HHS Public Access

Author manuscript

Am J Med Genet B Neuropsychiatr Genet. Author manuscript; available in PMC 2018 February 17.

Published in final edited form as:

Am J Med Genet B Neuropsychiatr Genet. 2016 March ; 171B(2): 276–289. doi:10.1002/ajmg.b.32402.

Genome-Wide Association Study Reveals Greater Polygenic Loading for Schizophrenia in Cases With a Family History of Illness

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Abstract

Genome-wide association studies (GWAS) of schizophrenia have yielded more than 100 common susceptibility variants, and strongly support a substantial polygenic contribution of a large number of small allelic effects. It has been hypothesized that familial schizophrenia is largely a consequence of inherited rather than environmental factors. We investigated the extent to which familiality of schizophrenia is associated with enrichment for common risk variants detectable in a large GWAS. We analyzed single nucleotide polymorphism (SNP) data for cases reporting a family history of psychotic illness (N = 978), cases reporting no such family history (N = 4,503), and unscreened controls (N = 8,285) from the Psychiatric Genomics Consortium (PGC1) study of schizophrenia. We used a multinomial logistic regression approach with model-fitting to detect allelic effects specific to either family history subgroup. We also considered a polygenic model, in which we tested whether family history positive subjects carried more schizophrenia risk alleles than family history negative subjects, on average. Several individual SNPs attained suggestive but not genome-wide significant association with either family history subgroup. Comparison of genome-wide polygenic risk scores based on GWAS summary statistics indicated a significant enrichment for SNP effects among family history positive compared to family history negative cases (Nagelkerke's $R^2 = 0.0021$; $P = 0.00331$; P-value threshold <0.4). Estimates of variability in disease liability attributable to the aggregate effect of genome-wide SNPs were significantly greater for family history positive compared to family history negative cases (0.32 and 0.22, respectively; $P = 0.031$).We found suggestive evidence of allelic effects detectable in large GWAS of schizophrenia that might be specific to particular family history subgroups. However, consideration of a polygenic risk score indicated a significant enrichment among family history positive cases for common allelic effects. Familial illness might, therefore, represent a more heritable form of schizophrenia, as suggested by previous epidemiological studies.

Keywords

schizophrenia; polygenic; GWAS; family history

INTRODUCTION

Schizophrenia is a common (~1%) and debilitating neuropsychiatric disorder, for which a family history of the condition is among the strongest known risk factors [Gottesman, 1991; Sullivan et al., 2003; Mortensen et al., 2010]. Familial clustering has long been recognized as being typical of schizophrenia, with the biological siblings and children of an affected person having a 10-fold greater risk of developing the illness compared to the general• population [Gottesman and Shields, 1982; Kendler and Diehl, 1993; Lichtenstein et al., 2006]. Studies of twins indicate that schizophrenia is highly heritable (~80%), and adoption studies reveal no such aggregation among the adoptive relatives of affected persons, suggesting that this familial clustering is due largely to genetic factors [Kety et al., 1971; Kety and Ingraham, 2000; Sullivan et al., 2003]. However, despite decades of family, twin, and adoption studies supporting a substantial aggregate genetic component for schizophrenia [Kety et al., 1971; Rosenthal et al., 1971; Gottesman and Shields, 1982; Gottesman, 1991; Kendler and Diehl, 1993; Kety and Ingraham, 2000; Sullivan et al., 2003; Lichtenstein et al., 2006; Mortensen et al., 2010], the mode of transmission is complex and there is no evidence of Mendelian inheritance in affected families nor of genes of large effect in the general population.

In recent years, genome-wide association studies (GWAS) of schizophrenia have yielded a burgeoning list of common (typically, minor allele frequency greater than 1%) susceptibility loci, providing strong support for a substantial polygenic contribution of a large number of small genetic effects, as well as copy number variants (CNVs) with larger effects [International Schizophrenia Consortium, 2008; Stefansson et al., 2008; Walsh et al., 2008]. A polygenic model, described first by R.A. Fisher [Fisher, 1918] and subsequently hypothesized to apply to schizophrenia [Gottesman and Shields, 1967], has been shown to better explain the molecular findings of schizophrenia than any other model, with an estimated third of the variability in disease liability attributable to common variants [International Schizophrenia Consortium, 2009; Cross-Disorder Group of the Psychiatric Genomics Consortium, Genetic Risk Outcome of Psychosis Consortium, 2013; Ripke et al., 2013]. Furthermore, assuming polygenic inheritance and modest family size, for a disease with the observed prevalence and estimated heritability of schizophrenia, more sporadic than familial cases are expected [Yang et al., 2010]. This might explain the somewhat surprising observation that the majority (~96%) of schizophrenia cases in the general population have no affected first-degree relatives [Kety et al., 1971; Kendler, 1987].

In the present study, we sought to determine whether allelic effects detectable in a large GWAS demonstrate greater specificity to schizophrenia cases with a family history of psychotic illness in the Psychiatric GWAS Consortium (PGC) study of schizophrenia [Schizophrenia Psychiatric Genome-Wide Association Study Consortium, 2011], and whether family history positive cases were enriched for common effects overall. We conducted GWAS using a single omnibus test of association among family history positive and negative cases and population controls, followed by model-specification in order to assess whether an observed association was best explained by case-control differences overall, or by one of these two family history subgroups. We also considered the effect of common variants in aggregate by two alternative but complementary methods: polygenic

risk score profiling based on SNP results from a large GWAS, as well as the GCTA method, which estimates the fraction of variability in disease liability attributable to common SNPs genome-wide [Yang et al., 2011; Lee et al., 2011a]. We sought to assess whether estimates obtained by either method differed significantly between cases with differing family history status.

METHODS

Samples, Ascertainment, and Assessment

The subsamples included in this study comprise Stage 1 of the Psychiatric Genomics Consortium Schizophrenia study [Schizophrenia Psychiatric Genome-Wide Association Study Consortium, 2011]. Ascertainment, diagnostic assessment, genotyping, and genotype quality control have been previously described [Schizophrenia Psychiatric Genome-Wide Association Study Consortium, 2011]. Briefly, 17 samples from the United States, Europe, and Australia comprising 9,394 cases were genotyped using a number of common Affymetrix and Illumina SNP array platforms. Imputation was performed with CEU+TSI HapMap phase 3 data (UCSC hg18/NCBI 36), resulting in a total of 1,252,901 autosomal SNPs, for GWAS analysis.

In the current study, we focus on family history of psychotic illness among affected subjects as the phenotype of interest, deriving this information directly from available clinical interviews and/or checklists from the individual PGC sites. A positive family history was defined as having at least one first- or second-degree relative with a diagnosis of psychotic illness. The individual sites and respective sample sizes are presented in Table I. Family history was determined using a variety of instruments including the DIGS, FIGS, OPCRIT, SCAN, and SCID, which we have detailed in the Supplementary Information.

Controls were mostly unscreened; this was justified given the low prevalence of schizophrenia in the population, and given the relatively large number of available controls. As family history information was largely unavailable for controls, this was not considered in these analyses.

Genome-Wide Association and Model Selection

We adopted a procedure analogous to that described by Huang et al. [2010] and Lee et al. [2011b], in which an omnibus test of association at each SNP, genome-wide, is followed by a model-selection approach to identify the configuration of outcomes most likely to be associated with a given variant. This entailed conducting a 2-df multinomial logistic regression (using the nnet package in R) [Venables and Ripley, 2002; R Core Team, 2013] in which allele frequencies can vary across three groups (family history positive cases, family history negative cases, and controls), and obtaining an estimate of the significance of this model relative to a null model in which allele frequencies are identical between groups. Imputed allelic dosages were analyzed, and sex, significantly associated ancestry principal components (PCs) [Schizophrenia Psychiatric Genome-Wide Association Study Consortium, 2011], and a study-site indicator were included as covariates. For those SNPs attaining suggestive significance by the omnibus test ($P < 5 \times 10^{-5}$), we compared the

following logistic models: specific to family history positive cases (family history positive cases ≠ [controls = family history negative cases]); specific to family history negative cases (family history negative cases ≠ [family history positive cases = controls]); and non-specific effect ([family history positive cases = family history negative cases] ≠ controls). We compared these sub-models on the basis of the Bayesian Information Criterion to determine the best-fitting model for the observed disease-SNP association. (i.e., family history positive, family history negative, or non-specific). This is reported alongside the omnibus *P*-value in the presented results in Table II.

Polygene Scores

To test whether family history subgroups differed in the extent of enrichment for common polygenic effects, scores for schizophrenia, bipolar disorder, and major depressive disorder risk were calculated as previously described, using results from the respective PGC primary GWAS of each disorder [Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011; Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium, 2013; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014]. Briefly, schizophrenia risk scores were generated for each study site in the PGC2 study of schizophrenia [Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014], using every other study as the training set in an iterative, “leave-one-out” procedure. This approach resolved any issues related to significance testing of a score among subjects included in the training set, while offering improved power and less sample attrition compared to subdividing the full cohort into approximate halves. Scores were computed based on varying *P*-value thresholds signifying the proportion of SNPs with smaller *P*-values in the training set; *P*-value thresholds ranged between 0.0001 and 1.0. We matched these PGC2 polygenic scores to the PGC1 samples used in the present analysis. We assessed the significance of the family history subgroup difference by standard logistic regression, including 10 ancestry-based principal component scores, sex and a study-site indicator as covariates.

Estimation of the Variance Explained by All the SNPs

We use the methods presented in Lee et al. [2011a], which have been implemented in the freely available GCTA software [Yang et al., 2010]. As described elsewhere, only those SNPs that had minor allele frequency >0.01 and imputation $R^2 > 0.6$ in all contributing cohort sub-samples (imputation cohorts) were retained [Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013]. Subjects were excluded to ensure that for all pairs of individuals, the genome-wide measure of genetic similarity was less than 0.05 (approximately second-cousins). Assuming a disease prevalence (K) of 1% [Gottesman, 1991], we estimated the heritability based on all schizophrenia cases and controls, and for each family history subgroup separately. For the comparison of family history subgroups, we assessed the significance of an observed difference in SNP-h^2 by comparison of the likelihood ratio test statistics obtained for each.

RESULTS

Genome-Wide Association and Model-Fitting

In total, we tested 1.25 M SNPs for association with schizophrenia by a 2-df omnibus test of any association between controls (N = 8,285) and family history positive (N = 978) and negative cases (N = 4,503). Total numbers of cases and controls contributed by each study site are given in Table I. The genomic inflation factor (l) was estimated as 1.127; scaled to a sample size of 1,000 cases and 1,000 controls (λ1,000), this was estimated as 1.018. No single variant attained significance at established genome-wide criteria ($P < 5 \times 10^{-8}$).

For variants demonstrating suggestive association by the omnibus test ($P < 5 \times 10^{-5}$), we performed model-fitting to determine whether the observed association was better explained by either of the family history subgroups or by case-control differences overall. Of 67 suggestively associated independent SNPs, 22 had already attained this level of significance in the primary PGC case-control analysis [Schizophrenia Psychiatric Genome-Wide Association Study Consortium, 2011]. For an additional 20 loci, our model-fitting procedure demonstrated non-specificity of the observed association to any particular family history subgroup, suggesting that a large fraction of these SNPs appear to be associated with both family history negative and positive forms of schizophrenia (Fig. 1). After excluding all SNPs within one megabase of a SNP attaining suggestive levels of significance in the primary case-control analysis [Schizophrenia Psychiatric Genome-Wide Association Study Consortium, 2011], 22 independent loci demonstrated specificity to a particular family history subgroup (Table II). We observe the strongest of these associations at SNPs on 2p22.1. These SNPs, for which family history positive was found to be the best-fitting model, fall upstream of *SLC8A1*, a sodium/chloride ion exchanger expressed ubiquitously across human tissues.

Polygenic Scoring Analyses

Following replicated evidence for a polygenic contribution to schizophrenia [International Schizophrenia Consortium, 2009; Schizophrenia Psychiatric Genome-Wide Association Study Consortium, 2011], we assessed whether weighted polygenic risk scores based on a training-set [Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014] of cases and controls could predict family history status in an independent target dataset, namely each constituent dataset included herein. Given the requirement that training and target datasets be independent, scores were generated via a “leave-one-out” procedure (see Methods section). Results for scores based on varying P-value thresholds are displayed in Figure 2. Overall, family history positive subjects demonstrated enrichment for common polygenic effects compared to subjects with no known family history of illness. We observed the most significant such enrichment for a score constructed of SNPs with *P*-values less than 0.4 in the PGC2 GWAS of schizophrenia (Nagelkerke’s $R^2 = 0.0021$; 1-sided $P = 0.00331$).

Similarly, family history positive cases were also enriched for polygene scores indexing risk of bipolar and major depressive disorders [Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011; Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium, 2013] (Fig. 2). For the bipolar disorder score, we observed the greatest

predictive ability for a score constructed from SNPs with *P*-values less than 0.4 (Nagelkerke's R^2 = 0.0014; 1-sided P = 0.0107). By comparison, enrichment of family history positive cases for major depressive disorder risk was more modest, with greatest predictive value at *P*-value inclusion threshold of 0.2 (Nagelkerke's R^2 = 0.00079; 1-sided P = 0.0424).

Estimation of the Variance Explained by All SNPs

It has been shown previously that the polygenic model explains a substantial proportion of the heritability of schizophrenia [Lee et al., 2012; Cross-Disorder Group of the Psychiatric Genomics Consortium, Genetic Risk Outcome of Psychosis Consortium, 2013; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013]. There is a tendency for polygenic scoring to underestimate the total variation in liability that is tagged by all SNPs because SNP effects are estimated with error [Wray et al., 2013]. We, therefore, sought to assess family history subgroup differences in the proportion of variability in liability explained by common SNPs using GCTA [Yang et al., 2011; Lee et al., 2011a]. Assuming a disease prevalence of 0.01 [Gottesman, 1991] and using a common set of control subjects, we obtained SNP heritability (SNP-h^2) estimates for the family history positive and negative case subgroups separately, as well as for schizophrenia overall,combining the two subgroups (Fig. 3). For the combined family history positive and negative group (5,365 cases and 8,101 controls), we estimated the heritability to be 0.239 (95% CI:[0.213,0.264]; $P = 2 \times 10^{-87}$); we obtained a slightly lower estimate of 0.220 (95% CI:[0.191,0.249]; $P = 1.2 \times 10^{-58}$) for the family history negative subgroup (4,412 cases and 8,104 controls); and 0.306 (95% CI: [0.213,0.399]; $P = 5 \times 10^{-12}$) for the family history positive subgroup (960 cases and 8,128 controls). Comparison of likelihood ratio test-statistics for SNP-h^2 estimates for family history negative and positive subgroups yielded a nominally significant, one-sided *P*-value of 0.031.

DISCUSSION

We have performed the first GWAS meta-analysis of schizophrenia aimed at identifying risk factors specific to familial versus non-familial illness. Although no novel genome-wide significant associations were detected, we did observe a small number of suggestively associated SNPs that demonstrated specificity to familial schizophrenia. We compared estimates of the aggregate contribution of common variants to disease liability in each family history subgroup by two alternative methods, demonstrating a modest but significant enrichment for common polygenic effects among familial schizophrenia cases.

In our primary analysis, we observed genome-wide significant associations in the vicinity of the major histocompatibility complex on chromosome 6p, albeit less significant than reported in the primary PGC1 study (Schizophrenia Psychiatric Genome-Wide Association Study Consortium) and demonstrating no specificity to either family history subgroup. Similarly, the majority of observed suggestive associations in other regions were also nonspecific, having yielded comparable levels of significance in the primary GWAS of schizophrenia. It follows that any inflation in the observed test-statistic distribution—indicating deviation from the null hypothesis of no association—is largely owing to the

power of the PGC1 discovery sample to detect genome-wide significant associations. That SNPs demonstrating specificity to family history negative cases achieved at least nominal significance in the primary GWAS is also not surprising, as the majority of schizophrenia cases are “sporadic” and, therefore, likely representative of the full PGC schizophrenia sample.

We observed the strongest evidence of an association demonstrating specificity to family history positive cases at SNPs upstream of *SLC8A1*. Despite not yielding previous evidence of association with schizophrenia, *SLC8A1* is potentially of interest given its role as a ubiquitous sodium/chloride ion exchanger. Complicating our interpretation of its putative etiological relevance are reported associations between variants in *SLC8A1* and both childhood obesity [Comuzzie et al., 2012] and electrocardiographic QT interval [Kim et al., 2012]. However, pleiotropy has been observed in even established schizophrenia and bipolar susceptibility genes, such *CACNA1C*, which is associated with the Brugada and Timothy Syndromes, both of which cause cardiac arrhythmias (http://www.omim.org/entry/114205). Of potential interest are SNPs demonstrating association to a specific family history subgroup despite having failed to yield even nominally significant [$P < 0.05$] associations in the primary GWAS of schizophrenia (Schizophrenia Psychiatric Genome-Wide Association Study Consortium). This includes variants in brain-expressed genes *BAIAP3* (16p13.3) and *THSD7A* (7p21.3) for the family history positive subgroup, and *MAP3K9* (14q24.2) for the family history positive subgroup.

In the present study, family history subgroups of schizophrenia were not distinguishable by individual genetic variants detectable in a large GWAS. We further asked whether these subgroups differed with respect to the total variability in liability attributable to common SNPs genome-wide. Using GCTA [Yang et al., 2011; Lee et al., 2011a], we obtained an estimate of SNP-heritability for family history positive cases that was slightly elevated relative to family history negative cases, an observation congruent with an underlying, continuous liability distribution. Comparison of schizophrenia polygene scores yielded additional support for this hypothesis, as family history positive cases were significantly enriched for common polygenic effects compared to family history negative cases. This supports a previous finding by our group demonstrating that the unaffected relatives of schizophrenia probands are similarly enriched for such effects [Bigdeli et al., 2013]. Taken together, these data might be construed as a positive—albeit somewhat preliminary—affirmation, using molecular genetic data, that familial schizophrenia is largely a consequence of inherited rather than environmental factors.

Polygenic scoring analyses also revealed enrichment of family history positive cases for common variants conferring risk of bipolar disorder and, to a lesser extent, major depressive disorder, although we note that these findings do not remain significant following correction for the number of scores examined. Nonetheless, the suggested pattern of enrichment is in keeping with several decades of findings from family studies demonstrating an elevated risk of psychotic and affective illness among the first-degree relatives of schizophrenia probands [Kendler and Gardner, 1997], as well as emergent molecular evidence supporting a shared genetic etiology for major psychiatric disorders [Cross-Disorder Group of the Psychiatric Genomics Consortium, Genetic Risk Outcome of Psychosis (GROUP) Consortium, 2013;

Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Ruderfer et al., 2014].

The conclusion that cases with a positive family history of psychosis carry a greater signature of polygenic liability than those with no known family history has potentially important implications for genetic studies of schizophrenia. Large, population-based studies might also benefit from consideration of family history status. To date, the use of unscreened controls has typically been justified by the relatively low prevalence of schizophrenia among the general population, with the ability to include a larger number of controls expected to offset any attendant loss of statistical power. It is conceivable that the use of thoroughly screened controls could potentiate polygenic risk score profiling because of their likely lower polygenic risk, potentially improving individual risk prediction. However, this would entail ascertainment of an equivalent number of such screened controls, likely at greater expense. This could apply in screening for family history of mood disorders as well, if our finding of enrichment for polygenic risk of both bipolar disorder and major depressive disorder is confirmed.

The findings presented herein should be interpreted in light of several key limitations. First, as familial cases represent a minority of all schizophrenia cases, attaining the requisite sample sizes for an adequately powered GWAS is likely to remain a difficult task. This limited statistical power is reflected in the observation that neither the SNP-heritability nor polygenic enrichment findings survive an experiment-wide Bonferroni correction for multiple testing. However, this would be over-conservative given the nested nature of the multiple P-value thresholds in enrichment analysis as well as the non-independence of enrichment and GCTA analyses. Furthermore, there are several well-established limitations of family history based methods, discussed in detail by Kendler and coworkers [Kendler, 1987, 1988; Kendler et al., 1991; Roy et al., 1996]. Like age-at-onset, accounts of family history are typically retrospective. It has also been demonstrated that a respondent's psychiatric diagnosis, as well as their relationship to the affected person (or proband) are relevant factors in the reporting of family history [Kendler et al., 1991; Roy et al., 1996]. It is important to note that, because we have defined family history based on first- and, if available, second-degree relatives, we cannot assume that family history negative cases are unequivocally "sporadic," thus precluding the traditional comparison with "familial" schizophrenia. Finally, given limitations posed by the design of participating studies, we were unable to address the occurrence of schizophrenia spectrum disorders among probands' relatives, and designations of "positive" family history were necessarily restricted to psychotic illness. The lower severity and diminished need for hospitalization in spectrum disorders would require them to be directly assessed in relatives, as they are unlikely to be reliably determined through case subjects' reports. This of course could be prohibitively expensive in large case-control studies.

In summary, we have demonstrated, using molecular genetic data, that familial schizophrenia is largely a consequence of inherited rather than environmental factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Statistical analyses were carried out on the Genetic Cluster Computer (http://www.geneticcluster.org) which is financially supported by the Netherlands Scientific Organization (NWO 480-05-003) along with a supplement from the Dutch Brain Foundation and the VU University Amsterdam. Work on the analyses specific to this paper was funded by a grant by the United States Department of Veterans Affairs Merit Review Program (5I01CX000278) to AHF. This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 279227.

Grant sponsor: United States Department of Veterans Affairs Merit Review Program; Grant number: 5I01CX000278; Grant sponsor: Netherlands Scientific Organization; Grant number: NWO480-05-003; Grant sponsor: Dutch Brain Foundation and the VU University Amsterdam.

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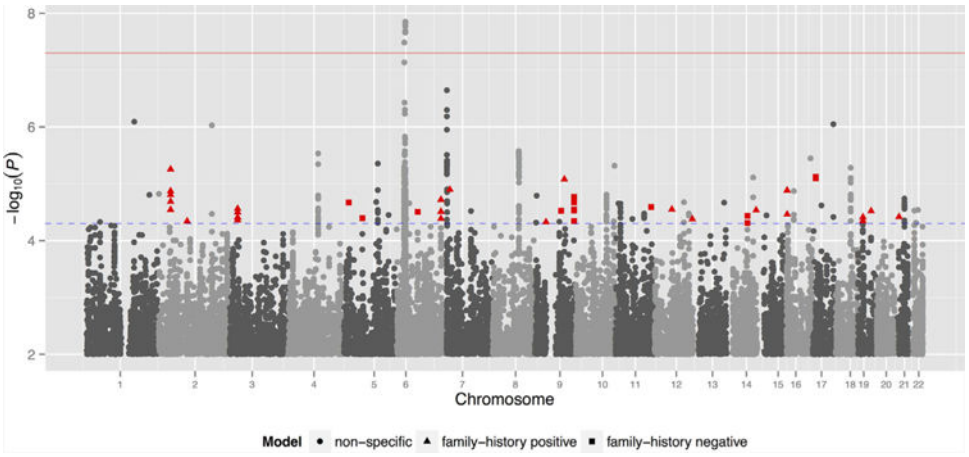

FIG. 1.

Manhattan plot of primary family history GWAS. Red and blue horizontal lines show thresholds for genome-wide (5×10^{-8}) and suggestive (5×10^{-5}) significance, respectively. Highlighted SNPs demonstrated specificity to a particular family history subgroup and were not within 1 Mb of any position attaining suggestive significance in the original schizophrenia analysis [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmgb].

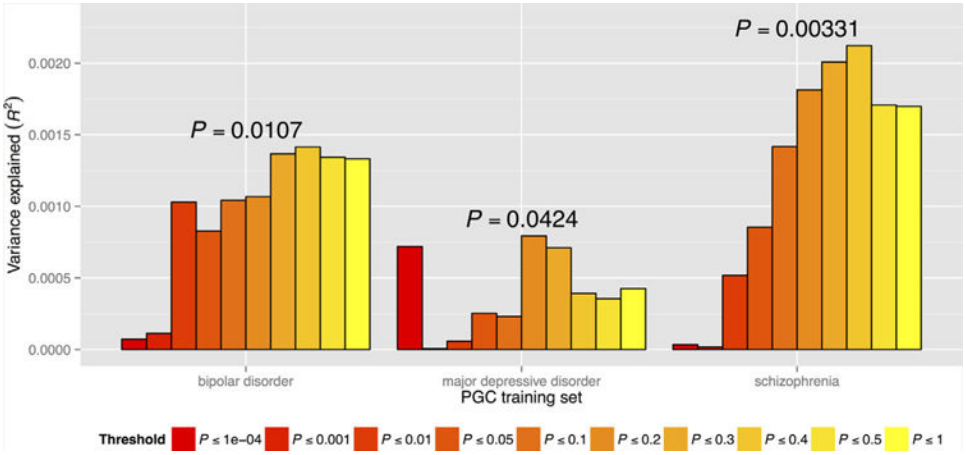

FIG. 2.

Predictive value of bipolar disorder, major depressive disorder, and schizophrenia polygene scores. Results based on varying SNP *P*-value inclusion thresholds are grouped by "training set." Proportion of variance explained (Nagelkerke's pseudo-R^2) is shown on y-axis, and represents comparison of family history positive and negative cases. Displayed *P*-values correspond to the inclusion thresholds yielding the largest proportion of variance explained and are one-sided [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmgb].

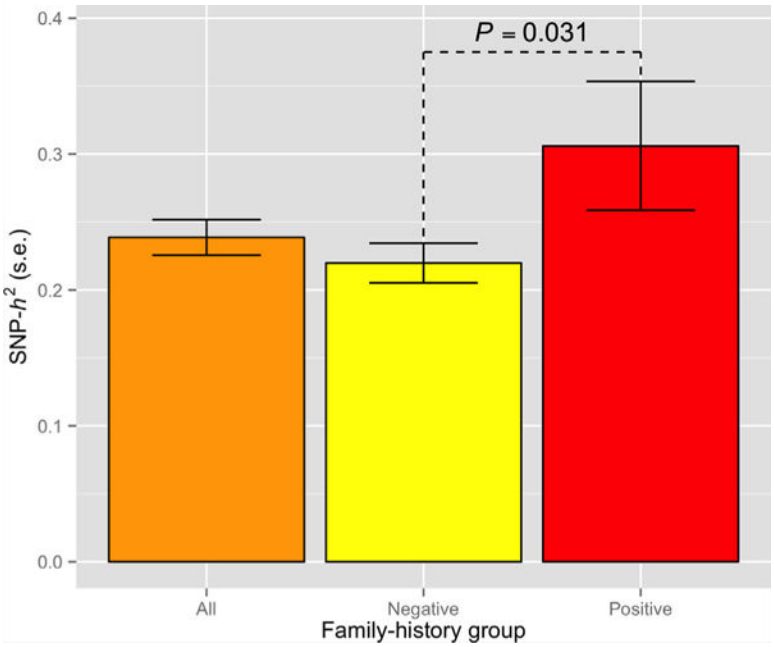

FIG. 3.

Estimated heritability of schizophrenia for family history positive and negative cases. SNP-heritability (SNP-h^2) estimates based on genome-wide SNPs based on family history positive, family history negative and all schizophrenia cases, assuming disease prevalence of 1%; error bars represent standard error (S.E.) of estimate. Displayed *P*-value is one-sided [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmgb].

TABLE I

Numbers of Cases With Given Family History Status and Controls by PGC1 Study Site

		Cases		
Study site	**Source**	**Positive**	**Negative**	**Controls**
ISC-Aberdeen	OPCRIT	106	521	698
ISC-Bulgaria	SCAN	83	302	609
ISC-Dublin	OPCRIT	37	138	860
ISC-Edinburgh	SADS-L	152	83	284
ISC-London	OPCRIT	99	355	492
ISC-Portugal	DIGS	53	216	216
MGS	DIGS	512	1,889	2,473
SGENE-Bonn	OPCRIT	129	342	1,304
SGENE-Copenhagen	OPCRIT	17	64	457
SGENE-Munich	SCID	122	311	351
SGENE-TOP3	SCID	37	158	351
Zucker hillside	SCID	42	124	190
Total		978	4,503	8,285

Abbreviations for study cohorts are as follows: SGENE, Schizophrenia Genetics Consortium; ISC, International Schizophrenia Consortium; TOP3, Thematic Organized Psychoses Research 3; UCLA, University of California at Los Angeles; MGS, Molecular Genetics of Schizophrenia.

Am J Med Genet B Neuropsychiatr Genet. Author manuscript; available in PMC 2018 February 17.

TABLE II

Novel SNPs Demonstrating Specificity to Particular Family History Subgroups

					$Freq_{cases}$					
CHR	**Mb**	**SNP (assoc allele)**	**Info**	**P_{PGC1}**	**Positive**	**Negative**	**$Freq_{cont}$**	**$P_{omnibus}$**	**Model**	**Nearest gene (kb)**
2	40.11	rs7568579 (A)	0.9956	0.036	0.075	0.103	0.11	5.53E-06	+	SLC8A1 (−81.33 kb)
17	10.22	rs3809738 (T)	0.7261	3.45E-04	0.868	0.841	0.854	7.51E-06	−	MYH13 (+0.324 kb) +
9	100.34	rs2779600 (A)	0.9197	2.42E-03	0.565	0.513	0.501	8.28E-06	+	GABBR2 (0)
7	11.6	rs2354954 (A)	0.6895	0.101	0.295	0.323	0.337	1.26E-05	+	THSD7A (0)
16	1.33	rs1132356 (A)	0.8486	0.187	0.132	0.099	0.104	1.30E-05	+	BAIAP3 (0)
9	133.34	rs12552460 (T)	0.9969	7.71E-05	0.851	0.872	0.849	1.70E-05	−	POMT1 (−29.86 kb)
6	150.94	rs9398022 (A)	0.8542	1.27E-03	0.609	0.571	0.559	1.90E-05	+	PLEKHG1 (−23.03 kb)
5	17.06	rs11959796 (A)	0.9155	0.033	0.136	0.161	0.14	2.13E-05	−	MYO10 (+70.02 kb)
11	121.55	rs17126243 (A)	0.9717	1.47E-04	0.058	0.051	0.064	2.54E-05	−	BLID (+62.75 kb)
3	27.57	rs12498098 (T)	0.9933	0.721	0.816	0.854	0.857	2.73E-05	+	SLC4A7 (+100.4 kb) +
12	58.05	rs2203391 (T)	0.981	0.002	0.775	0.802	0.815	2.80E-05	+	SLC16A7 (−314.6 kb)
14	99.69	rs35257667 (A)	0.7317	0.05	0.311	0.278	0.277	2.89E-05	+	DEGS2 (0)
9	89.17	rs1930057 (T)	0.9487	0.002	0.775	0.756	0.779	2.97E-05	−	DAPK1 (−132.9 kb)
19	44.54	rs1375910 (A)	0.7775	0.025	0.064	0.049	0.044	3.00E-05	+	SAMD4B (0)
6	71.8	rs2018220 (A)	0.9694	8.20E-04	0.379	0.4	0.376	3.11E-05	−	B3GAT2 (+78.74 kb) +
14	70.27	rs1476610 (T)	0.988	0.282	0.081	0.11	0.1	3.67E-05	−	MAP3K9 (0)
21	14.38	rs6516605 (C)	0.8042	0.007	0.653	0.614	0.604	3.80E-05	+	LIPI (−24.51 kb)
19	16.6	rs12461484 (C)	0.9134	0.007	0.46	0.424	0.416	3.83E-05	+	MED26 (+4.194 kb) +
5	63.41	rs7737133 (T)	0.7356	0.043	0.008	0.004	0.006	4.01E-05	−	RNF180 (−89.89 kb)
12	127.69	rs12099512 (T)	0.0145	0.801	0.995	0.995	0.995	4.14E-05	+	SLC15A4 (−148.9 kb)
2	96.56	rs11693625 (T)	0.7397	0.01	0.842	0.812	0.801	4.52E-05	+	ARID5A (−9.116 kb)
9	37.89	rs7030885 (A)	0.2433	0.579	0.995	0.998	0.998	4.69E-05	+	MCART1 (0)

For SNPs demonstrating specificity to family history positive or negative schizophrenia, CHR and Mb give its genomic coordinates (hg18); assoc allele represents the tested allele; INFO and P_{PGC1} are the imputation information and *P*-value as reported in the original PGC GWAS; $Freq_{cases}$ and $Freq_{cont}$ give the frequency of the tested allele in family history case subgroups and controls; $P_{omnibus}$ and Model give the significance by 2df omnibus test of “any association” and best-fitting model. For each SNP, the nearest gene within 1 Mb is shown; its position relative to a gene is given parenthetically (negative and positive kb values indicate up- and downstream positions).