Genetic heterogeneity of gene defects responsible for familial Alzheimer disease

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Abstract

Inherited Alzheimer’s disease is a genetically heterogeneous disorder that involves gene defects on at least five chromosomal loci. Three of these loci have been found by genetic linkage studies to reside on chromosomes 21, 19, and 14. On chromosomes 21, the gene encoding the precursor protein of Alzheimer-associated amyloid (APP) has been shown to contain several mutations in exons 16 and 17 which account for roughly 2-3% of familial Alzheimer’s disease (FAD). The other loci include what appears to be a susceptibility gene on chromosome 19 associated with late-onset (> 65 years) FAD, and a major early-onset FAD gene defect on the long arm of chromosome 14. In other early- and late-onset FAD kindreds, the gene defects involved do not appear to be linked to any of these three loci, indicating the existence of additional and as of yet unlocalized FAD genes. This review provides a historical perspective of the search for FAD gene defects and summarizes the progress made in world-wide attempts to isolate and characterize the genes responsible for this disorder.

Introduction

Alzheimer’s disease (AD) is a devastating neurodegenerative disorder that is characterized by dramatic personality changes and global cognitive decline (Terry & Katzman, 1983). It currently affects approximately four million Americans, taking more than 100,000 lives each year. Since mean survival from the time of diagnosis ranges from three to twenty years (average of eight years), a tremendous burden is placed on family members during the course of the disease. In fact, it is estimated that for patients living at home, the cost of care averages $18,000 annually. In the U.S., AD patients fill more than 50% of all nursing home beds at an annual cost of $36,000 for each patient. The overall cost to society is presently more than $90 billion per year. Presently, no effective therapy exists for this disorder and it is expected that by next century more than 14 million Americans will be affected (Alzheimer’s Association Statistical Data on Alzheimer’s Disease). Clearly, one of the major challenges to those studying the aging process will be deciphering the etiological events leading to AD.

The genetics of Alzheimer’s disease

The basic etiology of AD remains unknown, although advanced age and a positive family history of dementia (clustering of AD cases in kindreds) appear to represent prominent risk factors. Confirmed diagnosis of AD is only possible by autopsy or biopsy and depends on observing higher than expected amounts of beta-amyloid (βA4) plaques (senile plaques) and neurofibrillary tangles (NFT) in the brain (Glenner & Wong, 1984; Terry & Katzman, 1983). A major difficulty in developing rational therapies for AD stems from the lack of information regarding its etiology. The identification of particular environmental agents causing human neurodegenerative diseases is an arduous task. However, in some cases of AD the primary cause
lies not in the environment, but in the genome of the patient. In this review, we will concentrate on genetic studies of AD including the potential role(s) played by the genes encoding the amyloid βA4 precursor protein (APP) family, and a novel locus on chromosome 14.

The evidence for familial forms of Alzheimer's disease (FAD) derives from family-, survey-, and life table-based analyses (reviewed in St George-Hyslop et al., 1989). FAD has been clearly demonstrated to be a genetically heterogeneous disorder, involving multiple genetic loci on at least three chromosomes (chromosomes 14, 19, and 21). The actual proportion of AD that is considered to be inherited is debatable, since it is often difficult to assess whether the disorder is familial or sporadic in most kindreds where familial clustering of the disorder is observed. In many pedigrees, particularly in those with late onset (>65 years) AD, at-risk, presymptomatic family members may die of other age-related illnesses (e.g. heart disease) before showing symptoms of dementia, making it difficult if not impossible to determine if these cases of AD have a genetic component. Consequently, estimates of the proportion of AD that is inherited range from 10% to nearly 100%. Overall estimates of life-time risk of developing AD in first-degree relatives of probands with AD suggest that approximately 50% of AD is inherited (Farrer et al., 1991). Meanwhile, a relatively low concordance rate of 40% in monozygous twins (Breitner & Murphy, 1992) implicates non-genetic factors in the expression of AD.

The role of the amyloid β protein precursor gene

Perhaps the greatest clues to the etiology of AD have been derived from studies of the neuropathological lesions associated with AD, and particularly the amyloid-containing senile plaques. The cores of senile plaques are made up primarily of βA4, a 39-43 amino acid peptide (Glenner & Wong, 1984) derived from a much larger precursor protein, APP. The APP gene produces multiple mRNA transcripts (Kang et al., 1987; Goldgaber et al., 1987; Tanzi et al., 1987; Robakis et al., 1987; Ponte et al., 1988; Tanzi et al., 1988; Kitaguchi et al., 1988; De Sauvage & Octave, 1989; Jacobsen et al., 1991), the majority of which contain an alternatively-spliced exon encoding a Kunitz protease inhibitor (KPI) domain. The form(s) of APP that actually give rise to the βA4 in amyloid deposits remain unknown. The APP gene is expressed ubiquitously throughout the body and brain in a differential pattern (Tanzi et al., 1987, 1988). The predominant form of APP RNA in brain is APP695 (lacking the KPI domain) and is abundantly synthesized by large neurons such as cortical pyramidal cells (Bahnanyar et al., 1987; Palmert et al., 1987; Goedert, 1987; Higgins et al., 1987; Lewis et al., 1987; Neve, Finch & Dawes, 1988; Tanzi & Hyman, 1991; Tanzi/Hyman & Wemngier, 1993; Hyman, Wemnger & Tanzi, 1993).

The APP gene resides on chromosomes 21 and was mapped in 1987 to the same vicinity as that of a locus for early-onset FAD (Kang et al., 1987; Goldgaber et al., 1987; Tanzi et al., 1987; Robakis et al., 1987, St George-Hyslop et al., 1987). When APP was tested for genetic linkage to FAD in the same four early-onset FAD pedigrees that were used to show linkage of the disorder to DNA markers on chromosome 21, at least one obligate crossover event was detected in each pedigree in at least one affected individual displaying an early age of onset, thereby diminishing the possibility that the recombinants were due to the occurrence of sporadic AD. These results indicated that APP was not tightly linked to FAD in these families (Tanzi et al., 1987b). A further assessment of the potential genetic role of APP in FAD was prompted by the findings that FAD is a genetically heterogeneous disorder, thus the APP gene could still represent the gene defect in some pedigrees (Schellenberg et al., 1988; St George-Hyslop et al., 1990), and that a mutation in the βA4 region of APP segregates with hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D, Levy et al., 1990). Patients in these families generally die of hemorrhages in their fourth to fifth decade due to the accumulation of βA4 deposits in cerebral arteries.

In light of these reports, Goate and colleagues sequenced exon 17 of APP in patients from a chromosome 21-linked FAD pedigree that exhibited no apparent crossovers with APP. A missense mutation causing an amino acid substitution (V→I) at codon APP717 was found in affected individuals in two separate pedigrees (Fig. 1, Goate et al., 1991). Meanwhile, the same mutation is absent in 250 unrelated, normal individuals from the same popu-