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Molecular Genetic Risk for Psychosis Is Associated With Psychosis Risk Symptoms in a Population-Based UK Cohort: Findings From Generation Scotland

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Objective: **Subthreshold psychosis risk symptoms in the general population may be associated with molecular genetic risk for psychosis. This study sought to optimize the association of risk symptoms with genetic risk for psychosis in a large population-based cohort in the UK (*N* = 9104 individuals 18–65 years of age) by properly accounting for population stratification, factor structure, and sex.*Methods:* The newly expanded Generation Scotland: Scottish Family Health Study includes 5391 females and 3713 males with age *M* [SD] = 45.2 [13] with both risk symptom data and genetic data. Subthreshold psychosis symptoms were measured using the Schizotypal Personality Questionnaire-Brief (SPQ-B) and calculation of polygenic risk for schizophrenia was based on 11 425 349 imputed common genetic variants passing quality control. Follow-up examination of other genetic risks included attention-deficit hyperactivity disorder (ADHD), autism, bipolar disorder, major depression, and neuroticism.*Results:* Empirically derived symptom factor scores reflected interpersonal/negative symptoms and were positively associated with polygenic risk for schizophrenia. This signal was largely sex specific and limited to males. Across both sexes, scores were positively associated with neuroticism and major depressive disorder.*Conclusions:* A data-driven phenotypic analysis enabled detection of association with genetic risk for schizophrenia in a population-based sample. Multiple polygenic risk signals and important sex differences suggest that genetic data may be useful in improving future phenotypic risk assessment.**

Key words: schizotypal/schizophrenia/genetic/polygenic/risk/Generation Scotland

Introduction

Subthreshold psychosis symptoms, sometimes referred to as schizotypy,[1–7] have served as the basis for myriad studies of genetic risk for psychosis. Biometrical analyses of these symptoms have produced significant heritability estimates ranging from .3 to .5,[8–10] with elevations of negative/interpersonal symptoms typically being the most pronounced in high-risk youth and first-degree biological relatives.[3,9–15] Subthreshold psychosis risk symptoms are generally milder than overt symptoms, are observed to be continuously distributed in the general population, and may be measured continuously.[16–18]

However, association of subthreshold symptoms with molecular genetic risk for schizophrenia has not yet been detected in population-based samples. This is possibly due to light phenotyping in large studies of genetic risk, leading to limited psychometric and statistical analysis of risk symptoms. One previous study examined 2 cohorts of healthy male military recruits approximately 20–22 years of age (*N*s = 875 and 690). In the first cohort, at 1 of 6 PRS *P*-value thresholds (.3), some symptom factors evidenced a negative association with SZ PRS. But these results were not sustained on follow-up of the first cohort, nor replicated in the second cohort.[19] Another recent, well-powered molecular genetic analysis of psychotic

experiences (eg, auditory/visual hallucinations and delusions) detected shared genetic covariance with schizophrenia and with 4 other psychiatric disorders using interview data from UK Biobank.[4] These results are promising for genetic studies of subthreshold psychosis symptoms. Schizotypy measures provide increased variation and sensitivity with respect to risk—a key empirical finding from the literature on subthreshold negative symptoms.[20–22]

The availability of symptom and common variant genetic data in a large population-based cohort, the Generation Scotland Scottish Family Health Study (N = 9104 individuals aged 18–65), yielded a unique opportunity to examine associations of symptoms with genome-wide polygenic risk for schizophrenia. Additional follow-up analyses included an examination of risk for the 4 psychiatric disorders reported in the recent analyses of psychotic experiences in UK Biobank—major depression, bipolar disorder, autism spectrum disorder, and attention-deficit hyperactivity disorder (ADHD).[4] This was meant to account for clinically meaningful overlap of the SPQ-B items with diverse psychiatric conditions.

Recent data from the World Health Organization have also suggested that psychotic experiences may be much less specific to schizophrenia than previously thought.[1] Indeed, psychotic experiences appear to lie on the continuum of neuroticism and have been observed to either precede or follow the onset of a range of nonpsychotic psychiatric disorders.[23–26] Thus, it was also expected that risk symptoms would be associated with molecular genetic risk for neuroticism—consistent with dimensional conceptualizations of psychopathology and with evidence of significant shared genetic covariance of psychosis and neuroticism.[27–29]

Methods

Sample

Samples comprised adults aged 18–65 from Generation Scotland: The Scottish Family Health Study (GS; data available on request at http://www.generationscotland.co.uk). GS is a family- and population-based study consisting of 23 690 participants recruited from general medical practices across Scotland. The protocol and sample characteristics are described in detail elsewhere.[30] Briefly, participants were all adults and were not ascertained on the basis of having any particular disorder. The use of a population-based sample was thought to capture a cohort representative of the general population, though individuals with schizophrenia were excluded from these analyses. Sample characteristics for this study are presented in table 1. GS received ethical approval from the NHS Tayside Committee on Medical Research Ethics (REC Reference Number: 05/S1401/89).

Table 1. Demographics, Symptoms, and Empirically Derived Symptom Factor Scores

Sample	Entire Cohort	Male EFA	Females EFA
N	9104	3713	5391
Age, M (SD)	45.2 (13.4)	45.2 (13.7)	45.2 (13.3)
SPQ-B Score, M (SD)	3.9 (3.7)	3.9 (3.7)	3.9 (3.7)
Primary Factor Score, M (SD)	0.9 (1.1)	0.4 (0.9)	1.6 (1.8)

Note: M = mean, EFA = exploratory factor analysis. Schizotypy factor scores are specific to male and female EFAs.

Phenotypic Measurement

The oft-used and well-validated Schizotypal Personality Questionnaire (SPQ; Raine 1991) taps subthreshold psychosis symptoms and psychotic-like experiences.[31] Items are thought to reflect a phenotypic indicator of liability for schizophrenia-spectrum disorders.[32] The brief version (the 22-item SPQ-B)[33] measures a full range of symptoms based on the operational definition of schizotypal personality disorder (SPD).[34] These items reflect the same self-report information found on interview measures such as the Structured Interview for Schizotypy[2] and the Structured Interview for Prodromal Symptoms.[35] According to the International Consortium on Schizotypy Research and in current common parlance, *schizotypy* and *schizotypal* are now virtually interchangeable given the strong degree of measurement overlap. These symptoms are broadly cognitive (eg, paranoid ideation, ideas of reference), interpersonal (eg, anhedonia, no close friends), and behavioral (eg, odd behavior and language).[36,37] SPQ-B items have been widely used with schizophrenia probands, their first-degree relatives, adolescents, twins, outpatients, and college students,[3,7,33,38,39] and the SPQ is the most commonly utilized questionnaire for assessing these symptoms across cultures and languages. Notably, there is considerable variability in total and subscale scores across healthy cohorts (see table 1 for the means and variances of SPQ-B scores in Generation Scotland), but demonstrated reliability and several sources of evidence for validity of the measure.[39,40]

Factor Structure and Analysis of Measurement Invariance

Exploratory factor analysis (EFA) with oblique rotation identified 3 factors in the full cohort using the parallel analysis fa() function in the nFactors R package.[41] Weighted sum scores were derived for the primary factor in the full cohort. Follow-up confirmatory factor analysis using multiple group nested likelihood ratio tests indicated highly significant measurement noninvariance across sex in tests of metric invariance (loadings $\Delta X^2 = 744.54$, df = 60, $P < .001$), as well as tests of strict

measurement invariance (loadings, intercepts, residual variances ($\Delta X^2 = 2400.43$, df = 104, $P < .001$). To derive sex-specific factors, EFAs were fit separately in females and males (supplementary figure S1), and weighted sum scores were calculated from the primary factor item loadings. The use of only the primary symptom factor scores in subsequent regressions was intended to reduce the number of multiple tests, and the use of factor scores also bypassed zero-inflation concerns inherent in examination of psychosis risk items in population-based samples. Symptom factor scores were significantly negatively associated with age in males ($r = -.22$, $P < .0001$), but not females ($r = .01$, ns). Because the factor structure differed in males and females, we also ran follow-up analyses of symptom factor scores in females that were derived from the male EFA weights, and vice versa, to confirm that sex-specific factor scoring methods did not bias any of the results of sex-specific polygenic regression analyses.

Genotyping and Imputation

DNA collection and calling for Generation Scotland are detailed elsewhere.[30] Genotype imputation was performed on 559 363 single nucleotide polymorphisms (SNPs) using the Michigan Imputation Server pipeline v1.2.4 using the Haplotype Reference Consortium as a reference panel. Prior to imputation, the genotypes were filtered for ambiguous strand orientation, missingness rate > 5% (by marker exclusion, then by individual), and Hardy–Weinberg equilibrium violation ($P < 1e{-}6$). After imputation, SNPs with minor allele frequency below 0.001, average call rate < 90%, or imputation $R^2 < .5$ were also excluded. PLINK[42] was used to perform quality control. Final polygenic risk scoring was performed on 11 425 349 variants passing quality control.

Polygenic Risk Scoring

Polygenic risk scores were calculated using PRSice 2.0[43] based on genome-wide association summary statistic weights from the largest current genome-wide association study (GWAS) meta-analyses.[44–49] Previous studies have utilized multiple *P*-value thresholds to create PRS with increasing portions of genomic data to detect changes in R^2. To minimize the number of exploratory tests, a default a priori *P*-value threshold of 1.0 was selected using the maximum number of variants available.[50] For tests with significant signal, we than followed up with thresholds of .5 and .05, respectively. Significant differences were observed between males and females in PRS for schizophrenia, with higher PRS for schizophrenia in males ($t = 2.73$; $P = .006$). Other differences included ADHD PRS, which were calculated separately in males and females from established, sex-specific summary scores.

Regressions of Symptoms Onto Polygenic Risk

Generation Scotland evidenced normal distributions of all PRS and positive skew of the symptom factor score in both females and males. A cube-root transform was sufficient to correct this skew. No differences in prediction of any item by PRS were detected when using mixed models to account for cryptic relatedness (supplementary figure S2). Linear regressions of schizophrenia PRS onto the primary symptom factor included age and the first 10 ancestry principal components as covariates. Models in the full sample, then females and males were compared with and without PRS, examining Nagelkerke's pseudo-R^2 (rsq) and the PRS coefficient in the multivariate model, with false discovery rate correction for multiple testing. With rsq, the ratio of the likelihoods reflects the improvement of the full model over the intercept model and the range of possible values extends to 1. Follow-up tests examined the other PRS in similar model comparisons.

Results

A total of 5391 females and 3713 males were included in the final analyses. Sample characteristics and symptom factor scores for the entire cohort, males, and females are presented in table 1. Table 2 presents the EFA-derived primary factor item loadings in EFAs for the total sample, for males only, and for females only. In the sex-specific EFAs, male primary factor scores reflected higher loadings on negative/disorganized symptoms. In females, primary factor scores reflected a broader mix. In the full cohort, symptom scores were significantly positively associated with genetic risk for schizophrenia (rsq = .001, $t = 2.419$, $P = .02$, OR = 1.03, SE = 0.01), with signal largely evident in males (rsq = .003; $t = 2.516$, $P = .01$, OR = 1.04, SE = 0.02) rather than females (rsq = .0003, $t = 0.974$, $P = .33$, OR = 1.01, SE = 0.01).

In follow-up tests of associations with the genetic risks that were examined in UK Biobank,[4] significant associations of scores in males were observed with both major depressive disorder (rsq = .010, $t = 4.897$, $P = 1.0 \times 10^{-6}$, OR = 1.08, SE = 0.02) and neuroticism (rsq = .010; $t = 4.802$, $P = 1.6 \times 10^{-6}$, OR = 1.08, SE = 0.02). Symptom scores in females, again not associated with risk for schizophrenia, were also positively associated with genetic risk for major depressive disorder (rsq = .013, $t = 6.896$, $P = 6.0 \times 10^{-12}$, OR = 1.09, SE = 0.01) and neuroticism (rsq = .008; $t = 5.315$, $P = 1.1 \times 10^{-7}$, OR = 1.07, SE = 0.01). No other genetic risk associations were significant using factor scores from any of the EFAs. Overall, association with schizophrenia genetic risk was specific to males, whereas genetic risk for depression and neuroticism was not sex specific. Depression and neuroticism genetic risks accounted for the largest proportions of variance in population-based schizotypal symptom scores. Additional follow-up tests indicated that associations of scores with schizophrenia PRS in females were

Table 2. Items and Primary Factor Loadings From Exploratory Factor Analysis Models

Items (Paraphrased)	Entire Cohort	Male EFA	Female EFA
1. Aloof and distant (I)	0.12	−0.04	−0.06
2. Sense some person or force (CP)	0.14	−0.02	0.07
3. Unusual mannerisms and habits (D)	0.15	−0.02	−0.06
4. People can tell what you are thinking (CP)	0.29	0.13	0.25
5. Noticed special signs for you (CP)	0.33	0.23	0.15
6. People think I am very bizarre (D)	0.08	−0.05	−0.03
7. On my guard even with friends (I/CP)	0.33	0.19	0.05
8. People find me vague and elusive (I)	0.25	0.09	0.31
9. Often pick up hidden threats (I/CP)	0.35	0.26	0.5
10. People are taking notice of you (CP)	0.33	0.17	**0.53**
11. Discomfort with unfamiliar people (I)	0.13	0.04	**0.85**
12. Astrology, UFOs, ESP, sixth sense (CP)	0.15	−0.06	**0.63**
13. I use words in unusual ways (D)	0	−0.1	**0.87**
14. Not let people know about you (I/CP)	0.25	0.15	**0.75**
15. Tend to keep in background (I)	0.12	0	**0.86**
16. Distracted by distant sounds (D)	0.05	−0.14	**0.75**
17. Stop people from taking advantage (I/CP)	**0.77**	**0.74**	−0.03
18. Unable to get close to people (I)	**0.86**	**0.96**	−0.09
19. I am an odd, unusual person (D)	**0.54**	0.41	0.41
20. Hard to communicate clearly (D)	**0.67**	**0.65**	−0.04
21. Very uneasy talking to people (I)	**0.81**	**0.87**	0.07
22. Tend to keep my feelings to myself (I)	0.39	0.32	**0.55**

Note: Male EFA = loadings from the primary factor of the male-only EFA, female EFA = loadings from the primary factor of the female-only EFA. (I) = interpersonal/negative symptom item, (CP) = cognitive-perceptual/positive symptom item, (D) = disorganized symptom item. Loadings > .5 are presented in bold.

not significant even when loadings from a male-only EFA were applied to score females. None of the genetic risk scores were significantly associated with total SPQ-B or SPQ-B subscale scores in the full sample or in males or females separately.

Discussion

Polygenic analyses of Generation Scotland reflect the first detection of statistically significant association of risk symptoms with polygenic risk for schizophrenia in the general population. The use of empirically derived psychosis-spectrum symptom factors allowed for the detection of variation in molecular genetic schizophrenia risk signal. This association was limited to males.

Items comprising the primary factor in this cohort are strongly related to genetic risks for major depressive disorder and neuroticism across males and females. Of note, the items with the highest loadings in the female only primary factor (table 2) pertain to common cognitive and interpersonal experiences of individuals with broadly defined negative affect. It is possible that there was simply less self-reported risk in females in this cohort, though total SPQ-B scores did not significantly differ across males and females. Given a higher prevalence of depressive disorder in females relative to males, it is likely that females in this cohort had more depressive disorder symptoms. Associations of self-reported symptoms with genetic risk for depression and neuroticism in a very large population-based cohort of females warrant further study. It is possible that genetic data may be used to enhance future phenotypic measurement of psychosis risk in females.

Based on previous research on PRS associations with symptoms, there is ample reason to believe that genetic risk for conditions other than schizophrenia would predict SPQ-B endorsement. PRS for ADHD has predicted attention problems,[51] PRS for autism has predicted cognitive ability,[52] and PRS for major depression has predicted variation in antidepressant treatment response.[53] However, it is important to bear in mind that any PRS prediction, while statistically significant, accounts for a quite small amount of variance in any given phenotype.

The strongest associations observed in this study relate to genetic risk for major depressive disorder and neuroticism. This may be expected, given very high base rates of these symptoms relative to psychosis, and the population-based ascertainment of this cohort. Recent progress in psychiatric genetics has led to further consolidation and meta-analysis of phenotypic and molecular data, to more effectively model the latent structure of the psychosis spectrum.[54,55] Phenotypic studies of psychosis risk[56] suggest that it is possible that dimensional phenotypes will lead to higher rsq values. This is difficult to test empirically, however, since established summary statistics for polygenic risk calculation have been largely based on binary/threshold phenotyping. Enhanced quantitative approaches may further refine what we consider to be

psychosis risk and will ideally involve several methods and measures, multiple genetic risk metrics, and careful attention to the psychometrics within each population being measured.[57–60]

Limitations

One limitation of this study is a reliance on questionnaire rather than structured clinical interview data. The use of such questionnaires is a prerequisite of any large population study, and the measure does evidence strong overlap with conventional interview in nonclinical cohorts.[61] Another limitation is the lack of a clinical or preclinical comparison cohort. Factor analysis of psychotic-like symptoms in diverse psychiatric cohorts could generate different symptom dimensions that may more closely approximate "true" psychosis risk. However, our general goal was to approximate associations in a general population sample. Also, as noted above, it is important to understand that although statistical associations may be robust, any variance accounted for in the dependent variable is always modest, and in any given polygenic risk prediction, analysis rarely reaches 3%. It is possible that prediction methods using Bayes scoring could account for additional variance.[62,63] Finally, findings may not generalize to other ancestries despite the global appeal of SPQ-B items[64,65] because genome-wide association studies for these PRS still almost exclusively rely on Northern European cohorts. Fortunately, several recent studies have demonstrated enhanced GWAS discovery and generalizability following incorporation of non-European samples into discovery GWAS.[66–69]

Future Directions

Family and molecular genetic studies have provided evidence that a negative schizophrenia symptom dimension may hold predictive utility,[22,70–74] but phenotyping in genomic studies has been light, or samples too small, to adequately address questions about the common variant genetic architecture of symptom dimensions in the general population. Future comparison of GWAS effect sizes for symptom dimension factor scores in patients[75] with GWAS effect sizes for EFA-based factor scores in population controls (ie, an estimate of shared genetic covariance) could be informative.

Overall, it is possible that dimensional conceptualizations of a psychosis continuum that incorporate normative experience will compliment categorical approaches with respect to polygenic risk prediction. Given the observed relationships in this study, we believe it is likely that future genetic risk research (particularly with respect to psychosis and other low base-rate disorders) will benefit from attention to sex differences, measurement noninvariance, cohort factor structure, and perhaps association with polygenic risk for continuous, higher-order dimensions of psychopathology.[56,76]

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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