Problems and Pitfalls of the Family History Positive and Negative Dichotomy: Response to Dalén

by Anne Farmer, Peter McGuffin, and Irving I. Gottesman

Abstract

The authors defend the proposition that the simple division of schizophrenia into family history positive versus family history negative in the hope of uncovering etiological heterogeneity is too naive for a multifactorial disorder as contrasted with rare, mendelizing genetic conditions. Dalén is correct to forecast that a monolithic homogeneity view about the origins of schizophrenia is likely to be refuted and that it is important to pursue such a strategy. Using computed tomographic brain scan results and the simple dichotomy of family history positive versus family history negative as an illustration, we show the weakness (lack of statistical power) of the strategy. The problem arises from the fact that a negative family history for schizophrenia characterizes the vast majority of schizophrenic patients just as it does for insulin-dependent diabetes, another genetically influenced multifactorial disorder. A continuum from more genetic to less genetic variation in the etiology of schizophrenia fits the available familial patterns of risk.

Dr. Dalén’s proposition is that a family history method can be used to define a genetically distinct subgroup within schizophrenia and can provide a clear pointer to its etiology. He is, of course, correct to emphasize the importance of familiality as the best established etiological factor, and his suggestion is not new. Indeed, many authors have attempted to find clinical, biological, and anatomical differences between groups of schizophrenic subjects divided according to whether they are family history positive or negative. Unfortunately, all attempts thus far have been failures when submitted to the test of independent replication. For example, Reveley et al. (1984) from the Institute of Psychiatry, London, reported that cerebral ventricular enlargement was more frequent among schizophrenic twins without a family history of psychiatric illness. This finding led Lewis and Murray (1987) from the same unit to suggest that early brain damage was of etiological relevance and that this was related to obstetric complications. Subsequently, Nimgaonkar et al. (1988) and Owen et al. (1989), working with the same group and populations, found no significant differences between family history positive and negative schizophrenic subjects for clinical variables, ventricular enlargement, cortical sulcal widening, or history of obstetric complications. However, Owen et al. went on to suggest that the ventricular size in subjects with a family history of schizophrenia was larger than in those with a family history of affective disorder and then proposed that schizophrenic patients with a family history of affective disorder may constitute a different etiological group. The overall pattern across computed tomographic (CT) brain scan studies is confusing, with some supporting cerebral ventricular enlargement in schizophrenic patients without a family history of psychiatric illness (Cazzullo et al. 1985; Turner et al. 1986), while others (Nasrallah et al. 1983; Farmer et al. 1985) report a greater likelihood of a positive family history among patients with ventricular

Reprint requests should be sent to Dr. I.I. Gottesman, Dept. of Psychology, Gilmer Hall, University of Virginia, Charlottesville, VA 22903.
enlargement, and one from Japan (Kaiya et al. 1989) reporting three different kinds of enlargement for family history positive, family history positive for vertical transmission, and family history positive for horizontal transmission.

A further problem for those wishing to dichotomize schizophrenia according to the presence or absence of a positive family history is the one of definition. While some studies have restricted the term “family history positive” to include only those having first-degree relatives with a diagnosis of schizophrenia, other groups have broadened the definition to include any psychiatric disorder in any class of relatives. We have shown (Gottesman et al. 1987; McGuffin et al. 1987) that if the broader definition of “family history positive” is taken to include any major psychiatric disorder in any class of relatives, we have shown (Gottesman et al. 1987; McGuffin et al. 1987) that if the broader definition of “family history positive” is taken to include any major psychiatric disorder in any class of relatives, and if we assume that the population risk is about 10 percent, then by chance alone, anyone with five relatives has a 41 percent probability of being “family history positive.”

Given that clinicians have not been able to elicit replicable findings of differences between family history positive and negative groups, and given that the definition is imprecise, it is understandable that geneticists are, as Dalén puts it, “somewhat dismissive” of this approach. Yet a further difficulty which is often overlooked concerns statistical power. Eaves et al. (1986) examined the potential utility of the familial versus sporadic classification for the resolution of genetic and environmental etiologic factors in schizophrenia. These authors carried out a power analysis of the familial versus sporadic method assuming a multifactorial model where liability to illness is normally distributed within the population, resulting from the additive effect of polygenes and multiple environmental factors. They used various parameter estimates for risk factors to identify a component of either the genetic or environmental contribution to disease liability and found that almost without exception, very large sample sizes of probands and relatives were needed to have a reasonable probability of detecting etiologic heterogeneity.

The only way in which the required sample size could be dramatically decreased is if monozygotic twins are studied. Here “family history negative” probands would need to be schizophrenic monozygotic twins with unaffected cotwins and all first-degree relatives unaffected. Eaves et al. (1986) concluded that the familial versus sporadic design is useful only when pursued in the context of very large samples of nuclear families or moderate size studies of discordant monozygotic twins. Since both types of samples are difficult to obtain, the method is probably only of limited practical use, except perhaps in specialist centers which have the resources to collect discordant twin pairs.

Finally, we have to confront the issue of whether the clinical observation of phenotypic heterogeneity in schizophrenia necessarily means that there is genetic (etiologic) heterogeneity. The answer, of course, is that it does not. McKusick (1969) has pointed out that attempts at the classification of disease must take into account the possibility of pleiotropism (many forms, one cause) as well as etiologic heterogeneity (many causes, one form). We have discussed this distinction as applied to schizophrenia elsewhere (McGuffin et al. 1987). In brief, our findings were that all methods of subtyping schizophrenia, from classic Kraepelinian/Bleulerian categories to modern subtyping (Crow 1980; Farmer et al. 1984), tend to divide this disorder on a severity continuum. Thus, although several subtyping systems result in some degree of homotypia (the tendency for like to go with like in pairs of affected relatives), none provides perfect homotypia either in pairs of affected first-degree relatives or, more crucially, in monozygotic twins (Farmer et al. 1984; McGuffin et al. 1987). The familial transmission of subtypes is best explained using multiple threshold models, where liability to develop the disorder is approximately normally distributed in the population but only those whose liability at some point exceeds a certain threshold are affected (Reich et al. 1972). More severe subtypes represent a narrow category and lie beyond a second more extreme threshold. We have been able to show that such a model gives an excellent fit when applied to the extensive data of Kallmann (1938) on subtype resemblance in affected siblings and parent-offspring pairs (McGuffin et al. 1987).

In conclusion, a simple family history positive/negative split is insensitive and imprecise, and its limitations need to be recognized by researchers seeking the etiology of schizophrenia. We agree with Dr. Dalén that knowing that a patient with schizophrenia has one or more first-degree relatives affected gives us confidence that we are probably dealing with a genetic form of the disorder. It is important to realize, however, that the reverse is not true. Apparent absence of family history does not enable us to say that we have a nongenetic case. We also think that it might be worthwhile to
attempt to identify groups according to severity of liability. Those with the greatest familial liability to develop the disorder reflected in a high frequency of schizophrenia in first-degree relatives, may show greater differences from normal control subjects than those with a less strong family loading. To do this, however, we would need to perform a careful assessment of all available first-degree relatives instead of just taking a family history from one or two informants. We would then need to construct a quantitative index of family loading for each proband which would probably have to be a "family morbid risk." Here the numerator would be the number of affected relatives, but the denominator would need to be the total number of relatives corrected for the proportion of risk period through which the unaffected relative had lived. Such an approach would do better justice to the complexity of real life, where most evidence from family and twin studies (Gottesman and Shields 1982; Gottesman and Bertelsen 1989) points to a continuum from "more genetic" to "less genetic" schizophrenia rather than to a nongenetic/genetic dichotomy.

**References**


Reveley, A.M.; Reveley, M.A.; and Murray, R.M. Cerebral ventricular enlargement in "non-genetic"
schizophrenia: A controlled study. 


---

**The Authors**

Anne Farmer, M.D., M.R.C.Psych., D.P.M., is Senior Lecturer in the Department of Psychological Medicine, and Peter McGuffin, Ph.D., F.R.C.P., M.R.C.Psych., is Professor and Head of the Department of Psychological Medicine, University of Wales College of Medicine, Heath Park, Cardiff, Wales. Irving I. Gottesman, Ph.D., F.R.C.Psych. (Hon.), is Professor of Psychology, University of Virginia, Charlottesville, VA.

---

**Announcement**

TROPONWERKE Köln will sponsor the Hans-Jörg-Weitbrecht award to further biological-clinical research in the field of endogenous psychoses. The award will be presented together with Jörg-Weitbrecht medal to investigators of German-speaking countries. The purpose of the prize is to recognize exceptional scientific achievements in psychiatric research, especially in the field of cyclothymic—depressive and manic—as well as schizophrenic disorders including atypical and schizoaffective psychoses.

All entries must be submitted in seven copies in either German or English by October 31, 1990. For further information, please contact:

Prof. Gerd Huber  
Univ.-Nervenklinik  
D-5300 Bonn, 1  
Federal Republic of Germany

---

**Announcement**

The fourth Kurt Schneider Award will be presented for exceptional scientific achievements in 1991. The prize is sponsored by JANSSEN GmbH to encourage psychiatric research, especially in the areas of schizophrenia including basic research (clinical psychopathology, biochemistry, physiology, pharmacology, genetics, and epidemiology), diagnosis, therapy, and rehabilitation.

All entries must be submitted in seven copies in either German or English by February 28, 1991. For further information, please contact:

Prof. Gerd Huber  
Univ.-Nervenklinik  
D-5300 Bonn, 1  
Federal Republic of Germany