

Original Article

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Like father like daughter: sex-specific parent-of-origin effects in the transmission of liability for psychotic symptoms to offspring

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Abstract

Children of parents with major mood and psychotic disorders are at increased risk of psychopathology, including psychotic symptoms. It has been suggested that the risk of psychosis may be more often transmitted from parent to opposite-sex offspring (e.g., from father to daughter) than to same-sex offspring (e.g., from father to son). To test whether sex-specific transmission extends to early manifestations of psychosis, we examined sex-specific contributions to psychotic symptoms among offspring of mothers and fathers with depression, bipolar disorder and schizophrenia. We assessed psychotic symptoms in 309 offspring (160 daughters and 149 sons) aged 8–24 years (mean = 13.1, s.d. = 4.3), of whom 113 had a mother with schizophrenia, bipolar disorder or major depression and 43 had a father with schizophrenia, bipolar disorder or major depression. In semi-structured interviews, 130 (42%) offspring had definite psychotic symptoms established and confirmed by psychiatrists on one or more assessments. We tested the effects of mental illness in parents on same-sex and opposite-sex offspring psychotic symptoms in mixed-effect logistic regression models. Psychotic symptoms were more prevalent among daughters of affected fathers and sons of affected mothers than among offspring of the same sex as their affected parent. Mental illness in the opposite-sex parent increased the odds of psychotic symptoms (odds ratio (OR) = 2.65, 95% confidence interval (CI) 1.43–4.91, $P = 0.002$), but mental illness in the same-sex parent did not have a significant effect on psychotic symptoms in offspring (OR = 1.13, 95% CI 0.61–2.07, $P = 0.697$). The opposite-sex-specific parent-of-origin effects may suggest X chromosome-linked genetic transmission or inherited chromosomal modifications in the etiology of psychotic symptoms.

Introduction

Severe mental illness (SMI), including schizophrenia, bipolar disorder and major depression, runs in families. The familial risks for these major mood and psychotic disorders overlap substantially, and offspring of a parent with SMI are at elevated risk of developing any form of mental illness.^{1,2} Most cases of SMI are preceded by earlier antecedents that are not necessarily specific to a particular diagnosis. For example, psychotic symptoms in children and adolescents are associated with family history of either psychotic or mood disorders,^{3–5} and may predict the development of both schizophrenia and other forms of mental illness.^{6,7} It is desirable to understand the mechanism underlying the transmission of mental illness and its transdiagnostic antecedents to guide molecular genetic research and to inform parents who want to understand the risk for their children.

One line of enquiry into the genetic contribution to SMI risk has focused on the X chromosome and sex-specific patterns of risk transmission. Several studies found that individuals with an abnormal number of X chromosome(s) have higher rates of schizophrenia.^{8–10} Early molecular genetic investigations of SMI either did not identify any X chromosomal associations with illness¹¹ or did not include the X chromosome in the analysis.^{12,13} More recently, a genome-wide mega-analysis identified multiple loci on the X chromosome significantly associated with schizophrenia.^{12,14} In the New England Family Study, psychosis presented more frequently in female offspring when their father, rather than their mother, was affected, and male offspring were more likely to present with psychosis when their mother, rather than their father was unwell.¹⁵ This pattern was consistent across a range of disorders with psychotic features. Because of the nature of X chromosome inheritance (i.e., fathers transmit X chromosomes only to female offspring and males inherit X chromosomes only

from mothers), the authors suggested that this pattern of inheritance was consistent with X chromosome risk transmission. A similar pattern has also been found for mood disorders. In a sample of offspring of parents with major depression, sons of mothers, and daughters of fathers were more likely than offspring of the same sex as the affected parent to become unwell.¹⁶ These convergent findings prompt the examination of parent-of-origin effects in other populations at risk for SMI.

The presence of early, mild manifestations of SMI in childhood and adolescence has been linked to genetic liability for mental illness and predicts the development of SMI.^{4,7,17} These early antecedents, including psychotic symptoms and basic symptoms, occur a number of years before the onset of SMI.^{6,7,18} These antecedents have also been associated with family history of both psychosis⁴ and depression.^{3,5} Because they occur early in development and do not typically come to the attention of health services, these early manifestations are more likely to be direct effects of genetic factors and early development and less likely to be modified by external factors such as drug use and medication. However, sex-specific parent-of-origin effects on psychotic and basic symptoms in children have not been studied. Although we know that offspring of parents with SMI are at increased risk of experiencing antecedents, we do not know whether the sex of the affected parent impacts this risk. In the present study, we tested whether transmission of risk is impacted by the sex of the affected parent and their offspring. Specifically, we hypothesized that the risk of psychotic symptoms among offspring would be higher if their opposite-sex parent is affected by SMI.

Methods

Participants

We investigated the relationship between sex of a biological parent diagnosed with SMI and the presence of psychotic symptoms in a sample of 309 youth (160 females and 149 males) aged 8–24 years, who participated in the Families Overcoming Risks and Building Opportunities for Wellbeing (FORBOW) study.¹⁹ FORBOW is an accelerated cohort study, enriched for familial risk of SMI. We defined SMI as a diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder or major depressive disorder with the presence of at least two out of the following five severity criteria: (1) psychotic symptoms; (2) severity necessitating hospital admission; (3) recurrence with three or more episodes over 10 years; (4) persistence with a minimum 2-year duration of impairing symptoms and (5) a life-threatening suicide attempt. Of the youth included in the present study, 113 were biological offspring (69 daughters and 44 sons) of mothers with SMI and 43 were offspring (24 daughters and 19 sons) of fathers with SMI, and 165 (89 daughters and 76 sons) were control offspring of parents with no SMI (the numbers sum to more than 309, because 12 youth participants had both parents affected with SMI). FORBOW participants were recruited through parents attending psychiatric services for major mood and psychotic disorders in Nova Scotia, Canada, where clinicians systematically inquire if patients with major mood or psychotic disorders are parents. Control participants were recruited through parents of children attending the same schools as the high-risk participants. We invited all biological children of identified parents to participate and we assessed them annually with a retention rate of 95%. The inclusion criterion for the present study was age

8–24 years. We set the lower age limit at 8 years because reporting of psychotic symptoms may be less reliable in younger children. The exclusion criterion was intellectual disability of a degree that is incompatible with the assessments. The FORBOW study was approved by the research ethics board of the Nova Scotia Health Authority. Participants who had the capacity to do so provided written informed consent. Parents or guardians consented on behalf of children who were not able to give consent themselves.

Assessment of parents

We completed separate diagnostic interviews with both biological parents. We made multiple attempts to reach and directly assess each parent. When a parent was not available for an in-person interview, we offered a phone interview. Each parent was interviewed separately, by an interviewer blind to the diagnoses of other family members. We assessed psychopathology with semi-structured diagnostic interviews [the schedule for affective disorders and schizophrenia (SADS) and the structured clinical interview (SCID) for diagnostic and statistical manual (DSM)]^{20,21} supplemented by information from clinical notes. Diagnoses and severity criteria were established according to the DSM IV edition, text revision, in consensus meetings with psychiatrists blind to the diagnoses of relatives. When a biological parent was not available for in-person or phone interview, we obtained relevant information from their relatives using the Family Interview for Genetic Studies.²²

Assessment of offspring

Youth assessors were blind to information on parents and other family members. At baseline and then in yearly intervals for up to 4 years, psychotic symptoms experienced over the preceding 12 months were assessed in detail using four validated instruments. For the present study, we defined psychotic symptoms as reported hallucinations or delusions rated as ‘definite’ in consensus meetings with a child and adolescent psychiatrist blind to parent diagnosis or curated as a definite psychotic symptom by two independent assessors. We assessed psychotic symptoms using one or more of the following instruments: (1) Kiddie schedule for affective disorders and schizophrenia, present and lifetime version (K-SADS-PL), (2) funny feelings (FF), (3) structured interview for prodromal syndromes (SIPS) and (4) schizophrenia proneness instrument – child and youth version (SPI-CY).

K-SADS-PL

We interviewed all youth and parents with the K-SADS semi-structured interview.²³ In separate interviews, parents were interviewed about their offspring and the youth were interviewed about themselves. We administered the K-SADS psychosis module to all participants to comprehensively assess psychotic symptoms. Potential psychotic symptoms were consensus rated by a child and adolescent psychiatrist blind to parent psychopathology. Here, we only considered psychotic symptoms from the 12 months preceding the interview that were deemed clinically significant and confirmed as ‘definite’ in consensus meetings.

FF

We assessed self-reported psychotic symptoms experienced in the 12 months preceding the assessment with the ‘FF’ interview.^{4,24}

Initial positive responses to seven questions were further investigated using follow-up probes.^{4,7,24} We submitted the verbatim transcripts for independent clinical curation to establish the psychotic character of the experience. Potential psychotic symptoms were rated as 'none,' 'probable' or 'definite.' Two independent curators reached high agreement in rating the psychotic character of reported experiences ($\kappa=0.78$, 95% CI 0.75–0.80) and disagreements were resolved in consensus meetings. Here, we only considered psychotic symptoms rated as 'definite' by consensus between the two raters.²⁵

SIPS

In participants aged 11 and above, we also assessed psychotic symptoms with the SIPS, which allows the derivation of attenuated psychotic symptoms and definition of at-risk mental state for psychosis.²⁵ Here, we only considered SIPS ratings that met the threshold for at-risk mental state.

SPI-CY

We interviewed participants with the SPI-CY to assess basic symptoms.²⁶ Basic symptoms describe subjectively perceived deficits and abnormalities in multiple domains (perception, cognition, language, feelings) and have been shown to strongly predict the development of schizophrenia.¹⁸ Here, we only considered basic symptoms fulfilling criteria for the high-risk profiles of cognitive disturbances or cognitive-perceptive basic symptoms that were shown to predict psychosis with high specificity.²⁷

Statistical analysis

We defined the primary outcome as a dichotomous variable that had the value of 1, if one or more definite psychotic symptoms or a high-risk basic symptom profile was established with any one or more of the four assessment instruments (K-SADS, SIPS, FF and/or SPI-CY) on a given assessment, or 0 otherwise. The primary predictors were dichotomous variables that reflected whether the same-sex parent and opposite-sex parent had a lifetime diagnosis of SMI. Since both effects of same-sex and opposite-sex parent were included in each analysis, the offspring of two unaffected parents were the reference group. We used offspring age, sex and time in the study as covariates in all analyses. We tested the effects of parent diagnoses in a mixed-effects logistic regression with the same-sex parent SMI, opposite-sex parent SMI, offspring age, sex and time in the study entered as independent variables. The inclusion of offspring sex as a covariate was pre-specified to account for sex differences in the prevalence of psychotic symptoms separately from sex-specific parent-of-origin effects. The models included random effects of individual and family to account for the non-independence of repeated assessments within individual and individuals within families.²⁸ To provide the most generalizable estimates with respect to variation in psychopathology across the entire sample, the primary analysis included all offspring in the eligible age range, including offspring with only one biological parent directly interviewed and offspring with both biological parents affected with SMI. In three sensitivity analyses, we probed the robustness of the results to the inclusion of families where only one parent was directly interviewed, families with two affected parents and families where children were not in the care of both biological parents. In the first sensitivity analysis, we explored the effects of incomplete information on parent psychopathology by restricting the analyses to families

where both biological parents underwent diagnostic interviews. There were no missing data on other variables. In the second sensitivity analysis, we repeated the primary hypothesis test in a sample restricted to families where either none or only one biological parent was affected with SMI. In the third sensitivity analysis, we repeated the primary hypothesis test in a sample restricted to families where both biological parents live in the same household as the offspring. We quantified the magnitude of the relationships between predictors and the outcome as ORs with 95% CI. We completed all analyses using STATA 15.1 software.

Results

Psychotic symptoms

We included data from 839 assessments of 309 youth from 182 families. We assessed the youth an average of three times (mean number of assessments 2.72, range 1–5). We established definite psychotic symptoms in 222 (26.5%) of the 839 assessments. Of the 309 youth, 130 (42%) reported definite psychotic symptoms on one or more assessments. The rates of psychotic symptoms did not significantly differ between males and females (Table 1).

SMI in parents and psychotic symptoms in offspring

We examined the associations between SMI in a parent and the likelihood of psychotic symptoms in their offspring. Psychotic symptoms were reported on one or more assessments by 35% (58 of 165) of control offspring, and by 50% (72 of 144) of offspring with a parent affected with SMI. Across the assessments, SMI in a parent increased the odds of psychotic symptoms in offspring 1.8-fold (OR = 1.83, 95% CI 1.05–3.16, $P=0.032$).

Sex of the affected parent and psychotic symptoms in the offspring

Next, we examined if the sex of the affected parent influenced the likelihood of psychotic symptoms in the offspring irrespective of the offspring's sex. Psychotic symptoms were reported by 53% (60 of 113) of offspring of affected mothers and by 44% (19 of 43) of offspring of affected fathers. When father's SMI and mother's SMI were tested in a mixed-effect logistic regression model, the effect of mother's SMI on offspring psychotic symptoms was significant (OR = 1.97, 95% CI 1.12–3.46, $P=0.018$), whereas the effect of father's SMI was not (OR = 1.36, 95% CI 0.65–2.85, $P=0.418$).

Sex-specific parent-of-origin effects

We tested our primary hypothesis as contrasting effects of same-sex parent and opposite-sex parent being affected with SMI on the likelihood of psychotic symptoms in the offspring. Examination of same-sex parent-offspring pairs (mothers–daughters and fathers–sons) suggested no significant relationship between parent SMI and offspring's psychotic symptoms. Psychotic symptoms were reported by 44% (39 of 88) of offspring whose same-sex parent was affected compared with 41% (91 of 221) of youth whose same-sex parent was not affected with SMI. In contrast, examination of opposite-sex parent-offspring pairs (mothers–sons and fathers–daughters) revealed a positive relationship between parent's SMI and psychotic symptoms in offspring. Psychotic symptoms were reported by 59% (40 of 68) of offspring whose opposite-sex parent was

Table 1. Sample description

	Female offspring		Male offspring		Comparison	
	(n = 160)		(n = 149)		t	T
	Mean	s.d.	Mean	s.d.		
Number of assessments	2.68	1.41	2.76	1.38	0.53	0.600
Age at first assessment (years)	11.98	4.22	11.02	3.64	-2.15	0.033
Age at last assessment (years)	13.14	4.63	12.34	3.84	-1.65	0.100
	n	%	n	%	χ^2	P
Mother assessed						
Interview in person	138	86	127	85		
Interview on the phone	12	8	12	8		
Interview with relative	7	4	6	4		
Not assessed, co-parent report only	3	2	4	3	0.29	0.963
Father assessed						
Interview in person	74	46	75	50		
Interview on the phone	25	16	11	7		
Interview with relative	22	14	29	19		
Not assessed, co-parent report only	39	24	34	23	6.37	0.095
Living with biological parents						
Both biological parents	96	60	93	63		
Mother only	50	31	45	30		
Father only	4	3	5	3		
Not living with biological parents	10	6	6	4	1.03	0.794
Mother's diagnosis						
Schizophrenia	6	4	5	3		
Bipolar disorder	32	20	25	17		
Major depressive disorder	74	46	61	41		
None	48	30	58	39	2.76	0.431
Father's diagnosis						
Schizophrenia	3	2	2	1		
Bipolar disorder	11	7	9	6		
Major depressive disorder	32	20	29	20		
None	114	71	109	73	0.27	0.966
Offspring psychotic symptoms						
Hallucinations	38	24	33	22	0.11	0.738
Delusions	22	14	25	17	0.55	0.459
Basic symptoms	40	25	34	23	0.20	0.653
Any psychotic symptoms	68	43	62	42	0.03	0.874

Sample characteristics are given separately for female and male offspring. The numbers of offspring with psychotic symptoms correspond to the symptom being detected on one or more assessments. The comparison columns report statistics (t or χ^2) and P -value of comparison between female and male offspring

affected compared with 37% (90 of 241) of offspring whose opposite-sex parent was not affected with SMI (Fig. 1). The differential sex-specific parent-of-origin relationship was confirmed in a mixed-effect logistic regression model with no significant effect of same-sex parent's SMI (OR = 1.13, 95% CI 0.61–2.07, $P=0.697$) and a significant effect of opposite-sex parent's SMI (OR = 2.65, 95% CI 1.43–4.91, $P=0.002$) on offspring's likelihood of experiencing psychotic symptoms (see Table 2 for full model results).

Sensitivity analyses

We obtained direct diagnostic information with semi-structured interviews on the mothers of 289 offspring (94%) and fathers of 185 offspring (60%). Information on the mothers of 20 offspring (6%) and fathers of 124 offspring (40%) was obtained indirectly from relatives or from the other parent. In our primary analyses, we assumed that the indirect diagnostic information was valid. To confirm that our primary result did not rely on this assumption, we completed a sensitivity analysis restricted to the 175 offspring where both biological parents were directly interviewed. This analysis gave results with effect sizes very similar to the whole sample analysis, with non-significant effect of same-sex parent's SMI (OR = 1.32, 95% CI 0.54–3.19, $P=0.540$) and a significant effect of opposite-sex parent's SMI (OR = 2.91, 95% CI 1.14–7.40, $P=0.025$) on offspring's odds of experiencing psychotic symptoms. In our primary analysis, we included offspring with none, one or two biological parents affected with SMI. There were 12 offspring of two biological parents affected with SMI. Although this approach allowed us to model the variation across the entire sample, the families where both parents were affected with SMI could not directly contribute to the test of our primary hypothesis. Therefore, to test the robustness of our results to the inclusion of families with two affected parents, we completed a second sensitivity analysis, restricted to individuals with either none or one biological parent affected with SMI. This second sensitivity analysis gave results with effect sizes very similar to the whole sample analysis, with non-significant effect of same-sex parent's SMI (OR = 1.15, 95% CI 0.54–3.19, $P=0.6913$) and a significant effect of opposite-sex parent's SMI (OR = 2.77, 95% CI 1.38–5.57, $P=0.004$) on offspring's psychotic symptoms (Table 2). Finally, 104 (34%) of the included youth lived with only one of their biological parents and 16 (5%) youth did not live in the same household with either of their biological parents at the time of study participation. To examine whether the identified pattern of

transmission is robust to care arrangements, we completed a third sensitivity analysis, restricted to the 189 youth who shared household with both of their biological parents. This sensitivity analysis also confirmed the specific effect of opposite-sex parent's SMI (OR = 4.68, 95% CI 1.96–11.15) on offspring's psychotic symptoms (Table 2).

Discussion

Among offspring of parents with major mood and psychotic disorders, psychotic symptoms were more common in sons of affected mothers and daughters of affected fathers than in offspring of the same sex as their affected parent. Our findings are aligned with the results of studies demonstrating opposite-sex parent transmission of risk of psychotic disorders¹⁵ and major depressive disorder.¹⁶ These results suggest that offspring of the opposite-sex to their affected parent are more likely to experience psychotic symptoms during childhood and adolescence, before the typical age at onset of SMI. In addition, we observed a greater effect of mother's mental illness than father's mental illness on the development of psychotic symptoms, regardless of offspring sex.

The finding of preferential transmission of psychopathology from parent to opposite-sex offspring provides a replication of two previous studies.^{16,29} In addition to the overall effect of opposite-sex parent, each of the three studies found greater sex-specific transmission differential in male than in female offspring. This degree of consistency suggests that sex-specific transmission of liability to psychopathology may be most relevant to male offspring. In addition to replicating previous findings, the present study demonstrates that sex-specific parent-of-origin effects are relevant to early manifestations of psychopathology. These manifestations occur earlier in the development, predate the onset of major mental illness by a number of years and are unlikely to be influenced by help-seeking, drug or medication use. Therefore, the robust sex-specific parent-of-origin effects at this early developmental stage provide additional evidence in support to sex-specific genetic or early developmental mechanisms in the etiology of mental health and illness.

The present findings have potential implications for both clinical practice and research. Clinically, it is commonly observed that family members associate risk of mental illness with the physical characteristics of the affected individual, including their sex. As a result, there is often more concern expressed regarding SMI risk for offspring who are of the same sex as the affected parent. Given the fact that psychotic symptoms experienced in childhood are predictive of later mood and psychotic disorders,⁶ our findings suggest that it may be important to focus on daughters of affected fathers and sons of affected mothers in early risk identification and prevention efforts.

From a research perspective, our findings bring attention to the need to include sex chromosomes in molecular genetic investigations of SMI. Males inherit their single X chromosome from their mother and females receive one X chromosome from each parent. Our data show greater differential in transmission from fathers to their daughters compared with sons than in transmission of risk from mothers to their sons compared with daughters (see Fig. 1). This pattern replicates that reported by Goldstein *et al.*¹⁵ and is consistent with simple X-chromosome-linked inheritance, as the transmission of risk for psychotic symptoms seems to be approximately doubled in the relationships that involve a transfer of an X chromosome.³⁰ Although a simple

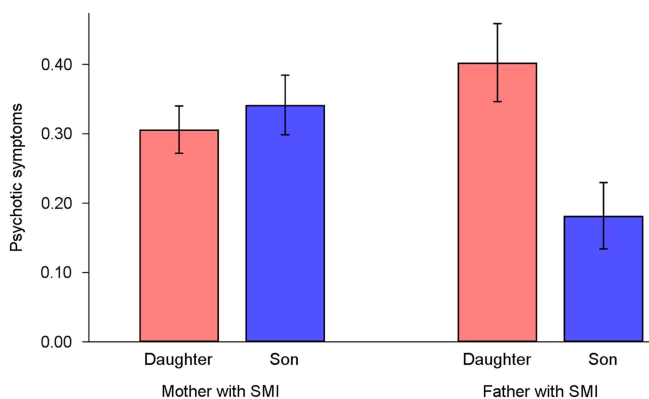


Fig. 1. Rate of psychotic symptoms in offspring by sex and affected parent. On the y-axis, we plot the proportion of assessments when definite psychotic symptoms were detected in each group. The error bars represent the standard error of measurement.

Table 2. Tests of sex-specific parent of origin effects: results of primary hypothesis test and sensitivity analyses

Parameter	OR	95% CI		P-value
		Lower	Upper	
1. Primary analysis (839 assessments of 309 youth from 182 families)				
Same-sex parent affected status	1.13	0.61	2.07	0.697
Opposite-sex parent affected status	2.65	1.43	4.91	0.002
Age (years)	1.03	0.97	1.09	0.381
Sex (female)	1.56	0.89	2.75	0.123
Constant	0.10	0.04	0.23	
2. Sensitivity analysis of youth with both parents directly assessed (451 assessments of 175 youth from 101 families)				
Same-sex parent affected status	1.32	0.54	3.19	0.540
Opposite-sex parent affected status	2.91	1.14	7.40	0.025
Age (years)	1.04	0.94	1.15	0.399
Sex (female)	1.16	0.49	2.75	0.742
Constant	0.06	0.02	0.23	
3. Sensitivity analysis excluding youth with two affected parents (801 assessments of 297 youth from 175 families)				
Same-sex parent affected status	1.15	0.58	2.25	0.691
Opposite-sex parent affected status	2.77	1.38	5.57	0.004
Age (years)	1.02	0.96	1.08	0.593
Sex (female)	1.66	0.93	2.95	0.087
Constant	0.11	0.04	0.25	
4. Sensitivity analysis restricted to youth who are in care of both biological parents (496 assessments of 189 youth from 114 families)				
Same-sex parent affected status	1.07	0.47	2.42	0.870
Opposite-sex parent affected status	4.68	1.96	11.15	0.001
Age (years)	0.98	0.90	1.08	0.741
Sex (female)	1.48	0.69	3.18	0.310
Constant	0.10	0.03	0.36	

CI, confidence interval; OR, odds ratio

In each analysis, the results of the parameter of interest (effect of opposite sex parent affected status) are printed in bold

contribution of X chromosome transmission offers a plausible explanation of the observed pattern, other mechanisms may also play a role. Although females carry two X chromosomes, one of the female X chromosomes is largely inactivated via chromosomal modifications, and the determination of which copy is inactivated may depend on the parent-of-origin.^{31,32} Because of the differences in copy number between males and females and female X-inactivation, the X chromosome poses unique analysis challenges and has thus been omitted from many of molecular genetic studies of various diseases and phenotypes.¹³ Some more recent searches for associations between mental illness and specific genetic loci have included the X chromosome;^{14,33} however, it is still not included in some recent genomic association studies.³⁴ A large genome-wide association study that included the X chromosome identified three independent X chromosome loci associated with schizophrenia, implicating genes linked to synaptic

plasticity and synaptic function.¹⁴ Another genomic study identified a risk region on Xq28, including *MECP2*, which encodes a protein in the methyl-CpG-binding domain family that is involved in modification of gene expression in the brain.³⁵ Finally, an analysis of families with multiple members affected by SMI identified a variant within the *SMARCA1* gene on the X chromosome associated with schizophrenia risk.³⁶ These emerging findings are examples of possible molecular substrates of X-linked inheritance of vulnerability to mental illness.

Our study has benefited from a detailed assessment of psychotic symptoms in a sample enriched for familial risk of SMI. However, the composition of our sample may also limit the generalizability of the present results. The majority of parents with SMI were diagnosed with bipolar disorders and major depressive disorder, with fewer parents diagnosed with schizophrenia. Although this may partly reflect the fact that individuals

with schizophrenia have fewer children,³⁷ it also means that we do not have adequate power to specifically test the effect of family history of schizophrenia. In addition, there were fewer affected fathers than mothers included, which may be due to greater negative effects of SMI on fecundity in males than in females.³⁷ Although we extended great efforts to reach all biological parents, we were not able to interview all of them and for about one-third of participants, information on the diagnosis of one of their biological parents depended on indirect information. A sensitivity analysis found very similar results in a sample of offspring where both biological parents were directly assessed, suggesting that the lack of direct information on some parents did not affect the findings. Although we obtained data from over 800 assessments of over 300 youth, the sample may be too small to interpret weaker effects. The effect of same-sex parent affected status on psychotic symptoms in offspring was not statistically significant in our analyses, but this is likely because of limited statistical power and it should not be interpreted as absence of effect until it is more accurately quantified in larger samples. Finally, in the absence of genetic design, the mechanism underlying the sex-specific parent of origin transmission remains unclear. Although the pattern of results is consistent with X-linked inheritance, environmental mechanism cannot be ruled out. A sensitivity analysis restricted to youth living with both biological parents confirmed the opposite-sex parent of origin effect, suggesting that the pattern of transmission is not substantially affected by the degree to which environment is shared between parent and offspring.

In summary, our findings refine the understanding of one of the strongest risk factors for mental illness, family history. Although children of any parent with SMI have increased risk of developing mental illness themselves, it may also matter *which* parent is affected. Offspring who are the opposite sex of their affected parent are at increased risk of experiencing psychotic symptoms, a known predictor of SMI, during childhood and adolescence. Even though most of these offspring will not go on to develop SMI, the early manifestation of risk in the form of psychotic symptoms suggests vulnerability and is often a distressing experience. The present study suggests that sex-specific parent-of-origin effects should be considered in genetic research and early identification of risk for mental illness.

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Conflicts of Interest. None.

Ethical Standards. The authors assert that all procedures contributing to this work comply with the Ethical Conduct for Research Involving Humans (Canada) and with the Helsinki Declaration of 1975, as revised in 2008. The FORBOW study was approved by the research ethics board of the Nova Scotia Health Authority.

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