

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 mutation¹. (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 described¹ 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.

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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 observations². 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 disease⁵. Others have also proposed that androgen receptor activity levels may be associated with prostate cancer susceptibility⁶.

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 receptor⁶. 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 expected⁶; 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.

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1. Monroe, K.R. *et al.* Evidence of an X-linked or recessive genetic component to prostate cancer risk. *Nature Med.* 1, 827-829 (1995).
2. Narod, S.A. *et al.* The impact of family history on early detection of prostate cancer. *Nature Med.* 1, 99-101 (1995).
3. Taplin, M.E. *et al.* Mutation of the androgen receptor gene in metastatic androgen-independent prostate cancer. *New Engl. J. Med.* 332, 1393-1398 (1995).
4. Visakorpi, T. *et al.* *In vivo* amplification of the androgen receptor gene and progression in human prostate cancer. *Nature Genet.* 9, 401-406 (1995).
5. La Spada, A.R. *et al.* Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy. *Nature* 352, 77-79 (1991).
6. Coetzee, G.A. & Ross, R.K. Prostate cancer and the androgen receptor. *J. natl. Cancer Inst.* 86, 872-873 (1994).

Animal experimentation

To the editor — In the July issue of *Nature Medicine*, a news piece, "Neurologists seek public support for animal research" (p. 607; 1995), painted a disturbing view of the controversy concerning animal experimentation. The article discussed a brochure being distributed by the American Academy of Neurology that promotes animal experimentation. One would believe from the article that the debate about the values of animal experimentation has scientists on one side and animal rights activists on the other.

In truth, the scientific value of animal experimentation is being contested by many scientists, researchers and physi-

cians. In a review of animal models of degenerative neurological diseases (amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's chorea and Parkinson's disease), Kaufman concluded that "animal models designed to improve our understanding and treatment of these conditions have had little impact, and their future value is highly dubious"¹. Animal models for these diseases differ clinically and pathophysiologically from their human counterparts. In an editorial discussing animal models of stroke, Wiebers and colleagues concluded, "Ultimately, the answers to many of our questions regarding the underlying pathophysiology and treatment of stroke do not lie with continued attempts to model the human situation perfectly in animals, but rather with the development of techniques to enable the study of more basic metabolism, pathophysiology and anatomical imaging detail in living humans"². Pulsinelli and Buchan note that of 25 different compounds 'proven' efficacious for treating stroke in animal models between 1978 and 1988, none was proven efficacious in treating human stroke victims³. Fisher stated, in a review article, that of all the animal models of epilepsy "none is fully trustworthy as an imitation of clinical epilepsy"⁴. Maiman noted, "In the last two decades at least 22 agents have been found to be therapeutic in experimental spinal cord injury... Unfortunately, to date none of these has been proven effective in clinical spinal cord injury"⁵.

As well as the scientific problems of animal experimentation, one cannot ignore the fact that the scientific community has been unable to ensure that animals used in these experiments receive humane care. Well-documented incidences of unnecessary and excessive suffering incurred by animals in experiments involving neurological injury and disease remain as blights on everyone involved in scientific pursuits.

As health care and research dollars remain precious, it is the responsibility of the medical and scientific communities to spend those dollars wisely in ways that will most benefit the people we are trying to help. It is my opinion that an examination of the history of medicine shows that animal experiments, although used for centuries, have not been a significant source of knowledge useful to improving human health. Scientists who accept animal experimentation without reservation need to reevaluate

their position. Likewise, the American Academy of Neurology.

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1. Kaufman, S.R. *et al.* Animal models of degenerative diseases. *Perspect. Med. Res.* 3, 9-48 (1991).
2. Wiebers, D.O., Adams, H.P. & Whitsnant, J.P. Animal models of stroke: Are they relevant to human disease? *Stroke* 21, 1-3 (1990).
3. Pulsinelli, W.A. & Buchan, A. The utility of animal ischemia models in predicting pharmacotherapeutic response in the clinical setting. in *Cerebrovascular Diseases* (eds Ginsberg M.D. & Dietrich, W.D.) 87-91 (Raven, New York, 1989).
4. Fischer, R.S. Animal models of the epilepsies. *Brain Res. Rev.* 14, 245-278 (1989).
5. Maiman, D. Symposium on spinal cord injury models: Introduction. *J. Am. Parap. Soc.* 11, 23-25 (1988).

Euthanasia

To the editor — You appear to have adopted a policy of publishing leader articles selected with more regard for their propensity to excite controversy than for their intrinsic merit or relevance to the interface between science and medicine, which seems to be the main focus of the rest of *Nature Medicine*. Janet Radcliffe Richards' arguments concerning euthanasia (July issue, p. 618-620; 1995) serve to continue this tradition.

Radcliffe Richards' argument rests crucially on the notion that since a liberal society does not regard suicide as wrong, but as a matter of individual liberty, it cannot therefore regard assisting suicide as wrong in itself. However, it is extremely doubtful that modern societies do regard suicide in this light. In Britain, whence she writes, suicide is no longer a criminal offence, and it would appear to be technically possible for somebody who had demonstrated that they were mentally competent to commit suicide without interference. In the real world things are quite different. In order to illuminate society's real attitude to suicide, we need only ask how we would expect a policeman, charged with enforcing the law, to behave if he came upon somebody who had hanged himself but was not yet dead. Personally, I would expect the policeman to cut the would-be suicide down, and I cannot believe that many people would expect him to behave otherwise. (Note that this situation differs from that in which a would-be suicide may die without medical inter-