British Journal of Psychiatry (1993), **163**, 2–5

Annotation

Alzheimer's Disease and Chromosome 14
Different Gene, Same Process?

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Over the past three years, progress in the molecular genetics of familial Alzheimer's disease has been fast and fundamental. The seminal finding that some cases are due to a mutation in the β-amyloid precursor protein (APP) gene has been followed by the discovery of a major additional locus for the disease on chromosome 14. The combined data suggest that the genetic sites accounting for most early-onset familial Alzheimer's disease cases have now been located. In addition, research is revealing the mechanisms by which the genes exert their pathogenicity. This promises to provide the explanatory link between the genes and the clinicopathological syndrome. The ultimate goal, an understanding in similar terms of the much commoner senile, sporadic form of Alzheimer's disease, is now a realistic target.

β-amyloid and Alzheimer's disease

There are several reasons for believing that the APP gene and its products are central to the cause of Alzheimer's disease (for review, see Hardy & Allsop, 1991; Harrison & Mullan, 1991; Joachim & Selkoe, 1992). Briefly, the evidence was initially circumstantial and came from identification of a fragment of APP, called β/A4, in the senile plaques and vascular amyloid characteristic of the disease. Subsequently, the gene which encodes APP was located on chromosome 21, which tied in with the frequent occurrence of Alzheimer's pathology in trisomy 21 (Down's syndrome) in early middle age. There were also indications that familial Alzheimer's disease was linked to a gene (of unknown identity, but generally assumed to be APP) on the same chromosome. At the same time, evidence has been accumulating that APP and β/A4 have a bewildering array of properties which may explain their pathogenic potential; although it has proved difficult to identify which particular process goes awry in Alzheimer's disease, a mechanism causing aberrant conversion of APP to β/A4 is the prime suspect.

Conclusive evidence that APP has a primary causal role in Alzheimer's disease, at least in the familial form, came with the finding of mutations in the APP gene which are the necessary and sufficient cause of the disease in affected families (Chartier Harlin *et al*, 1991; Goate *et al*, 1991; Murrell *et al*, 1991; Hendriks *et al*, 1992; Mullan *et al*, 1992*a*,*b*). These genetic data, taken together with the strength and depth of supporting evidence already available, led to the development of firm hypotheses proposing that an abnormality of APP metabolism and consequent deposition of β/A4 in the brain are central to the aetiology and pathogenesis of *all* forms of Alzheimer's disease. In cases due to an APP mutation, the mutation leads directly to APP mismetabolism (albeit by an unknown mechanism; see Citron *et al*, 1992; Hardy & Mullan, 1992); in other cases, a variety of initial insults are postulated which can each set off a cascade of events with the same final outcome (Hardy & Allsop, 1991; Hardy, 1992).

Despite the emphasis upon APP, there is more to the genetics of familial Alzheimer's disease than the APP gene. It was already clear that not all cases were linked to chromosome 21 (St George Hyslop *et al*, 1990) and, therefore, that APP could not be the only causative gene. It also soon became apparent that APP gene mutations are not common, occurring in less than a quarter of early-onset familial Alzheimer's disease and never in late-onset cases (which may be linked to chromosome 19; Pericak-Vance *et al*, 1991). Thus, there remained a large proportion of familial Alzheimer's disease to be accounted for in genetic terms.

A chromosome 14 gene is linked to many familial Alzheimer's disease cases

Once it was appreciated that APP gene mutations are only responsible for a small fraction of familial Alzheimer's disease, attention turned to locating the other gene, or genes. Progress in this search has been helped by the Human Genome Project, in which the chromosomal location of all genes is systematically being mapped. Arising from the project, many genetic markers have been identified which allow rapid scanning for possible linkage between a chromosomal region and a disease. By using a large number of markers, together spanning all the non-sex chromosomes, evidence has been found that early-onset familial Alzheimer's disease is linked to chromosome 14. This important discovery was made

Table 1
Alzheimer's disease gene loci

Chromosomal region[1]	Gene	Alzheimer's disease subtype
Chromosome 21q	APP	Early-onset familial[2]
Chromozome 14q	?	Early-onset familial[2]
Chromosome 19q	?	Late-onset familial
?[3]	?	Volga Germans, familial

1. q = Long arm of the chromosome.
2. Subtypes defined by causative gene locus. The only clinical or pathological feature which is currently known to distinguish them is age of onset, with APP-linked cases being older than those linked to chromosome 14 (Mullan, personal communication).
3. The loci on 21q, 14q, and 19q have all been excluded in these families.

in eight affected families, in which the APP gene had been excluded as the cause of the disease (Schellenberg *et al*, 1992). The data of Schellenberg and colleagues suggest strongly that in most or all of the eight families, a gene on chromosome 14 (more specifically, somewhere on the middle of its long arm) causes Alzheimer's disease. There are similar results from the former St Mary's group, now in Florida, using a different experimental and statistical approach (Mullan *et al*, 1992*b*). The data in total indicate that probably three-quarters of early-onset familial Alzheimer's disease cases are linked to this region of chromosome 14. Taken together with the APP mutations, the chromosome 14 findings allow most early-onset familial Alzheimer's disease to be accounted for in genetic terms. This in turn suggests that genetic testing using a combination of APP and chromosome 14 markers will be highly predictive for early-onset cases (Mullan, 1992). The main exception is families of Volga German descent, whose disease is not linked to any of the known familial Alzheimer's disease loci (Table 1).

How are the chromosome 14 gene and APP connected?

Two issues arise from the discovery of a familial Alzheimer's disease locus on chromosome 14. Firstly, to find the gene. To date, the evidence merely shows that an Alzheimer's disease-causing gene (or genes) is located on the middle of the long arm of chromosome 14; the identity of the gene, its precise location, and the mutation(s) which lead to the disease, remain to be established. Whether this question proves to be simple or difficult to answer is partly a matter of luck; one factor is the decision as to which gene (of the many) within the linked region is the most likely culprit, and which will be first to be targeted for study. As the number of genes known to reside on a given chromosomal region increases, there is a similar increase in the number of genes which can plausibly be proposed as candidate genes for a disease on the basis of what is known of the function of their gene products. For example, as mentioned above, it is believed that the proximate cause of β/A4 deposition in Alzheimer's disease is abnormal breakdown of APP or, possibly, altered regulation of the APP gene. A number of enzymatic and other processes are involved; thus, all genes encoding proteins functionally related to APP are legitimate candidates for being Alzheimer's disease-causing genes. Chromosome 14 contains its share of such genes, including those encoding proteases (which degrade APP), protease inhibitors, and stress proteins (which regulate APP gene expression).

The second issue concerns how the chromosome 14 data tie-in with the prevailing APP-based hypotheses of Alzheimer's disease (Hardy & Allsop, 1991). At the simplest level, the actions of the chromosome 14 gene and the APP gene must share a final common pathway, given the basic clinical and pathological homogeneity of all forms of Alzheimer's disease regardless of its aetiological origins. However, this does not mean that the two genes act via the same *causative* pathway; it may be that the interaction occurs far downstream in the pathological cascade (Fig. 1). The possibility that the two are closely causally linked is attractive to those who shave with Occam's razor and is in keeping with the view that changes in APP functioning are the key to all Alzheimer's disease. The examples given above of the candidate genes on chromosome 14 are based implicitly on the assumption of a connection with APP. However, at present there is no direct evidence to link the chromosome 14 gene to APP, and essentially independent disease processes for these subtypes of Alzheimer's disease cannot be ruled out. For example, the chromosome 14 gene might be pathogenic through its effect on *tau*, the cytoskeletal protein which is the main constituent of neurofibrillary tangles, with β/A4 production and senile plaque formation a secondary event. Alternatively, if the chromosome 14 gene turns out to encode a stress protein (e.g. the genes for heat shock protein HSPA2 and c-*fos* oncogene are within the linkage region), one can propose a process acting through the stress response, which has already been implicated in Alzheimer's disease (see Royston *et al*, 1992; Harrison *et al*, 1993), and which need not necessarily act through APP (Fig. 1). It is important, therefore, that future experiments are designed and interpreted without prior assumptions as to the relationship between the chromosome 14 gene and APP.

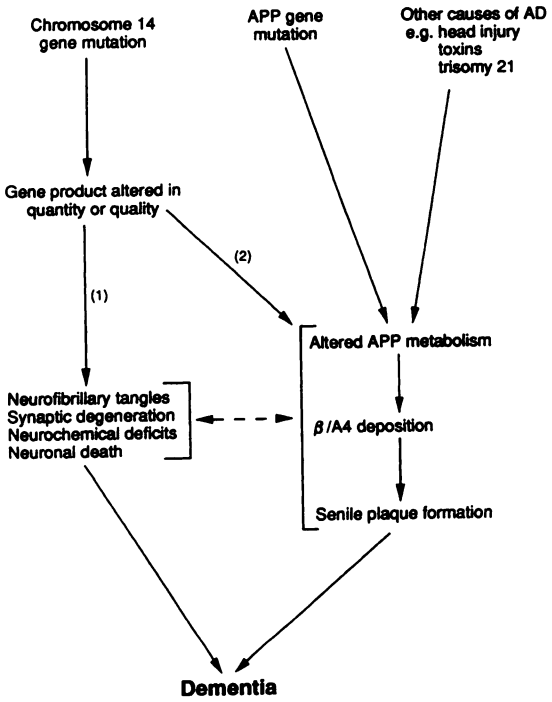

Fig. 1 Pathogenic pathways in Alzheimer's disease (AD). The right side of the diagram shows the amyloid hypothesis of AD in simple form. The central event in this process is a change in APP metabolism which may arise at any step in its synthesis or breakdown. The trigger for the alteration of APP metabolism can arise from an APP gene mutation in some familial cases, from excess APP production in Down's syndrome cases, or via unknown mechanisms in other circumstances (e.g. after head injury, environmental toxins). As a result of APP mismetabolism, β/A4 production is enhanced, leading to its deposition and formation of senile plaques. How the β-amyloid pathway produces the other aspects of AD pathology such as neurofibrillary tangles is unresolved, but it is assumed that the two are connected either directly or indirectly (dotted line).

The left side of the diagram indicates how the chromosome 14 gene may interact with APP. There are two main possibilities. (1) The chromosome 14 gene product is pathogenic through a direct effect on the APP gene or its metabolism. For example, it may regulate APP gene expression or APP processing. (2) Alternatively, the gene is pathogenic in its own right, acting largely in isolation from APP. In this instance, a primary effect on neurofibrillary tangle formation and neuronal death is emphasised; its influence on amyloid pathology is viewed as secondary, though still prominent pathologically.

The nature of the connection at the molecular level between the chromosome 14- and APP-linked forms of familial Alzheimer's disease may come to affect the definition and classification of the disease. It is apparent that different APP mutations can cause different clinical and pathological phenotypes, and it has been suggested that Alzheimer's disease be subsumed as one of the 'β-amyloidoses' to reflect this fact (Alzheimer's Disease Research Group, 1991). If the chromosome 14-linked cases of Alzheimer's disease were to turn out to have major pathogenic differences from APP-linked cases, there would be an equivalent argument for separating them into two disorders on aetiological grounds. While it is premature to discuss such issues in detail, they illustrate the reconceptualisation of all forms of Alzheimer's disease which may be called for in the next few years as the science progresses. A powerful recent precedent for this possibility is provided by the example of prion disease, the term which is now used to embrace several neurodegenerative disorders including Creutzfeldt–Jakob disease, Gerstmann–Sträussler syndrome, fatal familial insomnia, and thalamic dementia. The unifying category of prion disease is appropriate for these diverse clinico-pathological syndromes because they all share abnormalities of the same protein, prion protein, or its gene (Harrison & Roberts, 1991; Medori *et al*, 1992).

From familial to sporadic Alzheimer's disease

Familial Alzheimer's disease is rare. At present, clinicians may still have doubts about the relevance the research has for the understanding of senile, sporadic Alzheimer's disease or its impact on patient management. However, this view is probably too pessimistic and underestimates the speed and consequences of progress at the molecular level. Despite the current gaps in knowledge, it is virtually certain that the core disease process in all cases shares fundamental features; therefore insights into the familial subtype will be significant for Alzheimer's disease as a whole. For example, understanding how a mutation (in genetic cases) leads to aberrant functioning of the encoded protein and thence disease will help explain why similar problems can result even when there is no mutation (in sporadic cases). With regard to therapy, the discovery of APP mutations and the focus upon APP metabolism has already led to a large amount of cell biological research driven explicitly by the promise of impending treatments able to retard the disease process (see Gandy & Greengard, 1992; Mayer *et al*, 1992; Murphy, 1992). Viewed from this perspective, the discovery of a major locus on chromosome 14 allows an additional approach to the molecular basis and subsequent therapy of Alzheimer's disease. The critical step now, therefore, is to identify the gene.

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