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Affective Disorder on Paternal and Maternal Sides

Observations in Bipolar (Manic-depressive) Patients With and Without a Family History

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Introduction

Recent family studies of manic-depressive psychosis have emphasized the role of genetics in the aetiology of this bipolar illness (3, 8). However, the mode of genetic transmission is still unknown, the main controversy being between major gene and polygenic inheritance. Furthermore, it is not yet evident whether bipolar illness constitutes a homogeneous entity or whether it may be subdivided into different genetic subgroups. Mendlewicz, Fieve, Rainer, and Fleiss (1) recently produced some evidence that bipolar psychosis can be differentiated into two subgroups on the basis of family history data. Two matched samples of 30 patients each were studied, distinguished by the presence or absence of bipolar illness in their first degree relatives. The patients with a positive family history (FH+) in first degree relatives showed earlier onset of illness and more psychotic symptoms occurring in the manic phase. Alcoholism, if present, was of an episodic pattern. In patients with a negative family history (FH−), there was a later onset of illness; psychotic symptoms occurred usually in the depressive phase; and alcoholism, when present, tended to be chronic.

With bipolar patients thus appearing to have different clinical features of illness according to their genetic backgrounds, we have further analyzed the family history data in order to study the possible mode of inheritance in each subgroup. Slater (5), proposed a computational model to test whether single gene or polygenic inheritance is involved in a genetic disorder. This model is based on the analysis of ancestral secondary cases (affected ascendant relatives) on the maternal and paternal sides of the family.

If polygenic inheritance is involved, one would expect to find approximately twice as many unilateral pairs (two secondary cases on one side of the family) as bilateral pairs (one secondary case on maternal side and one secondary case on paternal side). In the case of dominant major gene inheritance this ratio would be significantly increased by the excess of unilateral pairs.

Slater and Tsuang (6) and Slater, Maxwell and Price (7) applied this 'ancestral secondary case' method to in-patients discharged from the Bethlem Royal and Maudsley Hospitals with the diagnosis of manic-depressive illness. The findings in both studies were more in accord with polygenic than with major gene transmission. Perris (4) in Sweden replicated the same study on the families of bipolar patients and came to the same conclusion. However, several methodological problems made these results difficult to interpret. In the first of Slater's studies (6), both bipolar and unipolar (with depression only) patients were counted as index cases. The data came from the examination of medical records, which tends to give excessive weight to one side of the family.

Another problem common to any family history study is the difficulty in obtaining complete psychiatric histories of ancestral secondary cases. As a result, underdiagnosis is frequent in many studies where second degree relatives are not available. This bias, however, should be distributed randomly on both sides of the family if the patients' father and mother are both available for interview.

Method

The diagnostic method and matching of our patients have been reported previously (1). All available first degree relatives were personally

interviewed. A detailed family history was obtained, including data on first and second degree relatives. To be suitable for the present study, a family must have at least two ancestral secondary cases with affective disorder or completed suicide or alcoholism among the second degree relatives. Ancestral secondary cases suffering from alcoholism (5 on paternal side and 2 on maternal side in the FH+ group versus 3 and 1 in the FH− group) have been included in the analysis as affective equivalents. This is supported by family studies (2, 9) providing some evidence for a genetic link between alcoholism and affective disorders.

Our study differs from previous ones in that patients' parents have not been counted as ancestral secondary cases. This is a sterner test, since the inclusion of parents as secondary cases would favour the number of unilateral pairs (especially in those patients with bipolar illness in their first degree relatives (FH+)).

Both parents were available for interview in 25 families in the FH+ group and 26 families in the FH− group. In the FH+ group 18 families were found to be suitable for the 'ancestral secondary case' analysis (i.e. two or more ancestral secondary cases were present), while in the FH− group, only 9 such families were found.

Results

The distribution of ancestral secondary cases in grandparents (*1*), sibs of grandparents (*1a*), uncles and aunts (*2*) and cousins (*3*) on maternal and paternal sides of the proband's families are presented in Tables I and II. The number of observed bilateral pairs (corrected to avoid giving excessive weight to families with many ill relatives and little weight to families with the required minimum of two secondary cases) can be derived from the following formula.

$$\text{No. of bilateral pairs} = \frac{2 \times \text{No. of maternal secondary cases} \times \text{No. of paternal secondary cases}}{\text{No. of secondary cases (mat. \& pat.)} - 1}$$

The number of unilateral pairs is available by subtracting the number of bilateral pairs from the total number of secondary cases.

Table III gives a comparison of observed and expected pairs in both the FH+ and FH−

Table I

FH+ groups: Secondary cases on paternal and maternal sides

Case no.	Paternal				Maternal				Total		Bilat. pairs
	1	*1a*	*2*	*3*	*1*	*1a*	*2*	*3*	Pat.	Mat.	
1	1	—	2	1	—	—	—	—	4	—	—
2	—	—	—	—	1	—	1	—	—	2	—
3	—	—	—	—	1	—	—	1	—	2	—
4	1	—	2	—	—	1	—	—	3	1	2·0
5	—	1	—	—	1	—	1	1	1	3	2·0
6	—	1	—	2	—	—	—	—	3	—	—
7	—	—	1	1	—	—	—	—	2	—	—
8	—	—	—	—	1	—	2	—	—	3	—
9	—	—	—	—	—	1	2	—	—	3	—
10	—	—	—	—	—	—	1	1	—	2	—
11	—	—	—	—	1	1	1	—	—	3	—
12	—	—	—	—	—	—	1	1	—	2	—
13	1	—	1	—	—	—	—	—	2	—	—
14	—	—	—	—	1	—	2	—	—	3	—
15	—	—	—	—	—	2	—	—	—	2	—
16	1	—	—	1	—	—	1	—	2	1	2·0
17	—	1	—	1	—	—	—	—	2	—	—
18	—	—	—	—	—	1	1	—	—	2	—
Total	4	3	6	6	6	6	13	4	19	29	6·0

1 = grandparents, *1a* = sibs of grandparents, *2* = uncles and aunts, *3* = cousins

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TABLE II

FH— group: Secondary cases on paternal and maternal sides

Case no.	Paternal				Maternal				Total		Bilat. pairs
	1	*1a*	*2*	*3*	*1*	*1a*	*2*	*3*	Pat.	Mat.	
1	1	—	—	—	—	1	—	1	1	2	2·0
2	—	—	1	1	—	—	1	—	2	1	2·0
3	1	—	2	1	—	—	—	—	4	—	—
4	1	—	—	—	—	1	—	—	1	1	2·0
5	—	—	1	1	—	—	2	—	2	2	2·67
6	—	—	—	—	—	1	—	1	—	2	—
7	—	1	1	—	—	—	—	—	2	—	—
8	—	—	—	—	1	—	2	—	—	3	—
9	—	—	1	1	—	—	1	1	2	2	2·67
Total	3	1	6	4	1	3	6	3	14	13	11·34

1 = grandparents, *1a* = sibs of grandparents, *2* = uncles and aunts, *3* = cousins

group. In the FH+ group, there is a highly significant deviation in the direction to be expected if dominance played a role. The distribution of secondary cases is preponderantly unilateral (42 unilateral pairs for 6 bilateral pairs). In the FH— group, the balance is shifted in the bilateral direction (15·66 unilateral pairs for 11·34 bilateral pairs).

TABLE III

FH+ group	Observed	Expected
Bilateral pairs	6·0	16·0
Unilateral pairs ..	42·0	32·0
Total	48·0	48·0

$\chi^2 = 9{\cdot}375$ ($p < {\cdot}01$); df = 1

FH— group	Observed	Expected
Bilateral pairs	11·34	9·0
Unilateral pairs ..	15·66	18·0
Total	27·0	27·0

$\chi^2 = 0{\cdot}9126$ (p — NS); df = 1

DISCUSSION

Our results support the presence of a single dominant gene in the transmission of affective disorder in a subgroup of bipolar patients with a positive family history (FH+). In the negative family history group the data are compatible with polygenic inheritance. The finding of major gene inheritance as a possible mode of transmission in the FH+ group differs from previously published data using the 'ancestral secondary cases' method (4, 7). These differences in genetic characterization of bipolar patients are compatible with the concept of genetic heterogeneity in bipolar illness. However, the numbers of families investigated in both groups are relatively small, and these results need to be confirmed on larger samples.

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REFERENCES

1. MENDLEWICZ, J., FIEVE, R. R., RAINER, J. D., and FLEISS, J. L. (1972). 'Manic-depressive illness: A comparative study of patients with and without a family history.' *British Journal of Psychiatry*, **120**, 523–30.
2. —— (1972). 'The nature of affective equivalents in relation to affective disorders.' Symposium on Affective Equivalents. *Proceedings of the Vth World Congress of Psychiatry, Mexico*. In press.
3. PERRIS, C. (1966). 'A study of bipolar (manic-depressive) and unipolar recurrent psychosis.' *Acta Psychiatrica Scandinavica* Supplementum 194.
4. —— (1971). 'Abnormality on paternal and maternal sides: observations in bipolar/manic-depressive and unipolar depressive psychosis.' *British Journal of Psychiatry*, **118**, 207–10.
5. SLATER, E. (1966). 'Expectation of abnormality on paternal and maternal sides: A computational model.' *Journal of Medical Genetics*, **3**, 159–61.

6. —— and TSUANG, M. T. (1968). 'Abnormality on paternal and maternal sides: Observation in schizophrenia and manic-depression.' *Journal of Medical Genetics*, **5**, 197–9.

7. —— MAXWELL, J., and PRICE, J. S. (1971). 'Distribution of ancestral secondary cases in bipolar affective disorders.' *British Journal of Psychiatry*, **118**, 215–8.

8. WINOKUR, G., and CLAYTON, P. (1967). 'Family history studies: I. Two types of affective disorders separated according to genetic and clinical factors', in *Recent Advances in Biological Psychiatry* (ed. Wortis), **9**, 35–50.

9. —— —— (1967). Family history studies: II. Sex differences and alcoholism in primary affective illness.' *British Journal of Psychiatry*, **113**, 973–9.

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