Familial Alzheimer's chromosome 14 mutations

To the editor — Five apparently pathogenic mutations in the gene S182 on chromosome 14 (ref. 1) and another mutation in a homologous gene, STM-2, on chromosome 1 (ref. 2), appear to cause early-onset (<65 years) forms of familial Alzheimer's disease (FAD). We have found two new and apparently pathogenic mutations within the same exon of S182 recently reported to contain the L286V mutation[1]. (We have also identified two polymorphisms in the intronic sequences flanking this exon: An A to C variant at nucleotide position –16 of the intron situated 3′ of the exon; and an A to G variant at nucleotide position –20 of the intron situated 5′ of the exon.) The exonic mutations are missense substitutions that occur immediately carboxy terminal to the sixth predicted transmembrane domain of the S182 protein. One substitution results in the replacement of a cysteine at position 263 with an arginine (C263R). The second mutation results in the substitution of a leucine for a proline at position 264 (P264L). C263R occurs in the proband (age of onset approximately 47 years) and in all of the four other affected individuals in pedigree MGH12. Autopsy confirmation of AD has been obtained for the proband, and the average age of onset in this kindred is 50 years. P264L occurs in the proband of pedigree MGH6. This patient had an age of onset of 45 years and also presented with thyroid problems. The proband's brother developed AD at 50 years of age, which was also confirmed by autopsy.

Screening for the C263R and P264L mutations was performed using a single-stranded conformational polymorphism (SSCP) assay capable of detecting both mutations. Amplification of the S182 exon harbouring the L286V mutation was carried out as previously described[1] and was subjected to SSCP analysis in affected individuals from 29 early-onset FAD kindreds (who are negative for the other five reported mutations in S182) and from 12 late-onset families. None of these families tested were positive for the two new mutations. Moreover, neither of these mutations were observed in 106 chromosomes from age-matched controls ascertained from the FAD pedigrees tested.

These data suggest that the two new mutations are most likely pathogenic. The potential pathogenicity of these mutations is also strongly supported by the profound amino acid substitutions that they impart to the protein. The C263R and P264L mutations residing in the predicted hydrophilic loop domain, and immediately following the C terminus of the sixth transmembrane domain, could extend the length of the transmembrane domain, aberrantly affecting the anchoring of the protein in the membrane. Alternatively, they may adversely affect the secondary or tertiary structure of the hydrophilic loop and/or the entire protein. Interestingly, the sixth transmembrane domain also contains the A246E mutation reported in the kindred, FAD1 (ref. 1). In the two families described and in that kindred, the average age of onset is very similar (approximately 50 years) indicating that disruptions in the S182 protein in or around the sixth transmembrane domain may carry similar pathogenic consequences. The C263R and P264L mutations are two of the most significant amino acid changes reported in S182, to date. They should be extremely valuable in experiments aimed at determining the normal role of this gene, and for developing experimental and animal models addressing the mechanism by which alterations in S182 cause Alzheimer's disease.

W. Wasco, W.P. Pettingell, P.D. Jondro, S.D. Schmidt, S. Gurubhagavatula, L. Rodes, T. DiBlasi, D.M. Romano, S.Y. Guenette, D.M. Kovacs, J.H. Growdon & R.E. Tanzi
Genetics and Aging Unit Department of Neurology
Massachusetts General Hospital
Building 149, 13th Street
Charlestown, Massachusetts 01219, USA

1. Sherrington, R. *et al.* Cloning of a novel gene bearing missense mutations in early-onset familial Alzheimer disease. *Nature* **375**, 754–760 (1995).
2. Levy-Lahad, E. *et al.* Candidate gene for the chromosome 1 familial Alzheimer's disease locus. *Science* (in the press).

Androgen receptor and familial prostate cancer

To the editor — From a population-based study of 55,000 American males, Monroe *et al.* estimate the relative risk of prostate cancer to be 5.3 for the brothers of cases; for the 14,738 white subjects in the study, the relative risk was 7.8 (ref. 1). Prostate cancer risks for brothers were significantly higher than risks for fathers in this study, confirming our earlier observations[2]. The authors propose that an X-linked susceptibility gene may account for the differences in risks among first-degree relatives and they consider the androgen receptor to be an interesting candidate. Somatic androgen receptor mutations, including gene amplification, have been seen in sporadic prostate cancers[3,4] and constitutional mutations are found in familial neurodegenerative disease[5]. Others have also proposed that androgen receptor activity levels may be associated with prostate cancer susceptibility[6].

If the excess familial clustering of prostate cancer among brothers were, in fact, due to a single X-linked locus, then the majority of affected brother pairs would share a common maternal X chromosome at this locus. To address the possibility that the androgen receptor is a prostate cancer susceptibility gene, we have typed constitutional DNA from 100 white males with familial prostate cancer (41 sib-pairs and six sib-trios) using a highly informative CAG-repeat polymorphism located within the androgen receptor[6]. Brothers were scored as concordant if they inherited the same maternal androgen receptor allele and discordant if they inherited different alleles. Only 18 of 41 sib-pairs were concordant, and only one of six sib-trios was concordant at this locus (both numbers are below expectation). Familial prostate cancer may occur at an earlier age than expected[6]; the average age of diagnosis of the 39 patients with concordant markers was 64.5 years, versus 64.9 years for the 61 patients with discordant markers. In summary, our data do not support the hypothesis that the observed clustering of prostate cancer among brothers in North America is attributable to genetic variation in the androgen receptor.