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GWAS meta analysis identifies TSNARE1 as a novel Schizophrenia / Bipolar susceptibility locus

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We carried out a GWAS meta-analysis of combined mixed-ancestry schizophrenia, schizoaffective, and bipolar cohorts that resulted in the identification of six genome-wide significant loci, including one novel locus at chr8q24.3, encompassing TSNARE1 ($P = 1.28 \times 10^{-9}$). The analysis included a total of 13,394 cases and 34,676 controls. While the function of TSNARE1 remains unknown, bioinformatic predictions based on phylogenetic ancestry indicate it may have a vertebrate-specific function in intracellular protein transport and synaptic vesicle exocytosis.

There is increasing epidemiological[1–3] and genetic evidence[4–8] of a shared genetic etiology between psychiatric disorders and, in particular, between schizophrenia (SCZ) and bipolar disorder (BP)[4]. Numerous genetic variants have been associated with susceptibility to schizophrenia. Many demonstrate overlapping susceptibility with bipolar disorder, including rare highly penetrant familial mutations (e.g. DISC1 gene[9]), numerous recurrent and *de novo* copy number variants (CNVs)[10] and an increasing number of common single nucleotide polymorphisms (SNPs)[4–6,11,12]. To date, 12 genome-wide significant loci have been associated with SCZ and/or BP, all with odds ratios of less than 1.2[6,10]. Taken together, evidence sugests genetic succeptibility to SCZ is highly heterogenous with multiple, common, polygenic variants contributing small effects.

The largest study to date, with genome-wide genotyping data on all samples, remains the phase I study of the PGC meta-analysis with 9,394 cases[9]. We carried out the largest single-phase meta-analysis of schizophrenia and bipolar cases, including data from 16 cohorts (Caucasian, African American and Asian cases and controls), to identify novel susceptibility loci.

Results

Following the meta-analysis of the combined mixed-ancestry schizophrenia, schizoaffective, and bipolar cohorts, 40 variants surpassed genome wide significance (P-values $< 5 \times 10^{-8}$) (Table 1). The 40 SNPs mapped to 6 loci, 5 of which had been previously associated with susceptibility to SCZ and/or BP (ITIH1, SDCCAG8, MHC, MAD1L1 and CSMD1; Figure 1). Two SNPs mapped to a novel locus containing a gene of unknown function, TSNARE1 (t-SNARE domain containing 1) on chr8q24.3 (top SNP rs10098073: fixed effects P 1.28×10^{-9} random effects P 1.28×10^{-9} OR 1.108; rs4129585 fixed effects P 2.38×10^{-8} random effects P 1.28×10^{-9} OR 1.108). In addition to the two genome-wide significant SNPs, multiple other SNPs in LD showed a trend towards association at the locus (Figure 2). Odds ratios for the most significantly associated SNP (rs10098073) across the 16 cohorts ranged from 1.003 to 1.258 (SD 0.06) with one outlier, the Dublin cohort, crossing 1 at OR 0.97. The genomic inflation factor of the meta-analysis was 1.08 indicating that population stratification had been adequately controlled. Analyzing the Caucasian cases and controls alone (n = 11,681 cases and 24,498 controls), the top TSNARE1 SNP, rs10098073, remains genome-wide significant (rs10098073 P-val 3.947×10^{-8} OR 1.12; rs4129585 P-val 1.061×10^{-7} OR 1.17).

While variants at TSNARE1 have not reached genome-wide significance in previous analyses, rs10098073 showed a consistent trend towards association with schizophrenia[12]. For the PGC discovery and replication analyses, the P-value for rs10098073 was 2.09×10^{-5}; OR 1.077; Analysis of the same SNP in the CLOZUK[10]

Table 1 | Genome wide significant variants following SCZ meta analysis

Gene	rsID	CHR	BP (hg18)	Freq	Pval	Direction effect	A1	A2	HetPVal	Imputed
SDCCAG8	rs10927013	1	241655779	0.436	8.09×10^{-9}	++++++++++++++++	G	T	0.91	Y
	rs2039839	1	241665293	0.564	1.28×10^{-8}	−−−−−−−−−−−−−−−	A	G	0.93	I
	rs6703335	1	241675590	0.562	3.71×10^{-9}	−−−−−−−−−−−−−−+	A	G	0.91	I
ITIH1	rs2710323	3	52790945	0.466	2.97×10^{-8}	−++−++−++++++++	C	T	0.39	A
MHC	rs9379858	6	26475668	0.106	1.42×10^{-8}	+++−++−++−++++++	C	T	0.35	A
	rs3799380	6	26575161	0.220	2.80×10^{-8}	+++−++−+++++++++	C	T	0.82	I
	rs6456728	6	26585758	0.779	2.36×10^{-8}	−−−+−−+−−−−−−−−−	A	G	0.82	I
	rs7749305	6	27554545	0.100	2.57×10^{-8}	+++−++++++++++++	C	T	0.29	Y
	rs6904596	6	27599278	0.896	3.06×10^{-8}	−−−+−−−−−−−−−−−	A	G	0.27	A
	rs17750424	6	27809101	0.085	1.99×10^{-8}	++++++++++++++++	C	T	0.38	Y
	rs17693963	6	27818144	0.904	1.61×10^{-9}	+++−++++++++++++	A	C	0.36	IA5
	rs34706883	6	27913234	0.909	3.14×10^{-8}	++++++++++++++++	A	C	0.39	Y
	rs13212651	6	27914964	0.909	3.34×10^{-8}	++++++++++++++++	A	G	0.39	Y
	rs13194781	6	27923618	0.909	3.51×10^{-8}	++++++++++++++++	A	G	0.42	A
	rs13199772	6	27942064	0.909	3.40×10^{-8}	++++++++++++++++	A	G	0.42	Y
MAD1L1	rs10275045	7	1887352	0.403	2.16×10^{-8}	−+−+−−−−−−+−−−+	C	T	0.36	N
	rs12537914	7	1914885	0.365	2.03×10^{-8}	−+−+−−−−−−+−−−−	C	T	0.47	Y
	rs4721184	7	1917310	0.369	2.74×10^{-8}	+−+−+++++++−+++−	C	T	0.47	Y
	rs2056480	7	1920827	0.632	1.54×10^{-8}	−−−+−−−−−−+−−−+	A	G	0.56	I
	rs4721190	7	1921258	0.596	3.83×10^{-8}	−−−+−−−−−−+−−−+	A	G	0.69	IA5
	rs12699477	7	1935479	0.352	8.78×10^{-9}	+−++++++++−++++	C	T	0.67	A
	rs2280550	7	1943082	0.639	3.80×10^{-8}	−+−+−−−−−−+−−−+	A	G	0.49	Y
	rs12666575	7	1970947	0.358	8.27×10^{-10}	−−−−−+−−−−+−−−+	C	T	0.19	A
	rs4721295	7	2003195	0.378	6.23×10^{-10}	+−++++−++++−+++−	G	T	0.07	I
	rs1107592	7	2007958	0.62	5.64×10^{-9}	+−++++−++++−+++−	A	G	0.04	IA5
	rs3778969	7	2106516	0.633	6.43×10^{-9}	−−−−−+−−−−+−−−+	A	G	0.16	N
	rs10224497	7	2116493	0.574	1.09×10^{-8}	++++++−++++−+++−	A	G	0.13	IA5
	rs10239050	7	2124916	0.615	1.11×10^{-8}	+−++++−++++−+++−	A	G	0.12	A
	rs3800913	7	2129763	0.604	4.03×10^{-8}	++++++−++++−+++−	A	G	0.15	A
	rs3800917	7	2134465	0.64	2.29×10^{-9}	−+−−−−+−−−−+−−−+	A	G	0.22	I
	rs3778991	7	2138981	0.656	2.21×10^{-9}	−−−−−−+−−−−+−−−−	A	G	0.20	A
	rs3778994	7	2142381	0.616	2.53×10^{-9}	−−−−−−+−−−−+−−−−	A	C	0.21	A5
	rs4721441	7	2150586	0.356	9.41×10^{-10}	++++++−++++−++++	C	T	0.29	Y
	rs3779003	7	2151428	0.347	2.33×10^{-9}	−−−−−−+−−−−+−−−−	C	T	0.23	IA5
	rs3757440	7	2239462	0.647	1.98×10^{-8}	++++++++++−−+++−	A	G	0.28	IA5
	rs7787274	7	2242519	0.651	1.08×10^{-8}	−−−−−−−−−−+−−−+	A	G	0.21	Y
	rs7799006	7	2244752	0.350	1.24×10^{-8}	−−−−−−−−−−+−−−+	C	T	0.23	A
CSMD1	rs6558872	8	4225547	0.571	4.75×10^{-8}	−−−−+−−−−+−−−−−+	A	G	0.46	IA5
TSNARE1	rs10098073	8	143307411	0.535	9.05×10^{-9}	++−++++++++++++++	A	C	0.93	I
	rs4129585	8	143310840	0.566	2.38×10^{-8}	++++++++++++++++++	A	C	0.99	I

The final column lists the imputation status of each SNP. Y: imputed in all cohorts; N: not imputed; I: imputed in cohorts genotypes on the Illumina chips; A: imputed in cohorts genotyped on the Affymetrix chips; A5: imputed in cohorts genotyped on the Affymetrix 5.0 and 500 arrays.

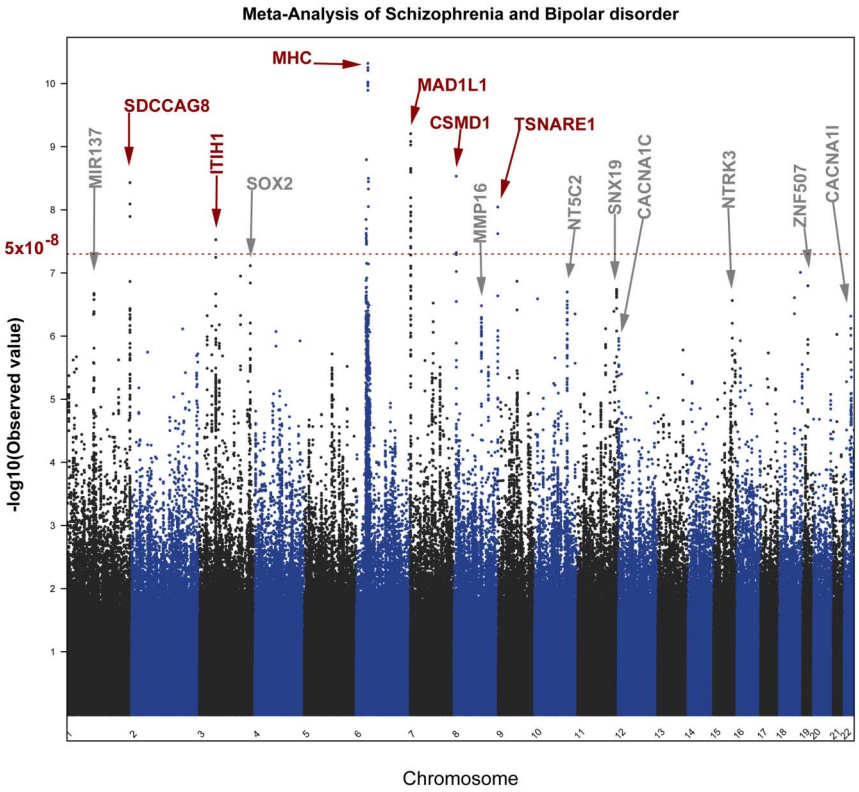

Figure 1 | Manhattan plot of the SCZ-BP meta-analysis. The red dotted line indicates genome wide significance threshold of 5×10^{-8}. Loci highlighted in red surpassed the genome-wide significance threshold in this study.

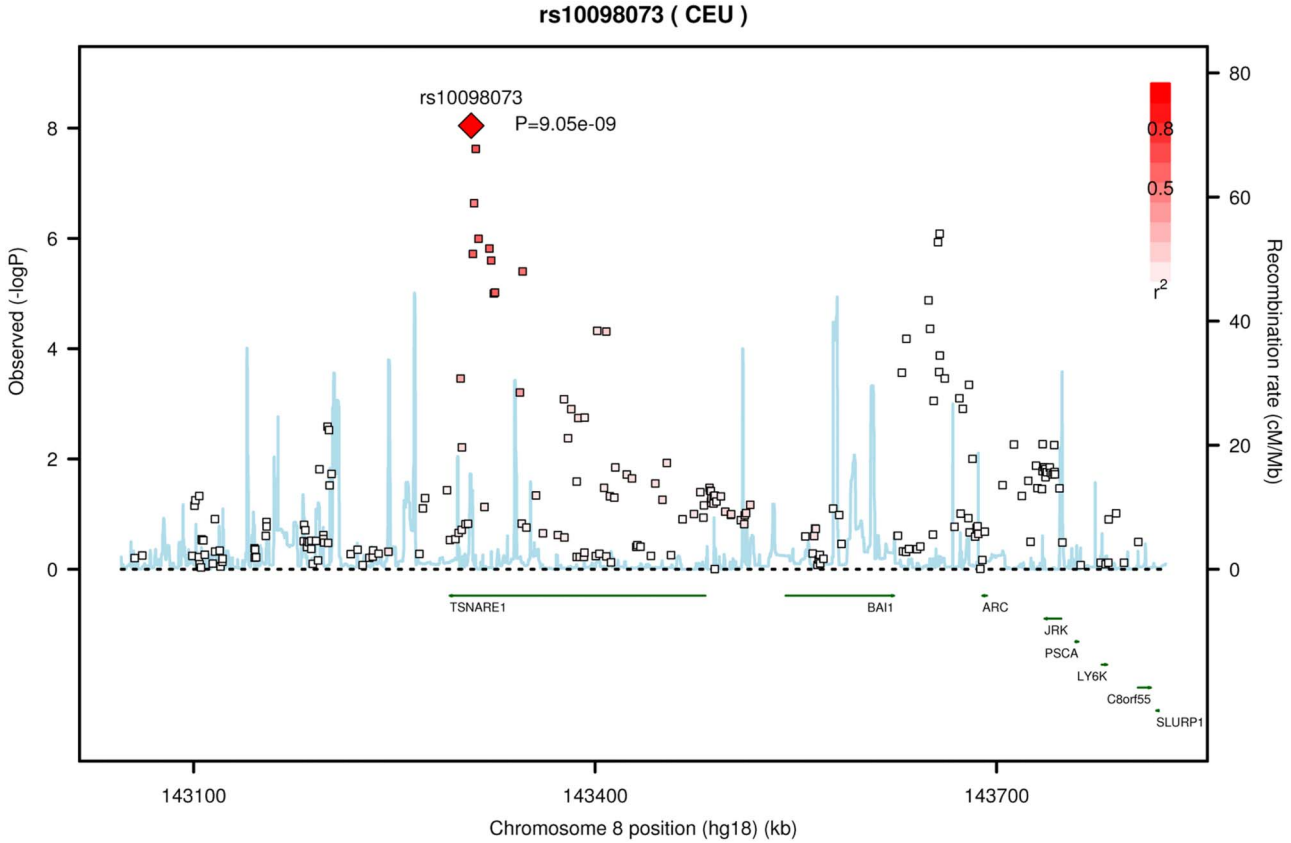

Figure 2 | TSNARE1 regional association plot.

study produced a *P*-value of 0.0165; OR 1.101. After combining the PGC and CLOZUK studies, analysis of rs10098073 resulted in *P* 1.19 $\times 10^{-6}$; OR 1.101. The CLOZUK sample (n = 2652) has not been included in any other GWAS apart from the primary study[12]. There are no overlapping samples between the CLOZUK study and our sample set and therefore the CLOZUK sample can serve as an inter-dependent replication of the association.

Discussion

The function of the TSNARE1 gene remains unknown. A recent publication suggests it may have evolved within the vertebrate lineage from the harbinger transposon superfamily[13]. Bioinformatic predictions based on phylogenetic ancestry indicate it may bind SNARE (soluble N-ethylmaleimide-sensitive factor attached protein receptor) proteins and have SNAP receptor activity. TSNARE1 may therefore have a vertebrate-specific function in intracellular protein transport and synaptic vesicle exocytosis.

Taken together, our meta-analysis confirmed 5 genome-wide significant loci previously reported and identified a novel sixth locus that has not previously been shown to associate with schizophrenia at genome-wide significance. The locus spans TSNARE1, a gene of unknown function that is predicted to have a vertebrate-specific function in synaptic vesicle exocytosis.

Methods

The study included 13,394 schizophrenia and bipolar cases and 34,676 controls (detailed in Supplementary table 1). Of these, 3,182 schizophrenia (of which 377 were classified as schizoaffective) cases and 1,032 bipolar I cases were collected from 28 clinical trials conducted by Janssen Research & Development, LLC (detailed description in Supplementary methods). These samples were matched to 15,277 and 8,000 controls, respectively, from the biorepository at the Center for Applied Genomics (CAG) of the Children's Hospital of Philadelphia (CHOP). All controls were recruited at CHOP and had no diagnosis or family history of psychiatric disease based on their medical record. All Janssen cases were genotyped on the Illumina 1M-DuoV3, while CHOP controls were analyzed using either the Illumina HumanHap550 or 610 Quad arrays.

In addition, 1,157 cases meeting DSM-IV-TR criteria for schizophrenia or schizoaffective disorder from the Center for Applied Genomics (CAG) at The Children's Hospital of Philadelphia and the Department of Psychiatry at the University of Pennsylvania, School of Medicine[14] and 2,107 controls from the biorepository at CAG were also included in the analysis. Samples were genotyped on the Affymetrix 6.0 array at The Children's Hospital of Philadelphia (CHOP) as previously described[14].

The remaining 8,023 schizophrenia cases and 9,292 controls were part of the Schizophrenia Psychiatric Genome-Wide Association Study Consortium (PGC), as previously described[11], and were obtained from the NIMH as schizophrenia distribution 9 (https://www.nimhgenetics.org/).

As different cohorts were genotyped on different platforms, we imputed genotypes based on HapMap 3 reference panel for all samples prior to meta-analysis to allow for direct comparison of variants across the entire cohort. Both fixed and random effect meta-analyses were then carried out. Detailed methods are presented in the supplementary materials.

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Author contributions

H.H. and N.C. conceived and initiated the project. Q.L. managed the Janssen samples and genetic data. P.S. performed the GWAS and meta-analysis. J.G. and D.H. performed a CNV analysis of the data. D.W. performed Janssen genotype data QC. R.E.G. assisted with phenotyping of the PENN cohort. P.S. and H.H. wrote the manuscript. The Janssen-CHOP Neuropsychiatric Genomics Working Group collected the samples and performed phenotype classification. All authors contributed to the data analysis review, discussions, and contributed to the final manuscript.

Additional information

Supplementary information accompanies this paper at http://www.nature.com/scientificreports

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