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Review

Current knowledge of chromosome 12 susceptibility genes for late-onset Alzheimer's disease

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Abstract

In the last decade, it has become more apparent the important role genes play in the development of late-onset Alzheimer's disease (AD). Great efforts, involving human genome scans and candidate gene studies, have been given towards identifying susceptibility genes for AD. A number of regions on different chromosomes have been reported to demonstrate linkage for AD. Of these, findings on chromosome 12 are some of the most compelling. Worldwide genetic association studies pre-dating and subsequent to recent linkage studies have identified and focused upon a number of genes that map to the areas of reported linkage on chromosome 12, however, analyses of those genes studied to date, on the whole, remain inconclusive and ambiguous. This paper reviews studies that have provided evidence of linkage for AD on chromosome 12 and in turn discusses the work conducted to date on candidate genes that have been identified and map to the chromosome 12 regions of interest.

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

1. Introduction

In less than two decades, great strides have been made in research of the molecular genetics of Alzheimer's disease (AD). Over 100 mutations in any of three genes (amyloid precursor protein (APP) [43], presenilin 1 (PSEN1) [109], and presenilin 2 (PSEN2) [124]) are considered deterministic in that they have been found to cause the disease as an early onset autosomal dominant form. Inheritance of a specific allele of a fourth gene, namely the ε4 allele of the apolipoprotein E (APOE) gene, has an entirely different character. Rather than being a deterministic mutation that results in disease through inheritance of at least a single copy, inheritance of one or more ε4 alleles, which are the result of a double polymorphism in the APOE gene, is considered to increase one's risk of developing late-onset AD, as well as some early onset forms [116]. However, in itself inheritance of the APOE ε4 allele is neither sufficient nor necessary for the development of AD and as many as 50% of AD patients with late-onset do not possess the ε4 allele [95]. Thus, APOE ε4 is likely to act in increasing AD risk in conjunction with environmental and/or other genetic factors.

On this basis, genes and biological markers have been identified and suggested to provide pre-symptomatic estimates of risk for the eventual development of the complex late-onset AD. There is widespread interest in obtaining such risk information, particularly as treatments are in use or continually being developed to slow or prevent the onset and progression of this degenerative disease. Many of the

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recently discovered susceptibility genes for late-onset AD have resulted from the findings of a number of recent genome wide linkage studies. These studies involved the examination of regularly spaced highly informative microsatellite genetic markers across the whole human genome of either extended families or affected siblings pairs with AD. The genome scans were designed to try and identify genetic regions in which there was greater sharing (inheritance) of alleles (at a number of adjacent sites on chromosomes) between affected relatives than would be expected by chance. As a result of these studies, various regions on different chromosomes were identified as having linkage for AD, although from all the studies conducted, no region. Subsequently, allelic-association studies on candidate genes chosen on the basis of their reported biological functions and their localisation within areas with reported AD linkage have been performed in attempts to refine the areas of linkage and look for specific susceptibility genes.

We reviewed clinical and epidemiological studies from the international literature between January 1997 and July 2005. We searched through Medline by the following keywords: dementia, Alzheimer's disease, chromosome 12, linkage, low density lipoprotein receptor-related protein 1, alpha-2-macroglobulin, oxidised LDL receptor 1, transcription factor LBP-1c/CP2/LSF. We started our search in 1997 because the first report on a new late-onset AD locus on chromosome 12 was published in that year [101]. Here we reviewed the results of those studies providing evidence of linkage for AD on chromosome 12, and then focused our attention on putative susceptibility genes that are and have been examined by genetic association studies and map within the areas of reported linkage on chromosome 12.

2. Genome scan studies on chromosome 12

Pericak-Vance and co-workers were the first to report evidence of a new late-onset AD locus on chromosome 12 following a complete genomic screen they had conducted on multiplex families with ages of onset greater than 60 years. They found the strongest evidence of linkage at 27.5 Mb in the peri-centromeric region of the chromosome [12p11] in subjects that were not carriers of the APOE ε4 allele [101]. Subsequent work by the authors in attempts to refine the area revealed the highest evidence of chromosome 12 linkage at the edge of the original peak [122] in APOE ε4 negative families and that it may be associated with dementia with Lewy bodies [123] (Fig. 1).

Additional evidence for linkage on chromosome 12 came from Wu and colleagues, as part of the first phase of another concurrent genome-wide scan on affected sibling pairs by Kehoe and colleagues [66,146]. In this study the strongest linkage was also found in APOE ε4 negative individuals but at some 35–40 cM distant from the Scott and co-workers peak [123,146]. These data were supported following the second phase of the Kehoe and colleagues genome screen which involved the use of a more dense series of markers in a larger sample of sibling pairs chromosomal regions of interest identified in phase I [91] (Fig. 1).

Independent confirmation of chromosome 12 linkage for AD was provided by Rogaeva et al. in 53 families with different ages at onset of AD [110]. These results implicated two separate regions, one which was adjacent to the peak reported by Wu and colleagues and the other within the region identified from more detailed mapping by Scott and colleagues [123,146] which encapsulated the 35–40 cM

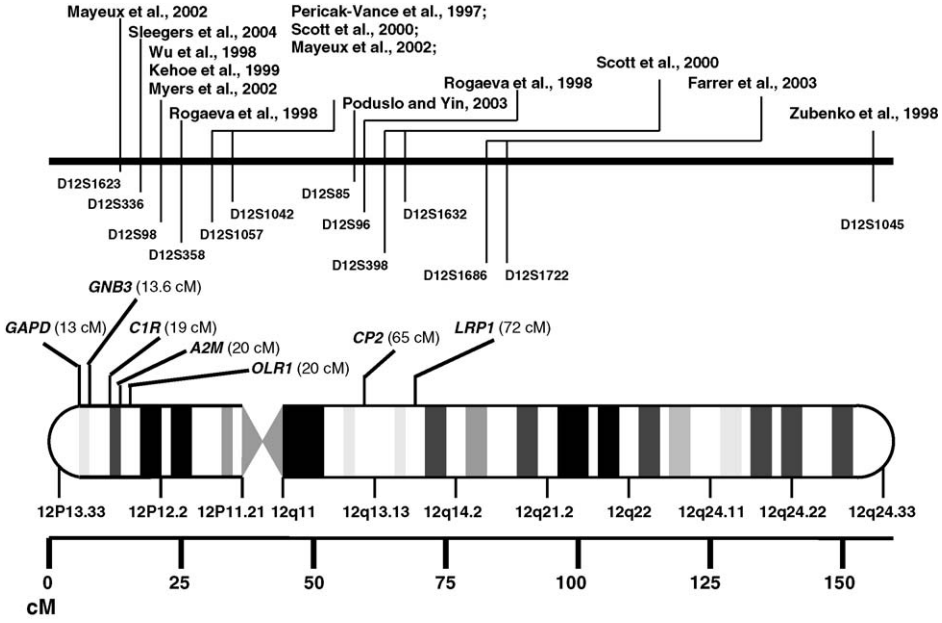

Fig. 1. Overview of linkage and linkage disequilibrium studies for Alzheimer's disease on chromosome 12. The location of the genes is given in centiMorgan (cM).