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The Prognostic Importance of Genetic Factors in Functional Psychoses

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1. *The Basic Clinical Material*

For a series of 972 first admissions of functional psychoses admitted to Gaustad Hospital between 1938 and 1950 a long-term clinical follow-up has been carried out. The prognostic importance of clinical, social and genetic factors was analysed in great detail (1).

In a new series of 706 first admissions between 1951 and 1957, long-term follow-ups have provided a control population for checking previous findings. Clinical symptomatology, social and genetic factors were analysed in the same way as for the 1938–50 series (2).

From the case histories and the central register of all first admissions of psychoses to Norwegian psychiatric hospitals since 1916, information was collected about the relatives hospitalized for functional psychoses. Case histories were borrowed from the hospitals where the relatives had been treated, and we were able to compare the clinical states of the followed-up probands and their relatives.

The classification of the followed-up cases was made independent of the classification of the relatives. Both follow-up cases and their relatives were classified into cases with non-schizophrenic outcome and 19 subgroups of schizophrenic defects according to the classification system of Leonhard (5). We operated also with three broader subgroups, paranoid, hebephrenic and catatonic defects, each of which were subdivided into "slight" and "severe". Judged from control studies on the Gaustad series of Fish and Astrup (4) there will probably be about 30 per cent. error in the classification of relatives into the 19 subgroups and about 10 per cent error in the classification into the broader subgroups of slight and severe defects. The errors are probably considerably smaller for the classifications of the followed-up patients, where more detailed information was available for the majority of the patients through personal re-examination. As a rule the relatives tend to have clinical pictures similar to those of the probands, although there are many exceptions.

2. *The Selection of Genetic Prognostic Factors in Models*

In a prognostic model based on a six point scale of favourable factors, Vaillant included an item of depressive heredity. From his data it is not possible to see how much this item by itself contributed to predictive validity, which is quite good from constellations of all six factors (6, 7).

We have for each patient coded genetic loading in two columns. In one column we coded presence or non-presence of functional psychoses (schizophrenic, manic-depressive or reactive psychoses) in the family in one of the following degrees of kinship: siblings, parents, grandparents, uncles, aunts, cousins, nephews or nieces. Here we included not only the hospitalized cases, but all relatives reported to have shown mental symptoms suspicious of functional psychoses. With this broad distinction, more than one-half of the followed-up patients were coded as having psychotic relatives. For a sample of 444 patients with functional psychoses, Noreik and Astrup coded independently the presence of psychoses in the family. The two investigators achieved 92 per cent. agreement on this distinction.

In another column the genetic loading was coded in more detail for siblings, parents, grandparents, uncles and aunts, where types of psychoses in relatives were coded from their case histories. When schizophrenic genetic loading could be ascertained from the case histories of sick relatives, code no. 1 was given.

If 1 was absent, but manic-depressive relatives found, 2 was coded. If both 1 and 2 were absent, but relatives with reactive psychoses found, 3 was coded. When none of these three categories could be ascertained from case histories, but suicides were noted, we coded 5. For unhospitalized, probably psychotic, relatives, 4 was coded. Code no. 6 was used for absence of any of the five above-mentioned types of genetic loading.

While Vaillant (6, 7) selected depressive psychoses in the family for his prognostic model, we have selected the presence of schizophrenic psychoses (code no. 1). This was done primarily because the number of schizophrenic relatives was considerably larger than the total number of relatives with manic-depressive and reactive psychoses (both types together designated as affective psychoses). It is important that a variable entering into a prognostic model should not have too few observations. Furthermore, it was noted that patients with both schizophrenic and affective psychoses among relatives predominantly took a schizophrenic course of illness, while those with only affective psychoses in relatives as a rule did not develop schizophrenic defects.

3. *Models Selecting Best Predictors among Clinical, Social and Genetic items*

Using computers, unstandardized regression coefficients between coded variables and clinical long-term outcome on a five-step scale from recovery to severe schizophrenic deterioration were calculated, using Pearson's method. The five steps were: 1. Recovered. 2. Improved, non-schizophrenic. 3. Improved with schizophrenic personality change. 4. Slight schizophrenic deterioration. 5. Severe schizophrenic deterioration. In this way we managed to obtain cut-off points for the symptom constellations which were possible for the three categories of non-schizophrenic outcome (steps 1 and 2), mild schizophrenic defects (steps 3 and 4), or severe schizophrenic deterioration (step 5)

We selected 31 items for possible inclusion in our prognostic models and operated with the presence or absence of these items as independent variables. The dependent variable was the clinical outcome along the five-step scale. In Table I the items are listed with unstandardized regression coefficients and partial correlation coefficients for the 1938–50 and 1951–57 series.

Using a computer programme developed by Efraymson, the computer selected the order of the factors containing most prognostic information with regard to the risk of developing schizophrenic defects (3). For our 1938–50 series the genetic variable, no. 15, came out as sixteenth in order of importance (not significant) while the genetic variable no. 31 was twenty-second (not significant) among the best predictors. This implies that the prognostic information of the two genetic factors was contained in other factors, selected as better predictors.

In the 1951–57 series variable 31 came out as the eighth best predictor, significant at the 0·001 level in unfavourable direction. Among the better predictors were the items of diagnosis (no. 2) and treatment (no. 17). These factors do not properly belong to a prognostic model, because they imply a considerable observation period after hospitalization. In further analyses these items have also been omitted. Variable 15 came out as predictor no. 18, significant at the five per cent. level in favourable direction. This appears to imply that the separation of unfavourable schizophrenic heredity in variable 31 produces favourable effect of the remaining genetic tainting variable 15, which predominantly is affective when presence of schiozphrenic psychosis is subtracted. The correlation coefficient between variables 15 and 31 was 0·41, expressing that variable 15 is a sub-category of variable 31.

The next step in our analysis was to calculate the prognostic weights of the two genetic variables along with 15 clinical items (nos. 3–16, 18 and 19) which according to the literature are considered to be prognostically relevant. We included also the social item of single marital status, as many authors consider this feature an important and reliable prognostic predictor.

We considered the predictors selected first as containing relatively most prognostic information. The regression coefficients were considered as measures of the prognostic weights, positive

TABLE I

Item	*1938–50 series* Regression coefficient	*1938–50 series* Partial correlation	*1951–57 series* Regression coefficient	*1951–57 series* Partial correlation
1. Male sex	−·14±·07	·06	·01±·06	·09
2. Discharge diagnosis of schizophrenia	·44±·06	·53	·33±·05	·54
3. Depression, excitation or confusion	−·34±·05	−·54	−·56±·04	−·58
4. Schizoid personality	·15±·09	·24	−·04±·06	·34
5. No abuse of alcohol	−·01±·09	−·07	·10±·07	·01
6. No known precipitating factors	−·04±·08	·25	·13±·07	·32
7. Change of character as initial symptoms	·23±·08	·43	·46±·06	·50
8. Psychomotor inhibition	−·11±·09	−·24	0·01±·08	−·18
9. Emotional blunting	·64±·07	·49	·32±·06	·50
10. Typical schizophrenic delusions	·17±·09	·14	·10±·07	·15
11. Schizophrenic thought disturbance	·34±·07	·31	·11±·06	·27
12. Schizophrenic hallucinations	·08±·08	·25	·27±·06	·32
13. Intelligence below average	·21±·10	·13	·23±·08	·14
14. Acute onset of illness	−·27±·08	−·39	−·22±·07	−·38
15. Functional psychoses among relatives	·11±·07	·06	−·11±·06	·05
16. Pyknic body type	·22±·08	−·04	−·11±·08	−·06
17. Treatment with psychotropic drugs			−·21±·07	−·06
18. Age of onset above 40 years	·22±·08	−·17	·24±·06	−·20
19. More than 2 years' duration of illness	·48±·08	·42	·25±·06	·42
20. Good working capacity	−·08±·08	−·20	−·11±·06	−·28
21. Under average social class	·25±·07	·32	·12±·05	·23
22. Poor housing conditions	·29±·06	·24	−·10±·05	·11
23. Non-migrant status	−·05±·07	−·06	·05±·06	·07
24. Single marital status	·13±·05	·27	·16±·04	·32
25. Children before admission	·04±·06	−·21	−·13±·04	−·29
26. No sexual experience	·09±·07	·20	·01±·07	·22
27. Living alone before admission	·02±·07	·15	−·09±·06	·12
28. Friendly attitudes of relatives	·05±·07	−·13	−·09±·06	−·19
29. Aggressive behaviour	·26±·09	·26	·06±·07	·17
30. Psychosomatic illness	−·10±·13	−·13	−·11±·08	−·11
31. Schizophrenic psychoses among relatives	·07±·09	·12	·31±·08	·18
Combined items	Multiple regression coefficient	Standard deviation of dependent variable	Multiple regression coefficient	Standard deviation of dependent variable
	·87	·99	·87	·90

coefficients being unfavourable and negative coefficients favourable prognostic features.

For the 1938–50 series the variable of schizophrenic relatives (31) came out as predictor no. 18 (not significant) and the genetic variable of presence of functional psychoses (15) as no. 12, statistically significant at the five per cent. level. However, in the 1951–57 series the former variable came out as no. 6. Here the prognostic weight was statistically significant at the 0·001 level in unfavourable direction. The variable of psychoses in the family came out as no. 11 with a prognostically favourable weight, statistically significant at the five per cent. level.

In several attempts at modelling we tried to evaluate the relative prognostic importance of clinical, social and genetic items. It turned out that the clinical variables contained most prognostic information. We decided then to construct a prognostic model which could be used for the total sample of functional psychoses, including both the 1938–50 and the 1951–57 series.

4. *A Model based on One Genetic and five Clinical items*

Social features came out quite differently in the two series and are very much dependent upon social structure and time periods. This decreases the general applicability of a model including social items, and we decided to omit the social items in this model. Furthermore, we found it practical to limit the number of clinical variables to five. Prediction is very little improved by using more than six items, and with more variables the predictive symptom constellations become very complex for practical applications.

Again we decided to select two favourable and three unfavourable items, which in several models were picked out as containing much prognostic information. These items were nos. 3, 9, 11, 12 and 14. Among these, 3 and 14 were favourable and the remaining unfavourable prognostic variables. The last variable included in the model was item 31, presence of schizophrenic psychoses among close relatives. From the preceding, it can be expected that this variable contains important prognostic information in addition to what can be derived from the clinical symptomatology. This model was used for the total 1938–57 sample.

The predictive variables came out in the order shown in Table II (unstandardized regression coefficients in parenthesis).

TABLE II

1. Syndrome of depression, excitation ($-\cdot 94 \pm \cdot 04$)
2. Emotional blunting ($\cdot 97 \pm \cdot 05$)
3. Acute onset of illness without prodromal symptoms ($-\cdot 48 \pm \cdot 05$)
4. Presence of schizophrenic psychoses among close relatives ($\cdot 27 \pm \cdot 06$)
5. Schizophrenic hallucinosis ($\cdot 17 \pm \cdot 05$)
6. Schizophrenic thought disturbance ($\cdot 15 \pm \cdot 04$)

The constant was 2·99, the multiple coefficient ·82 and the standard deviation of the dependent variable 1·04.

We have in this model operated with a five point scale for the dependent variable, from recovery to severe schizophrenic deterioration. All six variables had larger regression coefficients than three times the standard error, which conventionally gives a statistical significance at the ·001 level. The genetic variable turned out to be the fourth best predictor. Accordingly, we consider it well justified to include the genetic variable in a prognostic model.

The next step was to compare observed outcome with outcome calculated on the basis of the best predictive symptom constellations. The result of these calculations on a three-point outcome scale is shown in Table III. Twenty cases had to be excluded because the case histories gave insufficient information for ascertaining presence or absence of all six items.

TABLE III

Prognostic Model Calculated on both 1938–50 and 1951–57 Series

	Calculated Outcome			
Observed Outcome	Non-schizophrenic	Mild schizophrenic defects	Severe schizphrenic deterioration	Total
Non-schizophrenic ..	555	218	10	783
Mild schizophrenic defects	81	452	111	644
Severe schizophrenic deterioration ..	8	157	66	231
Total	644	827	187	1,658

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Items 1 and 3 were favourable and the remaining four items unfavourable. In cases with the favourable syndrome item (1), the unfavourable items 4, 5 or 6 could be present in the non-schizophrenic outcome group. Even a combination of 1 with items 3, 4 and 6, or 3, 5 and 6 could be allowed for in the best outcome group. Item 3 alone was possible, but had not sufficiently strong favourable weight to combine with any of the unfavourable items in the non-schizophrenic outcome group. If we consider all cases where observed and calculated outcome coincide as 100 per cent. correct, placements in adjoining groups as 50 per cent. correct and the remaining placements as 100 per cent. wrong, the model gave 82 per cent. correct predictions. For a dichotomous distinction between schizophrenic and non-schizophrenic outcome the model gave 81 per cent. correct predictions. Here the distribution was skewed, with 786 cases calculated and 875 observed in the schizophrenic outcome group, and 783 observed and 555 calculated in the non-schizophrenic outcome group.

Instead of operating with symptom constellations, the items can be weighted and added on a scale. For the 1951–57 series, item 1 gets a weight of +3, item 2 gets −5, item 3 gets +1, item 4 gets −2, item 5 gets −2 and item 6 gets −2. Scores can range from +4 to −11. A score of 0 or a positive score predicts non-schizophrenic outcome. A negative score predicts schizophrenic outcome. On the 1951–57 series, this scale gave 81 per cent. correct predictions of schizophrenic versus non-schizophrenic outcome. Gross validation of this scale on 35 recovered and 35 deteriorated followed-up patients from Phipps Clinic in Baltimore gave 86 per cent. correct predictions. For further attempts at international comparisons of prognostic models it is of some interest to be aware of the relatively high unfavourable prognostic weight of presence of schizophrenic psychoses in close relatives.

5. *Summary and Conclusions*

In two follow-up series of first admissions of functional psychoses to Gaustad Hospital we have 972 cases admitted between 1938 and 1950, and 706 cases admitted between 1951 and 1957. For these two series the genetic background has been analysed by comparing the clinical pictures of the probands with the clinical pictures of the relatives, evaluated from their case histories. As a rule the relatives tend to have clinical pictures similar to those of the probands, although there are many exceptions.

Utilizing computer techniques, prognostic models predicting the risk of schizophrenic defects were constructed based on coded clinical symptoms, social and genetic variables. The prognostic weights of the social variables varied considerably over the two time periods, which reduces the general applicability of their inclusion in a prognostic model. For the total sample of 1938–57 first admissions a model was constructed, containing five of the most predictive clinical items along with the genetic variable of presence of schizophrenic psychoses among siblings, parents, grandparents, uncles or aunts. The genetic variable turned out to be the fourth best predictor. Accordingly, we consider it well justified to include the genetic variable in a prognostic model. The model gives about 80 per cent. correct prediction of long-term outcome.

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