Schizotypal Personality Disorder in Parents and the Risk for Schizophrenia in Siblings

by Kenneth S. Kendler and Dermot Walsh

Abstract

With one exception, previous studies examining the familial relationship between schizotypal personality disorder (SPD) and schizophrenia have compared rates of SPD in relatives of probands with schizophrenia versus control probands. In the Roscommon Family Study, an epidemiologically based family study of major psychiatric disorders conducted in the west of Ireland, we used a Cox proportional hazards model to examine the impact of a parental diagnosis of SPD on the risk for psychiatric disorders in siblings of probands with schizophrenia or schizotypal spectrum disorders. In siblings of probands with schizophrenia or schizotypal spectrum disorders, a parental diagnosis of SPD significantly increased the risk for schizophrenia and schizotypal spectrum disorders, but not for affective illness or anxiety disorders. These findings replicate our previous results from the Roscommon Family Study, further supporting the hypothesis that SPD has a substantial familial relationship with schizophrenia and other schizotypal spectrum disorders, but not with affective illness.


Clinicians have observed for nearly a century that certain close relatives of patients with schizophrenia, although never psychotic, have odd, eccentric personalities clinically reminiscent of schizophrenia (Kendler 1985a). Based on interviews from the Danish Adoption Study of schizophrenia, Spitzer et al. (1979) developed specific criteria for a new diagnostic category that attempted to describe individuals with these personality characteristics. This syndrome, termed schizotypal personality disorder (SPD), was subsequently included in DSM-III (American Psychiatric Association 1980) and, with minimal change, in DSM-III-R (American Psychiatric Association 1987). We are aware of 10 previous studies that examined the prevalence of SPD in relatives of probands with schizophrenia and matched control probands. With one exception (Coryell and Zimmerman 1988), all found substantial evidence for a familial relationship between schizophrenia and SPD (Lowing et al. 1983; Kendler et al. 1984; Kendler and Gruenberg 1984; Baron et al. 1985b; Frangos et al. 1985; Coryell and Zimmerman 1988; Gershon et al. 1988; Onstad et al. 1991; Farnes et al. 1993). Results have been less clear in studies that began with SPD probands (Torgersen 1983; Baron et al. 1985a; Schulz et al. 1989; Siever et al. 1990; Battaglia et al. 1991; Kendler et al. 1993a; Thaker et al. 1993), perhaps because many of these studies had small sample sizes (and hence low statistical power) and used family history rather than family study methodology. However, two recent studies have reported a significantly elevated risk for schizophrenia in relatives of probands with SPD (Kendler et al. 1993a; Thaker et al. 1993).

The Roscommon Family Study is an epidemiologically based family study of major mental illness con-
ducted in a rural county in the west of Ireland (Kendler et al. 1993a). Compared with relatives of unscreened controls, we found in this study a substantially increased risk for SPD in relatives of probands with schizophrenia and other nonaffective psychoses, but not in relatives of probands with affective illness (AI) (Kendler et al. 1993b). This traditional analysis, while particularly powerful, does not contain all the information available in this study about the relationship between SPD and other psychiatric disorders. Further information is contained in the relationship between a parental diagnosis of SPD and the risk for schizophrenia spectrum and other psychiatric disorders in siblings of probands. While the strategy of examining the relationship between parental disorders and risks for illness in siblings was commonly used in early family studies of schizophrenia (e.g., Rudin 1916; Kallmann 1938), we are aware of only one recent application. Baron et al. (1983) found that a parental diagnosis of SPD significantly increased the risk for both schizophrenia and SPD in siblings of probands with schizophrenia.

Methods

Sample. Three proband groups were ascertained in the Roscommon Family Study: (1) schizophrenic—all cases with a diagnosis of schizophrenia from the Roscommon County Case Register (Walsh et al. 1980) (n = 303); (2) affective—a randomly chosen subsample of 75 percent of the cases from the case register with a diagnosis of major affective disorder (n = 99); and (3) control—age- and sex-matched controls chosen from the county electoral registry (n = 150). We tried to personally interview all probands and, blind to proband diagnosis, their first-degree relatives aged 16 and older residing in Ireland, Northern Ireland, and central and eastern England. To improve cooperation, the same interviewer was usually assigned to interview all members of a given family. All available psychiatric hospital records for probands and relatives were obtained and abstracted.

An adaptation of the Structured Clinical Interview for DSM-III-R Diagnoses (Spitzer et al. 1987) was used for the diagnosis of Axis I conditions; the interview-based assessment for Axis II disorders was performed with early versions of the Structured Interview for Schizotypy (SIS; Kendler et al. 1989).

DSM-III-R criteria were used by Kenneth S. Kendler or Alan M. Grunenberg to make blind, best-estimate diagnoses, using all available information, for probands and relatives for whom personal interviews and/or hospital records were available. Interrater reliability was assessed for 69 cases and both percentage agreement and chance-corrected agreement (Cohen 1960) were high: 83 percent and 0.77 ± 0.05, respectively (Kendler et al. 1993a).

A number of individuals and families in the Roscommon Family Study were ascertained more than once. To obtain the correct risk in relatives, we used the general proband method, in which all individuals are counted once for each time they are independently ascertained (Crow 1965). All counts of relatives in this report refer to numbers of ascertained relatives.

Using DSM-III-R diagnoses, we define the major diagnostic categories of interest as follows: all nonaffective psychoses (ANAP)—schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, and psychosis not otherwise specified (NOS); schizophrenia spectrum—ANAP plus SPD and paranoid personality disorder (PPD); AI—major depression, mixed, manic, and depressed bipolar disorder, and bipolar disorder NOS; anxiety disorder—generalized anxiety disorder or panic disorder, with or without agoraphobia; and alcoholism—alcohol dependence or alcohol abuse. Diagnoses were made at three levels of diagnostic certainty (Kendler et al. 1993a). In this article, we report only those analyses based on the broad criteria of definite, probable, or possible cases. Schizophrenia spectrum diagnoses reported here were based on a hierarchy: schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, psychosis NOS, SPD, and PPD. Diagnoses of AI, anxiety disorder, and alcoholism were made hierarchically, that is, after siblings with schizophrenia spectrum disorders had been removed from the analyses (Kendler 1988). We also repeated these analyses without a diagnostic hierarchy.

We were able to interview personally 85.8 percent of all living and traceable relatives of probands (n = 1,753). The analyses in this report were restricted to siblings from the approximately 50 percent of proband families that contained at least one parent and at least one sibling with a personal interview or hospital record. We focus on siblings of three groups of probands that reflect increasingly broad definitions of schizophrenia-related disorders: (1) schizophrenia only (n = 149 from 50 families—55.7% male, mean age [± standard deviation] 35.3 ± 9.1 years); (2)
ANAP (n = 290 from 88 families—54.8% male, mean age 35.9 ± 9.3 years), and (3) schizophrenia spectrum (n = 307 from 96 families, 53.8% male, mean age 35.8 ± 9.1 years).

Statistical Methods. We used a Cox proportional hazards model as operationalized in the PHREG program in SAS (SAS Institute 1990) to examine the impact of one or more parental diagnoses of SPD (there was only one family in our sample in which both parents had SPD) on the hazard rate for various psychiatric disorders in siblings of probands. Age at onset was not coded for SPD or PPD in our analyses, because these conditions represented, by definition, lifelong personality patterns. For the purpose of the Cox proportional hazards model, however, these personality disorders were assigned an age at onset of 18 years.

We present the risk ratio (calculated as $e^\beta$, where $e$ equals the natural logarithm and $\beta$ the regression coefficient estimated from the Cox regression), which represents the change in the hazard rate for a given disorder associated with a parental diagnosis of SPD.

In the analyses of schizophrenia spectrum disorders in siblings, we controlled for the presence of schizophrenia or schizoaffective disorder in parents. In the analyses examining other disorders in siblings (AI, anxiety disorder, and alcoholism), we controlled for the presence of the same disorder in parents. All analyses also controlled for the presence or absence of a personal interview with parents and with siblings.

Since this study represents an attempt to independently replicate a previous finding of a familial relationship between SPD and other schizophrenia spectrum disorders (Kendler et al. 1993b), one-tailed tests are used for these comparisons. Otherwise, two-tailed tests are employed. We report $p$ values greater than 0.05 but less than 0.10 as statistical trends.

Results

Risk for Schizophrenia Spectrum Disorders. The risk for a diagnosis of schizophrenia was significantly increased by a parental diagnosis of SPD in siblings of probands with schizophrenia ($x^2 = 3.09, df = 1, p = 0.04, \text{RR} = 4.24$), ANAP ($x^2 = 3.39, df = 1, p = 0.03, \text{RR} = 3.12$), or any schizophrenia spectrum diagnosis ($x^2 = 4.57, df = 1, p = 0.02, \text{RR} = 3.39$) (table 1). A similar pattern was seen for a sibling diagnosis of ANAP or schizophrenia spectrum. In particular, a parental diagnosis of SPD increased the risk for a diagnosis of schizophrenia spectrum disorder in siblings of schizophrenia spectrum probands by an RR of 2.96 ($x^2 = 8.28, df = 1, p = 0.004$).

Risk for Other Psychiatric Disorders. In examining siblings of probands with schizophrenia, ANAP, or schizophrenia spectrum, we found no evidence that a parental diagnosis of SPD increased sibling risk for AI or anxiety disorder (table 1). In siblings of schizophrenia probands, a parental

Table 1. The hazard ratio for psychiatric disorders in siblings, given a diagnosis of schizotypal personality disorder in parents

<table>
<thead>
<tr>
<th>Proband diagnosis</th>
<th>Schizophrenia</th>
<th>ANAP</th>
<th>Schizophrenia spectrum</th>
<th>AI</th>
<th>Anxiety disorder</th>
<th>Alcoholism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>4.24$^1$</td>
<td>2.49$^2$</td>
<td>2.49$^1$</td>
<td>0.25</td>
<td>0.00</td>
<td>4.11$^1$</td>
</tr>
<tr>
<td>ANAP</td>
<td>3.12$^1$</td>
<td>1.99$^2$</td>
<td>3.01$^3$</td>
<td>0.75</td>
<td>0.69</td>
<td>1.79</td>
</tr>
<tr>
<td>Schizophrenia spectrum</td>
<td>3.39$^1$</td>
<td>2.34$^1$</td>
<td>2.96$^3$</td>
<td>0.76</td>
<td>0.67</td>
<td>2.07</td>
</tr>
</tbody>
</table>

Note.—ANAP = all nonaffective psychoses (see text for definition); AI = affective illness.

$^1p < 0.05$.

$^2p < 0.10$.

$^3p < 0.01$. 
diagnosis of SPD significantly increased the risk for alcoholism ($\chi^2 = 5.39$, $df = 1$, $p = 0.02$, $RR = 4.11$). However, as the proband diagnosis was widened to include nonschizophrenic psychotic disorders and schizophrenia spectrum personality disorders (and statistical power increased), this effect diminished in magnitude and was no longer statistically significant, even at a trend level. These analyses were repeated without a diagnostic hierarchy in siblings, and similar results were obtained with one exception. A parental diagnosis of SPD now conveyed a significantly increased risk for alcoholism in siblings of probands with a diagnosis of schizophrenia, ANAP, or any schizophrenia spectrum disorder.

**Discussion**

The lifetime prevalence of SPD was significantly increased, compared with the prevalence in relatives of controls, in relatives of probands with schizophrenia, SPD, and other nonaffective psychoses, but not in relatives of probands with AI (Kendler et al. 1993b). We drew two major conclusions from these results: (1) consistent with the results of previous studies beginning with schizophrenia probands (Lowing et al. 1983; Kendler and Grueenberg 1984; Kendler et al. 1984; Baron et al. 1985b; Frangos et al. 1985; Coryell and Zimmerman 1988; Gershon et al. 1988; Onstad et al. 1991; Parnas et al. 1993), SPD shares familial etiologic factors with schizophrenia and related schizophrenia spectrum disorders, and (2) consistent with the results of some previous studies (Onstad et al. 1991) but not others (Squires-Wheeler et al. 1988, 1989), SPD does not have a substantial familial relationship with AI.

We sought to replicate these findings in an entirely independent manner in the same sample. To do this, we examined the pattern of illness in relatives of schizophrenia spectrum probands. We predicted that a diagnosis of SPD in parents would increase the risk for schizophrenia and schizophrenia spectrum disorders in siblings but that it would not increase the risk for AI.

Our results are in accord with our predictions. A parental diagnosis of SPD significantly increased the risk for schizophrenia in siblings of schizophrenia probands. A similar pattern of findings was seen if the proband or sibling diagnosis was widened to include ANAP or the total schizophrenia spectrum.

By contrast, a diagnosis of SPD in parents did not predict the risk for AI or anxiety disorders in siblings. Although this result is consistent with the previous results in this study, as well as those recently reported for relatives of Norwegian twins with schizophrenia and major affective illness (Onstad et al. 1991), it is inconsistent with the results of two studies from the New York sample of high-risk offspring of probands with schizophrenia and AI (Squires-Wheeler et al. 1988, 1989). Our results suggest that SPD reflects, with some specificity, familial vulnerability to schizophrenia and schizophrenia spectrum disorders.

Our findings on the relationship between SPD and alcoholism were somewhat more ambiguous, but they were not inconsistent with our previous finding that relatives of schizophrenia probands in the Roscommon Family Study had a nonsignificant increased risk for alcoholism (50% higher than the risk of relatives of matched controls; Kendler et al. 1993c). When diagnoses were made hierarchically, a parental diagnosis of SPD conveyed a significantly increased risk for alcoholism only in siblings of schizophrenia probands. However, when analyses were conducted without a diagnostic hierarchy, the same pattern was seen in siblings of probands with schizophrenia, ANAP, or schizophrenia spectrum. These results suggest that in siblings of schizophrenia spectrum probands, a parental diagnosis of SPD predicts a diagnosis of alcoholism in individuals with a schizophrenia spectrum diagnosis. Of the previous studies that have examined this question, most have not found evidence for a familial relationship between schizophrenia spectrum disorders and alcoholism (Rimmer and Jacobsen 1977; Bleuler 1978; Baron et al. 1985b; Frangos et al. 1985; Kendler 1985b; Kendler et al. 1985; Gershon et al. 1988), but a few have (Kallmann 1938; Vaziri 1961). Further research is clearly needed to clarify the possibility of a modest familial relationship between alcoholism and schizophrenia and associated disorders.

These results should be interpreted in the context of one potentially significant methodologic limitation. Interviewers often assessed more than one member of an individual proband family. Therefore, although they were blind to knowledge about proband diagnosis, they were not always blind to psychiatric diagnoses in nonproband relatives. It is possible that the findings described above were influenced by interviewer bias. But we consider this unlikely for two reasons. First, the inter-
References


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