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Schizophrenia scepticism

Sir—Jones and colleagues[1] report an alanine to valine substitution in codon 713 of the amyloid precursor protein gene (*APP*) in a single case of chronic schizophrenia. They were unable to detect this mutation in a further 100 unrelated patients with schizophrenia as well as in 105 individuals with presenile dementia and 100 non-demented controls. Nevertheless, they suggest that its position in a highly conserved portion of the *APP* gene suggests that it may prove to be pathogenic.

We have been studying the co-segregation of highly polymorphic microsatellite markers on chromosome 21 in 191 individuals from 24 families containing multiple cases of schizophrenia and related disorders. Eight of these families are from South Wales, 13 from South East England and 2 from Japan (ref. 2). Amongst the markers we have studied is 21-GT 12 (*D21S210*) which is located close to the *APP* gene. The table shows the two-point lod scores obtained when the data from this marker were analysed according to a range of genetic models. Individuals with RDC diagnoses of schizophrenia ($n=69$), schizoaffective disorder ($n=10$) and unspecified functional psychosis ($n=6$) were scored as affected. Overall, there was no evidence for linkage to this locus in these families nor was there any evidence for heterogeneity (the sum of all positive lod scores at $\theta = 0$ was <3 for all four models).

Lod scores from two-point analysis of *D215210* data under four different genetic models

Model	Penetrances A1A1	A1A2	A2A2	Frequency of A2	Lod score at θ = 0.0	0.01	0.05	0.1	0.2	0.3	0.4
1	0.001	0.95	0.99	0.02	−12.50	−9.40	−5.49	−3.32	−1.19	−0.36	−0.09
2	0.002	0.087	1.0	0.064	−4.64	−4.10	−2.60	−1.51	−0.45	−0.10	−0.02
3	0.0	0.061	0.656	0.04	−4.20	−3.51	−1.94	0.95	−0.13	−0.06	−0.03
4	0.0	0.00	1.0	0.10	–	−14.94	−7.00	−3.76	−1.20	−0.34	−0.07

A2 is assumed to be the mutant allele. Intermediate models (2 & 3) assume a population risk of 1% and are compatible with published recurrence risks in relatives[4].

Three of the families showed modestly positive lod scores with this marker (0.32 <Z> 0.78), but single strand conformation analysis (SSCA) of exon 17 of the *APP* gene in individuals with schizophrenia from each of these families failed to detect any abnormality. We have also screened 58 unrelated individuals for mutations in exon 17 of *APP* using SSCA and detected no abnormality.

We therefore conclude that susceptibility to schizophrenia in our multiply affected families is not determined by the codon 713 variant[1] or by other mutations in the *APP* gene. If this mutation is indeed pathogenic, it must be an extremely rare cause of schizophrenia. Although mutations within the *APP* gene can lead to a spectrum of different phenotypes[3], these all involve the abnormal deposition of β amyloid. In the absence of evidence that this is a neuropathological feature of schizophrenia we remain sceptical that mutations in *APP* cause the disorder.

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