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# Introduction: genetic determinants of mid- and late-life dementias

**G. M. Martin**

Departments of Pathology and Genetics and the Alzheimer's Disease Research Center, University of Washington, Seattle (Washington 98195-7470, USA), Fax +1 206 685 8356,
e-mail: gmmartin@u.washington.edu

**Abstract.** We introduce a series of papers dealing with genetic aspects of a subset of dementias of mid-life and late-life in order to illustrate four principles. First, there appear to be many genetic loci with the potential to modulate susceptibility to such dementias. Second, most of those so far discovered are autosomal dominants and none are autosomal recessives. Third, the autosomal dominant mutations are individually rare. Their frequencies in a given population are likely to be functions of genetic drift. Fourth, despite their rarity, they may inform us about the pathogenesis of more common late-life dementias, notably dementias of the Alzheimer type, which have polygenic determinants. The most important such modulation so far discovered involves polymorphic forms of the APOE locus.

**Key words.** Dementia; Alzheimer's disease; presenilins; $\beta$-amyloid; frontotemporal dementia; apolipoprotein E.

We are grateful to Professor Pierre Jollès and his staff for this opportunity to bring together a group of outstanding reviews of the current status of research on genetic determinants of mid- and late-life dementias. It has not been possible to cover all of the major advances in this field. Indeed, progress has been such of late that we are destined to be out of date by the time of publication.

The contributing authors have made highly original contribution to their subjects. Allison Goate pioneered the field by establishing the first gene mutation responsible for a form of relatively early onset familial Alzheimer's disease. The responsible locus, that coding for the $\beta$-amyloid precursor protein (APPp) is now at the epicenter of research on the pathogenesis of that most common of all the dementing illnesses of *Homo sapiens*. Rudy Tanzi has been involved in ground-breaking research on each of the three major autosomal dominant genes now established as playing a role in early-onset familial Alzheimer's disease. Ephrat Levy-Lahad played a key role in mapping the 'Volga German' Alzheimer gene to chromosome 1 while a postdoctoral fellow in the laboratory of Gerard D. Schellenberg. These workers, together with Wilma Wasco and Rudy Tanzi, identified the gene now known as presenilin 2 (*PS2*). Kurt Wilhelmsen was the first to demonstrate linkage of families with forms of frontotemporal dementia and parkinsonisms to chromosome 17. A different gene for a form of frontotemporal dementia was shown by Jerry Brown and his colleagues to be linked to chromosome 3. Finally, Elizabeth Corder and her colleagues bring us up to date on the role of polymorphic forms of the gene coding for the apolipoprotein E gene (*APOE*) in susceptibility to late-onset 'sporadic' forms of Alzheimer's disease. These forms are vastly more prevalent than the rare disorders described by our other contributors. (Although rare, however, the work is of course motivated by the proposition that elucidation of their pathogenetic mechanisms will guide us to a fuller understanding of the polygenic, late-onset disorders. Dr. Corder was a key player in the original observation that the epsilon 4 allele of *APOE* is an age-of-onset risk factor.)

What do we mean by 'early' vs. 'late' onset? These are rather arbitrary divisions, the boundaries being generally set at around 60 years of age by some authors and

around 65 years of age by others. The familial forms of Alzheimer's disease caused by the presenilin 1 mutations (by far the most common of the early onset familial forms) are the most virulent, with onsets often in the early forties. The range of onsets of the disease caused by presenilin 2 mutations is significantly later, with a very wide range. There are even some apparent escapees close to 90 years of age.

Readers should realize that the present group of papers does not reflect all known forms of dementias of mid- and late-life. For example, we do not have a review of a recently discovered entity that has come to be known as CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy linked to chromosome 19) [1]. The responsible mutation is in the *Notch3* gene [1]. *Notch3* is one of three highly conserved mammalian homologues of the *Drosophila Notch* gene [2]. It encodes a transmembrane protein important for some cell fate decisions in early development, particularly neurogenesis.

Moreover, it is certainly the case that the set of genes described in the following pages, while representing giant steps in our knowledge, merely scratches the surface of the genetic variables of relevance to the pathogenesis of dementias. Some years ago, I attempted to obtain some crude estimate of the number of genes that could be playing roles in our susceptibility to various aspects of the complex senescent phenotype [3]. Of the 2336 human loci identified as of 1975, 55 (2.4%) could be implicated as playing a role in the genesis of dementias or certain types of relevant degenerative neuropathology, or both. Assuming there are 100,000 genes in humans, that would implicate as many as 2400 relevant loci! It may be, of course, that only a relatively small proportion of that total may be of regular relevance in the vast majority of individuals within most populations. Given the increasing power of genetic analysis and continued refinements in phenotypic characterizations, we should have a much better estimate of the degree of complexity in the coming decades.

*After these papers went to press, three papers appeared that provided very strong evidence that at least a subset of frontotemporal dementias are caused by autosomal dominant mutations involving a locus coding for the synthesis of the microtubular binding protein, tau: P. Poorkaj et al., Ann. Neurol. 43:815–825, 1998; M. Hutton et al, Nature 393:702–705, 1998; M. G. Spillantini et al., Proc. Natl. Acad. Sci. USA 95:7737–7741, 1998.*

1 Joutel A., Corpechot C., Ducros A., Vahedi K., Chabriat H., Mouton P. et al. (1996) Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. Nature **383:** 707–710

2 Lardelli M., Dahlstrand J. and Lendahl U. (1994) The novel Notch homologue mouse Notch 3 lacks specific epidermal growth factor-repeats and is expressed in proliferating neuroepithelium. Mech. Dev. **46:** 123–136

3 Martin G. M. (1978) Genetic syndromes in man with potential relevance to the pathobiology of aging. Birth Defects **14:** 5–39