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PTSD has Shared Polygenic Contributions with Bipolar Disorder and Schizophrenia in Women

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Twin studies have demonstrated overlap between genetic contributions to posttraumatic stress disorder (PTSD) and other psychiatric disorders.[1] These findings have prompted interest in examining shared genetic risk between PTSD and other psychopathology at the molecular level. With genome-wide association studies (GWAS) and collaborative consortia-based efforts, replicable risk variants have been identified for schizophrenia and bipolar disorder.[2,3] Analyses of genetic loci in aggregate (polygenic effects[4]) have demonstrated shared genetic risk between schizophrenia, bipolar disorder, and major depressive disorder (MDD), with greatest overlap for schizophrenia and bipolar disorder.[3] Using 3,742 candidate single nucleotide polymorphisms (SNPs), an initial polygenic analysis of PTSD by our group[5] suggested overlap in genetic risk for bipolar disorder and PTSD in European American (EA) women that was replicated in a male EA sample with genome-wide data.[6]

Methods

Here we extend our previous investigation[5] by examining associations between polygenic scores computed on genome-wide data using results from the Psychiatric Genomics

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Consortium (PGC) for bipolar disorder, MDD, and schizophrenia (the discovery samples) with PTSD in 1,293 trauma-exposed EA women in the PTSD diagnostic subsample of the Nurses' Health Study II (the target sample). Interviews assessed participants' trauma history and the 17 *DSM-IV* PTSD symptoms subsequent to their worst trauma. Forty-four percent (*n*=563) of women met PTSD criteria; mean PTSD severity score (calculated by summing responses to the 17 symptoms) was 32.3 (*SD*=14.5; range=17-85). Mean age at study baseline was 35.9 (*SD*=4.3; range=24-43).

DNA was extracted from blood samples. Genotyping was performed with the Illumina Infinium PsychArray BeadChip (Psych Chip), which assesses 500,000+ psychiatric-relevant markers genome-wide. Standard GWAS quality control, phasing, and imputation procedures were performed as in the PGC Schizophrenia Working Group.[2] Overlap between previously-examined SNPs in this sample[5] and the genome-wide data was minimal. Using the PGC polygenic score approach,[4] we computed polygenic scores for bipolar disorder, MDD, and schizophrenia based on linkage disequilibrium-pruned results from the largest available studies of these disorders (http://www.med.unc.edu/pgc/downloads). For each disorder, polygenic scores at varying *p*-value thresholds were computed by summing the number of risk alleles for a participant weighted by the natural log of the odds ratio for each SNP. Polygenic scores were computed in PLINK 1.9 (https://www.cog-genomics.org/plink2). The first 10 principal components from a principal components analysis were covaried in analyses.

Results

Logistic and linear regressions predicting PTSD diagnosis and severity, respectively, from the polygenic scores demonstrated overlap in common genetic risk for bipolar disorder and schizophrenia with PTSD (Table 1). Associations generally became stronger with more liberal *p*-value thresholds. As is typical in polygenic score analyses,[5,6] nominal significance was set at $p<.05$, although we note that some associations with the schizophrenia-based scores survived Bonferroni correction ($p<.0014$)—a highly-conservative approach given that many tests were correlated. Bipolar disorder and schizophrenia polygenic scores accounted for a small percentage (<1.2%) of the variance in PTSD outcomes (Table 1). No significant associations emerged for MDD-based scores.

Discussion

Consistent with prior research,[5,6] our findings suggest that common genetic variants for bipolar disorder index genetic risk for PTSD in women. We extended these previous findings by further demonstrating significant overlap between polygenic scores for schizophrenia and PTSD. Effects were small but consistent with others in the literature[3] and with the notion of shared genetic vulnerability across diagnostic categories. The lack of significant results for MDD-based scores is consistent with two previous reports.[5,6] Although surprising given genetic overlap between MDD and PTSD in twin studies,[1] the results parallel the underpowered PGC MDD GWAS, which has no significant loci to date.[3] Additional research needs to assess generalizability of findings and whether results reflect

unique bipolar-PTSD and schizophrenia-PTSD variants or genetic variation associated with general psychopathology risk.

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Table 1

Associations between PTSD and polygenic scores for bipolar disorder, major depressive disorder, and schizophrenia results (latest PGC publications for each).

P-value threshold	Bipolar disorder score					Major depressive disorder score					Schizophrenia score				
	N_{SNPs}	$P_{PTSD\ Dx}$	Nagelkerke R^2	$P_{PTSD\ Sev.}$	R^2	N_{SNPs}	$P_{PTSD\ Dx}$	Nagelkerke R^2	$P_{PTSD\ Sev.}$	R^2	N_{SNPs}	$P_{PTSD\ Dx}$	Nagelkerke R^2	$P_{PTSD\ Sev.}$	R^2
0.05	6241	.302	.002	.211	.002	6030	.562	.000	.498	.001	7152	.006	.007	.001	.008
0.10	10478	.142	.003	.146	.002	10635	.853	.000	.914	.000	9953	.005	.008	.001	.009
0.20	17363	.006	.009	.006	.006	18281	.903	.000	.809	.000	13830	.010	.006	.001	.009
0.30	23099	.003	.010	.005	.007	24968	.885	.000	.724	.000	16754	.016	.006	.001	.009
0.40	28083	.002	.011	.004	.007	30858	.691	.000	.916	.000	19020	.017	.005	.001	.008
0.50	32275	.002	.011	.004	.007	36010	.695	.000	.833	.000	20777	.035	.004	.002	.007

Note. PTSD=posttraumatic stress disorder. PGC=Psychiatric Genomics Consortium. N_{SNPs}=number of SNPs used to derive the polygenic score for a given *p*-value threshold. PTSD_Dx=PTSD diagnosis. PTSD_Sev=PTSD severity. Models were adjusted for the first 10 principal components from a principal components analysis conducted in PLINK 1.9.

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