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Sex-specific rates of transmission of psychosis in the New England high-risk family study

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ABSTRACT

Recent molecular genetic studies have demonstrated X-chromosome abnormalities in the transmission of psychosis, a finding that may contribute to understanding sex differences in the disorder. Using our family high risk paradigm, we tested the hypothesis that there are sex-specific patterns of transmission of psychosis and whether there is specificity comparing nonaffective- with affective-type psychoses. We identified 159 parents with psychoses (schizophrenia psychosis spectrum disorders (SPS, n = 59) and affective (AP, n = 100)) and 114 comparable, healthy control parents. 203 high risk (HR) and 147 control offspring were diagnostically assessed (185 females; 165 males). We compared the proportion of male:female offspring with psychoses by affected parent sex and the consistency for SPS compared to AP parents, and tested (using exact logistic regression) whether the male:female ratio for affected offspring differed significantly between affected mothers and affected fathers. Risk of psychosis in offspring was a function of the sex of the parent and offspring. Among ill mothers, 18.8% of their male offspring developed psychosis compared with 9.5% of their daughters. In contrast, among ill fathers, 3.1% of their male offspring developed psychosis compared with 15.2% of their daughters. The male: female ratio for affected offspring differed significantly ($p<0.05$) between affected mothers and fathers. Similar patterns held for SPS and AP. Results demonstrated sex-specific transmission of psychosis regardless of psychosis-type and suggest X-linked inheritance. This has important implications for molecular genetic studies of psychoses underscoring the impact of one's gender on gene–brain–behavior phenotypes of SCZ.

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1. Introduction

Relative risk estimate for schizophrenia in first-degree relatives of persons with schizophrenia (SCZ) is ~10% (Gottesman, 1994), with a high schizophrenia (SCZ) heritability estimate of 80–85% (Cardno and Gottesman, 2000). Recent genomic studies have implicated a small number of SCZ susceptibility genes, including major histocompatibility complex (MHC) locus (Stefansson et al., 2009; Shi et al., 2009) and copy number variations (Sebat et al., 2009; Bassett et al., 2010) although not consistently (Craddock et al., 2010), and suggest that small effect genes act in aggregate to account for ≥one-third of SCZ liability (International Schizophrenia Consortium et al., 2009).

It was generally accepted that elevated risk among relatives did not vary by proband's gender. This was challenged by our group and others demonstrating that the risk was associated with proband or relative gender (Bellodi et al., 1986; Pulver et al., 1990; Goldstein et al., 1990). Another line of thinking hypothesized that a gene for psychosis was located on the sex chromosomes (DeLisi and Crow, 1989), based in part on the high rates of psychosis and schizophrenia traits in individuals with X chromosome anomalies (Boks et al., 2007; DeLisi et al., 2005; van Rijn et al., 2006; Roser and Kawohl, 2008). However, linkage studies investigating X chromosome reported weak evidence on Xp11, Xq21, and Xq26 (Paterson, 1999), and a consensus

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review report on X chromosome (Paterson, 1999) and a large sibling pair cohort study (DeLisi et al., 2000) reported overall negative evidence for X linkage with SCZ. Thus investigators have been less likely to pursue this hypothesis even though there has been recent molecular genetic evidence that there may be an X-chromosome contribution to understanding schizophrenia (Philibert et al., 2007; Carrera et al., 2009; Wei and Hemmings, 2006; Crow, 2008). Reasons for discrepancies across studies include: false-positive results, small sample sizes with insufficient statistical power to identify a locus, genetic and clinical heterogeneity of samples, and statistical methods unable to take into account the complexity of gene–gene or gene–environment transmission (Szatmari et al., 1998; Porteous et al., 2003; Alaerts and Del-Favero, 2009; Bearden et al., 2004).

Thus, in a recently completed high-risk (HR) study, we tested the hypothesis that there are sex differences in the risk for psychoses among adult offspring of parents with psychoses. Specifically, if there was evidence of X chromosome transmission, we predicted that fathers with psychoses would be more likely to produce daughters with psychoses than sons, given that fathers do not transmit an X chromosome to sons, and mothers with psychoses would be more likely to give birth to affected sons than daughters, given that only mothers transmit the X chromosome to sons. Given the previous literature, we further predicted that this sex-specific pattern would be consistent for schizophrenia spectrum psychotic disorders and for affective psychoses (e.g., bipolar disorder with psychosis).

2. Experimental/materials and methods

2.1. Sample ascertainment

The background for the study has been described previously (Goldstein et al., 2010). Briefly, the study sample originates from the Boston and Providence cohorts of the Collaborative Perinatal Project (CPP), also known as the New England Family Study (NEFS). The CPP includes 17741 individuals born to a community sample of 13464 women whose pregnancies were studied between 1959 and 1966 (Niswander and Gordon, 1972). We followed a subsample of the NEFS cohort for a study of families at HR for psychosis (Goldstein et al., 2010) (Buka et al., manuscript in preparation). The goal of this study was to ascertain approximately 200 of the original mothers and fathers (Generation 1: G1) who had psychoses, half with SCZ and half with affective psychoses, and a comparable group of unaffected parents and all of their CPP adult offspring (Generation 2: G2). Of 26928 G1 parents, 859 with a history of psychiatric treatment were identified through prior record review and record linkage with private and public psychiatric treatment facilities, out of which 755 were eligible for follow-up. Unaffected parents were selected to be comparable to affected parents based on number of offspring enrolled in the CPP, insurance status (public or private), parent's age, ethnicity (Caucasian or other), study site, and G2 offspring's age, sex, and history of chronic hypoxia (given that we wanted to test for the interaction of parent diagnosis and hypoxia). Eligible comparison parents included all CPP members who were not identified as potential psychotic parents and whose original records did not indicate a history of psychiatric treatment. Unaffected parents did not have spouses, parents, or siblings with psychoses, recurrent MDD, suicide, or psychiatric hospitalizations.

Located subjects were invited to participate in a two-part diagnostic interview including screening and the Structured Clinical Interview for Diagnosis (First et al., 1996) to assess DSM-IV Axis I diagnoses. Medical records were obtained with subject consent. Family history of psychiatric disorders was evaluated using the Family Interview for Genetic Studies (Maxwell, 1996). Expert diagnosticians (J.G., L.S. and June Wolf, Ph.D.) reviewed all information collected from interviews and medical records, if available, to determine final best estimate diagnoses.

Of the 755 eligible parents, 212 were confirmed DSM-IV psychotic disorders, including 153 (72%) mothers and 59 (27%) fathers. Based on past literature (Faraone and Tsuang, 1985; Kendler et al., 1985; Gottesman, 1991), parents with SCZ, schizoaffective disorder depressed type, delusional disorder, brief psychosis, schizophreniform, and psychosis NOS were classified into one higher order group (schizophrenia psychosis spectrum disorders, subsequently referred to as SPS), and schizoaffective disorder bipolar type, bipolar disorders with psychosis, and major depressive disorder (MDD) with psychosis were classified into a second group (affective psychoses, subsequently referred to as AP). We identified a matched sample of 219 potential comparison G1s, of which 132 were included in the final sample of unaffected controls, given exclusions.

The 212 parents with psychoses and 132 healthy control parents had 467 pregnancies: 167 offspring among APs, 114 offspring among SPS and 186 offspring among healthy controls (Goldstein et al., 2010). Among these 467 pregnancies, we successfully diagnosed 350 G2 offspring (mean age = 36.8 years (SD = 2.9)), reflecting a completed diagnostic rate of 78.7%. Diagnostic procedures for adult offspring were similar to parent procedures and blind to parent diagnosis. The 273 parents of the 350 offspring consisted of: 114 healthy comparison parents (12 fathers and 102 mothers) and 159 parents with psychosis (49 fathers and 110 mothers). There were 59 parents with SPS disorders and 100 parents with AP. Among 350 offspring, 28 (8%, 14 males and 14 females) developed psychosis in adulthood (n = 12 SPS; n = 16 AP). Human subject approval was granted by all institutions involved. Written consent was obtained and subjects compensated for participation.

2.2. Statistical analyses

Data analyses examined rates of psychopathology for male and female G2 offspring in relation to the parent's sex and diagnostic status (SPS and AP; and any psychosis (SPS and AP)). The unaffected parent group included G1s who neither had Axis I diagnoses nor Axis II disorders genetically related to psychoses (e.g., schizotypal personality disorder). This resulted in four parental clinical categories (i.e., Psychosis, SPS, AP, and healthy controls) and two parental genders. For each of these, we calculated the total number of G2 offspring ascertained, number of male and female G2 offspring, and rates of psychopathology. We compared the proportion of male and female offspring with psychoses among mothers and fathers with psychoses. Using an exact logistic regression model, we tested an interaction effect for the sex of offspring by the sex of parent, predicting that the ratio of male:female offspring with psychoses among mothers with psychoses would be higher compared with the ratio of male:female offspring among fathers with psychoses. We tested the specificity by calculating rates of affected male and female offspring among mothers and fathers with SPS and AP.

Potential confounders were: ethnicity, maternal education; parental socioeconomic status (SES); number of people in household; marital status; maternal and paternal age; and prior pregnancies. SES was a composite index of family income, education, and occupation (Myrianthopoulos and French, 1968) and ranged from 0.0 (low) to 9.5 (high).

3. Results

Table 1 shows the parental demographic characteristics. Parents with psychoses were comparable to healthy controls on all measures, except marital status, with ~5% more healthy control parents married than case parents. Average maternal age with psychosis was 25.7 years (s.e. = 0.5) compared to 26.8 years (s.e. = 0.6) for healthy controls. Mothers with psychosis had approximately 11 years of education and were living at mid-level SES at the time of their index pregnancy. Paternal age and housing density were similar among

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