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Genome-Wide Association Study of Psychosis Proneness in the Finnish Population

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The current study examined quantitative measures of psychosis proneness in a nonpsychotic population, in order to elucidate their underlying genetic architecture and to observe if there is any commonality to that already detected in the studies of individuals with overt psychotic conditions, such as schizophrenia and bipolar disorder. Heritability, univariate and multivariate genome-wide association (GWAs) tests, including a series of comprehensive gene-based association analyses, were developed in 4269 nonpsychotic persons participating in the Northern Finland Birth Cohort 1966 study with information on the following psychometric measures: Hypomanic Personality, Perceptual Aberration, Physical and Social Anhedonia (also known as Chapman's Schizotypia scales), and Schizoidia scale. Genome-wide genetic data was available for ~9.84 million SNPs. Heritability estimates ranged from 16% to 27%. Phenotypic, genetic and environmental correlations ranged from 0.04–0.43, 0.25–0.73, and 0.12–0.43, respectively. Univariate GWAs tests revealed an intronic SNP (rs12449097) at the *TMC7* gene (16p12.3) that significantly associated ($P = 3.485 \times 10^{-8}$) with the hypomanic scale. Bivariate GWAs tests including the hypomanic and physical anhedonia scales suggested a further borderline significant SNP (rs188320715; P-value $= 5.261 \times 10^{-8}$, ~572 kb downstream the *ARID1B* gene at 6q25.3). Gene-based tests highlighted 20 additional genes of which 5 had previously been associated to schizophrenia and/or bipolar disorder: *CSMD1, CCDC141, SLC1A2, CACNA1C*, and *SNAP25*. Altogether the findings explained from 3.7% to 14.1% of the corresponding trait heritability. In conclusion, this study provides preliminary genomic evidence suggesting that qualitatively similar biological factors may underlie different psychosis proneness measures, some of which could further predispose to schizophrenia and bipolar disorder.

Key words: genome-wide association study/heritability/Finnish population/psychoses proneness/schizophrenia/bipolar disorder

Introduction

Psychosis is a serious mental condition by which affected persons experience delusions, hallucinations and severe behavioral abnormalities usually leading to losing contact with reality. While acute forms of psychosis characterize disorders such as schizophrenia, schizoaffective disorder or psychotic bipolar disorder, subclinical types are also present in the general population in the form of odd behaviors, social withdrawal/anxiety, lack of feelings, perceptual abnormalities and magical ideation.[1] These psychotic-like experiences, also termed "schizotypy," are regarded as signs of an underlying predisposition (psychosis proneness) to undergo a clinically meaningful psychotic episode. Evidence from population data on this regard is steadily accumulating,[2,3] and as a consequence there is a current consensus amongst clinicians and researchers on the idea that psychosis proneness is a continuum ranging from a normal dissociative to full-blown diagnosable primary psychotic disorders.[4]

This continuum understanding of psychosis implies that individual differences exist in people's vulnerability due to the combined effect of their personal genetic background and certain environmental stressors, and only those most susceptible would be pushed over a disease threshold.[5,6] It is then possible that the genetic

bases of these psychosis-like feelings and experiences (the lower and central portion of the continuum) are to a certain extent common to those for schizophrenia and other disorders with psychotic components (the upper end of the continuum, beyond the disease threshold).[6] Consequently, unveiling the genes mediating psychosis proneness in nonpsychotic individuals could help to understand part of the genetic architecture of disorders with psychotic components, and in future to accurately identify individuals at putative risk prior to any clinical manifestation.

To date, large meta-analyses of multinational case-control samples on psychotic disorders have successfully identified numerous common polymorphisms with moderately robust effects, mainly on individuals diagnosed with schizophrenia.[7,8] However significant, many of these common polymorphisms showed very limited predictive power. This implies the need for complementary strategies capable of unveiling less common and population specific genetic polymorphisms of importance.[9] Studying psychosis proneness in the general population could make this feasible due to 2 main reasons. First, it allows incorporating standard psychiatric epidemiological data that provides information on carefully defined, quantifiable phenotypes and symptoms well below the disease threshold. Second, these data are normally gathered from well-characterized nation-wide registers and cohorts, which can take better advantage of population specific haplotype blocks and subtle linkage disequilibrium patterns to isolate less common, population specific variants with unanticipated roles that may well pass undetected in meta-analyses of multinational case-control samples.[10–12]

Current understanding of the genetics underlying psychosis proneness in the general population derives principally from traditional quantitative genetic methods, applied to phenotypic data alone, and obtained from close relatives such as twins or parents-offspring. These have offered heritability estimates ranging from 15% to 65% depending upon symptom evaluated or population age.[13–18] The most complete study thus far investigated phenotypic data on self-rated paranoia, hallucinations, cognitive disorganization, grandiosity, and anhedonia, as well as parent-rated negative symptoms, from 5059 adolescent twin pairs from England and Wales.[19] Consistent with findings from smaller studies, their results showed genetic influences ranging between 15% and 59%, and genetic correlations between 0.27 and 0.63. A relatively similar study in 3685 Australian young-adult twins focusing on Perceptual Aberration, Magical Ideation, Hypomania, Impulsivity, and Physical and Social Anhedonia, provided comparable genetic influences ranging from 24% to 50%.[20]

Importantly, recent methodological and experimental studies have suggested that heritability estimates obtained through traditional quantitative genetic methods would represent an upper bound estimate of the overall genetic effects on the trait, and that applying current association methods to the available genomic data may well never reveal a significant part of those overall effects.[21] This in turn imposes the need of finding distinctive, more conservative heritability estimates that can provide a sensible description of the extent to which psychoses proneness is affected by polymorphisms susceptible to be detected through the analyses of population genomic data. This type of lower level estimate can nowadays be obtained by applying modern statistical methods that rely on the joint analysis of phenotypic and genomic information from large samples of genetically unrelated individuals. At present, only the study by Sieradzka et al[22] has considered this methodological approach, which resulted in heritability estimates of 20% for anhedonia, 19% for cognitive disorganization, 17% for grandiosity and 14% for paranoia, and an estimate of 0 for hallucinations.

Given the relevance of the genetic effects on psychosis proneness in the normal population, and the current availability of genome-wide association (GWAs) data in psychiatric research, looking for specific genes and markers affecting these traits is a fundamental and sensible action. However, to date only a few studies have provided suggestive evidence for genetic loci of potential interest, such as the TCF4, COMT and DISC1 genes.[23–26] Therefore, we aim to elucidate the genetic architecture of psychosis proneness within a Finnish population-based cohort, maximizing the phenotypic and genomic information available in order to: compute an estimate of the heritability of psychoses proneness traits; disentangle whether shared genetic influences may account for the observed relation between different psychoses proneness scales; and examine genomic regions potentially harboring genes affecting 1 or more of the traits.

Methods

Participants

This study used data collected as part of the larger "Northern Finland Birth Cohort 1966" (NFBC66), a population based longitudinal cohort study comprising 12 058 persons (~96.3% of all possible) with an expected date of birth in 1966 in the northern Finnish provinces of Oulu and Lapland. Data from the participants and their mothers were recorded during pregnancy and at birth with additional follow-up data being collected when they were 1, 14, and 31 years of age, by means of postal questionnaires. Supplementary data was obtained from hospital records, national registers and a physical examination at age 31 years. This investigation analyzed the data gathered at the 31-year follow-up. A detailed explanation of the study protocol for this follow-up may be found elsewhere.[27] In brief, 8394 of the cohort members alive and living in Northern Finland or the Helsinki metropolitan area were initially contacted and invited to participate. A total of 6033 persons participated, of

which 5122 provided answers to a series of standard psychometric instruments. Here we focus on the study of the summary scores from the following scales: Perceptual Aberration Scale (PAS),[28] Hypomanic Personality Scale (HPS),[29] Revised Social Anhedonia Scale (SAS),[30] Revised Physical Anhedonia Scale (PHAS)[30] (also known as Chapman's Schizotypia Scales), and Schizoidia Scale (SCHS).[31] PAS consists of 35 true/false items evaluating psychotic-like experiences including uncommon bodily discomforts, discontinuities and experiences (eg, "My hearing is sometimes so sensitive that ordinary sounds become uncomfortable"). HPS includes 48 true/false items designed to identify hyperactive or exhibitionistic behaviors, feelings of euphoria, impulsivity, irritability, or mood swings (eg, "I have often been so excited about an involving project that I didn't care about eating or sleeping"). PHAS comprises 61 true/false items assessing difficulties experiencing pleasure from physical stimuli that are usually pleasurable such as food, sex, visual or acoustic settings, etc. (eg, "One food tastes as good as another to me"). SAS consists of 40 true/false items evaluating problems experiencing pleasure from nonphysical stimuli and social interactions such as people's company, talking, etc. (eg, "I prefer watching television to going out with other people."). Finally, SCHS includes 7 true/false items revealing key characteristics reckoned to be associated with schizotypal personality (eg, "I am more sensitive than most other people").

These scales are well described and characterized in clinical and epidemiological psychiatric literature and their reliability and validity have been extensively examined previously,[32–35] including in the current sample,[36] and deemed acceptable (eg, test–retest reliability values for the Chapman scales ranging between 0.75 to 0.85), which facilitates subsequent interpretation and understanding of the genetic results obtained. In addition a 12-item version of the Infrequency Scale was included to identify individuals offering random answers.[37]

Exclusion procedures were applied to maximize the quality of the phenotypic data. First, when a participant left 1 or more items of a psychometric scale blank, the rest of the items for that scale were rejected, as full information was required to accurately build the corresponding score. Further, data from participants endorsing >2 items of the Infrequency Scale were disregarded as it was considered evidence of careless response. As we were interested in understanding the genetic predisposition to undergo psychosis-like experiences in the general population without overt psychotic disorders, individuals diagnosed between 1982 (when the cohort members turned 18 years old, the legal age of majority in Finland) to 1997 (when this last 31-years follow-up was completed) with schizophrenia or other psychotic disorders (eg, schizophreniform disorder, schizoaffective disorder, delusional disorder, major depression with psychotic features, bipolar disorder with psychotic features, and psychotic disorders not otherwise specified) were excluded. This information was obtained from the Finnish Hospital Discharge Register. Finally, we disregarded participants who did not provide DNA or who showed any of the confounding characteristics for rejection of genomic information (see below). Supplementary table 1 summarizes the numbers excluded at every step and the final sample sizes available for each trait.

Genomic Data

The NFBC66 members participating at the 31-year follow-up were genotyped using the Illumina HumanHap CNV 370k array (Illumina Inc). Quality control analyses were performed on raw genotype data: genotypes missing in >5% of the samples or samples missing >5% of genotypes, as well as samples showing signs of excessive genome-wide heterozygosity, gender discrepancies, or close consanguinity were excluded.

These cleaned genotypes formed the basis for imputing additional genomic variants, using the IMPUTE2 software,[38] considering the reference genomes from the 1000 Genomes Project (Phase I integrated variant set release from March 2012, Includes 93 Finnish individuals), and outlined as in the National Center for Biotechnology Information (NCBI) human genome assembly 37 (GRCh37). Quality control filters were subsequently applied to reduce the number of SNPs to a highly informative set of ~9.8 million SNPs. The exclusion criteria were: poorly imputed (an imputation informativeness INFO statistic from IMPUTE software < 0.4), undefined genotypes (an allele posterior probability < .95, genotypes set to "missing"), too rare (a minor allele frequency < .001), poorly characterized (missing in >10% of the samples), or genetically unbalanced (Hardy-Weinberg Equilibrium test P-value < 1×10^{-6}).

Statistical Methods (Extended in Supplementary Information)

Descriptive statistics of the psychoses proneness traits were initially computed (supplementary table 2). Phenotypes were then corrected for sex and population substructure (10 principal components), and transformed to a Gaussian distribution by applying inverse normal transformation methods.

Estimates of the proportion of the phenotypic variances explained by the SNPs in autosomal chromosomes were obtained by genome-wide restricted maximum likelihood (GREML) models in the Genome-wide Complex Trait Analysis software (GCTA).[39] The patterns of association between pairs of psychoses proneness traits were studied through examining their pairwise Pearson correlation coefficients. To understand the influences underlying such patterns observed at the phenotypic level, we further computed estimates of their genetic and environmental correlation through GCTA methods.

Phenotypes showing a significant heritability were examined in univariate association analyses using conventional linear regression modeling, while correlated phenotypes also showing significant heritability were entered into a series of bivariate association tests using canonical correlation analyses.[40] Both univariate and multivariate phenotype-SNP association tests were implemented through the corresponding extensions of the PLINK software.[40,41]

Additional analysis of statistical power indicated that the sample size available here ($N = 4269$, or the maximum number of individuals with phenotypic and genetic data) conferred 86.4% power to detect SNPs explaining ≥1% of the total variance in the phenotypes analyzed (supplementary figure 1), assuming a type-I error rate of 5×10^{-8}, complete LD between genotyped and causal markers, and a MAF ≥0.001.[42,43]

Genomic regions harboring SNPs with a suggestive phenotype-SNP association P-value $< 5 \times 10^{-6}$ were followed-up for gene-based association tests, using Versatile Gene-Based Test for Genome-wide Association methods within the VEGAS2 software.[44] Because we are aware that this technique may have difficulties to pinpoint genes including one or very few significant SNPs (and depend somewhat on the LD structure of the region), we performed the analyses also taking into account only the top 10% most significant SNPs in each gene to partly correct for this limitation. Gene-based tests were consequently regarded in our study as an enhancement, rather than a replacement, to the single marker association tests.[45] Genes offering P-values < .05 after Bonferroni correction taking into account the number of genes tested for each phenotype, were taken as significant.

Results

Genetic influences, as estimated from the ~9.6 million autosomal SNPs accounted for a significant part of the total variance for most of the phenotypes. The specific heritabilities (and SE) were as follows: $h^2_{HPS} = 27.4\%$ (8.1); $h^2_{PAS} = 16.6\%$ (6.9); $h^2_{PHAS} = 26.6\%$ (7.9); $h^2_{SAS} = 20.4\%$ (7.9); and $h^2_{SCHS} < 0.1\%$ (6.9%). Since the heritability for SCHS was extremely low, we disregarded the phenotype from further tests.

Phenotypic correlations between traits were low to moderate (r_p = .04–.43), while genetic (r_g) and environmental (r_e) correlations were moderate to high (r_g = .25–.73), and low to moderate (r_e = .12–.43), respectively (table 1). The strongest of the pairwise phenotypic associations were $r_{p,PAS–HPS}$ = .43 and $r_{p,PHAS–SAS}$ = .41. However, similar in magnitude, different patterns were detected in their underlying architecture, and genetic factors tend to account for a higher proportion of the association between PHAS-SAS than between PAS-HPS ($r_{g,PHAS–SAS}$ = .73 [SE $r_{g,PHAS–SAS}$ = .20] vs $r_{g,PAS–HPS}$ = .36 [SE $r_{g,PAS–HPS}$ = .22]). Yet, given the wide standard error of these estimates this differential pattern would not be statistically significant.

The univariate GWAs analysis highlighted an intronic variant (rs12449097; P-value = 3.49×10^{-8}) at the *TMC7* gene (16p12.3) associated to HPS (table 2, figure 1). Interestingly, this marker alone explained a meaningful 2.9% of the trait heritability. As this marker was imputed in our study sample, and was relatively uncommon, its imputation accuracy was verified by contrasting its minor allele frequency with respect to that observed in the Sequencing Initiative Suomi (SISu, www.sisuproject.fi[46]) population reference exome set, which is based upon exome sequence data from 1918 Finnish individuals. Given that the marker was present in both populations at similar frequencies (MAF = 0.003 here vs MAF = 0.004 in SISu), there are grounds to imply that rs12449097 was statistically imputed with reasonable precision in our study sample.

In total, 211 SNPs with suggestive P-value $< 5 \times 10^{-6}$, in any of the 4 univariate traits tested, were mapped in or near to 108 different genes (HPS: 43 genes; PAS: 29 genes; PHAS: 23 genes; and SAS: 13 genes). The subsequent gene-based analyses pinpointed a series of loci harboring 6 significant genes for HPS, 4 genes for PAS, 1 gene for PHAS, and 3 genes for SAS (table 3, and supplementary figures 2, 4, and 5). Altogether, these loci accounted for a meaningful proportion of the heritability of the corresponding psychosis proneness phenotypes: 13.9% of h^2_{HPS},

Table 1. Phenotypic, Genetic, and Environmental Correlations Between Psychoses Proneness Traits

Trait 1	Trait 2	$N_{(pairwise)}$	r_p (SE)	P-value	r_g (SE)	P-value	r_e (SE)
HPS	PAS	3824	.432 (0.015)	<1.00E-16	.358 (0.217)	.084	.429 (0.056)
HPS	PHAS	3787	−.204 (0.016)	<1.00E-16	−.435 (0.197)	.023	−.119 (0.076)
HPS	SAS	3837	−.041 (0.016)	1.11E-02	−.297 (0.262)	.122	.140 (0.074)
PAS	PHAS	3812	.040 (0.016)	1.14E-02	.256 (0.261)	.148	−.122 (0.069)
PAS	SAS	3868	.229 (0.016)	<1.00E-16	.337 (0.263)	.121	.205 (0.062)
PHAS	SAS	3820	.410 (0.015)	<1.00E-16	.730 (0.203)	.005	.352 (0.062)

Note: PAS, Perceptual Aberration Scale; HPS, Hypomanic Personality Scale; PHAS, Revised Physical Anhedonia Scale. r_p, r_g, and r_e refers to estimates of phenotypic, genetic and environmental correlations (pair-wise); *SE* refers to standard errors of estimates; *P-value* obtained from tests on correlation estimates equal to 0 as null hypothesis.

Table 2. Relevant Loci Detected in Univariate and Bivariate Marker-Based Association Analyses

Trait	SNP	Chr	Position	Gene	Allele	INFO	MAF	Missing	HWE	Test Statistic	*P*-value	Beta
HPS	rs12449097	16	19005180	TMC7	A/G	0.606	0.003	0.045	1	−5.527	3.485e-08	−1.13
PAS–PHAS	rs188320715	6	156526681	ARID1B	C/T	0.690	0.005	0.065	0.117	16.830	5.261e-08	−.616/.609

Note: PAS, Perceptual Aberration Scale; HPS, Hypomanic Personality Scale; PHAS, Revised Physical Anhedonia Scale. *Chr* refers to chromosome; Position refers to marker position (NCBI human genome assembly 37, GRCh37); *Gene* refers to suggested candidate gene in the SNP region; *INFO* refers to imputation informativeness INFO statistic from IMPUTE2 software; *MAF* refers to minor allele frequency; missing refers to percentage of individuals with missing genotype; HWE refers to *P*-values from Hardy-Weinberg Equilibrium tests; *Test statistic* obtained the corresponding univariate (*t*-statistic) or bivariate (*F*-statistic) tests; *P-value* from the corresponding univariate or bivariate test; *Beta* from independent univariate association tests.

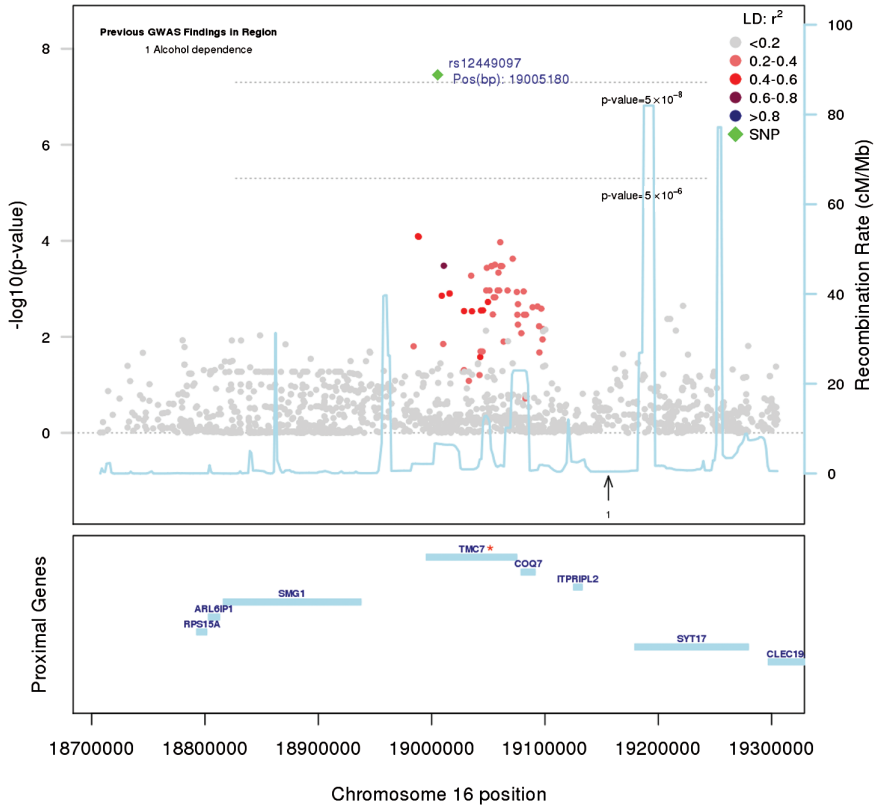

Fig. 1. Regional Manhattan plot (16p12.3) based on *P*-values from a univariate model including HPS. The candidate gene in the locus is marked with a star (*). The leading SNP within the locus is highlighted in green; other SNPs colored according their linkage disequilibrium (LD) with it. Genomic position as in the National Center for Biotechnology Information (NCBI) human genome assembly 37, GRCh37. Information on previous genome-wide association (GWAs) findings (with *P*-value < 5e-8) retrieved from the National Human Genome Research Institute (NHGRI): http://www.genome.gov.

10.4% of h^2_{PAS}, 3.7% of h^2_{PHAS} and 7.1% of h^2_{SAS}. When taking into account the genetic variance explained by the SNPs pinpointed in marker-based GWAs tests, the genomic findings explained as much as 14.1% of h^2_{HPS}.

The bivariate GWAs analyses suggested a further SNP with a borderline genome-wide significant *P*-value (rs188320715; *P*-value = 5.261×10^{-8}) to HPS–PHAS. This SNP is located within an intergenic region at 6q25.3 with the nearest gene being *ARID1B*, ~572 kb upstream (table 2 and supplementary figure 2). A total of 263 SNPs showed a suggestive *P*-value < 5×10^{-6} and they were mapped in or near to 125 different genes (HPS–PAS: 32 genes; HPS–PHAS: 57 genes; HPS–SAS: 40 genes; PAS–PHAS: 33 genes; PAS–SAS: 18 genes; PHAS–SAS: 38 genes). No signs of genomic inflation were detected (inflation factor λ = 1.01–1.03, supplementary figure 3).

The subsequent gene-based analyses showed that genes at 1q32.1, 8q24.13, and 9p21.3 primarily associated to HPS also had residual effects on PAS, PHAS and SAS. Similarly, the gene *CACNA1C* (12p13.33) primarily associated to HPS also had residual effects on PHAS, *MRC2* (17q23.2) associated with PAS also had effects on HPS, PHAS, and SAS; while *CCR4* (3p22.3) associated to SAS also had effects on PHAS. These analyses

Table 3. Results From Gene-Based Association Analyses, Including the Most Likely Candidate Genes for Each Region

Phenotype	Location	Gene	Start–End	N_{SNPs}	Sim_{GENE}	$VEGAS_{GENE}$	$P\text{-value}_{GENE}$	$Sim_{Top10\%}$	$VEGAS_{Top10\%}$	$P\text{-value}_{Top10\%}$	Best SNP	Position BP	$P\text{-value}_{SNP}$	h^2_{GENE}	h^2_{SNP}
HPS	1q32.1	KISS1	204159468–204165619	301	1.00E+05	884.125	2.740E-03	1.00E+07	569.956	**1.140E-05**	rs7513165	204147186	3.37E-07	0.965%	0.642%
	8q24.13	FBXO32	124510126–124553493	464	1.00E+07	1527.036	**9.220E-05**	1.00E+07	632.226	**9.120E-05**	rs61510724	124568658	2.67E-07	0.928%	0.628%
	9p21.3	CDKN2B-AS1	21994789–22121093	404	1.00E+07	2512.052	**5.400E-06**	1.00E+07	820.222	**6.300E-06**	rs3217992	22003223	6.57E-07	0.605%	0.604%
	9p21.3	CDKN2B	22002901–22009312	194	1.00E+07	1400.944	**2.280E-05**	1.00E+07	383.383	**1.290E-05**	rs3217992	22003223	6.57E-07	0.632%	0.604%
	12p13.33	CACNA1C	2162415–2807115	1814	1.00E+05	3722.052	2.530E-03	1.00E+07	2624.117	**2.040E-05**	rs34382810	2340798	9.98E-07	0.756%	0.612%
	13q32.1	CLDN10	96085852–96232010	816	1.00E+04	1819.670	1.050E-02	1.00E+07	940.510	**7.477E-04**	rs17235257	96071345	1.20E-06	0.895%	0.600%
HPS–PAS	1q32.1	KISS1	204159468–204165619	301	1.00E+05	783.959	6.290E-03	1.00E+07	485.473	**5.890E-05**	rs7513165	204147186	1.64E-06	0.965%/>0.001%	0.642%/0.020%
	8q24.13	FBXO32	124510126–124553493	464	1.00E+07	1291.855	**7.074E-04**	1.00E+07	539.489	**3.641E-04**	rs61510724	124568658	1.41E-06	0.928%/>0.001%	0.628%/0.019%
	9p21.3	CDKN2B-AS1	21994789–22121093	404	1.00E+07	2196.735	**2.580E-05**	1.00E+07	715.374	**2.790E-05**	rs3217992	22003223	3.98E-06	0.605%/0.211%	0.604%/0.117%
	9p21.3	CDKN2B	22002901–22009312	194	1.00E+07	1219.809	**9.330E-05**	1.00E+07	340.837	**4.630E-05**	rs3217992	22003223	3.98E-06	0.632%/0.173%	0.604%/0.117%
	13q12.2	MTIF3	28009775–28024739	447	1.00E+05	1231.000	7.810E-03	1.00E+05	510.123	**1.110E-03**	rs9581857	28027714	7.49E-07	>0.001%/0.188%	0.000%/0.535%
	17q23.2	MRC2	60704761–60770962	250	1.00E+05	694.994	6.170E-03	1.00E+07	437.334	**5.190E-05**	chr17:60762523:D	60762523	3.07E-06	0.302%/0.314%	0.130%/0.643%
HPS–PHAS	1q32.1	KISS1	204159468–204165619	301	1.00E+05	778.313	6.470E-03	1.00E+07	483.014	**7.110E-05**	rs7513165	204147186	1.89E-06	0.965%/0.012%	0.642%/>0.001%
	2q31.2	CCDC141	179694483–179914786	1008	1.00E+05	2765.664	1.340E-03	1.00E+07	1187.733	**4.911E-04**	rs16866587	179863363	4.40E-06	0.019%/1.002%	0.103%/0.559%
	6q22.32	TRMT11	126307575–126360420	128	1.00E+03	305.742	7.193E-02	1.00E+07	137.469	**8.470E-04**	rs141259875	126387618	4.30E-06	0.157%/1.002%	0.045%/0.449%
	8q24.13	FBXO32	124510126–124553493	464	1.00E+07	1367.177	**3.721E-04**	1.00E+07	514.114	**5.397E-04**	rs61510724	124568658	1.55E-06	0.928%/0.187%	0.628%/0.034%
	9p21.3	CDKN2B-AS1	21994789–22121093	404	1.00E+07	2185.916	**2.860E-05**	1.00E+07	706.810	**3.150E-05**	rs3217992	22003223	3.66E-06	0.605%/0.178%	0.604%/0.040%
	9p21.3	CDKN2B	22002901–22009312	194	1.00E+07	1263.299	**6.590E-05**	1.00E+07	343.480	**4.220E-05**	rs3217992	22003223	3.66E-06	0.632%/0.174%	0.604%/0.040%
	12p13.33	CACNA1C	2162415–2807115	1814	1.00E+05	3478.389	4.930E-03	1.00E+07	2267.963	**8.250E-05**	rs34382810	2340798	2.44E-06	0.756%/0.001%	0.612%/>0.001%
HPS–SAS	1q32.1	KISS1	204159468–204165619	301	1.00E+05	767.543	7.320E-03	1.00E+07	478.031	**7.680E-05**	rs7513165	204147186	2.01E-06	0.965%/0.044%	0.642%/>0.001%
	3p22.3	CCR4	32993065–32996403	343	1.00E+04	1031.097	1.130E-02	1.00E+07	588.986	**3.880E-05**	rs11919880	32962051	2.07E-06	>0.001%/0.455%	0.036%/0.587%
	8q24.13	FBXO32	124510126–124553493	464	1.00E+07	1469.779	**1.457E-04**	1.00E+07	587.502	**1.748E-04**	rs61510724	124568658	1.96E-07	0.928%/0.119%	0.628%/0.063%
	9p21.3	CDKN2B-AS1	21994789–22121093	404	1.00E+07	2032.304	**6.370E-05**	1.00E+07	684.368	**4.280E-05**	rs3217992	22003223	4.39E-06	0.605%/>0.001%	0.604%/>0.001%
	9p21.3	CDKN2B	22002901–22009312	194	1.00E+07	1134.339	**1.831E-04**	1.00E+07	319.903	**8.850E-05**	rs3217992	22003223	4.39E-06	0.632%/>0.001%	0.604%/>0.001%
	20p12.2	SNAP25	10199476–10288066	438	1.00E+05	1073.322	2.990E-03	1.00E+07	531.011	**3.029E-04**	rs6108491	10324253	2.81E-06	0.729%/0.386%	0.420%/0.148%
PAS	1p36.12	VWA5B1	20617411–20681387	552	1.00E+04	1101.382	2.810E-02	1.00E+05	618.233	**1.120E-03**	rs10916772	20677197	4.10E-06	0.364%	0.553%
	12q24.33	MMP17	132312940–132336316	299	1.00E+04	560.701	2.790E-02	1.00E+05	334.614	**1.080E-03**	rs11246807	132275765	3.01E-06	0.806%	0.538%
	16p13.11	ABCC1	16043433–16236930	742	1.00E+04	1407.935	2.010E-02	1.00E+07	806.508	**3.965E-04**	rs9931487	16204822	3.72E-06	0.448%	0.546%
	17q23.2	MRC2	60704761–60770962	250	1.00E+05	731.145	4.560E-03	1.00E+07	494.472	**1.340E-05**	chr17:60762523:D	60762523	6.71E-07	0.314%	0.643%
PAS–PHAS	8p11.22	ADAM18	39442086–39587583	524	1.00E+05	1508.380	5.840E-03	1.00E+07	673.844	**4.824E-04**	chr8:39394311:D	39394311	3.45E-06	0.111%/0.335%	0.205%/0.421%
	17q23.2	MRC2	60704761–60770962	250	1.00E+04	657.311	1.080E-02	1.00E+07	443.403	**4.150E-05**	chr17:60762523:D	60762523	2.52E-06	0.314%/0.104%	0.643%/>0.001%
PAS–SAS	2q31.3	CERKL	182401400–182521834	533	1.00E+05	1673.159	4.770E-03	1.00E+05	580.911	**1.950E-03**	rs13392054	182502438	3.76E-06	0.301%/0.330%	0.347%/0.379%
	3p22.3	CCR4	32993065–32996403	343	1.00E+05	1109.915	7.740E-03	1.00E+07	659.673	**1.220E-05**	rs11919880	32962051	6.12E-07	0.085%/0.455%	0.211%/0.587%
	17q23.2	MRC2	60704761–60770962	250	1.00E+04	638.890	9.399E-03	1.00E+07	423.914	**7.080E-05**	chr17:60762523:D	60762523	2.93E-06	0.314%/>0.001%	0.643%/>0.001%
PHAS	2q31.2	CCDC141	179694483–179914786	1008	1.00E+07	3050.673	**4.887E-04**	1.00E+07	1429.163	**1.130E-04**	rs16866587	179863363	1.62E-06	1.002%	0.559%
PHAS–SAS	3p22.3	CCR4	32993065–32996403	343	1.00E+05	1070.718	9.190E-03	1.00E+07	542.552	**8.330E-05**	rs11919880	32962051	4.18E-06	0.074%/0.455%	0.025%/0.587%
	11p13	SLC1A2	35272751–35441610	772	1.00E+07	2926.337	**2.665E-04**	1.00E+07	1261.179	**4.410E-05**	rs12804343	35244457	4.56E-06	0.148%/0.255%	0.291%/0.050%
SAS	3p22.3	CCR4	32993065–32996403	343	1.00E+05	1217.351	4.960E-03	1.00E+07	653.640	**1.520E-05**	rs11919880	32962051	6.90E-07	0.455%	0.587%
	8p23.2	CSMD1	2792874–4852328	14 485	1.00E+03	15907.856	2.478E-01	1.00E+05	7713.277	**3.580E-03**	rs4518695	3568201	3.72E-06	0.490%	0.521%
	12q14.3	CAND1	67663060–67708388	485	1.00E+07	2644.596	**1.838E-04**	1.00E+07	736.263	**1.900E-04**	chr12:67741435:I	67741435	4.89E-06	0.289%	0.522%

Note: PAS, Perceptual Aberration Scale; HPS, Hypomanic Personality Scale; SAS, Revised Social Anhedonia Scale; PHAS, Revised Physical Anhedonia Scale. *Start-End BP* refers to base-pair position for the gene start and end (NCBI human genome assembly 37, GRCh37); N_{SNP} refers to the number of SNPs mapped to the gene region and used in gene-based association tests; Sim_{GENE} indicates the number of simulations reached during the Vegas test for all markers mapped within the gene; $Sim_{Top10\%}$ indicates the number of simulations reached during the Vegas test for the top 10% most relevant markers; $VEGAS_{GENE}$ indicates the VEGAS statistic for the test all SNPs mapped within the gene; $VEGAS_{Top10\%}$ indicate the VEGAS statistic for the test the top 10% most relevant SNPs within the gene; $P\text{-value}_{GENE}$ refers to the *P*-value obtained in VEGAS tests all SNPs mapped within the gene; $P\text{-value}_{Top10\%}$ refers to the *P*-value obtained in VEGAS tests including the top 10% most relevant SNPs within the gene (significant *P*-values after Bonferroni correction are in **bold**); *Position BP* refers to the chromosomal base-pair position of the most relevant marker within the gene tested; $P\text{-value}_{SNP}$ refers to the *P*-value obtained in the corresponding univariate or bivariate SNP-based test; h^2_{GENE} refers to the heritability (genetic variance) explained by the gene region evaluated in VEGAS tests, using GCTA methods; h^2_{SNP} refers to the heritability (genetic variance) explained by the best SNP within the gene evaluated in VEGAS tests.

revealed additional new loci harboring significant genes that passed undetected to all previous tests: *SNAP25* (20p12.2) and *ADAM18* (8p11.22) associated to both HPS and SAS; *CERKL* (2q31.3) to both PAS and SAS; and *SLC1A2* (11p13) to both PHAS and SAS (table 3, and supplementary figures 2, 4, and 5).

Discussion

The initial part of this study provides heritability estimates for traits that relate to psychosis proneness, based on the analysis of ~9.6 million autosomal SNPs available from a large sample of unrelated individuals without overt psychotic disorders. It was earlier hypothesized that estimates obtained through this method would be lower than those detected in phenotypic analyses of twin samples.[21] Our results provide support to this hypothesis as the estimates here are either similar or lower than those from previous twin studies with matching psychometric instruments (current vs earlier): HPS: 27.4% vs 28%; PAS: 16.6% vs 33%–49%; PHAS: 26.6% vs 36%–57%; and SAS: 20.4% vs 45%–67%.[13,14,20] Accordingly, they constitute an upper estimate of genetic influences possible to identify by current genome wide association methods.[21]

Other results in this study provide further relevant conclusions. First, by employing multiple continuous measures of psychosis proneness and utilizing statistical methods that allowed scrutinizing genomic regions of interest, we were able to identify a series of genetic loci using a much smaller sample size than has been required to pinpoint most loci in earlier psychiatric case-control GWAs settings. These loci support some earlier findings from case based GWAs studies, but also provide novel insights on the molecular pathways potentially contributing to the development of clinical psychosis, such as schizophrenia or bipolar disorder, as well as other behavioral problems usually associated with psychoses proneness (eg, substance abuse,[47] post-traumatic stress disorder,[48] or some personality disorders[49]). For example, the locus at 1q32.1 showed multiple genes with significant *P*-values in gene-based association tests involving HPS. A detailed examination of the LD structure at this locus in relation to the leading SNP suggested that *KISS1*, a gene highly expressed in different brain regions is likely to be the candidate gene for the locus and explains a meaningful 3.5% of the trait heritability (2.3% accounted for by the leading SNP in the locus alone). The neuropeptide coded by this gene (kisspeptin) modulates neuronal calcium homeostasis in hypothalamic neurons involved in the production of gonadotropin-release hormone and initiates the hypothalamic–pituitary–gonadal axis.[50–52] Importantly, studies have recognized that gonadotropin alterations may prompt mood and behavioral changes.[53,54] Hypothalamic-pituitary dysfunctions have been earlier reported in relation to nonclinical psychotic feelings and experiences,[55] and are also characteristic of schizophrenia patients.[56–58] This finding thus provides preliminary molecular understanding on observations detected in earlier clinical studies among both psychiatrically healthy and ill populations.

Second, it is noticeable that our analyses also detected a series of genes previously linked to some extent either to schizophrenia alone or to both schizophrenia and bipolar disorder (*CSMD1*, *CCDC141, SLC1A2, CACNA1C,* and *SNAP25*).[7,8,59–61] These genes accounted here for 2.8% of the heritability of HPS, 3.8% of PHAS and 1.8% of SAS. Particularly noteworthy is the effect on PHAS of *CCDC141* alone (3.8% of the heritability), a gene that interacts directly with the schizophrenia candidate gene DISC1,[61] and had been identified previously in this cohort in a GWAs conditioned on DISC1 genotypes.[24] Altogether, these findings have important implications as they provide suggestive evidence of a genomic link between psychosis proneness in healthy adults and schizophrenia/bipolar disorder.

Previous positive evidence on this genomic link is limited. The study by Sieradzka et al investigated a large community sample of 2152 16-year-olds, utilizing the Specific Psychotic Experiences Questionnaire in relation to polygenic risk scores for schizophrenia and bipolar disorder, as well as 28 individual SNPs previously associated with schizophrenia, and reported 2 SNPs at the *TCF4* gene significantly associated with the paranoia subscale.[25] Smaller-sized candidate gene studies have also reported positive findings for some markers at the *COMT* gene associated with psychosis proneness scores in healthy samples of European and Chinese origin.[26,62,63]

Our results here provide preliminary support to the idea that a biological susceptibility to disorders such as schizophrenia or bipolar disorder may still be partly found even in individuals without a psychosis diagnosis. Still, observational studies have shown that very few of the persons who score high on psychosis proneness scales go on to develop psychotic disorders,[64] with subclinical negative psychotic symptoms (eg, physical and social anhedonia) carrying stronger predictive power than others.[65,66] Altogether this would imply that only those individuals most susceptible, who were further affected by key genetic and/or environmental influences (eg, an increased burden of large and rare chromosomal abnormalities[67]), would finally develop those diseases. Further evidence on this respect is nevertheless necessary.

A series of methodological considerations need to be acknowledged here. This study ensues from earlier recommendations on psychiatric genetics encouraging new investigations to explore approaches in which traits, rather than being classified as dichotomized entities, are deconstructed into a spectrum of lower-order, highly characterized set of traits with clinical relevance.[68] This would initiate a dynamic process, in which refined phenotypes would allow pinpointing of new genetic signals and in turn generating further phenotype refinements leading

to even lower-order traits.[69] Considering the findings in this study, in which the identified loci explained up to 14.1% of the estimated trait heritability, we believe that our methodological approach was indeed an advantage. The results reported here from an array of inter-related and carefully characterized traits represent only the first step in the genetic dissection of lower-order, high-resolution phenotypes regarding psychosis proneness, and new studies considering further phenotypic refinements are warranted to discover additional genomic regions of importance.

Due to the genomic link that our data suggested between psychosis proneness and schizophrenia/bipolar disorder, we believe that evaluating psychosis proneness even in nonpsychotic individuals is an advisable strategy to understand part of the genetic basis of severe mental disorders with psychotic components. This conclusion however is in contrast to that of Zammit et al[70] from an earlier GWAs study evaluating psychosis proneness in 3483 nonpsychotic adolescents. That previous study did not pinpoint any markers associated with psychotic-like experiences, and variants known to be associated with schizophrenia were also far from significant. The authors concluded that psychosis proneness in population-based samples may not share a comparable genetic architecture to schizophrenia, and thus utilizing a broader more common phenotype of psychotic experiences may not be an efficient approach to increase understanding of the genetic etiology of schizophrenia. This discrepancy with our conclusion is likely to be accounted for by 2 key methodological differences between the studies. Firstly our investigation evaluated a significantly larger pool of genetic markers (~9.8 million here vs ~2.5 million there). This in turn may explain the greater capability of our investigation to detect important loci, as variants that are in high LD with causal ones would be better captured. Secondly, and most importantly, we investigated here psychosis proneness utilizing summary (quantitative) scales built upon an ample number of answers provided to an array of questionnaires dissecting psychosis proneness into specific psychotic features. However, Zammit et al carried out a pre hoc categorization on participants as "cases and controls" depending on whether they displayed any type of psychotic-like experience during adolescence. Given that this categorization resulted in 424 "cases" (or 12.2% of the participants) and 3057 "controls," their statistical power to detect relevant loci was considerably lower compared to ours. To reach a reasonable statistical power similar to the one in our study (eg, ≥80%) with their strategy of categorizing individuals as "cases and controls," at least 7307 cases and as many as 52 682 controls would be required to detect variants significant genome-wide ($P < 5 \times 10^{-8}$) with a moderate effect (relative risk ≥ 1.5), not rare in the population (risk allele frequency ≥ 0.01), assuming a 12.2% prevalence, and 7.21 cases-to-controls ratio (as provided by Zammit et al). This illustrates further the high implications of utilizing quantitative endophenotypes in psychiatric genetic studies of persons not reaching a positive clinical diagnosis of schizophrenia or bipolar disorder.

Finally, it should be acknowledged that our study investigated a sample of adult individuals, while the 2 already mentioned genetic studies on the topic to date (by Sieradzka et al, and Zammit et al) investigated adolescents. Despite psychosis proneness features being more common among adolescents, it has been suggested that when observed at that period it may constitute a developmental phenomenon, carrying a somewhat different connotation and weight than when observed in adulthood.[71] It is very likely however, that most genetic influences involved in adolescence psychotic-like experiences may still be present during adulthood, although a considerable proportion of them may well be age-specific, as genetic studies on many other complex diseases seem to indicate. Further longitudinal studies to clearly determine transitory and persistent genetic and environmental causes are thus warranted. In addition, despite that our descriptive statistics showed significant sex differences within the psychoses proneness scores, our genomic tests were limited to sex-corrected data, as sex-stratified analyses to detect potential sex-heterogeneity of the genetic effects would have resulted in a substantial reduction of the statistical power of detection.

In summary, this study highlights the value of using population-based data without overt psychiatric disorders for genetic association analyses concerning predisposition to psychoses and their related psychiatric conditions. Our results confirm that the genetic predisposition to psychosis proneness is moderate for most traits evaluated. We provide further evidence for overlap in genetic risk between psychiatric endophenotypes related to both schizophrenia and bipolar disorder. We also found association of several of these traits with 5 loci previously reported in connection with schizophrenia and/or bipolar disorder, and provide initial evidence for 15 additional loci that had not previously been connected to any psychiatric trait.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin* online.

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