

## Linkage studies of major affective disorders: the impact of the extension of pedigrees

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Strongly discordant results have been obtained so far in linkage studies of major affective disorders.

Egeland *et al* (1987) reported preliminary evidence suggesting a linkage between a major locus for bipolar disorder and two markers on chromosome 11. However, linkage with the same markers was excluded (Kelsoe *et al*, 1989) after the pedigree had been extended and new subjects developing the illness were assessed.

Both studies were conducted with great accuracy as regards ascertainment of phenotype, laboratory techniques and statistical analysis. The authors suggested that the initial results may have been obtained by chance or, alternatively, that a genetic heterogeneity of the disease exists in the Amish population.

Whatever the cause of these discrepant findings, the only way to overcome such problems is by way of an extensive epidemiological-genetic study. The direct experience of our group is enlightening in this sense.

Bruni *et al* described in 1989 a family with a bipolar disorder segregating in an apparently dominant manner (fig 1): four generations of affected people, no generation skipped, male to male transmission, and an affected father, married twice, who had generated affected children from both wives. Subsequently, both affected and unaffected lines were extended vertically as well as horizontally, through a genealogical method called the blanket method (Foncin *et al*, 1988, 1989). Data on birth, marriage and death were collected from municipal archives dating back to 1809, and from parish archives dat-

ing back to the 17th century. The kindred, as reconstituted, contained not only blood relatives but also relatives by marriage and tended to be a description of an intermarrying population.

The extension of the pedigree (fig 2), with the presence of affected people in branches apparently not at risk raises doubts as to the initial evidence, generating new hypotheses of transmission related to peculiar features of the kindred, such as genetic isolation, inbreeding, apparently assortative mating.

We suggest that pedigrees in which major affective disorders are segregating should be submitted to a systematic investigation through this epidemiological genetic method, in order to clarify fundamental issues in the psychiatric field: model(s) of transmission, effects due to environment and/or genotype, comorbidity, assortative matings and phenocopies.

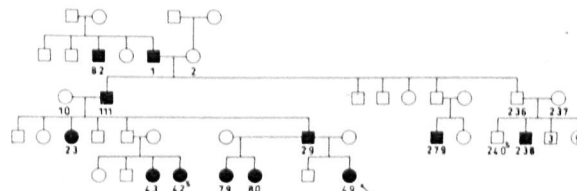
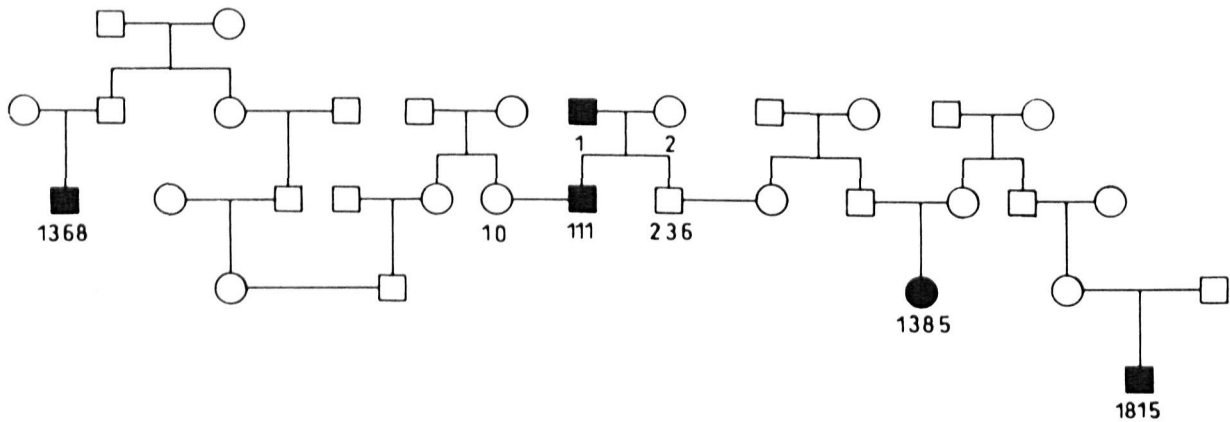


Fig 1. Original pedigree. Subjects are identified by their pedigree number. Black symbols = Major affective disorders; S = Suicide or attempted suicide.



**Fig 2.** A lateral extension of the original pedigree. The numbers identify the subjects reported in figure 1. Black symbols = major affective disorders.

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