al., 1998) or neuronal calcium homeostasis (Schneider et al., 2001).

Discovery of new mutations involved in monogenic familial forms could therefore help to decipher the pathophysiologic mechanisms in play. Our knowledge of monogenic forms is not yet complete: of 65 French families with early-onset AD, the causal mutation is not known for approximately 10% (Raux et al., 2005). These families may well carry pathogenic mutations not yet characterized in the PS1, PS2 and APP genes. A Dutch study, however, characterized significant linkage with a marker defining a region of 9.3 cM on chromosome 7 at q36 in at least one family with early-onset AD (Rademakers et al., 2005). This result underlines the well-known heterogeneity of the genetic component of AD and makes it possible to characterize one or more key new genes involved in the AD process.

3. Forms with non-Mendelian transmission

For the vast majority of AD cases, mainly late-onset forms, no familial aggregation is known; these forms are defined are "sporadic". Beyond the potential bias of censoring, this simple observation may therefore suggest that the genetic component of AD is relatively limited.

Although the first studies in twin populations sometimes suggested a slight increase in AD frequency in monozygous compared with dizygous twins, they mainly seemed to