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Smita N. Deshpande · Triptish Bhatia · Joel Wood · Jaspreet S. Brar · B. K. Thelma · Rohan Ganguli · Richard Day · Irving I. Gottesman · Vishwajit L. Nimgaonkar

Evaluation of familial influences on the course and severity of schizophrenia among US and Indian cases

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Abstract *Background* Prior studies suggest familial (possibly genetic) influences on the course of schizophrenia. *Aims* The aim of this study was to compare familial influences on the course and severity of schizophrenia in two independent samples. *Method* Thirteen selected measures were compared among affected sibling pairs (ASPs) from Pittsburgh, USA and New Delhi, India (48 US pairs, 53 Indian pairs). For each ASP proband, an unrelated patient was selected randomly from a suitable pool of cases ascertained in the same study (Sibpair proband – comparison case or S-C pairs). Correlations between these pairs were compared. *Results* The correlations varied by item and by site. Significant correlations for longitudinal course and pattern of severity were noted among the ASPs from USA, but did not remain significant following corrections for multiple comparisons. Comparisons between the correlations for ASPs and the S-C pairs, used to estimate familial effects, yielded trends for the ASP correlations to be numerically larger than the S-C correlations in both samples. Separate cross-site comparisons revealed several significant differences with regard to several demographic and clinical variables. The possible impact of the cross-site variations on the observed ASP correlations is discussed. *Conclusions* Though familial factors did not appear to have a significant impact on course/severity using this novel design, the suggestive trends need to be examined in larger samples.

Key words schizophrenia – course – severity – India – developing country – familial

S. N. Deshpande, MD
Dr Ram Manohar Lohia Hospital
New Delhi, India

T. Bhatia, PhD
Indo US Project on Schizophrenia Genetics
Dr Ram Manohar Lohia Hospital
New Delhi, India

J. Wood, BS · J. S. Brar, MD · R. Ganguli, MD · V. L. Nimgaonkar, DPhil, MRC Psych (✉)
Dept. of Psychiatry, WPIC Room 443
3811 O'Hara Street
University of Pittsburgh School of Medicine
Pittsburgh, Pa 15213, USA
Tel.: +1-412/246-6353
Fax: +1-412/246-6350
E-Mail: nimga+@pitt.edu

B. K. Thelma PhD
Dept. of Genetics
Delhi University
New Delhi, India

R. Day, MD
Dept. of Biostatistics
Graduate School of Public Health
University of Pittsburgh
Pittsburgh, USA

I. I. Gottesman, PhD, FRCPsych
Depts. of Psychiatry and Psychology
University of Minnesota
Minneapolis, USA

Introduction

It is important to identify familial influences on clinical characteristics of schizophrenia. If such influences are demonstrated to be genetic, they may be useful for gene-mapping studies. For example, genetic influences on negative features of schizophrenia have been proposed (Cardno et al. 2001; Chen and Faraone 2000; Malaspina et al. 2000; Ross et al. 2000). Genetic influences have also been suggested by retrospective analyses of linkage studies among multiply affected Irish families (Kendler et al. 2000) and by sub-type similarity among concordant twins (Inouye 1961; Gottesman and Shields 1972). On the other hand, familial influences may also reflect shared environment factors that may enable identification of risk factors.

Familial influences can be examined by estimating the correlation for selected characteristics among affected pairs of relatives. Correlations among affected siblings represent the most convenient design for variables influenced by age, as they involve comparisons among indi-

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viduals of similar age. In the present study, we also examined correlations between one member of each pair and randomly selected unrelated cases. The second set of correlations, also denoted as S-C correlations, were contrasted against the affected sib-pair (ASP) correlations to estimate familial influences. The design of the analyses entailed that shared genetic and environmental influences would be estimated. Our null hypothesis stated that no shared familial influences would be detected for selected indices of course and outcome.

We investigated a US as well as an Indian sample. The dual strategy enabled us to examine two ethnically distinct samples. Such investigations are potentially important, because the course and outcome of schizophrenia may be more favorable in developing countries such as India, when compared with highly industrialized or 'developed' nations (Sartorius et al. 1986; Jablensky et al. 1992). It has also been suggested that a more supportive familial environment may explain the cross-national differences (Waxler 1979; Leff et al. 1987, 1990). Thus, greater familial resemblance in outcome would be predicted in India, compared with US samples.

Subjects and methods

Analytical design

We used a novel modification on the intra-sib-pair correlation method. One member of each affected sib-pair (ASP) was compared with a randomly selected unrelated case from a "singleton case" pool. Two sets of correlations (intra-ASP and Sibpair proband – comparison case, S-C) were computed for selected items related to course and severity. Thus, shared familial effects could be teased from non-familial effects.

Recruitment design

The analyses are part of ongoing investigations into the genetic epidemiology of schizophrenia being conducted simultaneously by US and Indian investigators, using identical strategies. Participants are sought at Pittsburgh and New Delhi from a variety of treatment settings in order to sample the range of care available. Individuals clinically diagnosed with any psychotic illness are eligible for inclusion. Persons with or without affected siblings are recruited. Participation from available parents is also sought, in order to obtain family history information, as well as clinical information as appropriate. Thus, families are divided into those with affected sib-pairs ('ASP families') and those without affected sib-pairs ('singleton families').

Site details

Pittsburgh

Recruitment occurred primarily at the Western Psychiatric Institute and Clinic, a University affiliated tertiary care center, which also serves as a catchment area hospital for a defined region of Allegheny County, PA. Inpatients and outpatients were also sought at 35 University hospitals, non-academic community centers, hospitals and state facilities located within a 500-mile radius of Pittsburgh.

New Delhi

The primary recruitment site was the Dr. Ram Manohar Lohia Hospital (RMLH), a large publicly funded tertiary care center providing inpatient and outpatient care. In addition, all major hospitals and psychiatric rehabilitation facilities in New Delhi were approached regularly. Though most patients at such facilities resided in the metropolitan limits, approximately one-third were also drawn from rural areas surrounding New Delhi.

Assessment

Potential participants, who fulfilled eligibility criteria (a clinical diagnosis of psychosis) were informed about the study by their clinicians. If agreeable, they were contacted by project staff. They were then screened using a checklist based on DSM-IV criteria. Detailed clinical information was next obtained, using the English or Hindi versions of the 'Diagnostic Interview for Genetic Studies' (DIGS) (Nurnberger et al. 1994; Deshpande et al. 1998) (http://www-grb.nimh.nih.gov/gi.html). The DIGS is a comprehensive semi-structured interview schedule that includes extensive clinical as well as demographic information. It incorporates OPCRIT, a diagnostic checklist (McGuffin 1991). Additional information about each case was obtained from available medical records and appropriate relatives. At both sites, consensus diagnoses were established by psychiatrists in conjunction with the research associate who interviewed the patient. Cases with a consensus diagnosis of schizophrenia or schizoaffective disorder (DSM-IV) were included in the study.

All participants provided written informed consent, as approved by the Institutional Review Boards at the RMLH, Delhi University and the University of Pittsburgh.

Measures used for comparison

Thirteen measures of course/severity were selected from the DIGS (Table 3). The items included Return to normalcy (Psychosis section, item #4) Pattern of symptoms (Psychosis section, item #100), Longitudinal course (Psychosis section, item #101), Pattern of severity (Psychosis section, item #102), Deterioration in social, occupational, and emotional function (OPCRIT section, items 8a, b, c) and Global Assessment Scale (GAF): most severe and during the past month of the current episode (GAF section, item #2 and item #3). For age at onset, we selected the age at onset of psychosis. Due to differences in health care practices, we anticipated cross-national differences in the age at first hospitalization, an alternative measure of onset age. For similar reasons, we anticipated difficulties in using the age when psychiatric symptoms were first noted.

Selection of unrelated comparison cases

For each proband among the affected sib-pairs (ASP), an unrelated case with the same gender, nationality and diagnosis was selected randomly from approximately 250 cases in the singleton family group. The singleton cases were drawn from the same settings as the sibpairs.

Quality control

Uniform training in the use of the DIGS was provided to all research associates and co-investigators by the Principal Investigator at Pittsburgh (VLN) prior to the start of the studies. Semi-annual training sessions have been continued throughout the study, with bi-annual bilateral visits to the recruitment sites by the respective PIs (VLN and SND). Inter- and intra-site reliability are checked quarterly, using live sessions, video-taped interviews and transcripts of the DIGS. Kappa values over 0.6 for diagnoses were required for inter-rater reliability tests among research associates and psychiatrists during their initial training. During the study, diagnostic reliability was compared between the principal psychiatrists at New Delhi and Pittsburgh (SND and VLN). Significant agreement was obtained ($\kappa = 0.89, n = 13$ cases).

Statistical analysis

We used the Spearman's correlation coefficient for quantitative variables. The Cramer's V statistic was used for variables with more than two classes and the Phi coefficient was used for comparisons involving two categories. The correlation for each variable was calculated separately for the ASP and the S-C sets. The statistical significance of the differences between these sets of correlations was estimated using Fisher's z transformation (Cohen and Cohen 1983). The Bonferoni correction for multiple comparisons was utilized. The Statistical Package for Social Sciences (SPSS, version 10.0.0 for Windows) was used for all analyses.

Results

All US and Indian participants were first compared with respect to demographic and clinical variables. The comparisons were intended to identify variables that differed across the sites and that might also impact of the subsequent analyses involving ASP/S-C sets (Table 1). A number of significant cross-site differences were noted, These differences would remain even following corrections for multiple comparisons. A diagnosis of schizoaffective disorder was made more often among the US patients. The Indian patients were younger, but had a later age at onset of psychotic features. The US patients were more likely to be living alone and to be unmarried. The Indian patients were more likely to report normalcy between episodes. In contrast to the US patients, the majority of whom were rated as having continuous illness under the item 'longitudinal course', the Indian patients were more likely to report episodic illness with varying degrees of inter-episode residual symptoms. Consistent with this result, the ratings on patterns of severity suggested that the Indian patients were more likely to have mild deterioration, while the US patients were more likely to have severe deterioration. The US patients were more likely to have attempted suicide. Paradoxically, the Indian patients received significantly worse ratings on the Global Assessment Scale. No significant group-wise differences were noted for the gender distribution, pattern of symptoms or deterioration in social, occupational or emotional function.

The demographic characteristics of the ASP samples are described in Table 2. Members of US ASPs were more likely to be living alone compared with Indian ASPs, but

Table 2 Characteristics of affected sib-pairs

	US sample (96 cases, 48 pairs)	Indian sample (106 cases, 53 pairs)
Age	44±9.0	37±9.4
Gender (male/female)	51/45	57/49
Age at onset of psychosis	21±7.2	24±7.0
Living alone	12	0
Diagnosis (schizophrenia/ schizoaffective disorder)	58/38	98/8

Ages are presented as mean ± standard deviation

Table 1 Characteristics of US and Indian cases

	US sample (144 cases)	Indian sample (159 cases)	
Diagnosis (schizophrenia/schizoaffective disorder)	89/55	150/9	$\chi^2 = 48.72$ (df = 3, $p < 0.001$)
Age	39.5 (9.3)	33.3 (9.5)	$t = -5.62$ (df = 297, $p < 0.001$)
Gender (male/female)	72/72	84/75	$\chi^2 = 0.24$ (df = 1, $p = 0.62$)
Age at onset of psychosis	20.6 (7.1)	23.3 (6.6)	$t = -3.20$ (df = 260, $p = 0.002$)
Living alone	22	0	$\chi^2 = 93.48$ (df = 7, $p < 0.001$)
Marital status (married/unmarried/unknown)	14/108/22	52/106/1	$\chi^2 = 22.67$ (df = 4, $p < 0.001$)
Return to normalcy (yes/no/uncertain)	41/55/48	89/45/25	$\chi^2 = 12.79$ (df = 1, $p < 0.001$)
Pattern of symptoms (1/2/3/4/5/6)	43/8/8/0/5/55	74/7/17/0/59/2	$\chi^2 = 2.35$ (df = 3, $p = 0.50$)
Longitudinal course (1/2/3/4/5/6/7)	24/7/40/4/1/2/66	60/17/58/14/4/6	$\chi^2 = 8.84$ (df = 5, $p = 0.116$)
Pattern of severity (1/2/3/4/5/6)	8/7/27/39/8/55	34/32/62/24/4/3	$\chi^2 = 35.09$ (df = 4, $p < 0.001$)
Deterioration in social function (yes/no/uncertain)	53/26/65	83/32/44	$\chi^2 = 0.58$ (df = 1, $p = 0.45$)
Deterioration in occupational function (yes/no/uncertain)	62/18/64	85/30/44	$\chi^2 = 0.33$ (df = 1, $p = 0.57$)
Deterioration in emotional function (yes/no/uncertain)	55/19/70	82/33/44	$\chi^2 = 0.21$ (df = 1, $p = 0.65$)
Ever attempted suicide (yes/no/uncertain)	57/50/37	37/110/12	$\chi^2 = 20.98$ (df = 1, $p < 0.001$)
Global Assessment Scale, during the most severe period of the current episode	43.5 (15.7)	28.2 (13.8)	$t = -7.68$ (df = 225, $p < 0.001$)
Global Assessment Scale, past month	51.0 (16.5)	42.4 (20.2)	$t = -3.59$ (df = 245, $p < 0.001$)

All participants were used for the comparisons, i. e., affected sibling pairs as well as the unrelated comparison cases. Values for continuous variables are presented as mean ± standard deviation and were compared using the Student's t-test. Levels of statistical significance are shown without corrections for multiple comparisons.
Ratings for categorical descriptors of clinical course are rated as follows in the DIGS:
Pattern of symptoms: 1 = continuously 'positive', 2 = predominantly 'negative' symptoms, 3 = predominantly 'positive' symptoms converting to predominantly 'negative' symptoms, 4 = 'negative' symptoms converting to 'positive' symptoms, 5 = continuous mixture of positive and negative symptoms, 6 = uncertain.
Longitudinal course of illness: 1 = episodic with inter-episode residual symptoms, 2 = episodic with no inter-episode residual symptoms, 3 = continuous, 4 = single episode in partial remission, 5 = single episode in full remission, 6 = other, or unspecified, 7 = uncertain.
Pattern of severity: 1 = episodic shift, 2 = mild deterioration, 3 = moderate deterioration, 4 = severe deterioration, 5 = relatively stable, 6 = uncertain.

it was not possible to determine from the DIGS how many of the ASPs were living together at the time of the study.

When the measures of course/severity were examined separately at each site among the ASPs, considerable variation was noted. A significant correlation was obtained among the US ASPs for the longitudinal course of the illness ($r = 0.71$, $p < 0.01$) and pattern of severity ($r = 0.60$, $p < 0.02$). Among the Indian ASPs, correlations were noted for marital status ($r = 0.36$, $p < 0.03$). There was significant correlation for current living status among ASPs from both samples (US: $r = 0.60$, $P < 0.01$; India: $r = 0.80$, $p < 0.01$). No statistically significant correlation remained after corrections for multiple comparisons, possibly due to the fact that some data were missing (Table 3).

Correlations among the S-C pairs were next computed. Significant correlations emerged for the GAS score at the most severe phase in both samples (US: $r = 0.51$, $P < 0.03$; India: $r = 0.32$, $p < 0.04$, uncorrected for multiple comparisons). These correlations were compared with the respective values from the ASPs using Fisher's z transformation. The z values differed by item and across sites, suggesting highly variable familial influences. No significant differences were noted between ASP and S-C pair correlations, apart from living situation among the Indian patients ($z = 4.27$, $P < 0.01$, uncorrected for multiple comparisons). Other interesting trends also emerged. On all but three measures, the correlations for ASPs were numerically larger than the S-C correlations in the US sample. There was greater scatter within the Indian sample. Even so, seven measures exhibited this trend among the Indian patients. The ASP vs. S-C differences were present in both samples with regard to five variables (living situation, pattern of symptoms, deterioration in social, occupational and emotional function, and age at onset).

Discussion

We evaluated the role of familial factors in the course and severity of schizophrenia in two culturally distinct settings. Using conservative corrections for multiple comparisons, our analyses do not support a predominant role for familial factors in either the US or the Indian samples. However, inspection of the data indicates a trend for siblings to be more alike with regard to the course and severity measures than genetically unrelated individuals. These results are of potential interest, since the selected DIGS items are relatively crude measures. Hence, the suggestion that familial factors influence the course and outcome of schizophrenia needs to be evaluated in a larger sample.

The nature of the sample and the analytical design do not enable us to say whether the greater similarity among ASPs is determined by genetic factors, environment factors or gene-environment interactions. Since the majority of ASPs might not be living together at the time of the study, the term 'familial factors' is likely to encompass shared environmental factors during childhood and adolescence. A prior study of 256 Irish ASPs with schizophrenia revealed that global course and outcome, along with major symptoms except hallucinations, were modestly but significantly correlated in sibling pairs concordant for schizophrenia (Kendler et al.

Table 3 Correlation among affected sibling pairs and unrelated pairs

	US sample								Indian sample							
	r1	p1	df (n-2)	r2	p2	df (n-2)	Z	p	r1	p1	df (n-2)	r2	p2	df (n-2)	Z	p
Marital status	0.37	0.20	36	0.36	0.38	32	0.04	0.48	0.36	0.03	51	0.38	0.03	50	−0.06	0.48
Living situation	0.60	< 0.01	32	0.46	0.55	30	0.70	0.24	0.80	< 0.01	47	0.21	0.97	48	4.27	< 0.01
Return to normalcy	−0.03	0.89	22	0.01	0.97	23	−0.13	0.46	0.11	0.50	36	−0.22	0.20	34	1.36	0.09
Pattern of symptoms	0.48	0.13	20	0.43	0.36	16	1.74	0.04	0.32	0.06	50	0.16	0.96	49	0.17	0.44
Longitudinal course	0.71	0.01	18	0.46	0.24	11	1.02	0.16	0.27	0.58	48	0.33	0.18	47	−0.07	0.48
Pattern of severity	0.60	0.02	20	0.55	0.24	15	0.56	0.29	0.25	0.66	50	0.25	0.71	48	0	0.50
Deterioration in social function	0.26	0.25	21	−0.30	0.24	13	1.58	0.06	0.34	0.06	28	−0.06	0.74	26	1.49	0.07
Deterioration in occupational function	0.05	0.83	21	−0.25	0.33	13	0.84	0.20	0.24	0.20	28	0.06	0.77	26	0.70	0.24
Deterioration in emotional function	0.33	0.17	21	−0.28	0.31	11	1.63	0.05	0.20	0.27	28	−0.09	0.64	26	0.77	0.23
Ever attempted suicide	−0.15	0.43	24	−0.19	0.32	27	0.14	0.44	0.01	0.96	43	0.20	0.20	42	−0.83	0.21
Age at onset	0.29	0.14	25	0.16	0.42	27	0.49	0.31	0.22	0.13	47	0.06	0.69	49	0.80	0.21
Global Assessment Scale, most severe	0.31	0.17	19	0.51	0.03	17	−0.70	0.24	0.17	0.28	41	0.32	0.04	41	−0.72	0.24
Global Assessment Scale, past month	0.23	0.21	28	0.06	0.77	25	0.62	0.27	0.01	0.94	41	0.09	0.58	41	−0.36	0.36

For each data set, r1, p1 and r2, p2 denote the correlation coefficients and p values (uncorrected) for affected sibling pairs (ASPs) and the Sibpair proband – comparison case pairs (S-C), respectively. The standardized z scores and p values are also presented. Please refer to Table 1 for an explanation of the categories employed for each variable

1997). Sample size difference is a more plausible explanation than ethnic variation for the different conclusions between the Irish study and the present analyses.

Our samples enabled evaluation of patients from two distinct cultures. It has been speculated for over 30 years that the course and outcome of schizophrenia is more favorable for individuals in developing countries such as India, when compared with highly industrialized or 'developed' nations (Waxler 1979; Leff et al. 1990). An independent prospective study also reported better course and outcome in less developed countries ('Determinants of outcome of severe mental disorders', DOSMD) (Sartorius et al. 1986; Jablensky et al. 1992). Re-appraisal of these variations may be timely because of profound recent and ongoing changes in the developing and developed countries. Rapid urbanization and industrialization have led to breakdown of traditional family supports and deteriorating health care in India. Indeed, a recently concluded follow-up of Indian cases deemed to have a poor 2-year course in the DOSMD studies suggested that such individuals had very high risks of premature death (Mojtabai et al. 2001).

Convincing replication of the DOSMD results may require representative cross-national first-episode samples. Such studies are impractical for logistical and economic reasons. However, the DOSMD and other cross-national studies have generated testable predictions. For example, it has also been speculated that familial support, as well as lesser expectations may explain the differences (Waxler 1979). Our novel design enables rapid cross-sectional evaluation of potential familial influences on the measures of interest. The availability of the sibling-control groups in each venue enables comparison of each site internally, circumventing many of the inherent biases in cross-national comparisons.

Some of the cases were diagnosed with schizoaffective disorder, a disorder that may differ from schizophrenia in its course. Even though the proportion of individuals with schizoaffective disorder differed between the US and India sites, the overall results with regard to ASP-SC correlations were similar in both samples. Analysis of the combined sample, however, did not yield significant results (data not shown). Our analyses may have over-estimated the correlation for S-C pairs, who were all concordant for gender in contrast with the affected sib-pairs (ASPs). Separate analysis of gender concordant ASPs did not improve correlation for any of the measures. On the other hand, the randomly selected controls in the S-C pairs may not be as close in age as the ASPs. As age is an important covariate for some of the measures, our design is likely to over-estimate differences in correlation among ASP versus S-C pairs. No significant correlation for age of onset of psychosis was detected among the US or the Indian ASP samples, unlike prior reports (Kendler et al. 1997). This may reflect different definitions for age of onset, or the relatively small sample in our study.

The present analyses have some limitations. The patients were recruited from a range of facilities selected to represent the available treatment facilities, but selection bias can not be excluded. Data were also unavailable for some items. Such bias may account for some of the differences (Table 1). Other differences, such as the greater likelihood for the Indian patients to live together and higher rates of marriage reflect important cultural and economical differences between these sites. On the other hand, as the samples were not selected with regard to specific course or severity, bias towards selection of patients with a particular profile is unlikely. Hence the differences in the longitudinal course and patterns of severity are of interest. The Indian patients were more likely to report episodic illness, with greater likelihood of inter-episode resolution, as well as lower ratings for deterioration. The later age at onset among the Indian cases is consistent with the more favorable course. The higher rates of reported suicide attempts in the US sample may also reflect the greater likelihood of chronicity and social isolation. These differences are consistent with the patterns reported in the earlier studies. However, the more severe Global Assessment Scale (GAS) ratings in the Indian sample are inconsistent with the other comparisons and are difficult to explain. As the GAS ratings evaluate function as well as symptom severity, they may be influenced by the local social context.

To sum up, suggestive but inconclusive evidence for familial influences on indices of course and outcome were detected in two independent samples. Our analyses do not support greater familial influences on these indices among Indian ASPs compared with US ASPs, as would be predicted by prior studies. Further analyses, using larger samples are warranted in order to evaluate these trends.

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