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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-

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Conflict of Interest:

Drs. Goldstein, Cherkerzian, Seidman, Petryshen, Fitzmaurice, Tsuang, and Buka report no biomedical financial interests or potential conflicts of interest.

Contributors:

Drs. Goldstein, Buka, Seidman and Tsuang designed the study. Dr. Cherkerzian managed the literature search. Statistical analyses were managed by Drs. Cherkerzian and Fitzmaurice. Dr. Goldstein oversaw the writing of the manuscript, and all authors contributed to and have approved the final manuscript.

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 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.

Keywords

schizophrenia; psychosis; genetic transmission; sex differences; high risk; X-linked inheritance

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 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 genetics 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 were 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 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 17 741 individuals born to a community sample of 13 464 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 26 928 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, 102 mothers) and 159 parents with psychosis (49 fathers, 110 mothers). There were 59 parents with SPS disorders and 100 parents with AP. Among 350 offspring, 28 (8%, 14 males, 14 females) developed psychosis in adulthood (n=12 SPS; n=16 AP). Human subjects 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 sex of offspring by 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. = 0.4) 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 parents with psychosis and healthy controls. Parental measures did not differ by sex of parent, except for marital status for which fathers compared to mothers with psychosis were significantly more likely to be married (95.9% v. 82.7%, χ^2_1 , $p=0.03$).

Among the 203 offspring of parents with psychosis, 12.3% (n = 25) developed psychosis. The rate of psychosis was highly comparable between the 96 male offspring (13.5%) and 107 female offspring (11.2%) of parents with any psychosis. As expected, rates were significantly higher than those of offspring of unaffected controls, where 2% of the 147 unaffected offspring developed psychoses. Taking into consideration the sex of the affected parent only, there were modest differences in the proportion of affected offspring. For fathers with psychosis, 9.2% of their 65 offspring developed psychosis compared to 13.8% of the 138 offspring of affected mothers (see Table 2).

When rates of offspring psychoses were stratified by parent *and* offspring gender, a sex-specific pattern of transmission emerged. Among mothers with psychosis, 18.8% (12/64) of their sons developed psychosis compared with 9.5% (7/74) of their daughters (m:f ratio = 2.0). Among fathers with psychosis, following a pattern opposite that found among the mothers with psychosis, 3.1% (1/32) of their sons developed psychosis compared with 15.2% (21/33) of their daughters (m:f ratio = 0.2). Using an exact logistic regression model to test for the difference in the ratios of male:female offspring among affected mothers versus fathers, results showed that the ratio of male:female offspring of mothers with psychosis was significantly greater than that among offspring of fathers with psychosis (respectively, 2.0 vs. 0.2, $p < 0.05$).

The difference in sex-specific transmission of psychosis in offspring was consistent when parents were separated into AP and SPS disorders. Among mothers with AP, 19.5% (8/41) of their sons developed psychosis, whereas only 8.9% (5/56) of their daughters developed psychosis. In contrast, among fathers with AP, 0% (0/15) of their sons developed psychosis compared with 25.0% (5/20) of their daughters. Similar to that found among mothers with psychosis, the ratio of male:female offspring with psychosis among mothers with AP was significantly greater than that found among fathers with AP ($p=.02$). Among mothers with SPS, 17.4% (4/23) of their sons developed psychosis and 11.1% (2/18) of their daughters developed psychosis. Among fathers with SPS, there was only one child who developed psychosis, and therefore the data were too sparse to make any formal comparison of transmission through mothers or fathers with SPS.

Finally, when we included non-psychotic spectrum disorders in the schizophrenia and affective psychoses spectrum (e.g., schizotypal personality disorder for schizophrenia spectrum and bipolar without psychosis and recurrent major depression in the affective spectrum), the pattern of sex-specific transmission was substantially attenuated and not significant, suggesting specificity of this sex-specific pattern was for psychosis. (Data are available on request).

4. Discussion

Consistent with prior literature, this study found elevated rates of psychosis among offspring of affected parents generally comparable for males and females, when parent gender was not taken into consideration. However, we also demonstrated a sex-specific pattern of transmission when parent gender *and* offspring gender were considered. The rate of psychosis among sons of mothers with psychosis was substantially higher (18.8%) than among the daughters of these women (9.5%). In contrast, the rate of psychosis in daughters was higher when the father was affected (15.2%) compared with that among the sons of these fathers (3.1%). Findings demonstrated a significant difference in the male:female ratio of ill offspring among ill mothers versus ill fathers. Similar patterns were observed when analyses were restricted to SPS or AP, suggesting non-specificity of the sex-dependent risk for type of psychosis, although we had insufficient power to fully test this formally. In addition, inclusion of non-psychotic spectrum disorders attenuated the sex-specific transmission pattern, suggesting specificity of the sex-dependent effect for risk of *psychosis* and not spectrum disorders per se.

This observed pattern of transmission is, in part, suggestive of X-linked inheritance. As XY males receive their Y chromosomes from fathers, a psychosis risk variant on the X chromosome would never be transmitted from affected fathers to sons. In our sample, only one son of a father with psychosis developed the disease, resulting in prevalence similar to control parent rates and to baseline occurrence of psychosis in the general population. In contrast, an X-linked risk variant would be transmitted from affected XX mothers to 50% of

sons on average, assuming each maternal X chromosome has equal chance of transmission. As the psychosis rate in sons of affected mothers was ~19% instead of 50%, the putative X-linked risk variant appears to have reduced penetrance, most likely due to other genetic, epigenetic, and environmental factors contributing to the development of psychosis.

The approximately 2:1 ratio of the risk of psychosis in daughters of affected fathers versus mothers also suggests X-linked inheritance, since an X-linked risk variant would be transmitted from affected XY fathers to all daughters, but to only 50% of daughters of affected mothers (i.e., our data showed: 15.2% versus 9.5% psychosis in daughters of fathers versus mothers with psychosis; Table 2). However, the risk of psychosis in daughters of affected fathers was lower than the expected 100% if the putative risk variant was sufficient for the development of psychosis or a 50% rate if it acted in a recessive manner. This suggests reduced penetrance or multifactorial effects, or X inactivation of the risk chromosome may decrease susceptibility in females, which was previously suggested for psychosis (Crow, 2007) and bipolar disorder (Rosa et al., 2008). Lower penetrance in females compared to males was indicated by the lower proportion of psychosis in daughters compared to sons of affected mothers (9.5% versus 18.8%). Since both sexes have an equal chance of receiving the putative mutant X chromosome from affected mothers, the disparity in psychosis risk suggests sex-dependent disease penetrance.

Our findings seem to suggest that an X-linked variant with a relatively large effect influences risk of psychosis. However, linkage and association studies have not identified a large-effect gene on the X chromosome, thus studies may have been underpowered due to incomplete penetrance, small sample sizes, insufficient numbers of affected parents, or allelic heterogeneity. Alternatively, the relevant variation may be epigenetic and thereby undetectable by conventional linkage and association analyses. Epigenetic regulation is gaining increasing attention as an important factor in the etiology of psychosis (Pidsley and Mill, 2011).

An alternative explanation for the observed findings could conceivably be due to differential attrition related to both parent and offspring gender. For example, the low prevalence of psychosis among male offspring of affected fathers might have occurred due to a high level of attrition of affected offspring of this type. However, participation rates according to parent and offspring gender were generally quite uniform, ranging from 70% to 90%, with no evidence of a pattern of higher attrition due to gender of the parent or offspring.

The primary limitation of this study is the small sample size when separated by sex of parent and offspring. Thus, it is possible that the observed rates of psychosis are indicative of sex-dependent transmission, and specifically X-linked inheritance, by chance. However, while these findings clearly require replication, we had an a priori hypothesis (and thus we were not “fishing” for significant findings), and the results show a sex-specific pattern that is consistent even though we had low power to reach significance in some of the tests. The 1945 study of a large sample of familial pairs by Penrose (Penrose, 1991) suggested increased frequency of psychosis in mother-son pairs compared with father-son pairs, although mother-son transmission was only higher in affective psychoses and not in schizophrenia. However, the early definitions of “schizophrenia” and “affective” categories were very heterogeneous compared with current criteria, thus most likely contributing to differences between our findings and those of Penrose when applied to schizophrenia per se. In fact, when examined by psychosis in general, their findings were consistent with ours.

Recent molecular genetic studies have further implicated X chromosome loci in the risk for psychosis and schizophrenia, specifically. For example, male-specific association with SCZ has been reported for haplotypes of the MAOB gene on Xp11.23 (Carrera et al., 2009), and

association between a MAOB polymorphism and psychotic disorders (Bergen et al., 2009). Furthermore, the SYP/CACNA1F locus in the Xp11 region (Wei and Hemmings, 2006), the GPR50 gene at Xq28 (Thomson et al., 2005), and the HOPA gene at Xq13 (Philibert et al., 2001; Sandhu et al., 2003; Philibert et al., 2007) have been associated with schizophrenia or psychosis in general. In addition, the protocadherin 11 X-linked (PCDH11X) gene has been proposed in the etiology of psychosis (Crow, 2008). Further, the distal long arm (q) of the X chromosome has been linked to schizophrenia spectrum diagnoses in females with Fragile X syndrome (Reiss et al., 1988), juvenile-onset mood disorders (Wigg et al., 2009), bipolar and related affective disorders, such as schizoaffective bipolar disorder (Del Zompo et al., 1984; Zandi et al., 2003; Mendlewicz et al., 1980; Baron et al., 1987), suggesting that polymorphisms in this region of the X chromosome may be associated with psychosis in general rather than specific to schizophrenia. Interestingly, rare variants in microRNA genes, which negatively regulate gene expression, located on the X chromosome were implicated in SCZ risk (Feng et al., 2009). Of possible further relevance to our data is the finding that a missense mutation in the Xq28 gene methyl-CpG binding-protein 2 (MECP2), which epigenetically regulates transcription via binding methylated DNA, is responsible for PPM-X syndrome, a male-specific X-linked mental retardation syndrome with psychosis, pyramidal signs, and macro-orchidism (Klauck et al., 2002). These recent molecular genetic studies are consistent with the findings in our high risk study that the X-chromosome is implicated in the development of psychosis and may contribute to understanding sex differences in schizophrenia.

In fact, partial or full X chromosome monosomies in Turner's syndrome (Ross et al., 2000; Murphy et al., 1997; Haberecht et al., 2001) have been associated with cognitive deficits, such as memory, spatial working memory, language ability, and attention, functions in which sex differences in schizophrenia have been reported (Goldstein et al., 1998). Further, structural brain abnormalities and brain activity deficits in hippocampus, amygdala, orbitofrontal cortex, have also been reported in Turner's syndrome (e.g., (Murphy et al., 1997; Haberecht et al., 2001; Molko et al., 2004)), i.e., brain regions that are "normally sexually dimorphic" (Goldstein et al., 2001; Ross et al., 2000), and for which we and others have previously demonstrated sex differences in brain volumes in schizophrenia (Goldstein et al., 2002; Gur et al., 2004; Elsabagh et al., 2009; Abbs et al., 2010 - resubmitted). In addition, sex chromosome dosage related to cerebral asymmetry in Turner's and Klinefelter's syndromes suggesting relevance to the genetic basis of psychosis (Rezaie et al., 2009)). Furthermore, Weickert and colleagues (Weickert et al., 2009) reported specific genes on the sex chromosomes that influenced the development of prefrontal cortex in a sex-specific manner, a key brain region contributing to schizophrenia pathology. These findings thus provide some evidence that sex-specific transmission of psychosis related to the sex chromosomes has functional relevance for understanding sex differences in the neurobiology of schizophrenia and potentially other psychoses.

Future work in our high risk study includes molecular genetic work in these families. One of the advantages of this high risk study is that offspring were followed from the maternal pregnancy and offspring birth until age 48 years and includes prenatal stored sera. Therefore, we have a unique opportunity to investigate genetic variation in the context of potential prenatal environmental insults and childhood developmental pathways, thus contributing to understanding potential gene-environment interactions in explaining sex differences in psychoses.

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References

- Abbs B, Liang L, Makris N, Tsuang MT, Seidman LJ, Goldstein JM. Covariance modeling of MRI brain volumes in memory circuitry in schizophrenia. Sex differences are critical. 2010 resubmitted.
- Alaerts M, Del-Favero J. Searching genetic risk factors for schizophrenia and bipolar disorder: Learn from the past and back to the future. *Hum. Mutat.* 2009; 30:1139–1152. [PubMed: 19626716]
- Baron M, Risch N, Hamburger R, Mandel B, Kushner S, Newman M, Drumer D, Belmaker RH. Genetic linkage between X-chromosome markers and bipolar affective illness. *Nature.* 1987; 326:289–292. [PubMed: 3493438]
- Bassett AS, Scherer SW, Brzustowicz LM. Copy number variations in schizophrenia: critical review and new perspectives on concepts of genetics and disease. *Am. J. Psychiatry.* 2010; 167:899–914. [PubMed: 20439386]
- Bearden C, Reus V, Freimer N. Why genetic investigation of psychiatric disorders is so difficult. *Curr. Opin. Genet. Dev.* 2004; 14:280–286. [PubMed: 15172671]
- Bellodi L, Bussoleni C, Scorza-Smeraldi R, Grassi G, Zacchetti L, Smeraldi E. Family study of schizophrenia: exploratory analysis for relevant factors. *Schizophr. Bull.* 1986; 12:120–128. [PubMed: 3485816]
- Bergen SE, Fanous AH, Walsh D, O'Neill FA, Kendler KS. Polymorphisms in SLC6A4, PAH, GABRB3, and MAOB and modification of psychotic disorder features. *Schizophr. Res.* 2009; 109:94–97. [PubMed: 19268543]
- Boks MP, de Vette MH, Sommer IE, van Rijn S, Giltay JC, Swaab H, Kahn R. Psychiatric morbidity and X-chromosomal origin in Klinefelter sample. *Schizophr. Res.* 2007; 93:399–402. [PubMed: 17459660]
- Cardno A, Gottesman I. Twin studies of schizophrenia: from bow-and-arrow concordances to star wars Mx and functional genomics. *Am. J. Med. Genet. C Semin. Med. Genet.* 2000; 97:12–17.
- Carrera N, Sanjuan J, Molto MD, Carracedo A, Costas J. Recent adaptive selection at MAOB and ancestral susceptibility to schizophrenia. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 2009; 150B:369–374. [PubMed: 18553363]
- Craddock N, Hurles ME, Cardin N, Pearson RD, Plagnol V, Robson S, Vukcevic D, Barnes C, Conrad DF, Giannoulatos E, Holmes C, Marchini JL, Stirrups K, Tobin MD, Wain LV, Yau C, Aerts J, Ahmad T, Andrews TD, Arbury H, Attwood A, Auton A, Ball SG, Balmforth AJ, Barrett JC, Barroso I, Barton A, Bennett AJ, Bhaskar S, Blaszczyk K, Bowes J, Brand OJ, Braund PS, Bredin F, Breen G, Brown MJ, Bruce IN, Bull J, Burren OS, Burton J, Byrnes J, Caesar S, Clee CM, Coffey AJ, Connell JM, Cooper JD, Dominiczak AF, Downes K, Drummond HE, Dudakia D, Dunham A, Ebbs B, Eccles D, Edkins S, Edwards C, Elliot A, Emery P, Evans DM, Evans G, Eyre S, Farmer A, Ferrier IN, Feuk L, Fitzgerald T, Flynn E, Forbes A, Forty L, Franklyn JA, Freathy RM, Gibbs P, Gilbert P, Gokumen O, Gordon-Smith K, Gray E, Green E, Groves CJ, Grozeva D, Gwilliam R, Hall A, Hammond N, Hardy M, Harrison P, Hassanali N, Hebaishi H, Hines S, Hinks A, Hitman GA, Hocking L, Howard E, Howard P, Howson JM, Hughes D, Hunt S, Isaacs JD, Jain M, Jewell DP, Johnson T, Jolley JD, Jones IR, Jones LA, Kirov G, Langford CF, Lango-Allen H, Lathrop GM, Lee J, Lee KL, Lees C, Lewis K, Lindgren CM, Maisuria-Armer M, Maller J, Mansfield J, Martin P, Massey DC, McArdle WL, McGuffin P, McLay KE, Mentzer A, Mimmack ML, Morgan AE, Morris AP, Mowat C, Myers S, Newman W, Nimmo ER, O'Donovan MC, Onipinla A, Onyiah I, Ovington NR, Owen MJ, Palin K, Parnell K, Pernet D, Perry JR, Phillips A, Pinto D, Prescott NJ, Prokopenko I, Quail MA, Rafelt S, Rayner NW, Redon R, Reid DM, Renwick, Ring SM, Robertson N, Russell E, St Clair D, Sambrook JG, Sanderson JD,

Schuilenburg H, Scott CE, Scott R, Seal S, Shaw-Hawkins S, Shields BM, Simmonds MJ, Smyth DJ, Somaskantharajah E, Spanova K, Steer S, Stephens J, Stevens HE, Stone MA, Su Z, Symmons DP, Thompson JR, Thomson W, Travers ME, Turnbull C, Valsesia A, Walker M, Walker NM, Wallace C, Warren-Perry M, Watkins NA, Webster J, Weedon MN, Wilson AG, Woodburn M, Wordsworth BP, Young AH, Zeggini E, Carter NP, Frayling TM, Lee C, McVean G, Munroe PB, Palotie A, Sawcer SJ, Scherer SW, Strachan DP, Tyler-Smith C, Brown MA, Burton PR, Caulfield MJ, Compston A, Farrall M, Gough SC, Hall AS, Hattersley AT, Hill AV, Mathew CG, Pembrey M, Satsangi J, Stratton MR, Worthington J, Deloukas P, Duncanson A, Kwiatkowski DP, McCarthy MI, Ouwehand W, Parkes M, Rahman N, Todd JA, Samani NJ, Donnelly P. Genome-wide association study of CNVs in 16,000 cases of eight common diseases and 3,000 shared controls. *Nature*. 2010; 464:713–720. [PubMed: 20360734]

- Crow T. How and why genetic linkage has not solved the problem of psychosis: review and hypothesis. *Am. J. Psychiatry*. 2007; 164:13–21. [PubMed: 17202538]
- Crow TJ. Craddock & Owen vs Kraepelin: 85 years late, mesmerised by “polygenes”. *Schizophr. Res.* 2008; 103:156–160. [PubMed: 18434093]
- Del Zompo M, Bocchetta A, Goldin LR, Corsini GU. Linkage between X-chromosome markers and manic-depressive illness. *Acta Psychiatr. Scand.* 1984; 70:282–287. [PubMed: 6333780]
- DeLisi L, Maurizio A, Svetina C, Ardekani B, Szulc K, Nierenberg J, Leonard J, Harvey P. Klinefelter's syndrome (XXY) as a genetic model for psychotic disorders. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 2005; 135B:15–23. [PubMed: 15729733]
- DeLisi LE, Crow TJ. Evidence for a sex chromosome locus for schizophrenia. *Schizophr. Bull.* 1989; 15:431–440. [PubMed: 2683040]
- DeLisi LE, Shaw S, Sherrington R, Nanthakumar B, Shields G, Smith AB, Wellman N, Larach VW, Loftus J, Razi K, Stewart J, Comazzi M, Vita A, De Hert M, Crow TJ. Failure to establish linkage on the X chromosome in 301 families with schizophrenia or schizoaffective disorder. *Am. J. Med. Genet.* 2000; 96:335–341. [PubMed: 10898911]
- Elsabagh S, Premkumar P, Anilkumar A, Kumari V. A longer duration of schizophrenic illness has sex-specific associations within the working memory neural network in schizophrenia. *Behav. Brain Res.* 2009; 201:41–47. [PubMed: 19428614]
- Faraone SV, Tsuang MT. Quantitative models of the genetic transmission of schizophrenia. *Psychol. Bull.* 1985; 98:41–66. [PubMed: 4034818]
- Feng J, Sun G, Yan J, Noltne K, Li W, Buzin CH, Longmate J, Heston LL, Rossi J, Sommer SS. Evidence for X-chromosomal schizophrenia associated with microRNA alterations. *PLoS ONE*. 2009; 4:e6121. [PubMed: 19568434]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical interview for DSM-IV Axis I Disorders - Patient Edition (SCID -I/P, vers. 2.0). Washington, D.C.: Am Psych Press; 1996.
- Goldstein J, Faraone S, Chen W, Tolomiczenko G, Tsuang M. Sex differences in the familial transmission of schizophrenia. *Br. J. Psychiatry*. 1990; 156:819–826. [PubMed: 2207512]
- Goldstein JM, Buka SL, Seidman LJ, Tsuang MT. Specificity of familial transmission of schizophrenia psychosis spectrum and affective psychoses in the New England family study's high-risk design. *Arch. Gen. Psychiatry*. 2010; 67:458–467. [PubMed: 20439827]
- Goldstein JM, Seidman LJ, Goodman JM, Koren D, Lee H, Weintraub S, Tsuang MT. Are there sex differences in neuropsychological functions among patients with schizophrenia? *Am. J. Psychiatry*. 1998; 155:1358–1364. [PubMed: 9766767]
- Goldstein JM, Seidman LJ, Horton NJ, Makris N, Kennedy DN, Caviness VS Jr, Faraone SV, Tsuang MT. Normal sexual dimorphism of the adult human brain assessed by in vivo magnetic resonance imaging. *Cereb. Cortex*. 2001; 11:490–497. [PubMed: 11375910]
- Goldstein JM, Seidman LJ, O'Brien LM, Horton NJ, Kennedy DN, Makris N, Caviness VS Jr, Faraone SV, Tsuang MT. Impact of normal sexual dimorphisms on sex differences in structural brain abnormalities in schizophrenia assessed by magnetic resonance imaging. *Arch. Gen. Psychiatry*. 2002; 59:154–164. [PubMed: 11825137]
- Gottesman I. Schizophrenia epigenesis: past, present, and future. *Acta Psychiatr. Scand.* 1994; 90:26–33.

- Gottesman, II. Schizophrenia Genesis: The Origins of Madness. New York: W.H. Freeman and Company; 1991.
- Gur R, Kohler C, Turetsky B, Siegel S, Kanes S, Bilker W, Brennan A, Gur R. A sexually dimorphic ratio of orbitofrontal to amygdala volume is altered in schizophrenia. *Biol. Psychiatry*. 2004; 55:512–517. [PubMed: 15023579]
- Haberecht M, Menon V, Warsofsky I, White C, Dyer-Friedman J, Glover G, Neely E, Reiss A. Functional neuroanatomy of visuo-spatial working memory in Turner syndrome. *Hum. Brain Mapp*. 2001; 14:96–107. [PubMed: 11500993]
- Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, Sklar P. International Schizophrenia Consortium. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*. 2009; 460:748–752. [PubMed: 19571811]
- Kendler KS, Masterson CC, Davis KL. Psychiatric illness in first-degree relatives of patients with paranoid psychosis, schizophrenia, and medical illness. *Br. J. Psychiatry*. 1985; 147:524–531. [PubMed: 4075047]
- Klauck S, Lindsay SJ, Beyer K, Splitt M, Burn J, Poustka A. A mutation hot spot for nonspecific X-linked mental retardation in the MECP2 gene causes the PPM-X Syndrome. *Am. J. Hum. Genet*. 2002; 70:1034–1037. [PubMed: 11885030]
- Maxwell, ME. FIGS. Clinical Neurogenetics Branch, Intramural Research Program. Bethesda, MD: NIMH; 1996.
- Mendlewicz J, Linkowski P, Wilmotte J. Linkage between glucose-6-phosphate dehydrogenase deficiency and manic-depressive psychosis. *Br. J. Psychiatry*. 1980; 137:337–342. [PubMed: 7448473]
- Molko N, Cachia A, Riviere D, Mangin J, Bruandet M, LeBihan D, Cohen L, Dehaene S. Brain anatomy in Turner syndrome: evidence for impaired social and spatial-numerical networks. *Cereb. Cortex*. 2004; 14:840–850. [PubMed: 15054057]
- Murphy D, Mentis M, Pietrini P, Grady C, Daly E, Haxby J, De La Granja M, Allen G, Largay K, White B, Powell C, Horwitz B, Rapoport S, Schapiro M. A PET study of Turner's syndrome: effects of sex steroids and the X chromosome on brain. *Biol. Psychiatry*. 1997; 41:285–298. [PubMed: 9024951]
- Myrianthopoulos NC, French KS. An application of the U.S. bureau of the census socioeconomic index to a large diversified patient population. *Soc. Sci. Med*. 1968; 2:283–299. [PubMed: 5760819]
- Niswander, KR.; Gordon, M. The Collaborative Perinatal Study of the National Institute of Neurological Diseases and Stroke: The Women and Their Pregnancies. Washington, D.C.: Government Printing Office, U.S. Department of Health, Education, and Welfare; 1972.
- Paterson AD. Sixth world congress of psychiatric genetics X chromosome workshop. *Am. J. Med. Genet*. 1999; 88:279–286. [PubMed: 10374746]
- Penrose LS. Survey of cases of familial mental illness. L. S. Penrose, July 1945. *Eur. Arch. Psychiatry Clin. Neurosci*. 1991; 240:315–324. [PubMed: 1831662]
- Philibert RA, Bohle P, Secrest D, Deaderick J, Sandhu HK, Crowe RR, Black DW. The association of the HOPA (12bp) polymorphism with schizophrenia in the NIMH Genetics Initiative for Schizophrenia sample. *Am. J. Med. Genet. B Neuropsychiatr. Genet*. 2007; 144B:743–747. [PubMed: 17299734]
- Philibert RA, Sandhu HK, Hutton AM, Wang Z, Arndt S, Andreasen NC, Crowe RR, Wassink TH. Population-based association analyses of the HOPA12bp polymorphism for schizophrenia and hypothyroidism. *Am. J. Med. Genet*. 2001; 105:130–134. [PubMed: 11424983]
- Pidsley R, Mill J. Epigenetic studies of psychosis: Current findings, methodological approaches, and implications for postmortem research. *Biol. Psychiatry*. 2011; 69:146–156. [PubMed: 20510393]
- Porteous DJ, Evans KL, Millar JK, Pickard BS, Thomson PA, James R, MacGregor S, Wray NR, Visscher PM, Muir WJ, Blackwood DH. Genetics of schizophrenia and bipolar affective disorder: Strategies to identify candidate genes Cold Spring Harbor Symp. Quant. Biol. 2003; 68:383–394.
- Pulver AE, Brown CH, Wolyniec P, McGrath J, Tam D, Adler L, Carpenter WT, Childs B. Schizophrenia: age at onset, gender and familial risk. *Acta Psychiatr. Scand*. 1990; 82:344–351. [PubMed: 2281804]

- Reiss AL, Hagerman RJ, Vinogradov S, Abrams M, King RJ. Psychiatric disability in female carriers of the fragile X chromosome. *Arch. Gen. Psychiatry*. 1988; 45:25–30. [PubMed: 3337608]
- Rezaie R, Daly EM, Cutter WJ, Murphy DG, Robertson DM, DeLisi LE, Mackay CE, Barrick TR, Crow TJ, Roberts N. The influence of sex chromosome aneuploidy on brain asymmetry. *Am J Med Genet B Neuropsychiatr Genet*. 2009; 150B:74–85. [PubMed: 18454450]
- Rosa A, Picchioni M, Kalidindi S, Loat C, Knight J, Touloupoulou T, Vonk R, van der Schot A, Nolen W, Kahn R, McGuffin P, Murray R, Craig I. Differential methylation of the X-chromosome is a possible source of discordance for bipolar disorder female monozygotic twins. *Am. J. Med. Genet. B Neuropsychiatr. Genet*. 2008; 147B:459–462. [PubMed: 17955481]
- Roser P, Kawohl W. Turner syndrome and schizophrenia: A further hint for the role of the X-chromosome in the pathogenesis of schizophrenic disorders. *World J. Biol. Psychiatry*. 2008; 11:1–4. [PubMed: 18609442]
- Ross DE, Kirkpatrick B, Karkowski LM, Straub RE, MacLean CJ, O'Neill FA, Compton AD, Murphy B, Walsh D, Kendler KS. Sibling correlation of deficit syndrome in the Irish Study of High-Density Schizophrenia Families. *Am. J. Psychiatry*. 2000; 157:1071–1076. [PubMed: 10873913]
- Sandhu HK, Sarkar M, Turner BM, Wassink T, Philibert RA. Polymorphism analysis of HOPA: A candidate for schizophrenia. *Am. J. Med. Genet. B Neuropsychiatr. Genet*. 2003; 123B:33–38. [PubMed: 14582143]
- Sebat J, Levy DL, McCarthy SE. Rare structural variants in schizophrenia: one disorder, multiple mutations; one mutation, multiple disorders. *Trends Genet*. 2009; 25:528–535. [PubMed: 19883952]
- Shi J, Levinson DF, Duan J, Sanders AR, Zheng Y, Pe'er I, Dudbridge F, Holmans PA, Whittemore AS, Mowry BJ, Olincy A, Amin F, Cloninger CR, Silverman JM, Buccola NG, Byerley WF, Black DW, Crowe RR, Oksenberg JR, Mirel DB, Kendler KS, Freedman R, Gejman PV. Common variants on chromosome 6p22.1 are associated with schizophrenia. *Nature*. 2009; 460:753–757. [PubMed: 19571809]
- Stefansson H, Ophoff R, Steinberg S, Andreassen O, Cichon S, Rujescu D, Werge T, Pietiläinen O, Mors O, Mortensen P, Sigurdsson E, Gustafsson O, Nyegaard M, Tuulio-Henriksson A, Ingason A, Hansen T, Suvisaari J, Lonnqvist J, Paunio T, Børglum A, Hartmann A, Fink-Jensen A, Nordentoft M, Hougaard D, Norgaard-Pedersen B, Böttcher Y, Olesen J, Breuer R, Möller H, Giegling I, Rasmussen H, Timm S, Mattheisen M, Bitter I, Réthelyi J, Magnusdottir B, Sigmundsson T, Olason P, Masson G, Gulcher J, Haraldsson M, Fossdal R, Thorgeirsson T, Thorsteinsdottir U, Ruggeri M, Tosato S, Franke B, Strengman E, Kiemeny L, Genetic Risk and Outcome in Psychosis (GROUP). Melle I, Djurovic S, Abramova L, Kaleda V, Sanjuan J, de Frutos R, Bramon E, Vassos E, Fraser G, Ettinger U, Picchioni M, Walker N, Touloupoulou T, Need A, Ge D, Yoon J, Shianna K, Freimer N, Cantor R, Murray R, Kong A, Golimbet V, Carracedo A, Arango C, Costas J, Jönsson E, Terenius L, Agartz I, Petursson H, Nöthen M, Rietschel M, Matthews P, Muglia P, Peltonen L, St Clair D, Goldstein D, Stefansson K, Collier D. Common variants conferring risk of schizophrenia. *Nature*. 2009; 460:744–747. [PubMed: 19571808]
- Szatmari P, Jones MB, Zwaigenbaum L, MacLean JE. Genetics of autism: Overview and new directions. *J. Autism Dev. Disord*. 1998; 28:351–368. [PubMed: 9813773]
- Thomson PA, Wray NR, Thomson AM, Dunbar DR, Grassie MA, Condie A, Walker MT, Smith DJ, Pulford DJ, Muir W, Blackwood DH, Porteous DJ. Sex-specific association between bipolar affective disorder in women and GPR50, an X-linked orphan G protein-coupled receptor. *Mol. Psychiatry*. 2005; 10:470–478. [PubMed: 15452587]
- van Rijn S, Aleman A, Swaab H, Kahn R. Klinefelter's syndrome (karyotype 47,XXY) and schizophrenia-spectrum pathology. *Br. J. Psychiatry*. 2006; 189:459–460. [PubMed: 17077438]
- Wei J, Hemmings G. A further study of a possible locus for schizophrenia on the X chromosome. *Biochem. Biophys. Res. Commun*. 2006; 344:1241–1245. [PubMed: 16650384]
- Weickert CS, Elashoff M, Richards AB, Sinclair D, Bahn S, Paabo S, Khaitovich P, Webster MJ. Transcriptome analysis of male-female differences in prefrontal cortical development. *Mol. Psychiatry*. 2009; 14:558–561. [PubMed: 19455171]
- Wigg K, Feng Y, Gomez L, Kiss E, Kapornai K, Tamas Z, Mayer LS, JBaji I, Daroczi G, Nbenak I, Osvath VK, Dombovari E, Kaczvinszki E, Besnyo M, Gadoros J, King N, Szekely J, Kovacs M,

- Vetro A, Kennedy JL, Barr CL. Genome scan in sibling pairs with juvenile-onset mood disorders: Evidence for linkage to 13q and Xq. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 2009; 150B: 638–646. [PubMed: 19035515]
- Zandi P, Willour V, Huo Y, Chellis J, Potash J, MacKinnon D, Simpson S, McMahon F, Gershon E, Reich T, Foroud T, Nurnberger JJ, DePaulo JJ, McInnis M. National Institute of Mental Health Genetics Initiative Bipolar Group. Genome scan of a second wave of NIMH genetics initiative bipolar pedigrees: chromosomes 2, 11, 13, 14, and X. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 2003; 119B:69–76. [PubMed: 12707942]

TABLE 1
Demographics of the n = 273 Study Sample G1 parents in the NEFS High Risk Study

Categorical variables	Fathers						Mothers					
	Parents with Psychosis			Healthy Control Parents			G1 Psych			G1 Healthy Control		
	n = 159	n = 114	n = 49	n = 114	n = 49	n = 114	n = 110	n = 102	n = 110	n = 102	n = 110	n = 102
	N	%	N	%	N	%	N	%	N	%	N	%
Race (white)	146	91.8%	106	93.0%	45	91.8%	12	100.0%	101	91.8%	94	92.2%
Married *	138	86.8%	105	92.1%	47	95.9%	12	100.0%	91	82.7%	93	91.2%
Gravida (prior pregnancies)	107	67.3%	83	72.8%	32	65.3%	8	66.7%	75	68.2%	75	73.5%
Continuous and count variables	Fathers						Mothers					
	Parents with Psychosis			Healthy Control Parents			G1 Psych			G1 Healthy Control		
	n = 159	n = 114	n = 49	n = 114	n = 49	n = 114	n = 110	n = 102	n = 110	n = 102	n = 110	n = 102
	Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.
Maternal age (years)	25.7	0.4	26.7	0.6	25.6	0.9	25.6	1.6	25.7	0.5	26.8	0.6
Maternal education (years)	11.0	0.2	11.3	0.3	11.4	0.3	11.1	0.6	10.8	0.2	11.4	0.3
Socioeconomic status	5.6	0.2	5.8	0.2	5.3	0.3	6.3	0.5	5.7	0.2	5.7	0.2
Housing density (log)	0.02	0.04	0.00	0.04	-0.03	0.06	0.11	0.06	0.05	0.06	-0.02	0.04
Paternal age (log years)	3.40	0.02	3.40	0.02	3.37	0.04	3.35	0.06	3.36	0.03	3.37	0.02

* $P < 0.05$, G1 fathers with psychosis were significantly more likely to be married than G1 mothers with psychosis (95.9% v. 82.7%, $P = 0.0310$) No other significant differences were found between groups

TABLE 2
Sex-Specific Transmission of Psychosis: Stratified by Sex of the Parent and Sex of the Offspring^{*}

Parent Psychopathology [†]	All Offspring				Male Offspring Only				Female Offspring Only			
	No. Parents	No. Offspring	Psychosis [‡]	No. Parents	No. Offspring	Psychosis [‡]	No. Parents	No. Offspring	Psychosis [‡]	No. Parents	No. Offspring	Psychosis [‡]
	N	N	%	N	N	%	N	N	%	N	N	%
Healthy Control	114	147	3	2.0%	54	69	1	1.4%	60	78	2	2.6%
Father	12	14	0	0.0%	6	8	0	0.0%	6	6	0	0.0%
Mother	102	133	3	2.3%	48	61	1	1.6%	54	72	2	2.8%
Psychosis	159	203	25	12.3%	79	96	13	13.5%	80	107	12	11.2%
Father	49	65	6	9.2%	26	32	1	3.1%	23	33	5	15.2%
Mother	110	138	19	13.8%	53	64	12	18.8%	57	74	7	9.5%

^{*} Using an exact logistic regression model to test for the difference in the ratios of male:female offspring among affected mothers versus fathers: ratio of male:female offspring of mothers with psychosis was significantly greater than that among offspring of fathers with psychosis (respectively, 2.0 vs. 0.2, $p < 0.05$)

[†] Parent psychopathology. Psychosis includes the following dxs: schizophrenia, schizoaffective depressed, psychosis NOS, delusional dx, brief psychosis, schizophreniform, hx of psychosis NOS, hx of psychosis NOS due to organicity, schizoaffective bipolar, bipolar w/psychosis, major depressive disorder w/psychosis, bipolar w/psychosis, bipolar w/psychosis unknown, hx of MDD with psychosis, hx of bipolar with psychosis. The healthy control group consists of those parents who had no axis I or axis II disorders found to be genetically related to psychoses.

[‡] Offspring psychopathology. Psychosis includes the following dxs: schizophrenia, schizoaffective depressed, psychosis NOS, delusional dx, brief psychosis, schizophreniform, schizoaffective bipolar, bipolar w/psychosis, major depressive disorder w/psychosis, bipolar w/psychosis unknown