Short reports

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Linkage analysis of manic depression in an Irish family using H-ras 1 and INS DNA markers

Manic depression (bipolar affective disorder) is one of the major psychiatric illnesses. It is distinguished from unipolar major depression by the occurrence of manic episodes, symptoms of which show a variable combination of heightened and expansive mood, restlessness, irritability, pressure of speech, disinhibition, increased energy, and grandiose ideas or delusions. It has a lifetime risk of slightly less than 1% in most populations studied. A large genetic component has been shown using twin and adoption studies.

Egeland *et al*¹ have shown linkage between the manic depressive phenotype in one North American pedigree and two polymorphic DNA markers on the tip of the short arm of chromosome 11. Other studies^{2,3} have failed to show this linkage in Icelandic and other North American pedigrees.

We have ruled out tight linkage between these DNA markers and the manic depressive phenotype, assuming that the disorder is segregating as an autosomal dominant trait in a large Irish pedigree. A single, unilateral source of the manic depression is likely but cannot be proven.

The diagnoses were based on the Research Diagnostic Criteria of Spitzer *et al*,⁴ compiled using a combination of interviews, a review of the case notes, and the Schizophrenia and Affective Disorders Schedule-Lifetime Version (SADS-L).

All cases were of bipolar affective disorder, apart from one case of unipolar depression. Of the unaffected subjects only those over the age of 55 were used to minimise the risk of false negative phenotype assignment. The pedigree is shown in the figure.

DNA samples from members of the pedigree were

digested with the restriction enzymes *PvuII* and *SacI*. They were separated by electrophoresis on agarose gels and transferred to nylon membranes. Hybridisations were carried out with the DNA probes H-ras 1 to *SacI* digests and INS to *PvuII* digests. Both of these loci show high frequency restriction fragment length polymorphisms owing to the insertion or deletion of short, repeated DNA sequences (variable tandem repeats). The resulting genotypes are shown in the figure.

Lod scores were calculated using the computer program LIPED and the results are presented in the table. These data exclude the possibility of close linkage between manic depression and the chromosome 11 markers H-ras 1 and INS, under the assumption that there is an autosomal dominant gene responsible for the disorder in this family. This would indicate that the gene or genes responsible for manic depression in this family are at other, as yet unknown, loci. Further work is needed to identify other manic depressive gene loci in this and other pedigrees. Isolation and examination of these genes will lead to a better understanding of the pathogenesis of the disease and its interactions with the environment.

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FIGURE Pedigree of family showing age, H-ras 1 alleles (A, B, C), and INS alleles (1, 2, 3, 4).

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TABLE Lod scores calculated between the two marker loci, H-ras 1 and INS, and the manic depression phenotype, for various values of recombination fraction (θ), using three selected penetrance values for the susceptible genotypes (AA and Aa); 0.85 was the maximum penetrance of the susceptible genotype found in the Amish study¹ and 0.63 was the average penetrance found in their sample.

	Penetrance	Recombination frequency θ							
		0.00	0.001	0.002	0.005	0.025	0.050	0.100	0.300
H-ras 1	1.00	— ∞	-5.40	-4.80	-4.00	-2.51	-1.76	-0.93	-0.02
	0.85	— ∞	-4.66	-4.06	-3.26	-1.85	-1.25	-0.66	-0.03
	0.63	— ∞	-4.44	-3.84	-3.06	-1.70	-1.14	-0.62	-0.06
INS	1.00	— ∞	-2.70	-2.40	-2.01	-1.31	-1.02	-0.73	-0.17
	0.85	— ∞	-2.69	-2.39	-2.00	-1.30	-1.00	-0.67	-0.14
	0.63	— ∞	-2.67	-2.38	-1.99	-1.28	-0.96	-0.63	-0.11

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Prenatal diagnosis of mosaicism for del(18)(q12·2q21·1) and a normal cell line

A 37 year old single Hispanic woman had amniocentesis because of maternal age. She had had five pregnancies, resulting in two normal children with a previous partner, one elective abortion, and one tubal ectopic pregnancy with the present 20 year old partner. The medical and family histories were unremarkable.

Two separate primary amniotic fluid cell cultures at 21 weeks' gestation showed mosaicism for 46,XY/46,XY, del(18)(q12·2q21·1)(fig 1). Six of 25 cells (24%) from one primary culture and eight of 25 cells (32%) from the other primary culture showed the deletion. The chromosomes of the parents were normal.

The pregnancy was electively terminated by prostaglandin at 24 weeks' gestation. The fetus weighed 740 g (at about the 50th centile). Noted were the following craniofacial anomalies: high and narrow forehead, long philtrum, small and thin lips especially the lower (fig 2), long and broad thumbs, contractures at the middle interphalangeal joints, bilateral transverse palmar creases, long and broad big toes, and long toes. Necropsy showed a large foramen

FIG 2 The fetus at 24 weeks.

ovale that was indistinguishable from an atrial septal defect.

The deletion was found in 24% (6/25) of cultured cells from amniotic fluid, in 2% (1/50) of cells from cord blood, and in 47% (35/75) of cells from umbilical cord tissue obtained at the time of pregnancy termination.

Since this pregnancy, the couple has had another pregnancy resulting in a normal son.

Mosaicism for a structural anomaly at prenatal diagnosis is an uncommon event, occurring in only 15 of about 60 000 genetic amniocenteses.¹ Since de Grouchy *et al*² first described a syndrome associated with partial deletion of the long arm of chromosome 18, several other physical anomalies associated with deletion of 18q12·2→q21·1 have been described.³ This deletion was found in a proportion of cells from the present fetus, who showed some craniofacial features similar to those of the child previously reported, including a high and narrow forehead and long philtrum. The deletion responsible for this case is more proximal than the deletion associated with de Grouchy syndrome, which appears to involve 18q21 (probably q21·3).

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FIG 1 Partial GTG banded karyotype from an amniotic fluid cell. The arrows indicate the breakpoints in the normal chromosome 18 (left) and in the idiogrammatic 18 (right). The dark band q12·3 and some of the light staining band q21·1 are deleted in the anomalous chromosome 18.

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