Published in final edited form as:

Schizophr Res. 2010 February ; 116(2-3): 133. doi:10.1016/j.schres.2009.10.023.

Tailoring the Definition of the Clinical Schizophrenia Phenotype in Linkage Studies

Verena Krause^a, Olga Krastoshevsky^a, Michael J. Coleman^a, J. Alexander Bodkin^a, Jan Lerbinger^a, Lenore Boling^a, Fred Johnson^a, Anne Gibbs^a, Jonathan O. Cole^{a,†}, Zhuying Huang^b, Nancy R. Mendell^b, and Deborah L. Levy^{a,*}

^a Psychology Research Laboratory, McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA

^b Department of Applied Mathematics & Statistics, Stony Brook University, Stony Brook, NY 11794, USA

Abstract

The delineation of schizophrenia-related symptomatology is critical to informative clinical phenotyping in linkage studies. A minority of first-degree relatives of schizophrenia and schizoaffective probands (RelSZSA) qualifies for a clinical diagnosis in the schizophrenia spectrum. Schizotypal personality disorder (SPD) is a key component of this spectrum, largely because of its relatively specific familial aggregation in relatives. The criteria for SPD were not developed for the purpose of identifying RelSZSA, however, and SPD is not a homogeneous clinical disorder, potentially introducing false positives and false negatives into affectedness classifications. In this study we used logistic regression (LR) to identify the combination of clinical signs and symptoms that maximized the discrimination between nonpsychotic first-degree RelSZSA (n=241) and controls (n=161). Three variables contributed significantly to optimizing this distinction: no close friends or confidants other than family members, social isolation and irritability. The combination of deviant LR scores and schizophrenia spectrum psychotic disorders had greater sensitivity for identifying RelSZSA, 23.7%, than SPD and schizophrenia spectrum psychotic disorders, 16%. Importantly, the diagnosis of SPD and deviant LR scores were not significantly correlated. Most individuals with deviant LR scores did not meet criteria for a diagnosis of SPD and only a minority of those who were diagnosed with SPD had deviant LR scores. Since misclassification of gene carriers as non-gene carriers in linkage analyses increases the risk of false negatives, it may be advantageous to tailor the definition of the clinical phenotype to those aspects of social-interpersonal dysfunction that optimize the discrimination of RelSZSA from controls.

Keywords

Schizophrenia; Schizotypal Personality Disorder; Schizotypy; Linkage Analysis; Schizophrenia Relatives

*Corresponding author. Psychology Research Laboratory, McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA. Tel.: +1 617 855 2854; fax: +1 617 855 2778. dlevy@mclean.harvard.edu.

†deceased

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1. Introduction

One of the challenges facing genetic studies of schizophrenia (SZ) is accurate identification of non-penetrant gene carriers. Although genetic factors play a major role in the etiology of schizophrenia (Kety et al., 1968; Gottesman, 1991), recurrence risk in first-degree relatives of schizophrenia and schizoaffective probands (RelSZSA) is only on the order of ~8% – 10% (Gottesman, 1991; Kendler et al., 1993a; Lichtenstein et al., 2006), substantially lower than risk for a disorder with Mendelian transmission. Thus, in a traditional linkage study, the vast majority of RelSZSA are classified as non-gene carriers because they do not have a clinical diagnosis of schizophrenia.

Schizotypal (SPD), schizoid (SZD) and paranoid (PPD) personality disorders also aggregate in RelSZSA at a significantly higher rate than in the general population (Stephens et al., 1975; Baron et al., 1985; Frangos et al., 1985; Kendler et al., 1993c; Varma et al., 1997). Indeed, because of these familial aggregations, the clinical definition of “affectedness” is sometimes expanded to include one or more of these disorders. Inherent in the rationale for broadening the definition of affectedness to include other traits, including nonpsychotic disorders and endophenotypes, is the concept of variable expressivity or pleiotropic effects of genetic liability (Holzman and Matthysse, 1990). Expanding the definition of affectedness has had varying effects on linkage and association results, sometimes improving power (Brzustowicz et al., 1999), but not always (Brzustowicz et al., 2000; Vladimirov et al., 2007). Possible reasons for this inconsistency include the limited specificity of PPD (Marneros et al., 1991; Tienari et al., 2003) and the rarity of SZD (Kendler et al., 1993c).

Among SZ spectrum personality disorders SPD has the most consistent support for a relatively specific familial aggregation in schizophrenia families (Lowing et al., 1983; Onstad et al., 1991; Parnas et al., 1993; Kendler et al., 1993c; Asarnow et al., 2001). However, identifying potential carriers of schizophrenia susceptibility genes based on this diagnosis is potentially problematic for two reasons. First, the original diagnostic criteria for SPD (DSM-III) were not designed to optimize the distinction between RelSZSA and individuals who are not related to a schizophrenic (Gunderson et al., 1983; Kendler, 1985). Rather, they were based on a re-analysis of the signs and symptoms most commonly found in individuals who received a diagnosis of “borderline schizophrenia” in the Danish Adoption Study (Kety et al., 1976; Spitzer et al., 1979). Most of the individuals who were assigned a diagnosis of borderline schizophrenia were biological relatives of schizophrenics, but a substantial proportion, 39%, were not. Thus, the diagnostic criteria for SPD, which have changed little since the original formulation, were optimized to detect the Kety et al. diagnosis of borderline schizophrenia, but not to identify biological RelSZSA *per se*.

Second, SPD is not a homogeneous clinical entity. The specific constellations of signs and symptoms that are present in individuals who meet diagnostic criteria vary at least in part as a function of genetic relatedness to a schizophrenic individual (Kendler et al., 1985; Torgersen, 1985; Torgersen et al., 2002). Substantial evidence supports the predominance of the social-interpersonal features of SPD (attenuated “negative” symptoms) in RelSZSA whereas the cognitive-perceptual features (attenuated “positive” symptoms) seem to be more characteristic of clinical populations independent of biological relatedness to a schizophrenic (Marneros et al., 1991; Maier et al., 1994; Kendler et al., 1995; Torgersen et al., 2002; Tsuang et al., 2002; Calkins et al., 2004). Thus, SPD seems to be made up of relatively distinct clinical subgroups. Extending the definition of affectedness to include the diagnosis of SPD without taking this heterogeneity into account carries the risk of introducing false positive as well as false negative classifications into the gene carrier status of nonpsychotic RelSZSA. For example, if RelSZSA who meet criteria for SPD based on cognitive-perceptual symptoms are actually false positives (i.e., misclassified as gene carriers), power to detect linkage would be reduced (Greenberg,

1992; Matthyse and Parnas, 1992). Conversely, RelSZSA who have conspicuous social-interpersonal symptomatology but fail to meet the threshold for a diagnosis of SPD or who have deviant clinical traits not included in the diagnostic criteria (e.g., social dysfunction and avoidant behaviors) (Gunderson et al., 1983; Kendler et al., 1995; Calkins et al., 2004) may be misclassified as non-gene carriers (i.e., false negatives). These false negative classifications reduce penetrance, making it more difficult to detect linkage when it is present (Greenberg, 1992).

In this study we assessed a broad array of signs and symptoms in RelSZSA and nonpsychiatric controls with two aims: 1) to identify the cluster of nonpsychotic clinical traits (and their weightings) that optimizes the distinction between nonpsychotic RelSZSA and nonpsychotic controls, and 2) to compare the sensitivity of this group of traits with the DSM-IV diagnosis of SPD. We hypothesize that: 1) the clinical traits that optimize the distinction between nonpsychotic RelSZSA and controls will include some but not all of the signs and symptoms in the diagnostic criteria for SPD as well as others that are not included in the diagnostic criteria, and 2) logistic regression scores for traits that distinguish RelSZSA from controls will have significantly better sensitivity for identifying RelSZSA than the diagnosis of SPD.

2. Methods

2.1. Subjects

The subject groups included 241 non-psychotic first-degree relatives from 114 families of individuals who met DSM-IV criteria for a diagnosis of schizophrenia or schizoaffective disorder (RelSZSA) and 161 nonpsychiatric control (NC) subjects from 129 families. On average there were 2 members/family in the RelSZSA group (range: 1–6), and 1.3 members/family in the NC group (range: 1–4). The sample considered here was purposefully restricted to individuals who did *not* meet diagnostic criteria for any psychotic disorder (lifetime); the RelSZSA sample is a subset of a larger subject pool ($n=275$) that includes RelSZSA with psychotic conditions. The control subjects were ascertained through one of three sources: a website for classified advertisements, poster advertisement, or through flyers placed in the waiting room of the internal medicine department of a large local medical center. Control subjects were screened for not having a family or personal history of psychosis prior to being recruited. All subjects met the following inclusion criteria: 1) >16 years old; 2) fluency in English; 3) estimated verbal IQ ≥ 80 ; 4) no diagnosed neurological disorder or brain injury; and 5) no alcohol or drug abuse/dependence within one year prior of participating in this study. Table 1 presents the breakdown of age, sex, estimated verbal IQ, and level of education for the RelSZSA and NC groups. The only variable that shows a statistically significant difference between the groups was age ($t_{(365)} = -5.98$, $P < 0.001$).

2.2. Procedures

In all subjects Axis I disorders were assessed using the Structured Clinical Interview for DSM-IV (SCID) (Spitzer et al., 1994). A modified version of the Structured Interview for Schizotypal Symptoms (SIS) (Kendler et al., 1989) was used to evaluate symptoms and signs of the three schizophrenia spectrum disorders, paranoid, schizoid, and schizotypal personality disorder. A group of senior diagnosticians independently assigned all applicable Axis I diagnoses and Axis II schizophrenia spectrum personality disorder diagnoses based on review of the interview narrative and all available medical records. Axis II diagnoses were assigned at three levels of certainty: definite (meets diagnostic criteria), probable (approaches required number of signs and symptoms, but falls short of meeting threshold for a diagnosis) or possible (one or two diagnostic criteria are met at a mild level). Both the interviewers and diagnosticians were blind to subject group. The distributions of non-psychotic Axis I and definite SZ spectrum disorders are shown in Tables 2 and 3, respectively.

The diagnosticians also rated each of the diagnostic criteria for SPD on a three point ordinal scale: 0 (absent), 1 (mildly present), or 2 (strongly present). For the analyses in this paper, we combined scores of 1 and 2 into one score, 1 (present). The diagnosticians also assigned scores on each of the six dimensions included in the Chapman Psychosis Rating Scale (CPRS): transmission of ones' own thoughts, passivity experiences, voice and auditory hallucinations, thought withdrawal, aberrant beliefs, and visual experiences (Chapman and Chapman, 1980; Kwapil et al., 1999; Kwapil et al., 2008).

In our modified version of the SIS, every item received a quantitative score, with higher scores corresponding to more severe psychopathology. For yes/no and true-false items, the more and less pathological answers received scores of 1 and 0, respectively. The sum of the items in each SIS section yielded a total score for that section. In addition, SIS sections and SIS items that were conceptually related based on *a priori* considerations were combined to produce SIS summary scores. Table 4 lists these SIS summary scores and their corresponding SIS sections as well as the SIS items that make up each SIS section.

2.3. Statistical Methods and Data Reduction

The initial dataset consisted of 6 CPRS scores, 9 SPD signs and symptoms and the various scores from the SIS described above. A series of exploratory analyses was carried out to identify any variables on which the groups had equal average scores or the NC had average scores indicating greater pathology than RelSZSA). Such variables were excluded from further consideration. For the remaining SIS and SPD variables and CPRS scores (supplementary section 1) logistic regression (LR) analyses were used to identify the combinations of clinical variables that optimized the distinction between RelSZSA and NC (supplementary section 2). Separate LR analyses were carried out on the following three combinations of variables:

1. SIS summary scores, SPD variables, and CPRS scores
2. Refined SIS section scores (supplementary section 3), SPD variables, and CPRS scores
3. SIS items, SPD variables, and CPRS scores

The variables that were included in each LR equation were statistically significant independent predictors at the 0.05 level as evaluated by the Wald Chi-Square Test. The predictive power of each LR equation was evaluated on the basis of the Receiver Operating Characteristic Curve (ROC) (Swets, 1988); the larger the ROC c-value, the better the predictive accuracy of the LR equation. The goodness of fit of the distribution of LR scores (to the observed log odds of being a RELSZSA in the sample) was assessed using the Hosmer-Lemeshow (HL) test; the more *non-significant* the HL p-value, the better the fit.

A LR score based on each of the three LR equations was assigned to each subject, with higher scores corresponding to more pathology. A specificity of 97.5%, the percentile for the specificity of a diagnosis of SPD in the control group, was chosen as the cutoff point for pathological deviance. The sensitivities of the three LR equations were compared using McNemar chi square tests.

The second LR equation (see above) was significantly better at identifying RelSZSA than the first LR equation (McNemar $\chi^2_{(1)} = 5.04$, $p = 0.02$). The second and third LR equations did not differ statistically; since the sensitivity of the second equation was higher than that of the third and the fit of the data to the second model was better, we used the second LR equation as the final model (see supplementary section 2).

In order to ensure that the inclusion of several members per family did not influence the outcome of the LR analyses, we ran an ANOVA testing for significant intraclass correlation

between family members. Among the three variables found to distinguish RelSZ from NC, irritability was the only one with a significant between family variance (i.e., intraclass correlation greater than 0.0) [$F_{(68)}=1.77$, $p=0.003$]. We therefore repeated the LR analysis, including only one member per family (closest in age to the proband). Irritability continued to be a significant independent predictor. Therefore, all family members were included in the analyses reported here.

3. Results

3.1. Logistic Regression Model

The LR equation that best distinguished RelSZSA from NC was based on the refined SIS section scores (supplementary section 3), SPD variables, and CPRS scores. The resulting logistic regression equation was:

$$Y = -1.1 + 0.59 * C + 0.46 * S + 0.26 * I$$

Here $Y = \ln$ (odds of being a RelSZSA vs. Control), C = no close friends or confidants score, S = social isolation score and I = irritability score.

We thus calculated an individual's logistic regression score (LR score) as $LR \text{ score} = 10(Y + 1.1)$ resulting in LR scores ranging from 2.45 to 43.49.

This LR equation had the best fit based on the c value ($c=0.67$), HL p value ($p=0.73$), and the best sensitivity (12.9%) for a specificity of 97.5%. Corresponding values for the other two LR equations can be found in supplementary section 2. Three variables contributed significantly to optimizing the distinction between RelSZSA and NC: no close friends or confidants other than family members ($p=0.03$; SPD criterion), social isolation ($p=0.0007$; refined SIS section score) and irritability ($p=0.001$; refined SIS section score).

3.2. Logistic Regression Scores, SPD Diagnosis, and Nonpsychotic Axis I Disorders

RelSZSA had a significantly higher mean LR score than NC (Wilcoxon Rank Sum: $Z = -5.86$, $p < 0.0001$). Summary statistics are shown in Table 5 and the distribution of the LR scores is shown in Figure 1.

The horizontal line in Figure 1 denotes the 97.5% specificity cutoff), which corresponds to a logistic score of 23.6. Based on this cutoff, 31/241 (12.9%) of nonpsychotic RelSZSA would be classified as clinically deviant compared with 4/161 (2.5%) of NC (Fisher's Exact $p=0.0002$). In contrast, 10/241 (4.1%, orange) nonpsychotic RelSZSA and 4/161 (2.5%, dark blue) NC met DSM-IV criteria for SPD. Thus, the LR score identified 3 times more nonpsychotic RelSZSA as clinically deviant than who met criteria for SPD (McNemar $X^2_{(1)} = 11.4$, $p=0.0007$). The estimate of the odds ratio for paired data is 4.0. Most of the RelSZSA with deviant LR scores (24/31, 77.4%) did not meet criteria for an SZ-related PD (24/31, 77.4%), for SPD (3/31, 9.7%), or for multiple SZ-related PDs (30/31, 96.8%) (see Figure 2). Further, only a modest proportion of those who did meet criteria for a schizophrenia-related PD (7/20, 35%, of RelSZSA; 1/12, 8.3%, of NC) or for SPD specifically (3/10 or 30% of RelSZSA; 1/4 or 25% of NC) had elevated LR scores. Deviant LR scores and the diagnosis of SPD were not significantly associated with each other (Fisher's Exact = 0.1235).

The rate of Axis I disorders did not distinguish between RelSZSA who were and were not identified as clinically deviant by the logistic score ($X^2_{(1)} = 92$, $p=0.6$; see Figure 3). The same result was obtained when specific categories of Axis I diagnoses were examined (Table 6; all

X^2 p-values ≥ 0.15), indicating that deviant logistic scores were not a function of co-morbid non-schizophrenia-spectrum psychopathology.

Broad definitions of the schizophrenia spectrum sometimes include nonaffective and affective psychosis and SPD in addition to SZ and SA disorders. The prevalence of these psychotic disorders and SPD in RelSZSA was 16% (44/275) (54/275, 19.6%, for psychotic disorders plus SSPD). Using the deviant LR score instead of SPD (or SSPD), the rate increases to 23.7% (65/275).

4. Discussion

The primary aim of this study was to identify those nonpsychotic clinical traits (and their weightings) that optimize the distinction between nonpsychotic RelSZSA and nonpsychiatric controls. In order to compare the sensitivity of this group of clinical traits with that of the formal diagnosis of SPD, all nonpsychotic RelSZSA were included in the analyses, irrespective of co-morbidity with a schizophrenia-related personality disorder. Based on data from the SISS, SPD diagnostic criteria, and the CPRS, LR analysis identified three clinical traits that significantly distinguished nonpsychotic RelSZSA from controls and each trait's relative weight as a discriminator: no close friends or confidants, social isolation, and irritability. We found that 12.9% (31/241) of nonpsychotic RelSZSA met criteria for a deviant LR score on the basis of 97.5% specificity in the control group, a rate that was significantly higher than that of SPD. Indeed, most of the RelSZSA with deviant LR scores did not qualify for a diagnosis of SPD, and fewer than half of those who did had deviant LR scores. Further, having an Axis I disorder was not significantly associated with having an elevated LR score. The combination of deviant LR scores and psychotic diagnoses identified 23.7% of RelSZSA with a clinical phenotype in a broadly defined schizophrenia spectrum, a substantial improvement over use of the SPD diagnosis. These findings are discussed below.

4.1. Clinical Traits that Distinguish Non-Psychotic RelSZSA from NC

The cluster of traits identified by the LR analysis has clear relevance to social-interpersonal functioning. The symptom with the highest weight, no close friends or confidants, attests to a notable degree of interpersonal disengagement that is supported by the independent contribution of social isolation. Irritability reflects intemperate modulation of emotional reactions, particularly anger, in interpersonal contexts.

The strong role of traits that pertain to aspects of interpersonal engagement in optimizing the distinction between RelSZSA and controls is consistent with findings from other studies, although the specific features of social-interpersonal dysfunction vary across studies (Marneros et al., 1991; Kendler et al., 1995; Torgersen et al., 2002; Tsuang et al., 2002; Calkins et al., 2004). Notably, each of the individual symptoms that independently contributed to a significant proportion of the variance in identifying RelSZSA replicates findings by other groups (Torgersen et al., 2002; Calkins et al., 2004). In 7 out of the 10 studies examined by Kendler (1985), RelSZSA were characterized as "irritable-unreasonable." Several studies reported signs associated with "negative schizotypy" to be independent discriminators of RelSZSA (Kendler et al., 1995; Fanous et al., 2001; Torgersen et al., 2002; Calkins et al., 2004), but none of those signs individually contributed to the discrimination between RelSZSA and NC in this study. However, traits in the latter category are implicated in ones that maximized the discrimination of RelSZSA in this sample, suggesting that this difference is one of semantics more than substance. Odd speech did not contribute significantly to the discrimination of RelSZSA from NC in this study, as it has in some other studies (Kendler et al., 1995; Fanous et al., 2001; Torgersen et al., 2002). However, we have found significantly elevated levels of thought disorder characterized by idiosyncratic use of language in this sample of RelSZSA

(Levy et al., 2009; Sung et al., 2009) using a metric designed to detect subtle instances of thought slippage.

4.2. Logistic Regression Score vs. SPD - False Positives/False Negatives and Sensitivity/Specificity

The LR score identified 12.9% (31/241) of nonpsychotic RelSZSA as clinically deviant, including 3 of 10 RelSZSA who met criteria for SPD. RelSZSA with deviant LR scores, combined with RelSZSA with psychotic diagnoses, accounted for 23.7% of RelSZSA with a clinical phenotype in a broadly defined schizophrenia spectrum. This rate is substantially higher than the rate of 16% of RelSZSA who were identified as deviant on the basis of a psychotic condition or a diagnosis of SPD. Importantly, elevated logistic scores were not a function of having a co-morbid non-schizophrenia-spectrum Axis I disorder.

Deviant LR scores and a clinical diagnosis of SPD were not significantly associated. Indeed, the odds that a RelSZSA would be classified as clinically deviant are 4 times higher based on the LR score than the diagnosis of SPD. Importantly, the vast majority of RelSZSA with elevated LR scores did not meet criteria for a diagnosis of SPD. The discordance between a deviant LR score and the diagnosis of SPD is not surprising since only one of the diagnostic criteria for SPD was an independent predictor of being a RelSZSA and the other two predictors are not included in the diagnostic criteria for SPD. Indeed, the sensitivity of a diagnosis of SPD is only 4.1% with a specificity of 97.5%, whereas the sensitivity of the LR score is 12.9% with a specificity of 97.5%.

The LR analysis was carried out on the combined sample of RelSZ and RelSA. The McNemar test showed that a deviant score defined by the LR was significantly better than the diagnosis of SPD in identifying RelSZ and RelSA ($X^2_{(1)} = 11.43$, $p=0.0007$). The corresponding odds ratio estimate was 4.0 (95% CI: 1.71–10.85). Separate analyses were also done on RelSZ and RelSA and the results were in the same direction, with the odds ratio estimate being higher for the RelSA (12.5) than for the RelSZ (2.5), but these estimates were not significantly different from each other (Wald Chi square = 1.11, $df=1$, $p>0.3$) (see Figure 4).

The RelSZSA and NC in this study are largely comparable to samples described in other studies. The pattern of Axis I disorders in RelSZSA and NC is similar to other major studies such as the Danish Adoption Study (Kety et al., 1976; Kendler and Gruenberg, 1984), the Iowa Family Study (Kendler, 1985), and the Roscommon Family Study (Kendler et al., 1993a; Kendler et al., 1993b; Kendler et al., 1993c). Schizophrenia, schizoaffective, and nonaffective psychotic disorders shared a significant familial aggregation in biological RelSZSA, whereas mood and anxiety disorders did not. The rates of substance disorders reported here cannot be compared with those described in other studies, because participants with current substance disorders were excluded (due to the potential confounding effect on other measures not reported here). Like studies that reported a significantly increased risk for SPD in relatives of schizophrenia probands (RelSZ) (excluding RelSA) (Kendler and Gruenberg, 1984; Kendler et al., 1985; Kendler et al., 1993c), we found a higher rate of SPD in nonpsychotic RelSZ (7.14%, 8/112) than in NC (2.5%, 4/161) based on blind interviews and diagnostic assessments. This difference was in the expected direction but did not reach statistical significance ($p=0.12$). Also like other studies (e.g., (Kendler et al., 1993c)), the rate of SPD in nonpsychotic relatives of schizoaffective patients (RelSA) in this sample (2/129) did not differ from that of controls ($p=0.9$). SPD occurred more often in siblings of schizophrenia probands (5/60, 8.3%) than in parents of schizophrenia probands (3/49, 6.1%), consistent with other findings (Kendler et al., 1993c). Too few RelSA ($n=2$) had a diagnosis of SPD to do the corresponding calculation. The proportion of parents and siblings with a deviant LR score did not differ among RelSZSA, RelSZ or RelSA ($p\geq 0.47$; see Figure 5), however.

4.3 Implications

Whether the LR score or the diagnosis of SPD more accurately classifies some carriers of SZ susceptibility genes cannot be determined from this study. However, it is noteworthy that most RelSZSA with deviant LR scores did not qualify for a diagnosis of SPD or for an SZ-related PD. Conversely, most RelSZSA who met criteria for SPD did so on the basis of cognitive-perceptual symptoms that did not discriminate RelSZSA from NC and did not have deviant LR scores. Two points are relevant to these findings. First, although the magnitude of the difference between the LR score and the diagnosis of SPD in detecting clinical deviance in RelSZSA is moderate (16% vs. 23.9%), the nonpsychotic relatives who are identified by each method are largely independent of each other. In either case, misclassification of relatives as “affected” could lead to false positives or false negatives, diluting power to detect linkage. Second, any useful designator of affectedness status would identify a maximum of 50% of relatives as potential gene carriers. Thus, if the LR score is more accurate than a diagnosis of SPD in this regard, the increased detection afforded by the LR score may be advantageous. Which of the two methods of identifying potential gene carriers in nonpsychotic RelSZSA actually improves power to detect linkage is an empirical question, but these results provide two different approaches for addressing this issue. The recent study by Fanous et al (Fanous et al., 2007) is potentially relevant in this regard. They did not find statistical evidence that schizotypy, defined as a continuous trait, was genetically related to schizophrenia. Based on the results of this study, it would be interesting to know whether power would be improved by defining schizotypy in terms of signs and symptoms that optimize the distinction between RelSZSA and NC, even if such traits are not part of the diagnostic criteria for SPD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

- Asarnow RF, Nuechterlein KH, Fogelson D, Subotnik KL, Payne DA, Russell AT, Asamen J, Kuppinger H, Kendler KS. Schizophrenia and schizophrenia-spectrum personality disorders in the first-degree relatives of children with schizophrenia: the UCLA family study. *Archives of General Psychiatry* 2001;58:581–588. [PubMed: 11386988]
- Baron M, Gruen R, Rainer JD, Kane J, Asnis L, Lord S. A family study of schizophrenic and normal control probands: implications for the spectrum concept of schizophrenia. *American Journal of Psychiatry* 1985;142:447–455. [PubMed: 3976917]
- Brzustowicz LM, Hodgkinson KA, Chow EWC, Honer WG, Bassett AS. Location of a major susceptibility locus for familial schizophrenia on chromosome 1q21–q22. *Science* 2000;288:678–682. [PubMed: 10784452]
- Brzustowicz LM, Honer WG, Chow EWC, Little D, Hogan J, Hodgkinson K, Bassett AS. Linkage of familial schizophrenia to chromosome 13q32. *American Journal of Human Genetics* 1999;65:1096–1103. [PubMed: 10486329]
- Calkins ME, Curtis CE, Grove WM, Iacono WG. Multiple dimensions of schizotypy in first degree biological relatives of schizophrenia patients. *Schizophrenia Bulletin* 2004;30:317–325. [PubMed: 15279049]
- Chapman LJ, Chapman JP. Scales for rating psychotic and psychotic-like experiences as continua. *Schizophrenia Bulletin* 1980;6:477–489. [PubMed: 7403809]
- Fanous A, Gardner C, Walsh D, Kendler KS. Relationship between positive and negative symptoms of schizophrenia and schizotypal symptoms in nonpsychotic relatives. *Archives of General Psychiatry* 2001;58:669–673. [PubMed: 11448374]
- Fanous AH, Neale MC, Gardner CO, Webb BT, Straub RE, O'Neill FA, Walsh D, Riley BP, Kendler KS. Significant correlation in linkage signals from genome-wide scans of schizophrenia and schizotypy. *Molecular Psychiatry* 2007;12:958–965. [PubMed: 17440434]

- Frangos E, Athanassenas G, Tsitourides S, Katsanou N, Alexandrakou P. Prevalence of DSM III schizophrenia among the first-degree relatives of schizophrenic probands. *Acta Psychiatrica Scandinavica* 1985;72:382–386. [PubMed: 4072739]
- Gottesman, II. *Schizophrenia Genesis*. Freeman; New York, N.Y: 1991.
- Greenberg DA. There is more than one way to collect data for linkage analysis. What a study of epilepsy can tell us about linkage strategy for psychiatric disease. *Archives of General Psychiatry* 1992;49:745–750. [PubMed: 1514880]
- Gunderson JG, Siever LJ, Spaulding E. The search for a schizotype. Crossing the border again. *Archives of General Psychiatry* 1983;40:15–22. [PubMed: 6849615]
- Holzman PS, Matthysse S. The genetics of schizophrenia: A review. *Psychological Science* 1990;1:279–286.
- Kendler KS. Diagnostic approaches to schizotypal personality disorder: a historical perspective. *Schizophrenia Bulletin* 1985;11:538–553. [PubMed: 3909377]
- Kendler KS, Gruenberg AM. An independent analysis of the Danish Adoption Study of Schizophrenia. VI. The relationship between psychiatric disorders as defined by DSM-III in the relatives and adoptees. *Archives of General Psychiatry* 1984;41:555–564. [PubMed: 6732417]
- Kendler KS, Gruenberg AM, Tsuang MT. Psychiatric illness in first-degree relatives of schizophrenic and surgical control patients. A family study using DSM-III criteria. *Archives of General Psychiatry* 1985;42:770–779. [PubMed: 4015321]
- Kendler KS, Lieberman JA, Walsh D. The Structured Interview for Schizotypy (SIS): a preliminary report. *Schizophrenia Bulletin* 1989;15:559–571. [PubMed: 2623438]
- Kendler KS, McGuire M, Gruenberg AM, O'hare A, Spellman M, Walsh D. The Roscommon family study: I. Methods, diagnosis of probands, and risk of schizophrenia in relatives. *Archives of General Psychiatry* 1993a;50:527–540. [PubMed: 8317947]
- Kendler KS, McGuire M, Gruenberg AM, O'hare A, Spellman M, Walsh D. The Roscommon family study: III. Schizophrenia-related personality disorders in relatives. *Archives of General Psychiatry* 1993c;50:781–788. [PubMed: 8215802]
- Kendler KS, McGuire M, Gruenberg AM, Spellman M, O'hare A, Walsh D. The Roscommon family study: II. The risk of nonschizophrenic nonaffective psychoses in relatives. *Archives of General Psychiatry* 1993b;50:645–652. [PubMed: 8343035]
- Kendler KS, McGuire M, Gruenberg AM, Walsh D. Schizotypal symptoms and signs in the Roscommon family study: their factor structure and familial relationship with psychotic and affective disorders. *Archives of General Psychiatry* 1995;52:296–303. [PubMed: 7702446]
- Kety, SS.; Rosenthal, D.; Wender, PH.; Schulsinger, F. The types and prevalences of mental illness in the biological and adoptive families of adopted schizophrenics. In: Rosenthal, DE.; Kety, SS., editors. *The Transmission of Schizophrenia*. Pergamon; Oxford: 1968. p. 345–362.
- Kety SS, Rosenthal D, Wender PH, Schulsinger F, Jacobsen B. Mental illness in the biological and adoptive families of adopted individuals who have become schizophrenic. *Behavior Genetics* 1976;6:219–225. [PubMed: 973827]
- Kwapil TR, Barrantes-Vidal N, Silvia PJ. The dimensional structure of the Wisconsin Schizotypy Scales: factor identification and construct validity. *Schizophrenia Bulletin* 2008;34:444–457. [PubMed: 17768308]
- Kwapil TR, Chapman LJ, Chapman J. Validity and usefulness of the Wisconsin Manual for Assessing Psychotic-like Experiences. *Schizophrenia Bulletin* 1999;25:363–375. [PubMed: 10416737]
- Levy DL, Coleman MJ, Sung H, Ji F, Mendell NR, Titone D. The genetic basis of thought disorder and language and communication disturbances in schizophrenia. *Journal of Neurolinguistics*. 2009 In press. 10.1016/j.jneuroling.2009.08.003
- Lichtenstein P, Bjork C, Hultman CM, Scolnick E, Sklar P, Sullivan PF. Recurrence risks for schizophrenia in a Swedish national cohort. *Psychological Medicine* 2006;36:1417–1425. [PubMed: 16863597]
- Lowing PA, Mirsky AF, Pereira R. The inheritance of schizophrenia spectrum disorders: a reanalysis of the danish adoptee study data. *American Journal of Psychiatry* 1983;140:1167–1171. [PubMed: 6614222]

- Maier W, Lichtermann D, Minges J, Heun R. Personality disorders among the relatives of schizophrenia patients. *Schizophrenia Bulletin* 1994;20:481–493. [PubMed: 7973465]
- Marneros, A.; Andreasen, NC.; Tsuang, MT. Negative versus positive schizophrenia. Springer Verlag; Berlin: 1991.
- Matthysse S, Parnas J. Extending the phenotype of schizophrenia: implications for linkage analysis. *Journal of Psychiatric Research* 1992;26:329–344. [PubMed: 1491357]
- Onstad S, Skre I, Edvardsen J, Torgersen S, Kringlen E. Mental disorders in first-degree relatives of schizophrenics. *Acta Psychiatr Scand* 1991;83:463–467. [PubMed: 1882700]
- Parnas J, Cannon TD, Jacobsen B, Schulsinger H, Schulsinger F, Mednick SA. Lifetime DSM-III-R diagnostic outcomes in the offspring of schizophrenic mothers. Results from the Copenhagen High-Risk Study. *Arch Gen Psychiatry* 1993;50:707–714. [PubMed: 8357296]
- Spitzer RL, Endicott J, Gibbon M. Crossing the border into borderline personality and borderline schizophrenia. The development of criteria. *Archives of General Psychiatry* 1979;36:17–24. [PubMed: 760694]
- Spitzer, RL.; Williams, J.; Gibbon, M.; First, M. Structured Clinical Interview for DSM-IV - Patient edition. American Psychiatric Association; Washington, D.C: 1994.
- Stephens DA, Atkinson MW, Kay DWK, Roth M, Garside RF. Psychiatric morbidity in parents and sibs of schizophrenics and non-schizophrenics. *British Journal of Psychiatry* 1975;127:97–108. [PubMed: 1182396]
- Sung H, Ji F, Levy DL, Matthysse S, Mendell NR. The power of linkage analysis of a disease-related endophenotype using asymmetrically ascertained sib pairs. *Computational Statistics and Data Analysis* 2009;53:1829–1842.
- Swets JA. Measuring the accuracy of diagnostic systems. *Science* 1988;240:1285–1293. [PubMed: 3287615]
- Tienari P, Wynne LC, Laksy K, Moring J, Nieminen P, Sorri A, Lahti I, Wahlberg KE. Genetic boundaries of the schizophrenia spectrum: evidence from the Finnish Adoptive Family Study of Schizophrenia. *Am J Psychiatry* 2003;160:1587–1594. [PubMed: 12944332]
- Torgersen S. Relationship of schizotypal personality disorder to schizophrenia: genetics. *Schizophrenia Bulletin* 1985;11:554–563. [PubMed: 3909378]
- Torgersen S, Edvardsen J, Oien PA, Onstad S, Skre I, Lygren S, Kringlen E. Schizotypal personality disorder inside and outside the schizophrenic spectrum. *Schizophrenia Research* 2002;54:33–38. [PubMed: 11853976]
- Tsuang MT, Stone WS, Tarbox SI, Faraone SV. An integration of schizophrenia with schizotypy: identification of schizotaxia and implications for research on treatment and prevention. *Schizophrenia Research* 2002;54:169–175. [PubMed: 11853991]
- Varma SL, Zain AM, Singh S. Psychiatric morbidity in the first-degree relatives of schizophrenic patients. *Am J Med Genet* 1997;74:7–11. [PubMed: 9033998]
- Vladimirov V, Thiselton DL, Kuo P-H, Fanous A, Wormley B, Vittum J, Ribble R, Moher B, van den Oord E, O'Neill FA, Walsh D, Kendler KS, Riley BP. A region of 35 kb containing the trace amine associate receptor 6 (TAAR6) gene is associated with schizophrenia in the Irish study of high-density schizophrenia families. *Molecular Psychiatry* 2007;12:842–853. [PubMed: 17505468]

Figure 1.

Nonpsychotic RelSZSA and NC are divided into individuals who either met diagnostic criteria for schizotypal personality disorder (SPD), schizoid personality disorder (SZD), or paranoid personality disorder (PPD) in a hierarchy corresponding to this order or who did not meet diagnostic criteria for one of these schizophrenia spectrum personality disorders (No PD). The horizontal line in Figure 1 marks the 97.5% specificity cutoff, which corresponds to a logistic score of 23.6.

Figure 2.

Distribution of logistic regression scores in RelSZSA with no schizophrenia-related personality disorder (No PD), who meet criteria for a diagnosis of schizotypal personality disorder (SPD), paranoid personality disorder (PPD), schizoid personality disorder (SZD), SPD and PPD, or SPD, PPD and SZD.

Figure 3.

Nonpsychotic RELSZSA and NC are divided into individuals who met (yes) or did not meet (no) diagnostic criteria for an Axis I nonpsychotic disorder.

Figure 4.

Distribution of logistic regression scores in relatives of schizophrenia probands (RELSZ) and relatives of schizo-affective probands (RELSA). Individuals who met diagnostic criteria for SPD are specified.

Figure 5. Distribution of logistic regression scores in controls and RelSZSA as a function of relation to proband (parent, sibling, or offspring).

Table 1

Demographic Characteristics of Study Subjects

Group	N	Age (yrs) ^a	Sex	Estimated Verbal IQ ^b	Education (yrs)
Relatives of Schizophrenia/Schizoaffective Patients	241	50.1 (16.4)	147F, 93M	106.8 (13.4)	15 (2.6)
Controls	161	40.6 (14.9)	99F, 62M	105.8 (11.9)	15.1 (2.3)

Mean (standard deviation)

^a_t (365) = -5.98, P<0.001

^bBased on the vocabulary subtest of the WAIS-R (Wechsler, 1981)

Table 2

Lifetime Prevalence of Primary Nonpsychotic Axis I Disorders in Relatives of Schizophrenia/Schizo-affective Patients and Controls*

Group	N	Mood Disorders	Anxiety Disorders	Substance Abuse/Dependence Disorders (in remission)	Other Disorders	No Axis I Disorders
Relatives of Schizophrenia/Schizo-affective Patients	241	79 (32.8%)	12 (5%)	39 (16.2%)	4 (1.6%)	107 (44.4%)
Controls	161	61 (37.7%)	14 (8.6%)	18 (11%)	5 (3.1%)	63 (39.5%)

* The following diagnostic hierarchy was used: mood disorders, anxiety disorders, substance abuse/dependence, other mental disorders, and no Axis I disorder. Only data on the primary Axis I diagnosis are presented. Rates for substance abuse/dependence should not be considered epidemiologic estimates because the samples were screened for current abuse/dependence, which was an exclusion criterion for participating.

Table 3

Lifetime Prevalence of Schizophrenia Spectrum Disorders in Relatives of Schizophrenia/Schizoaffective Patients and Controls^a

Group	N	Schizophrenia or Schizoaffective Disorder ^b	Affective Psychosis ^b	Nonaffective Psychosis ^b	Schizophrenia Spectrum Personality Disorders (SSPD)	No Current or Past Psychotic Disorder or SSPD
Relatives of Schizophrenia/Schizoaffective Patients	275	19 (6.9%)	9 (3.3%)	6 (2.2%)	20 (10 SPD, 1 SZD, 9 PPD) (7.3%)	221 (80.3%)
Controls	161	0	0	0	12 (4 SPD, 0 SZD, 8 PPD) (7.5%)	149 (92.5%)

^aThese lifetime prevalence rates for psychotic disorders should not be considered epidemiologic estimates in controls, since these individuals were screened for a personal or family history of psychosis.

^bNot included in statistical comparisons of RelSZSA and NC

Table 4

Composition of SIS Summary Scores

SIS Summary Score	SIS Section(s)	SIS Items
Referential thinking/Suspiciousness	Ideas of reference	<p>F1 and F3– feeling of being watched</p> <p>F5– reason for being watched</p> <p>F8– likelihood of being watched at future time</p> <p>G1– special messages from environment</p> <p>G2– number of special messages</p> <p>G5– TV/radio broadcaster knows you are listening</p> <p>H1–being talked about in public</p> <p>H2– frequency being talked about in public</p> <p>H3– laughed at in public</p> <p>H4– talked about/laughed at more than others</p> <p>H5– reason for being talked about/laughed at</p> <p>H6– people dropping hints about you in public</p> <p>H8– double talk about you</p> <p>H9– frequency of double talk</p> <p>H10– types of feelings in public</p> <p>I1– how trusting</p> <p>I2, I3 and I4– trusting others</p> <p>I5– people making life difficult</p> <p>I6– take precautions to protect from others</p> <p>I7–relationship with neighbors</p> <p>I9– reason for suspiciousness</p> <p>U20– suspiciousness/guardedness</p> <p>U21– verbal suspiciousness</p>
	Suspiciousness	
Intimate relationships		B10– number of close friends as teenager
		C1– number of friends today
		C7– number of close friends can confide in

SIS Summary Score	SIS Section(s)	SIS Items
Interpersonal aversiveness	Social anxiety	E1– discomfort in social situations E2– anxiety in social situations E3– worrying about what others might think of you E4– worry about appearing foolish E5– avoiding social situations
	Social avoidance	C2– frequency of contact with friends C3– closeness to friends
	Social isolation	C4– frequency of contact with relatives C6– any close relationships C14– loner
	Introversion	C15 C16 and C17– outgoingness C14– loner C15 C16 and C17– outgoingness J1– reserved in showing of emotions
Reserved emotion		
Speech		U10– organization of speech U11– organization of associations U12– rate of speech U13– frequency of speech U14– poverty of content of speech
Behavior		U16– odd behavior U17– social appropriateness U18– appropriateness of clothing
Liability	Irritability	O14– losing temper frequently O15– bad temper O16– frequency of anger O17– yelling when angry O18– violence when angry
	Affective instability	Q1– mood changes

SIS Summary Score	SIS Section(s)	SIS Items
Affect	Impulsivity	Q2–frequency of mood changes from ok to depressed S1– regrets impulsivity S2– cut or burnt self S3– frequency of cutting/burning S4– impulsive actions
		U5– range of emotions U6– appropriateness of affect U7– stability of affect
Cognitive perception	Illusions	L1– mistaking object for person L2– hearing sounds that are not real L3– imagine calling of name L4– hearing whispering/voices when quiet L5–frequency of whispers/voices when quiet L6– person/force around when alone L7–frequency of person/force around when alone L8– sensitivity to sensations
	Psychotic-like phenomena	M1– frequency of confused thoughts M2– frequency of losing train of thought M3– outside power stopping thoughts M4– frequency of thoughts in mind that don't belong M5– frequency of thoughts in mind not your own M6– frequency of outside power putting thoughts in mind M7– who puts thoughts in mind M9– others hear your thoughts M10– number of others who hear your thoughts M11– frequency of feelings that don't belong M12– feelings that are not yours M13– outside power putting feelings in you N1– surroundings seem unreal
	Derealization	

SIS Summary Score	SIS Section(s)	SIS Items
	Magical thinking	N2– outside body experience N3– number of outside body experiences N4– outside body experience during illness or taking drugs N5– frequency of déjà vu K1, K4, and K6– endorsement of superstitious beliefs & acts K2– endorsement of magical thinking K9– strength of superstitious beliefs K10– number of superstitious beliefs K12– practical effect of superstitious beliefs K13– frequency of effect on behavior of superstitious beliefs
Interpersonal signs		U1– eye contact U2– body language U3– emotional rapport U5– fullness of affect U6– appropriateness of affect U7– stability of affect U8– general warmth vs. coldness of affect U16– odd movements U17– social appropriateness U18– appropriateness of dress

Table 5
Logistic Score Summary Statistics in Relatives of Schizophrenia/Schizo-affective Patients and Controls

Group	N	Mean (SD)	Median	Minimum	Maximum	97.5 th Percentile
Relatives of Schizophrenia/Schizo-affective Patients	241	16.2 (7.3)	14.3	3.1	43.5	35.2
Controls	161	12.1 (4.5)	11.6	2.5	25.1	23.6

Table 6

Proportion of Non-Psychotic Axis I Disorders in Relatives of Schizophrenia/Schizoaffective Patients Identified as Deviant and Non-Deviant based on the Logistic Regression Score

Group	N	Mood Disorders	Anxiety Disorders	Substance Abuse/ Dependence Disorders (in remission)	Other Disorders	No Axis I Disorders
Relatives of Schizophrenia/Schizoaffective Patients Identified as Clinically Deviant by Logistic Score	31	29%	3%	19%	0%	48%
Relatives of Schizophrenia/Schizoaffective Patients <i>Not</i> Identified as Clinically Deviant by Logistic Score	210	33%	5%	16%	2%	44%