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Stratifying empiric risk of schizophrenia among first degree relatives using multiple predictors in two independent Indian samples

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ABSTRACT

Background: Schizophrenia (SZ) has an estimated heritability of 64–88%, with the higher values based on twin studies. Conventionally, family history of psychosis is the best individual-level predictor of risk, but reliable risk estimates are unavailable for Indian populations. Genetic, environmental, and epigenetic factors are equally important and should be considered when predicting risk in 'at risk' individuals.
Objective: To estimate risk based on an Indian schizophrenia participant's family history combined with selected demographic factors.
Methods: To incorporate variables in addition to family history, and to stratify risk, we constructed a regression equation that included demographic variables in addition to family history. The equation was tested in two independent Indian samples: (i) an initial sample of SZ participants (N = 128) with one sibling or offspring; (ii) a second, independent sample consisting of multiply affected families (N = 138 families, with two or more sibs/offspring affected with SZ).
Results: The overall estimated risk was 4.31 ± 0.27 (mean ± standard deviation). There were 19 (14.8%) individuals in the high risk group, 75 (58.6%) in the moderate risk and 34 (26.6%) in the above average risk (in Sample A). In the validation sample, risks were distributed as: high (45%), moderate (38%) and above average (17%). Consistent risk estimates were obtained from both samples using the regression equation.
Conclusions: Familial risk can be combined with demographic factors to estimate risk for SZ in India. If replicated, the proposed stratification of risk may be easier and more realistic for family members.

1. Introduction

Aggregation of schizophrenia in families was studied extensively by twin and adoption studies through which genetic basis of schizophrenia came to be accepted (Gottesman et al., 1987; Sullivan et al., 2003). The mechanism of inheritance is not clear (Tandon et al., 2008). Thus the family members of schizophrenia

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patients are at risk for the disorder, depending, to some extent, upon the type of relationship to a proband.

Empiric risks are derived from the observed frequencies of the condition of interest in relatives of a person who has the condition (Henquet et al., 2005; Krabbendam and van Os, 2005). Empiric risks for SZ using only family history for assessing risk are available (Kendler and Zerbin-Rudin, 1996; Niemi et al., 2004; Austin and Peay, 2006), but very few considered other biological and environmental factors. Moreover, most reliable risk estimates stem from studies of Caucasian samples. How these genetic and environmental risk factors interact for predicting risk in a particular individual is uncertain (Cougnard et al., 2007), but empiric risk for SZ is well established and risk charts are available as a rough guide to genetic counselors (Gottesman, 1991). In a Danish national register study, the heritability of liability of developing schizophrenia was estimated at 0.67 (95% confidence interval (CI) 0.64–0.71) (Wray and Gottesman, 2012). The risk for SZ among first-degree relatives ranged from 6% to 13% and for second-degree relatives from 2 to 4% (Bassett et al., 2009). In a review of family studies, McGue et al. used a multifactorial threshold model to estimate that the averaged recurrence risk for confirmed plus probable diagnoses of SZ in relatives was 12.84% for offspring and 3.46% for nieces and nephews (McGue et al., 1983).

Several authors reported simple behavioral interviews for prediction among high risk populations (Johnstone et al., 2005), incorporating neurobehavioral, structural, physiological, and neurochemical brain alterations (Keshavan et al., 2004; Tandon et al., 2012), as well as cannabis use as risk factors for developing psychosis (Dragt et al., 2010), and studying them for prevention of psychosis (Fusar-Poli et al., 2013). Shah et al. developed a formula to predict schizophrenia using familial, neurobiological, socio-environmental, cognitive and clinical data (Shah et al., 2012).

Familial risk for SZ may be modified by exposure to environmental factors such as urban living, minority status, immigration,cannabis use, season of birth, low birth weight, prenatal exposure to certain infectious agents or to trauma (Golimbet et al., 2004; Henquet et al., 2005; Krabbendam and van Os, 2005; van Os et al., 2005a,b; Veling et al., 2008; Spauwen et al., 2004). Environmental risks for psychosis may act additively in vulnerable subjects (Cougnard et al., 2007) and as a function of severity of the Index patient's (IP's) illness (Gottesman et al., 1976), the latter estimated as total length of hospitalization and outcome on follow up (Gottesman and Shields, 1966). IP is associated with increased risk among blood relatives, presumably because the overall familial risk affects both variables (Valles et al., 2000).

Older paternal age at conception of the IP has been associated with an approximate doubling of the risk for developing SZ (Wohl and Gorwood, 2007), but the rationale is uncertain. Age (risk period for SZ ranges between 15 and 55 years) – (Gottesman and Erlenmeyer-Kimling, 2001; Hafner, 2000; Hodgkinson et al., 2001), and sex (males are at 1.4 fold greater risk of SZ than females) – (McGrath et al., 2004; Selten et al., 2003) are also factors that can modify risk, e.g., a greater lifetime risk of SZ was estimated in the relatives of female than those of male patients (Goldstein et al., 1992). There is an association between urban birth, upbringing (up to the age of 15) and an increased risk of developing SZ (Kirkbride et al., 2006; Lewis et al., 1992; Mortensen et al., 1999; McGuffin and Gottesman, 1999), but the cause for the increased risk is uncertain.

Multiple psychiatric illnesses in a single family or from both paternal and maternal lineage make risk calculation more complex (Gottesman and Shields, 1976). Risk may be expressed as probability and numbers, but individuals at all levels of education experience difficulty in understanding probability and data (Kendler and Zerbin-Rudin, 1996) particularly when presented numerically (Hallowell and Richards, 1997). In view of these problems, it has been suggested that numerical information should be replaced with simple verbal categorization of risk (i.e. high, moderate or above average risk) (Gottesman and Bertelsen, 1996). Klaning et al. (2016) repeated the original twin studies in Danish population using ICD-10 diagnostic criteria and reported increased heritability and less variance attributable to environmental factors but their sample size was relatively smaller (Klaning et al., 2016). Concerns and anxiety of relatives of patients with SZ were reduced with genetic counseling that utilized available empiric risk estimates (Costain and Bassett, 2012). Stratifying risk categorically while incorporating familial and environmental risk factors should make risk more understandable. Individuals considered at high risk can be offered more intensive education to inform their decisions towards disease prevention. In addition, this can help in following up high risk individuals and ascertain which risk factors provide more predictive power (Keshavan et al., 2004). Eventually, more nuanced conversations can be held and specific issues addressed, as desired.

There are no familial risk studies in India but there is evidence that the prevalence and incidence of schizophrenia is similar across the world (Ayesa-Arriola et al., 2013); risk factors are also similar, except for contributions from infectious agents. The present study was designed to stratify the risk of schizophrenia for first degree relatives of an index patient (IP) into above average, moderate and high risk categories to make it easier for family members to understand their risk for SZ in a less abstract fashion. To do so, we applied the risk stratification process described by Scheuner and Yoon (Scheuner et al., 2004; Kendler and Zerbin-Rudin, 1996), endorsed by the US Surgeon General for stratification of risk for complex diseases (Yoon et al., 2003). We evaluated our risk analysis scheme in two samples. The first sample was clinic based, prospectively recruited and included singly affected and multiply affected families. The second, independent sample for validation comprised multiply affected families recruited in previous research studies. We predicted that if our risk prediction equations were valid, members of the second sample would be estimated to have moderate or high risk values since two or members had already been affected.

2. Methods

2.1. Sample

2.1.1. Sample A (n = 144)

Participants were recruited from Dr. Ram Manohar Lohia Hospital (RMLH), New Delhi, India. Dr.R.M.L. Hospital is a combined primary, secondary and tertiary care hospital. Thus, patients with all levels of severity can seek treatment directly. Only a relatively small number of patients are referred by other departments. Thus, RML is essentially a General Hospital Psychiatry Unit, a variety of patients seek treatment from all over Delhi and indeed, North India.

Each consecutively registered patient diagnosed with SZ in the Psychiatry Outpatient Department was referred to the research staff by their treating physician following discussions between the physician and the patient. Participation was voluntary and required written informed consent. IPs diagnosed with SZ using DSM-IV-TR criteria (and no history of substance abuse, mental retardation or neurological illness, with or without family history of SZ) and at least one healthy sibling or offspring (18–60 years of age) were eligible for inclusion. The study was approved by the Institutional Ethics Committee of PGIMER-Dr R.M.L. Hospital.

2.1.2. Sample B (retrospective) (n = 138)

Families with two affected children, or a parent and offspring 'duo' affected with SZ who had participated in our earlier studies, where complete family pedigrees were available, were included