Clinical Variables and Genetic Loading for Schizophrenia: Analysis of Published Danish Adoption Study Data

by Alastair G. Cardno, Katherine Thomas, and Peter McGuffin

Abstract

Schizophrenia shows considerable clinical variation, but the relationship between clinical variables and degree of genetic loading for schizophrenia is unclear. We investigated this by analyzing published data from the adoption study of Kety et al. (1994) in Denmark. We sought to determine which clinical variables in proband adoptees with chronic schizophrenia predicted risk of schizophrenia in their biological relatives, using logistic regression analysis. We found that risk of chronic schizophrenia in relatives was predicted by the presence of pervasive negative symptoms (odds ratio [OR] = 9.44, 95% confidence interval [CI] = 1.98–45.01) and absence of pervasive positive symptoms (OR = 0.09, 95% CI = 0.01–0.78) in probands. Pervasive negative symptoms were defined by the presence of all of the symptoms: social withdrawal, autistic behavior, poverty of thought/speech, and flat affect. Pervasive positive symptoms were defined by the presence of all of the symptoms: suspiciousness/ideas of reference, delusions, auditory hallucinations, and other hallucinations. These clinical variables may be useful for refining phenotypic definitions of schizophrenia in molecular genetic studies.

Keywords: Schizophrenia, symptom, adoption, genetic.


It is well established that genetic factors make an important contribution to the etiology of schizophrenia (Gottesman 1991; McGuffin et al. 1995) and that multiple genes are involved in most, or all, cases (O’Rourke et al. 1982; Risch 1990). This genetic complexity makes the process of identifying specific susceptibility genes a formidable task (Risch 2000); however, the endeavor may be considerably facilitated by identifying clinically relevant variables that are markers of particularly high genetic loading (or liability) for schizophrenia. Such variables could then be used to improve phenotypic definitions of schizophrenia in molecular genetic studies, for example, by including the variables as covariates in linkage analyses (Greenwood and Bull 1999).

Previous studies aimed at identifying clinical variables associated with high genetic loading for schizophrenia have generally been based on data from families or pairs of monozygotic (MZ) twins and have sought to determine whether clinical variables in affected probands are associated with risk of schizophrenia or related disorders in their biological relatives. Greater familial risk has been associated in some studies with earlier age of onset (Kendler et al. 1987; Dworkin et al. 1988; Kendler and MacLean 1990; Pulver and Liang 1991; Suvisaari et al. 1998), female sex (Goldstein et al. 1989, 1990; Sham et al. 1994a), poor premorbid adjustment (Dworkin et al. 1988), the hebephrenic or nonparanoid subtype of schizophrenia (Gottesman and Shields 1972; Kendler and Davis 1981; Farmer et al. 1984; McGuffin et al. 1987), and severity of negative (Dworkin and Lenzenweger 1984; McGuffin et al. 1987, 1991; Van Os et al. 1997; Malaspina et al. 2000) or disorganized (Cardno et al. 1997; Van Os et al. 1997) symptomatology. However, such studies are unable to distinguish between genetic and shared environmental effects.

In contrast, pairs of biological relatives from adoption studies of schizophrenia do not share a family environment, which implies that variables in probands that are associated with risk of schizophrenia in their relatives are likely to be markers of genetic loading for schizophrenia.

The adoption studies of Kety and colleagues (1968, 1975, 1994) in Denmark provide vital evidence for the role of genetic factors in the etiology of schizophrenia. Furthermore, in the definitive report on the “provincial sample” (Kety et al. 1994), covering adoptees in Denmark...
outside Copenhagen, information is provided on the core clinical features shown by each adoptee proband with chronic schizophrenia, along with pedigree diagrams for each proband giving details of the illness status of their biological relatives.

The aim of the current study was, therefore, to determine which clinical features of adoptee probands from the provincial adoption sample of Kety et al. (1994) are associated with the level of risk of schizophrenia in their biological relatives and hence which clinical features are likely to be markers of relatively high genetic loading for schizophrenia.

Methods

Sample. The sample is described in detail in the original article (Kety et al. 1994). Briefly, the records of the Danish Department of Justice were searched for every recorded adoption, other than those to biological relatives, that took place outside Copenhagen between 1942 and 1947. Adoptees who had developed schizophrenia were identified via the Danish National Psychiatric Register, which provides discharge diagnoses from all hospital admissions; their biological parents, full siblings, and half-siblings were identified via adoption and population registers. In one family, there were two putative biological fathers, both of whom were included in the study. Psychiatric illness in the relatives was also identified via the National Psychiatric Register. Control adoptees and relatives were also identified, but data on these were not analyzed in the current study.

Initial clinical abstracts based on hospital records were augmented by structured research interviews conducted by researchers blind to illness and family status. Consensus diagnoses were then made on the basis of all relevant clinical information. The core diagnoses were chronic schizophrenia—based on the descriptions of Kraepelin, Bleuler, and DSM—II—and latent schizophrenia, which was described as “analogous but not identical with the DSM—III diagnoses of schizotypal and paranoid personality disorders” (Kety et al. 1994, p. 444).

Clinical Variables. Table 2 of the original article (Kety et al. 1994) gives details of 14 illness history and clinical variables shown by each adoptee proband with chronic schizophrenia ($n = 29$). In addition, the sex of each proband is given in the pedigree diagrams shown in figure 1 of that article. After researchers combined certain variables that appeared a priori to be closely related, there were eight variables for analysis in the current study: (1) gender; (2) premorbid difficulties (defined as the presence of both poor premorbid adjustment and premorbid schizoid features); (3) age at onset (defined as age at first hospitalization); (4) insidious onset; (5) chronic course; (6) pervasive positive symptoms (defined by the presence of all of the symptoms: suspiciousness/ideas of reference, delusions, auditory hallucinations, and other hallucinations); (7) pervasive negative symptoms (defined by the presence of all of the symptoms: social withdrawal, autistic behavior, poverty of thought/speech, and flat affect); and (8) loose associations. All variables were categorical (present/absent) except age at onset.

Statistics. These items were entered as independent variables into two forward stepwise (conditional) logistic regression analyses in the Statistical Package for the Social Sciences, Windows Version 10. The criterion for entry of a variable in the analyses was $p = 0.05$. In the first analysis, the dependent variable was the presence/absence of chronic schizophrenia in each biological relative ($n = 171$). In the second analysis, the dependent variable was the presence/absence of chronic or latent schizophrenia in each biological relative.

For variables showing a significant effect on risk of schizophrenia in relatives, further analyses were performed to determine whether risk changed significantly when alternative definitions of combined variables were employed.

Results

The results of the logistic regression analysis for chronic schizophrenia are shown in table 1. Chronic schizophrenia in relatives was significantly predicted by the presence of pervasive negative symptoms and the absence of pervasive positive symptoms in probands. There was no significant interaction between these two variables ($Wald = 0.04, df = 1$)
There was a higher OR when these variables were combined into a variable defined as the presence of pervasive negative symptoms and the absence of pervasive positive symptoms (Wald = 9.85, df = 1, p = 0.002, OR = 13.37, 95% CI = 2.65 to 67.51); however, it should be noted that this result was largely due to the fact that the one proband who had this combined variable present (in family 069) had three siblings with chronic schizophrenia. The schizophrenia spectrum of chronic or latent schizophrenia in relatives was not significantly predicted by any variable in probands.

The association between negative and positive symptoms in probands and risk of chronic schizophrenia in relatives was not strengthened by using narrower definitions of symptoms or quantitative symptom scores. For a narrower definition of negative symptoms (poverty of thought/speech and flat affect), Wald = 1.64, df = 1, p = 0.20, OR = 2.60 (95% CI = 0.60–11.18); for a narrower definition of positive symptoms (delusions and auditory hallucinations), Wald = 0.02, df = 1, p = 0.88, OR = 1.19 (95% CI = 0.12–11.76). For negative symptom score (number of negative symptoms present; range = 0–4), Wald = 1.34, df = 1, p = 0.25, OR = 1.42 (95% CI = 0.78–2.60); for positive symptom score (number of positive symptoms present; range = 0–4), Wald = 2.45, df = 1, p = 0.12, OR = 0.57 (95% CI = 0.28–1.15).

Discussion

The main findings of this study are that the presence of pervasive negative symptoms and the absence of pervasive positive symptoms in adoptee probands significantly predicts the presence of chronic schizophrenia in their biological relatives. This is consistent with these two variables being markers of relatively high genetic loading for schizophrenia.

Several previous studies have found that more prominent negative symptoms are associated with greater familial risk of schizophrenia and related psychoses. In a study that involved making symptom ratings from published case summaries of MZ twins with clinically defined schizophrenia, Dworkin and Lenzenweger (1984) found that concordance for schizophrenia was greater when probands had high negative symptom scores than when they had low negative symptom scores. These authors used a broad definition of negative symptoms that included social withdrawal in addition to poverty of speech and restricted affect. However, McGuffin et al. (1991) found a similar trend using Crow’s (1980) narrow definition of negative symptoms (i.e., not including social withdrawal) when they rated the case summaries from one of the twin series (Gottesman and Shields 1972) rated by Dworkin and Lenzenweger (1984).

In a family history study of probands with Research Diagnostic Criteria (RDC) schizophrenia or schizoaffective disorder, McGuffin et al. (1991) found a significantly higher morbid risk of schizophrenia or other nonaffective psychosis in parents of probands with narrowly defined negative symptoms compared with parents of probands with no negative symptoms, and similar trends for morbid risks in siblings and offspring of probands. In a family history study, this time of all psychoses, Van Os et al. (1997) found that higher familial risk was associated with higher scores on a negative dimension derived from factor analysis that was characterized by blunted affect but also by early and insidious onset. In a family history study of probands with DSM-III-R schizophrenia, Malaspina et al. (2000) found an association between a family history of schizophrenia-related psychosis and severity of negative symptoms in probands, particularly symptoms related to social withdrawal.

Other studies have found no clear relationship between negative symptoms and familial morbid risk. In a family history study of probands with RDC schizophrenia (Cardno et al. 1997) based on a subset of the data analyzed by McGuffin et al. (1991), no significant relationship was found between negative symptom factor scores (poverty of speech and restricted affect) and morbid risk of schizophrenia or other nonaffective psychosis in first degree relatives. In the epidemiologically based Roscommon family study of probands with DSM-III-R schizophrenia, Kendler et al. (1994b) found that total score on the broad Scale for the Assessment of Negative Symptoms (Andreasen 1984) weakly predicted morbid risk of schizophrenia in relatives (Cox model risk ratio 1.09) but that the trend weakened when the risk of schizophrenia spectrum disorders was included and when other definitions of negative symptoms (based on factor scores) and other analytical approaches (presence/absence of a family history) were used. However, it is notable that the approach that produced the strongest effect has consistency with the approach that produced the strongest effect in the current study—namely, using a broad rather than narrow definition of negative symptoms and investigating familial risk of schizophrenia rather than wider definitions including spectrum disorders.

There is also interest in persistent negative symptoms or the deficit syndrome. We were unable to specifically analyze persistent negative symptoms in the current study. However, most previous studies have found either no relationship with familial risk of illness or a nonsignificant trend toward higher familial risk when probands have persistent negative symptoms (Fenton and McGlashan 1994; Verdoux et al. 1996; Kirkpatrick et al. 2000; Malaspina et al. 2000).

In contrast to the above results, one family study (Baron et al. 1992) found an association between promi-
ment negative symptoms (broadly defined) in probands who fulfilled criteria for both RDC and DSM-III schizophrenia, and lower morbidity risk of schizophrenia in their first degree relatives. The reasons for this discrepancy are unclear, but possibly relevant factors include definitions of schizophrenia in probands that do not emphasize negative symptoms, and cross-sectional (rather than lifetime) evaluation of symptoms. The result could also potentially have been due simply to sampling variation.

Most previous studies have found no clear relationship between level of positive symptoms and familial risk of schizophrenia (Dworkin and Lenzenweger 1984; Baron et al. 1992; Kendler et al. 1994b; Cardno et al. 1997; Van Os et al. 1997). However, in a further analysis of MZ twin data, Dworkin et al. (1988) found that concordance for schizophrenia was predicted by probands having fewer paranoid symptoms in addition to more negative symptoms, which is consistent with the results of the current study.

Two family history studies (Cardno et al. 1997; Van Os et al. 1997) have found that the strongest predictor of familial risk of psychoses in relatives of probands with RDC schizophrenia is higher levels of disorganized symptoms (positive formal thought disorder, inappropriate affect, bizarre behavior). This dimension of psychopathology could not be investigated in the current study because "loose associations" was the only symptom characteristic of this dimension that was described in probands.

No significant association was found for age at onset in the current study. Early age at onset has been associated with higher familial liability in some studies of schizophrenia (Kendler et al. 1987; Dworkin et al. 1988; Kendler and MacLean 1990; Pulver and Liang 1991; Suvisaari et al. 1998) but not others (Kendler et al. 1987, 1996; Neale et al. 1989). It is possible that the positive results are type I errors; however, the consistency of the direction of results suggests that there may be a small effect that is difficult to replicate consistently.

The lack of significant findings for sex in the current study is consistent with most previous studies (Cannon et al. 1998; Sham et al. 1994b; Kendler and Walsh 1995; Suvisaari et al. 1998) but inconsistent with studies that have reported an association between female sex and higher familial loading for schizophrenia (Goldstein et al. 1989, 1990; Sham et al. 1994a). The positive studies could have detected a subtle effect not found in previous studies, although Goldstein et al. (1989) reported a risk ratio of 2.4, so the relationship between sex and familial risk of schizophrenia remains unclear.

Poor premorbid social adjustment has been less investigated than the above variables but was associated with higher concordance for schizophrenia in the twin analysis of Dworkin et al. (1988). The reasons for the discrepancy with the results of the current study are unclear, but potential differences in definitions of this variable and difficulties with making retrospective assessments may be relevant.

Limitations. The diagnoses of chronic and latent schizophrenia were based on criteria established by Kety and colleagues, which were based on classical descriptions rather than on published operational criteria. This issue is discussed in the original article (Kety et al. 1994), where it is argued that it may not be a limitation because, although the narrower operational definitions enhance reliability, they do not appear to be more genetically valid than the authors' global diagnostic criteria, on the evidence of the Danish adoption studies (Kendler et al. 1994a; Kety et al. 1994). Also, in twin studies, the heritability of schizophrenia defined clinically in Scandinavia and operationally in the United Kingdom is almost identical (Cannon et al. 1998; Cardno et al. 1999). An important issue for the current study, however, is that negative symptoms have probably been given more prominence in the diagnosis of chronic schizophrenia than they are in narrower operational definitions of schizophrenia, so negative symptoms are probably relatively prevalent in this proband sample compared with samples defined by narrower operational criteria. However, this may have provided greater sensitivity for detecting a relationship between prominent negative symptoms and familial risk of schizophrenia than if narrower diagnostic criteria with less emphasis on negative symptoms had been employed.

The symptoms shown by probands were listed but not explicitly defined in the original article (Kety et al. 1994); however, the authors state that they based their assessments on the descriptions of Kraepelin, Bleuler, and DSM-II. As with most genetic studies, some symptoms were rated retrospectively on the basis of hospital records. The effects of this are not entirely predictable, but it is most likely to have resulted in an underestimate of the true frequency of symptoms in probands because routine clinical assessments may not inquire in detail about all symptoms relevant to a particular research study. This in turn is likely to somewhat reduce the power to detect associations between particular symptoms in probands and familial risk of illness.

The ages of probands and relatives are not known, but the assessment process included "careful follow-up" (Kety et al. 1994, p. 445). It would have been interesting to analyze risks of chronic schizophrenia separately in parents, full siblings, and half-siblings. However, the small number of relatives in each category with chronic schizophrenia meant that we could obtain meaningful results only for parents: for prominent negative symptoms, Wald = 1.49, df = 1, p = 0.22, OR = 5.32; and for prominent positive
symptoms, Wald = 0.72, df = 1, p = 0.40, OR = 0.32. In the main analysis we made no weighting for half-siblings because Kety (1983) has argued strongly against doing so.

Although this adoption sample is particularly informative for investigating the relationships between clinical variation and genetic loading for schizophrenia, some caution is required when extrapolating the results to general populations. Adoptees and their relatives are atypical in various respects (Gottesman 1991). For example, adoptees frequently have a family history of psychiatric illness, so the proband sample in this study may have had higher than average genetic loading for schizophrenia than people with schizophrenia in the general population. Again, this may have given us more power to detect associations between clinical variables and familial risk of schizophrenia.

Conclusions. The results of this study are consistent with the presence of pervasive negative symptoms and the absence of pervasive positive symptoms (which is not the same as the absence of positive symptoms) being markers of relatively high genetic loading for schizophrenia. These symptom groups may therefore be useful for refining the schizophrenia phenotype in molecular genetic studies. For example, a weighting function may be incorporated into linkage analyses based on presumed level of genetic liability of an individual (Greenwood and Bull 1999), and there may also be applications in association studies. Based on the liability-threshold model (Falconer 1965), any given susceptibility locus is more likely to be present in individuals with high genetic liability to schizophrenia than in individuals with schizophrenia in general. Therefore, if, for example, an association is found between a particular genetic polymorphism and schizophrenia, the effect size of this association should be greater in the subsample of probands with high genetic liability to schizophrenia than in the whole sample, if the association is true.

References


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