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Candidate genes for late-onset Alzheimer's disease: Focus on chromosome 12

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Abstract

In recent years, there was an increasing interest on candidate genes may play an important role in the development of Alzheimer's disease (AD). Several genome wide screens have undertaken so far or expanded recently, and suggested a number of genomic areas that may contain novel susceptibility genes for AD, in particular most compelling have been the findings on chromosome 12. Polymorphisms in different susceptibility genes on chromosome 12 (A2M, LRP1, CP2 and OLR1) are now being suggested as possible genetic markers for increased risk of developing AD. However, many of these studies are controversial and have shown conflicting results. Thus far, the search for the chromosome 12 Alzheimer's gene must continue and there are several other genes in this region that we are looking at. In this article, we focused on the current knowledge of the genetics of familial late-onset and sporadic AD linked to the chromosome 12, and the future search for other candidate genes.

Keywords: Dementia; Alzheimer's disease; Chromosome 12; Low density lipoprotein receptor-related protein 1; Alpha-2-macroglobulin; Oxidised LDL receptor 1; Transcription factor LBP-1c/CP2/LSF

1. Introduction

The progress made in the last decade in dementia genetics highlighted the important role that genes play in the development of dementia and particularly in Alzheimer's disease (AD), the most common cause of dementia in the elderly. Apart from the three genes (amyloid precursor protein [APP], presenilin [PS] 1 and 2) known to be involved in the autosomal dominant forms of AD with early-onset, only another gene, the apolipoprotein E (APOE), has been recognised as a common susceptibility gene for both late-onset familial AD and sporadic AD (Saunders et al., 1993). A susceptibility gene is a gene that not causes the disease but convey an increased risk for the disease. In fact, having the APOE ε4 allele may increase the risk for AD and decrease age at onset of the disease, whereas the ε2 allele seems to have a protective effect. However, as APOE gene accounts for only 45–60% of the genetic risk for late-onset AD (Rubinsztein and Easton, 1999), and it represents only 7–9% of the total variance in age of onset of familial AD (Daw et al., 2000), it becomes evident that additional risk factors should be involved in the etiology of late-onset AD.

In the attempt to identify these other factors, two main approaches have been used: candidate gene studies and human genome scans. The candidate gene approach assesses the association between a particular allele (or a set of alleles) of the gene that may presumably play a role in the disease and the disease itself, and it is performed with unrelated cases and control subjects or with families including probands and unaffected relatives. While, in a genome scan, linkage analyses search and map disease genes by typing polymorphic DNA markers and looking whether the alleles cosegregate with disease among related subjects, and when the mode of transmission of the disease is complex, as in late-onset AD, a common way is to examine allele-sharing between pairs of affected relatives. In this case, if the marker is linked to the disease gene the alleles will be shared between affected sib pairs more often than expected. Both the approaches outlined above have been applied to studying late-onset AD but have not yet produced definitive results.

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This review focused on the current knowledge of genetic loci of chromosome 12 likely linked to familial late-onset and sporadic AD, through the analysis of clinical and epidemiological studies from the international literature. Searching National Library of Medicine (PubMed) using the key words Alzheimer's disease AND chromosome 12, OR low density lipoprotein receptor-related protein 1, OR alpha-2-macroglobulin, OR oxidised LDL receptor 1, OR transcription factor LBP-1c/CP2/LSF, (OR "A2M" or "LRP1", OR "OLR1", OR "CP2") for papers published from January 1997 to July 2005, retrieved several studies. The time criterion was chosen according to the publication of the first evidence for a late-onset AD chromosome 12 locus (Pericak-Vance et al., 1997).

2. Chromosome 12 and late-onset Alzheimer's disease

Several genome wide screens have been undertaken or expanded recently which suggested a number of genomic areas that may contain novel susceptibility genes for late-onset AD. Most compelling have been the chromosome 12 findings (Fig. 1).

The first evidence for a novel late-onset AD locus within the chromosome 12 came from a linkage study by Pericak-Vance et al. (1997). They performed a complete genomic screen using two independent data sets of late-onset AD pedigrees, and showed evidence for a new late-onset AD locus on the pericentromeric region of chromosome 12 between the markers D12S373 and D12S390 in subjects non-APOE ε4 bearers. Subsequent work by the authors in attempts to better localize the gene involved in late-onset AD detected evidence for linkage in a broad area surrounding the centromeric region of the chromosome highlighted in the original report (Scott et al., 1999). A follow-up study in 53 white families with different age at onset of AD confirmed the evidence for linkage within a wider region of the chromosome 12p (Rogaeva et al., 1998). Wu et al. (1998) tried to replicate these findings in a selected samples from 230 US families with two or more siblings affected by AD and found only a moderate linkage signal in the same region of 12p reported by previous work (Fig. 1).

The refining of the original work showed a stronger evidence for linkage within the long arm of chromosome 12 conditional on the presence of APOE ε4 allele and Levy body dementia in post-mortem material from family members (Scott et al., 2000). A genome screen (Kehoe et al., 1999) performed in 292 sib pairs with late-onset AD provided little evidence of linkage on chromosome 12p, further supported by a subsequent screen in the same population that found linkage with AD at two 12p different sites (Myers et al., 2002). In a systematic survey of the human genome, allelic association with AD was found for the marker D12S1045, close to the telomeric end of the chromosome (Zubenko et al., 1998). Two further linkage studies performed in Caribbean Hispanics with familial AD provided modest support for linkage to regions on chromosome 12p (Mayeux et al., 2002; Lee et al., 2004). A more recent genome scan detected evidence of association on chromosome 12 in a inbred Arab community (Farrer et al., 2003), but the exact region of linkage was distal to that observed in previous studies. Using extended families with late-onset AD, Poduslo and Yin (2001) found markers on chromosome 12 linked with the disease, which were downstream from the gene of alpha-2 macroglobulin (A2M). Similarly, in a very recent population-based study from the Netherlands it has been reported evidence of association of a marker near to A2M gene with late-onset AD (Sleegers et al., 2004) (Fig. 1).

All these studies, although highlighting different regions of maximum linkage, strengthen the argument that an AD susceptibility gene maps on the chromosome 12. The different results showed by the above reported genome scans may be related either to the genetic heterogeneity, or to the methodology itself, because of different genetic markers and marker maps, variations in statistical analysis and the varying power of different studies. Furthermore, in a complex disease, linkage analyses generally result in a large disease-correlated region that span from 10 to 20 Mb, and can contain several candidate genes.

3. Low density lipoprotein receptor-related protein 1 and alpha-2-macroglobulin genes in Alzheimer's disease

The identity of the chromosome 12 locus is at the moment unclear and a number of plausible candidate genes for late-onset AD map in the reported linkage areas. Looking at the published association studies, two candidate genes located in the regions of interest have received firstly considerable attention: the low density lipoprotein receptor-related protein 1 (LRP1) (Kang et al., 1997) and the alpha-2-macroglobulin (A2M) (Blacker et al., 1998) genes.

LRP1 gene is a ligand for proteins involved in AD pathogenesis, such as APOE, APP and A2M, and is expressed in immunoreactive senile plaques, dystrophic neurites and reactive astrocytes. A silent C → T polymorphism in the exon 3 of the gene has been identified and associated with late-onset AD in some studies (Kang et al., 1997; Hollenbach et al., 1998; Lambert et al., 1998; Baum et al., 1998; Kolsch et al., 2003), while just a weak association modulated by APOE ε4 allele and gender (Hatanaka et al., 2000; Bullido et al., 2000) or totally no association have been reported in others (Table 1). The conflicting results can be explained by a possible linkage disequilibrium (LD) with other causative polymorphisms, or another close biologically relevant locus, or by differences in genetic background among different populations, as suggested in our recent study. In fact, we reported a statistically significant decreasing geographical trend from Northern to Southern regions of Europe for the LRP1C allele and CC genotype frequency in AD patients, and supposed that these regional differences in allele and genotype frequencies may influence the different patterns of association between this polymorphism and AD in various populations (Panza et al., 2004a,c). However, the low statistical power of some studies, the use of not well-matched groups, the different diagnostic criteria utilised or publication bias have to be considered as possible cause of spurious associations and the inconsistent results among studies.

To better clarify the role of this polymorphism in the disease, two meta-analyses have been conducted. The first one was performed in 2001 by Sanchez-Guerra and colleagues using seven studies, and showed a statistical significant difference in the frequency of the CC genotype between patients and