

## Distribution of Ancestral Secondary Cases in Bipolar Affective Disorders

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Perris (1966) has produced evidence that affective disorders which manifest both manic and depressive phases are genetically distinct from recurrent affective illnesses characterized by a series of depressive phases only. One of the most challenging aspects of this most interesting work by Perris is the suggestion that these bipolar illnesses might be transmitted in at least a fair proportion of cases by major genes at one or more loci. According to the calculations of Edwards (1960) the expectation of disease in the first degree relatives of probands with a polygenically determined disorder is approximately the square root of the expectation in the general population. In Perris's material the expectation in the first degree relatives of the 138 bipolar probands was 0.098 (9.8 per cent) for bipolar psychosis, and 0.185 (18.5 per cent) with the inclusion of other affective disorders which might be considered to be incomplete forms of bipolar psychosis. Although in population studies the cases of bipolar psychosis have been included with unipolar psychosis, and therefore the expectation of bipolar psychosis is not known, it is very unlikely to be as high as 0.03 (3.4 per cent) which is the square of 0.185.

One of the ways of testing between the major gene and polygenic models of genetic transmission is an analysis of the distribution of the ancestral secondary cases of the disorder between the paternal and the maternal sides of the family (Slater, 1966). This method has already been used to study manic-depressive psychoses including both bipolar and unipolar cases (Slater and Tsuang, 1968) with negative results. In view of the findings of Perris it was of interest to do a more extensive study limited to the bipolar affective disorders.

### METHOD

A list of in-patients discharged from the Bethlem Royal and Maudsley Hospitals during

the years 1960-1967 inclusive, having the diagnostic code number 301.0 (manic, manic-depressive and circular psychoses and reactions) was kindly prepared by the staff of the Records Department of the Maudsley Hospital. The case records of these patients were scrutinized by the authors to confirm the diagnosis of bipolar affective psychosis (as defined by Perris, 1966), and 193 patients were so ascertained. The family histories of these patients were then examined, and those patients were selected for study who had two or more parents, grandparents, aunts, uncles or cousins affected by some form of psychiatric illness (the criteria were the same as those used by Slater and Tsuang, 1968). The method of analysis was also the same as that in the previous paper and will not be recapitulated in full. Briefly, the polygenic model expects approximately twice as many unilateral pairs of ancestral relatives as bilateral pairs (after weighting for the number of pairs in any one family). The major gene model expects a greater number of unilateral pairs. The hypothesis of major gene transmission is therefore supported if the number of unilateral pairs exceeds that to be expected from the polygenic model.

Because the number of secondary cases is likely to depend on the source of the family history, a record was kept of those cases in which information had been obtained from the mother or one of her relatives, the father or one of his relatives, or from both sides of the family.

### RESULTS

Twenty-six of the 193 patients were found to have two or more ancestral cases (as defined above) recorded in the case notes of either the patients or of relatives who had attended the Joint Hospital. The distribution of these cases is set out in Table I, and the comparison of the observed with the expected distribution is given

TABLE I  
*Secondary cases on paternal and maternal sides*

Case No.	1*	Paternal			1	Maternal			Total		Bilateral 2pm/(n-1)
		2a	2b	3		2a	2b	3	Pat.	Mat.	
A7022	—	—	—	—	1	1	—	—	—	2	—
F0528	1	—	—	—	—	—	1	—	1	1	2·0
K7150	1	—	1	—	—	—	—	—	2	—	—
L2457	1	1	—	—	—	—	—	—	2	—	—
L9223	—	—	1	—	1	—	—	—	1	1	2·0
M0896	—	—	1	—	—	—	1	—	1	1	2·0
M1928	1	—	2	—	1	1	—	—	3	2	3·0
M1992	—	1	—	—	—	1	—	—	1	1	2·0
M2025	1	1	—	—	—	—	1	—	2	1	2·0
M2425	—	—	—	—	1	—	1	—	—	2	—
N1926	1	—	1	—	—	—	2	—	2	2	2·67
N2394	1	—	1	—	—	—	—	—	2	—	—
N7171	1	—	—	—	1	1	—	—	1	2	2·0
P0222	1	—	—	—	—	—	1	—	1	1	2·0
P0927	—	1	2	—	—	—	—	—	3	—	—
P1756	1	1	2	—	—	—	—	—	4	—	—
R0520	—	—	—	—	1	—	1	—	—	2	—
S0703	—	—	2	—	1	—	—	—	2	1	2·0
S7132	1	—	—	—	1	—	—	—	1	1	2·0
T0377	—	—	2	—	—	—	—	—	2	—	—
T0530	1	—	—	—	—	—	—	1	1	1	2·0
T1557	1	—	—	—	—	1	1	1	1	3	2·0
T2655	—	—	—	—	1	—	1	—	—	2	—
V1401	—	—	—	—	—	—	2	—	—	2	—
V1513	—	—	1	—	1	—	—	3	1	4	2·0
V7032	—	—	2	—	—	—	—	—	2	—	—
Totals	13	5	18	0	10	5	12	5	36	32	29·67

\* 1 = parent; 2a = grandparent; 2b = uncle or aunt; 3 = cousin.

*N.B.* The corrected number of unilateral pairs need not be calculated directly, but can be found by subtracting the corrected number of bilateral pairs (29·67) from the total number of secondary cases observed (68), i.e. in the present case 38·33.

in Table II. It will be seen that not only was there no excess of unilateral pairs, as would be expected with major gene transmission, but there was actually a marked though not quite significant deficit of such pairs. This deficit is not meaningful, and may be due to one or more of the biases discussed later.

Unfortunately the data cannot be considered very satisfactory for such a family study. For only 57 (less than one-third) of the patients was there a family history given by a member of the parental generation. The proportion of patients for whom an affected ancestral relative was reported was slightly (but not significantly) greater in the group for whom a family history had been obtained from one or both parents

(Table III). There was a tendency for the family history to be more positive on the side of the relative who acted as informant, but the numbers concerned are small (Table IV).

In the case of one of the patients (N 1926), three of the father's brothers had married three of the mother's sisters. Three of the offspring of these unions (cousins of the patient) had suffered mental illness; but they are excluded from the calculations because they provide no information relevant to the testing of the hypothesis.

#### DISCUSSION

The findings do not lend support to the hypothesis of major gene transmission of bipolar

TABLE II

	Observation	Expectation
Unilateral pairs	38.33	45.33
Bilateral pairs	29.67	22.67
Totals	68.00	68.00

$\chi^2 = 3.24$  (1 d.f.)  $0.10 > p > 0.05$ .

TABLE III

	Affected ancestral relatives		Total
	None	1 or more	
History from parental generation	29	28	57
No history from parental generation	80	56	136
Total	109	84	193

$\chi^2 = 0.73$  (1 d.f.)  $0.50 > p > 0.30$ .

TABLE IV

History from:	More illness on:	
	Father's side	Mother's side
Father's side only	2	1
Mother's side only	1	9

affective psychoses. The negative result should be viewed with some reserve, however. Not only does the lack of informants of the parental generation in over two-thirds of the cases add a degree of random error to the data, but there are several biases which may be operating both for and against the hypothesis of major gene transmission.

*Biases for the hypothesis*

(1) Where either the mother alone or the father alone acted as informant there is likely to be a tendency for an excess of secondary cases to be as reported on the side of the informant, leading to an excess of unilateral pairs.

(2) Even where neither parent acted as

informant, the cultural transmission of knowledge of ancestral mental illness down the generations of a family may be an all or none affair, so that a patient or his sibs may be aware of several cases on one side of the family but be ignorant of several cases which have occurred on the other.

*Biases against the hypothesis*

(1) Assortative mating for family history of mental illness, for mental illness itself, or for personality traits associated with a predisposition to mental illness would tend to produce an excess of bilateral pairs.

(2) If mental illness in one marriage partner tends to induce mental illness in the other, there will be an excess of patients whose mothers and fathers are secondary cases; three of the patients in the present material had two affected parents. Even if the actual incidence of mental illness is not affected by the marriage partner, it may be that there is a greater tendency for one to be hospitalized for an illness if the other has already been hospitalized. Similarly, a cultural tendency to deal with emotional upsets by adopting the patient role may pass from one set of in-laws to the other, resulting in an increase in bilateral pairs not only including the two parents, but involving other members of both families also.

(3) It is possible that the existence of a known history of mental disorder on one side of the family might increase the chances of ascertaining a history of mental disorder on the other side. This would lead to a tendency for mental disorder to be reported either on both sides of a family or on neither side, with consequent systematic error.

SUMMARY

Of 193 in-patients diagnosed as bipolar affective disorder, 26 had two or more secondary cases of mental illness among parents, grandparents, uncles, aunts and cousins. The distribution of the secondary cases was more in accord with polygenic than with major gene transmission. The family histories were probably far from complete, and in less than one-third

was there an informant from the parental generation. Several biases which might affect the data are mentioned.

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