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The dichotomy of schizophrenia and affective disorders in extended pedigrees

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Abstract

The paper reports the first controlled family study investigating not only 1st but also 2nd and 3rd degree relatives of patients with schizophrenia by direct diagnostic interviews. Regardless of their degree of relationship, all biological relatives of the patients were found to be at an elevated risk of schizophrenia (5.0% in 1st, 3.1% in 2nd, 1.5% in 3rd degree relatives compared to 0.8% among controls). Schizoaffective and affective disorders have also been found to be more common in the three groups of relatives but without a monotone decline of prevalence rates across the groups. Other psychiatric disorders were not found to be at an elevated risk in relatives of patients compared to controls. Thus, our findings support the hypothesis that psychotic, as well as affective disorders, aggregate in families of individuals with schizophrenia. However, in our study, the risk of schizophrenia and the risk of affective disorders correlated. Particularly, the magnitude of the risk of schizophrenia among relatives of probands with schizophrenia varied with the occurrence of affective disorders in relatives. In relatives, the risk of schizophrenia was maximal in absence of a family history of affective disorder. This constellation holds true even if only families of index cases without any affective syndrome during lifetime are considered.

Keywords: Family studies; Coaggregation; Schizophrenia; Affective disorders

1. Introduction

For decades, the familial-genetic relationship between schizophrenia and other disorders has been disputed (Gershon et al., 1988; Taylor, 1992; Maier et al., 1993). Recently, the discussion was supplemented by linkage studies in schizophrenia and bipolar disorder; nearly half of the candidate areas on the human genome linked to schizophrenia overlap with candidate areas linked to bipolar disorder, i.e., on chromosomes 10p, 13q, 18p and 22q (Berrettini et al., 1994; Pulver et al., 1994; Collins et al., 1997; Rice et al., 1997; Blouin et al., 1998; Schwab et al., 1998a,b; Wildenauer et al., 1999). Although overlap of linked areas on the genome does not necessarily mean sharing of the susceptibility genes, the extent of overlap is far beyond random variation. A susceptibility gene has not been identified for any of both disorders; therefore,

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Table 1
Relative risk[a] (odds ratio) for schizophrenia and affective disorders among 1st degree relatives of schizophrenic probands in previous controlled family studies

Study	Odds ratio for		
	Schizophrenia	Bipolar disorder	Unipolar depression
Iowa Family Study (Tsuang et al., 1980)	39.7 (2.3–672.3)	1.6 (0.3–7.8)	0.9 (0.6–1.4)
NIMH (Gershon et al., 1988)	5.1 (2.0–10.9)	4.0 (0.8–100.1)	2.2 (1.2–3.2)
Danish Adoption Study (Kendler et al., 1994)	9.1 (0.9–90.2)	–	1.8 (0.6–4.9)
Roscommon Family Study (Kendler et al., 1993a,b)	16.2 (3.7–70.2)	2.2 (0.6–8.1)	1.7 (1.2–2.6)
Mainz Family Study (Maier et al., 1993)	9.0 (1.0–80.2)	1.0 (0.2–20.5)	1.7 (1.1–2.6)

[a] With relatives of control probands recruited in the general population as comparator.

the family-genetic relationship between both disorders still has to be discussed on a phenotypic level.

Several controlled family studies found a coaggregation of schizophrenia and affective disorders in families and, therefore, argued against a strict dichotomy of schizophrenia and affective disorders. The majority of family studies, however, did not report a significant excess of affective disorders in families of index cases with schizophrenia. A recent review of family studies exploring the familial relationship between schizophrenia and other disorders demonstrated that even the studies most frequently cited in favor of a nosological dichotomy also revealed an excess of affective disorders in families of probands with schizophrenia (Kendler and Gardner, 1997); the excess rate (odds ratio) ranged between 1.6 and 2.2 either for bipolar disorder or for unipolar depression among 1st degree relatives of probands with schizophrenia compared to control families (Table 1). Given the limitation of sample size, this elevation of the odds ratios failed to be significant. The meaning of this excess remains obscure.

One putative interpretation is that the excess of depression among 1st degree relatives of probands with schizophrenia is due to the fact that life together with an individual with schizophrenia creates a serious burden for all relevant family members. This possibility could be verified by investigating 2nd degree relatives who are not living in close relation with the affected index case. An excess of affective disorders among these 2nd degree relatives would view the excess of depression in 1st degree relatives as a reaction to the index case as unlikely.

Another putative reason for the coaggregation between both disorders is misclassification. Although the currently available interview and diagnostic instruments and all the available diagnostic information are combined into a best-estimate diagnosis, misclassification is still possible if inappropriate diagnostic concepts are used. In the following are the two major possibilities.

- The diagnosis of schizophrenia relies on a convention claiming a hierarchical relationship between schizophrenia and affective disorders; co-occurrence of both syndromes (at different times during lifetime in the same subject) is compatible with the lifetime diagnosis of schizophrenia but not with a lifetime diagnosis of affective disorders. This convention might be inappropriate. Therefore, the sample of index cases classified as schizophrenia might falsely comprise also subjects with both schizophrenic and affective symptoms. Stringent inclusion criteria for schizophrenic index cases (e.g., absence of full depressive or manic syndromes) in controlled family studies are therefore warranted.
- Schizophrenia might be heterogeneous, with one subtype representing an alternative variant of affective disorders; i.e., this subtype of schizophrenia is associated with affective disorders in relatives.

The present study explores these putative sources of cosegregation of schizophrenia and affective disorders in a sample of extended families (including 1st, 2nd and 3rd degree relatives of probands with schizophrenia).

2. Methods

2.1. Recruitment of psychiatrically ill probands

For an extensive family study, psychiatrically ill probands were recruited at the psychiatric hospitals of