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Genome-Wide Association Study of Schizophrenia in Ashkenazi Jews

Fernando S. Goes,[1*] John McGrath,[1] Dimitrios Avramopoulos,[1,2] Paula Wolyniec,[1] Mehdi Pirooznia,[1] Ingo Ruczinski,[3] Gerald Nestadt,[1] Eimear E. Kenny,[4,5,6,7] Vladimir Vacic,[8] Inga Peters,[5] Todd Lencz,[9,10,11,12,13] Ariel Darvasi,[14] Jennifer G. Mulle,[15] Stephen T. Warren,[16] and Ann E. Pulver[1*]

[1]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland

[2]Institute of Genetic Medicine, Johns Hopkins University, Baltimore, Maryland

[3]Department of Biostatistics, Bloomberg School of Public Health, Baltimore, Maryland

[4]The Charles Bronfman Institute of Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York City, New York

[5]Department of Genetics and Genome Sciences, Icahn School of Medicine at Mount Sinai, New York City, New York

[6]Institute of Genomics and Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York City, New York

[7]Center of Statistical Genetics, Icahn School of Medicine at Mount Sinai, New York City, New York

[8]New York Genome Center, New York City, New York

[9]Division of Research, Department of Psychiatry, The Zucker Hillside Hospital Division of the North Shore—Long Island Jewish Health System, Glen Oaks, New York

[10]Center for Psychiatric Neuroscience, The Feinstein Institute for Medical Research, Manhasset, New York

[11]Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York

[12]Department of Psychiatry, Hofstra University School of Medicine, Hempstead, New York

[13]Department of Molecular Medicine, Hofstra University School of Medicine, Hempstead, New York

[14]Department of Genetics, The Institute of Life Sciences, The Hebrew University of Jerusalem, Givat Ram, Jerusalem, Israel

[15]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia

[16]Departments of Human Genetics, Pediatrics and Biochemistry, Emory University, Atlanta, Georgia

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Schizophrenia is a common, clinically heterogeneous disorder associated with lifelong morbidity and early mortality. Several genetic variants associated with schizophrenia have been identified, but the majority of the heritability remains unknown. In this study, we report on a case-control sample of Ashkenazi Jews (AJ), a founder population that may provide additional insights into genetic etiology of schizophrenia. We performed a genome-wide association analysis (GWAS) of 592 cases and 505 controls of AJ ancestry ascertained in the US. Subsequently, we performed a meta-analysis with an Israeli AJ sample of 913 cases and 1640 controls, followed by a meta-analysis and polygenic risk scoring using summary results from Psychiatric GWAS Consortium 2 schizophrenia study. The U.S. AJ sample showed strong evidence of polygenic inheritance (pseudo-R^2 ~9.7%) and a SNP-heritability estimate of 0.39 ($P = 0.00046$). We found no genome-wide significant associations in the U.S. sample or in the combined US/Israeli AJ meta-analysis of 1505 cases and 2145 controls. The strongest AJ specific associations (P-values in 10^{-6}–10^{-7} range) were in the 22q 11.2 deletion region and included the genes *TBX1*, *GLN1*, and *COMT*. Supportive evidence (meta $P < 1 \times 10^{-4}$) was also found for several previously identified

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*Correspondence to:
Fernando Goes, M.D., Department of Psychiatry and Behavioral Sciences, Meyer 4-119A, 600 N. Wolfe Street, Baltimore, MD 21287.
E-mail: fgoes1@jhmi.edu
Ann Pulver, Sc.D., Department of Psychiatry and Behavioral Sciences, 550 N. Broadway, Room #, Baltimore, MD 21205
E-mail: aepulver@jhmi.edu
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genome-wide significant findings, including the HLA region, *CNTN4*, *IMMP2L*, and *GRIN2A*. The meta-analysis of the U.S. sample with the PGC2 results provided initial genome-wide significant evidence for six new loci. Among the novel potential susceptibility genes is *PEPD*, a gene involved in proline metabolism, which is associated with a Mendelian disorder characterized by developmental delay and cognitive deficits.

Key words: schizophrenia; genetics; polygenic; GWAS; Ashkenazi

INTRODUCTION

Schizophrenia is a common, clinically heterogeneous disorder associated with substantial life-long disability and increased mortality [Murray et al., 2012; Jaaskelainen et al., 2013; Laursen et al., 2013]. Schizophrenia is highly heritable, with a genetic architecture that is likely to include contributions from both common and rare variation [Sullivan et al., 2012]. In the era of genome-wide approaches, numerous linkage studies have been performed on familial samples, but lack of consistent replication was consistent with the presence of prominent genetic heterogeneity across families [Holmans et al., 2009; Ng et al., 2009]. Although initial genome-wide association studies of schizophrenia proved to be underpowered, large scale meta-analyses have reached sample sizes necessary to find convincing associations, with 108 genome-wide significant loci recently identified by the Psychiatric genome-wide association study (GWAS) Consortium 2 Schizophrenia (PGC2) analyses [Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014]. While the proportion of heritability accounted for by the genome-wide significant findings remains small, larger sample sizes will likely yield more genome-wide significant findings and will potentially account for far higher heritability estimates [Robinson et al., 2014].

To date, most studies of schizophrenia have been based on outbred Caucasian populations, primarily of Northern European ancestry. Here, we report a GWAS of schizophrenia among Ashkenazi Jews (AJ), an ethnically based population that likely represents one of the more common and "accessible" population isolates. The AJ population has undergone several population bottlenecks, which have led to a number of potentially useful properties for genetic mapping such as greater haplotype lengths, and higher frequencies of pathogenic rare alleles for certain disorders [Bray et al., 2010; Palamara et al., 2012; Ostrer and Skorecki, 2013]. These properties have been particularly evident in certain Mendelian diseases such as lysosomal and glycogen storage diseases, where the frequency of the causal rare alleles is significantly higher in AJ populations [Ostrer, 2001]. For common diseases, the AJ population has facilitated the discovery of rare Mendelian forms of diseases such as hereditary cancer and Parkinson's disease [Friedman et al., 1995; Ozelius et al., 2006], and has led to the earlier identification of several genome-wide significant loci in Crohn's Disease [Kenny et al., 2012]. Although there is no evidence that the prevalence of schizophrenia is higher among the AJ, the history of population bottlenecks and the relative ethnic homogeneity may result in a simpler overall genetic architecture.

Prior analyses of schizophrenia in our AJ samples have identified copy-number variation deletions (3q29) and duplications (7q11.23) that have been replicated across several samples. [Mulle et al., 2010, 2013] In addition, a recent study of schizophrenia among Israeli AJ found genome-wide significant evidence for a marker on the 4q26 region in a sample of 904 schizophrenia cases and 1640 controls [Lencz et al., 2013], providing an initial indication that the AJ population may provide distinct advantages for mapping of complex disorders such as schizophrenia and bipolar disorder.

In this report, we perform a GWAS of a carefully ascertained U.S. AJ sample of schizophrenia cases and controls. However, unlike the previous AJ GWAS study of schizophrenia, we find no evidence of genome-wide significant association in the Johns Hopkins Epidemiology Genetics AJ Sample (Epi Gen AJ SZ) sample or in a meta-analysis with the Israeli AJ sample. These results suggest that common variation in the AJ increases risk for schizophrenia in a polygenic manner, and that most common variants identified in outbred European samples also increase the risk of schizophrenia in the AJ population.

MATERIALS AND METHODS

Study Samples

Epidemiology genetics program AJ schizophrenia case-control samples (Epi Gen AJ SZ). Individuals affected with schizophrenia were collected between 1996 and 2007 by the Epidemiology Genetics Program at The Johns Hopkins University School of Medicine. Cases and family members were identified nationally through research advertisements placed in Jewish periodicals, a study website, and through outreach to Jewish community and mental health organizations. All subjects were examined in person by trained PhD clinicians using a modified version of the Diagnostic Interview for Genetic Studies [Nurnberger et al., 1994], which included additional questioning about developmental milestones and behaviors. A consensus diagnosis, based on DSM-IV criteria, was made by two supervising research clinicians who reviewed the interview along with case vignettes, psychiatric records, and reports from family informants. All subjects underwent a detailed family history interview, which included determination of the ethnic origins of all grandparents. For the current study, we included unrelated subjects with a diagnosis of schizophrenia or schizoaffective disorder and Ashkenazi descent in all grandparents. Ashkenazi controls were ascertained between 2003 and 2007 and were screened for a lifetime history of psychotic symptoms, manic or depressive episodes, and for a history of attempted suicide or psychiatric hospitalizations. The initial pre-quality control (QC) GWAS sample consisted of 648 cases and 591 controls. Cases were primarily male (66.%) while the control sample was more evenly matched (55.7% male). The average age of the cases was 44, with a standard deviation (S.D.) of 11.9, and the mean age of controls was 61.4 (S.D. = 13.4). Controls for the Epi Gen AJ SZ study were purposefully ascertained to be older in order to be past the age of risk for developing schizophrenia.

Hebrew university genomic resource AJ schizophrenia case-control sample (HUGR). GWAS data for this AJ sample was obtained from dbGaP (phs000448.v1.p1). This sample is part of the Hebrew University Genetic Resource (HUGR) and consists of 1044 cases and 2052 controls [Lencz et al., 2013]. Patients were recruited from specialized treatment centers and were assigned a DSM-IV diagnosis of schizophrenia or schizoaffective disorder based on an interview with the Structured Clinical Interview for DSM-IV. DNA Samples from healthy AJ individuals were collected from volunteers at the Israeli Blood Bank; these subjects did not undergo psychiatric screening but reported no chronic disease and were not taking any medication at the time of the blood draw. All cases and controls reported having four grandparents of AJ origin. Males were over-represented in both the HUGR case (63.2%) and control (73.3%) samples. The average age was 45.3 years (S.D. = 3.9) for cases and 42.6 (S.D. = 16.8) for controls. This dataset was analyzed by the JHU group using the available data from dbGaP, which led to essentially identical results compared with the published study [Lencz et al., 2013]

Meta-analysis with the PCG2 schizophrenia study. For the purposes of a meta-analysis, summary data was downloaded from the recently performed PGC2 GWAS of schizophrenia consisting of 36,989 cases and 113,075 controls (https://pgc.unc.edu/) [Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014].

Genotyping and Imputation

Epi Gen AJ SZZ sample. DNA from whole blood was genotyped using the Affymetrix Human Genomewide SNP Array 6.0 as previously described [Mulle et al., 2013]. Genotypes were called using the Corrected Robust Linear Model with Maximum Likelihood Distance (CRLMM) R-package [Scharpf et al., 2011], which provides quality scores for each genotype and incorporates multilevel modeling to adjust for batch effects. We used a CRLMM quality score cut off of 0.991 call genotypes based on the overall behavior of genome-wide QQ-plots. As cases and controls were genotyped in separate batches, we removed SNPs that showed association to specific batches using a *P*-value threshold of 0.0001. Following the primary AJ specific meta-analysis, we also tested whether our top findings showed evidence of unusual batch effects by specifically testing 22 genotyped markers that were in linkage-disequilibrium with the index SNPs shown in Table I. We found no evidence of batch effects on these markers, with an average batch effect P-value of 0.51 (95% CI: 0.49, 0.53). Subsequently, we used highly stringent quality control steps excluding markers with: (1) a MAF <1%; (2) genotype missing rate >1%, (3) HWE *P*-value <0.001 in cases or controls; (4) and subject missing rate >1%. Following these QC steps, 600 cases and 508 controls remained for further analysis. We used the GCTA software [Lee et al., 2013] to remove subjects with cryptic relationships (using the command—grm-cutoff 0.025), but found no unexpected relationships among the remaining subjects.

HUGR schizophrenia case-control sample. We downloaded raw Illumina Omni-1 genotype data for 1,044 cases and 2,052 controls of AJ descent from dbGaP and followed the QC steps described in the original GWAS report [Lencz et al., 2013]: SNP missing rate >2%; HWE p-value $<1 \times 10^{-6}$; minor allele frequency <1%; and subject missing rate >2%. The final filtered file included 790, 901 genotyped SNPs.

Imputation reference panel. As allele frequencies in the AJ population may differ from Caucasian European American allele frequencies, we initially used a specific AJ reference panel consisting of 98 subjects of AJ ancestry genotyped on both the Affymetrix and Illumina platforms as previously described [Kenny et al., 2012]. However, with emerging evidence suggesting that newly available 1000 Genomes based multi-reference panels may be the preferred method to perform imputation in general [Li et al., 2010], we also performed imputation using IMPUTE2 and the 1000G phase 3 project as the reference dataset. We compared the results and found strong similarities across both imputation strategies (correlation of ORs in markers with imputation INFO > 0.6 = 0.95). Given the comparability of both methods and the greater coverage of the 1000 Genomes imputation, we elected to use the later for all further analyses.

1000Genomes (1000G) imputation. We followed IMPUTE2's best practice recommendations by (1) mapping our filtered datasets to UCSC hg19 coordinates; (2) performing strand alignment between our datasets and the reference panel; (3) performing prephasing of our datasets with the SHAPEIT2 software; and (4) using a multi-ethnic 1000G reference panel [Howie et al., 2011]. After imputation we excluded variants with an INFO score <0.6 and a minor allele frequency < 1%, leading to a final datasets comprising of 9, 411,141 markers in the Epi Gen AJ SZ dataset and 9,792,010 markers in the HUGR dataset.

Principal component analysis (PCA). To exclude subjects of mixed ancestry, we performed PCA of each dataset separately but in the presence of population reference panels from the Human Genome Diversity Project (www.hagsc.org/hgdp/files.html) and from a study of Jewish and Middle Eastern populations [Behar et al., 2010]. Common SNPs (MAF > 5%) from each AJ dataset were merged with the reference panels and PCA was performed using EIGENSOFT [Price et al., 2006]. As shown in Supplementary Figure 1, the majority of the AJ samples clustered between middle-eastern and European populations. Plotting the first and third principal component led to the easy identification of an AJ cluster (Supplementary Figure 2a). Samples outside of the AJ cluster were excluded (Supplementary Figure 2b), leading to a final AJ dataset of 592 cases and 505 controls in the Epi Gen AJ SZ sample, and 913 cases and 1640 controls in the HUGR sample. Most of the dropped "non-AJ" participants were from the HUGR controls, who were ascertained from a blood bank sample.

Association and Meta Analysis

We initially performed within study association analyses using the imputed Epi Gen AJ SZ and HUGR datasets. Association was performed using logistic regression in PLINK1.9 [Chang et al., 2015] with 5 principal components as covariates to correct for any residual confounding. Meta-analysis was performed in PLINK using the summary results from the two AJ samples. We prioritized the results of a fixed-effect meta-analysis but also provided the results of the random effect meta-analysis for further evaluation of SNPs with evidence for heterogeneity of effects (defined as a Cochran's Q value <0.05). The results of the meta-analysis were

TABLE I. Top Results ($P < 5 \times 10^{-5}$) from the AJ Specific Meta-Analysis of the Epi Gen AJ SZ and HUGR GWAS

				Meta-analysis		Epi Gen AJ SZ GWAS		HUGR GWAS		
Marker	Chr	Location (hg19)	Risk allele	OR	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	Nearest gene(s)
rs41297816	22	19763978	A	0.74	1.08×10^{-7}	0.74 (0.69–0.78)	3.16×10^{-3}	0.74 (0.71–0.77)	1.00×10^{-5}	*TBX1, GNB1L*
rs11345859	4	55535377	AC	0.77	5.16×10^{-7}	0.73 (0.69–0.77)	9.19×10^{-4}	0.79 (0.77–0.81)	1.28×10^{-4}	*KIT*
rs12412942	10	2357702	G	0.78	8.20×10^{-7}	0.80 (0.77–0.83)	1.08×10^{-2}	0.77 (0.75–0.80)	2.26×10^{-5}	*LINC00701*
rs10812882	9	28891817	T	1.30	1.46×10^{-6}	1.24 (1.19–1.30)	2.35×10^{-2}	1.33 (1.28–1.37)	1.81×10^{-5}	*LINGO2, MIR873, MIR876*
rs58880514	7	70404837	T	0.77	1.61×10^{-6}	0.68 (0.63–0.74)	2.07×10^{-4}	0.80 (0.78–0.83)	9.20×10^{-4}	
rs11211309	1	47045213	A	1.41	2.11×10^{-6}	1.55 (1.38–1.73)	8.33×10^{-4}	1.36 (1.29–1.43)	5.28×10^{-4}	*MKNK1, KCN1, MOBKL2C*
rs76569837	12	45959763	G	2.70	2.70×10^{-6}	3.33 (1.62–6.85)	7.75×10^{-5}	2.22 (1.40–3.51)	6.78×10^{-3}	
rs4685495	3	2236857	A	1.29	2.84×10^{-6}	1.32 (1.25–1.39)	2.99×10^{-3}	1.27 (1.23–1.31)	2.73×10^{-4}	*CNTN4*
rs66831316	2	139194862	C	0.78	3.36×10^{-6}	0.72 (0.67–0.76)	6.87×10^{-4}	0.81 (0.78–0.83)	8.93×10^{-4}	
rs11864208	16	50277214	C	1.27	3.67×10^{-6}	1.25 (1.19–1.31)	3.25×10^{-2}	1.28 (1.24–1.32)	3.98×10^{-5}	*PAPD5*
rs55970365	20	38725186	T	0.52	3.79×10^{-6}	0.74 (0.63–0.87)	2.71×10^{-1}	0.46 (0.36–0.59)	2.17×10^{-6}	
rs369019574	9	81,886,747	AT	0.67	4.05×10^{-6}	0.64 (0.55–0.74)	7.86×10^{-3}	0.68 (0.63–0.74)	1.58×10^{-4}	
rs2144051	14	97544573	G	3.56	4.14×10^{-6}	5.12 (0.59–44.52)	1.55×10^{-2}	3.31 (1.63–6.74)	7.49×10^{-5}	
rs144759648	7	156736023	A	1.79	4.18×10^{-6}	1.61 (1.31–1.98)	3.23×10^{-2}	1.89 (1.56–2.29)	3.84×10^{-5}	*LMBR1,NOM1*
rs67900830	21	44615872	T	0.68	4.24×10^{-6}	0.74 (0.68–0.81)	4.96×10^{-2}	0.65 (0.60–0.71)	2.53×10^{-5}	
rs6083	15	58838010	A	1.29	4.60×10^{-6}	1.31 (1.24–1.38)	7.44×10^{-3}	1.28 (1.24–1.33)	1.96×10^{-4}	*LIPC*

The association results have been clumped (500 kb and $R^2 > 0.2$) to represent approximately independent loci. Genes shown are those within the clumped region.

subsequently grouped into individual loci by using PLINK1.9's clumping utility (grouping variants within 500 kb of each other and an $r^2 > 0.2$). To aid visualization of the highlighted loci, we created regional plots using Locus Zoom[Pruim et al., 2010].

We also performed a meta-analysis between the recently published PGC2 schizophrenia analysis [Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014] and the Epi Gen AJ SZ sample, while excluding the HUGR sample which was part of the original PGC2 study. We matched the PGC2 summary results with our filtered imputed dataset (INFO $\geq$0.6 and MAF $\geq$0.01), leading to a combined dataset of 7,158,791 high-quality markers that were used for meta-analysis. Given the lesser accuracy of indel calling [Fang et al., 2014] as well as the difficulties in matching the indels from the 1000 genomes phase 1 based PGC2 imputation and our phase 3 based imputation, we restricted the meta-analysis to biallelic SNPs.

Polygenic and Secondary Analyses

Gene based, gene set, and eQTL analyses. To further explore the findings of our primary AJ based analysis, we performed gene-based testing of the results of the Epi Gen AJ SZ and HUGR GWAS meta-analysis using the Versatile Gene-based Association Study 2 (VEGAS2) software, which performs gene based association testing and calculates empirical P-values based on simulation [Mishra and Macgregor, 2015]. We also performed gene-set enrichment analyses using the most recent version of the DEPICT (Data-driven Expression-Prioritized Integration for Complex Traits) software tool, which was adapted for meta-analyses based on 1000 Genomes imputation [Pers et al., 2015]. Finally we used a regional brain expression quantitative trait loci (eQTLs) resource [Ramasamy et al., 2014] to identify whether any of our top associated loci harbored a brain eQTL. A list of all strictly defined local brain eQTLs (defined as associations within 1 Mb of the target gene with a false-discovery rate (FDR) of <1%) was obtained from supplementary Table 2 of the original publication.

Subphenotype analysis of the Epi Gen AJ SZ sample. In a previous study including samples that overlap with the current study, we identified nine phenotypic factors that showed evidence for familial aggregation [McGrath et al., 2009]. Three of these factors were normally distributed and the remaining six factors were log-transformed to yield approximately normal distributions (shown in supplementary Fig 6a). Given the limited size of the Epi Gen AJ SZ sample, we restricted the number of multiple test performed with these phenotypic factors by only testing the 108 index SNPs that were identified by the recent PGC2 study. Out of these 108 loci, 102 were found in our imputed dataset, including 84 markers with an INFO score >0.9, and 18 markers with an INFO score between 0.3 and 0.9.

Polygenic analyses. We performed complimentary polygenic analyses using the polygenic scoring method first described by Purcell et al. [International Schizophrenia Consortium et al., 2009] and the mixed linear modeling approach implemented in genome-wide complex trait analysis (GCTA) software [Lee et al., 2013]. For the Epi Gen AJ SZ sample, we restricted the analysis to high confidence imputed SNPs with INFO >0.6 (9, 411,141 markers). Polygenic scoring was performed in PLINK1.9 using the PGC2 pruned polygenic risk profile training dataset (N = 102,636 markers). We removed 45 markers with multiple alleles in our dataset and calculated polygenic scores based on the imputed data across several PGC2 association based *P*-value thresholds. Subsequently, we tested whether the polygenic scores were associated with phenotype status in Epi Gen AJ SZ sample using logistic regression model and 5 ancestry based principal components as covariates. The effect of the polygenic scores was obtained by subtracting the Nagelkerke pseudo-R^2 of the baseline model with just covariates from the full model including the polygenic scores.

Genomewide complex trait analysis (GCTA) analysis. GCTA analysis was performed on the Epi Gen AJ SZ dataset using SNPs imputed with high quality (INFO >0.6). Dosage files were converted into PLINK format in PLINK1.9 using the default threshold parameters. After an additional QC step to remove SNPs that were multi-allelic or newly classified as missing after conversion to most-likely genotypes (−geno 0.05), we used GCTA to create a genetic relationship matrix (GRM) file. We subsequently performed a "SNP-heritability" analysis based on a restricted maximum likelihood (REML) analysis using 5 principal components as covariates to estimate the variance explained by the genome-wide SNPs. Analyses were performed assuming an underlying risk scale and a disease prevalence of 1%.

RESULTS

GWAS of the Epi Gen AJ SZ Cases and Controls

We initially performed a GWAS of the imputed Epi Gen AJ SZ sample of 592 cases and 505 controls. Logistic regression analyses with five principal components as covariates ($\lambda_{GC} = 1.02$) revealed eleven independent regions with association *P*-values in the 10^{-6} range (results shown in supplementary Table 1) with no marker meeting genome-wide significance. Notably, we found no evidence for association of the 4q26 region that was previously reported to have genome-wide significance in the HUGR GWAS sample [Lencz et al., 2013]. The top marker highlighted by the original HUGR study (rs11098403) did not replicate in the Epi Gen AJ SZ sample and showed a weak association in the opposite direction (risk allele: A; OR = 1.06; $P = 0.48$).

Meta-Analysis of Epi Gen AJ SZ and HUGR AJ Samples

We obtained raw genotypes from a recently published AJ schizophrenia case-control GWAS (HUGR sample) [Lencz et al., 2013], which had previously found genome-wide significant evidence for association to an intergenic region upstream of *NDST3*. Although this dataset consisted of subjects of nominally bilineal Ashkenazi descent, principal component analysis showed evidence of mixed ancestry (Supplementary Figure 2a and b), which led to the exclusion of 131 cases and 412 controls outside the AJ cluster and resulted in a final dataset of 913 cases and 1640 controls. After QC there were 790,901 genotyped markers in the HUGR dataset that were used for 1000 Genomes imputation. The final imputed filtered dataset consisted of 9,792,010 high quality markers. To perform an AJ specific meta-analysis of both samples, we first performed logistic regression analysis of the HUGR sample using 5 ancestry principal components ($\lambda_{GC} = 1.06$, top results shown in

supplementary Table 2, with QQ plot shown in supplementary Figure 3). As in the original report, this GWAS found genome-wide significant evidence to the 4q26 region (best marker: rs35553880, OR = 0.71, $P = 9.25 \times 10^{-9}$). However, the meta-analysis ($\lambda_{GC} = 1.06$; Supplementary table 3 and Supplementary Figure 3) revealed no associations meeting genome-wide significance criteria, with the best *P*-values in the 10^{-6} to 10^{-7} range (Table I). The top marker on 4q26 in the HUGR dataset (rs35553880) showed no association in the Epi Gen AJ SZ dataset (OR = 1.05, $P = 0.56$), thereby attenuating the strength of the association seen in the meta-analysis (random effect OR = 0.86, $P = 0.43$, Cochran's Q = 0.0002). Table I shows the 16 independent loci with a meta-analysis $P < 5 \times 10^{-6}$, with regional plots for each of these associations shown in Supplementary Figure 4. Among the loci with a meta-analysis $P < 1 \times 10^{4}$ were five regions identified as genome-wide significant by the PGC2 study, including the chromosome 6 *HLA* region and three single gene loci encompassing *CNTN4*, *IMPP2L*, and *GRIN2A*.

Meta-Analysis With PGC2

To uncover novel loci potentially driven by the Epi Gen AJ SZ sample, we used the summary data from the PGC2 meta-analysis of 36,989 cases and 113,075 controls to perform a meta-analysis with the imputed Epi Gen AJ SZ GWAS. There were 7,158,791 high quality (INFO >0.6) markers that overlapped between the Epi Gen AJ SZ and PGC2 datasets. As expected, the Epi Gen AJ SZ PGC2 meta-analysis test-statistics deviated strongly from the null ($\lambda_{GC} = 1.45$, QQ plot shown in Supplementary Fig 3, top results in supplementary Table 4), although this level of deviation was similar to that reported in the original PGC2 study ($\lambda_{GC} = 1.47$). To test whether the risk alleles of the top PGC2 findings were over-represented in the Epi Gen AJ SZ sample compared to what would be expected by chance, we performed a one-sided sign test at various PGC2 *P*-value thresholds using an LD-pruned version of our dataset. As shown in Table II, the majority of the PGC2 findings showed evidence for consistent association in the Epi Gen AJ SZ sample (all one sided binomial test $P \leq 4 \times 10^{-9}$). The meta-analysis of these two datasets generally showed evidence for the loci already discovered by the PGC2 analysis; however, there was also evidence for new genome-wide significance ($P < 5 \times 10^{-8}$) in 6 loci that are highlighted in Table III and shown in Supplementary

TABLE II. Percentage of Independent Loci Showing the Same Direction of Effect in the Epi Gen AJ SZ Sample Stratified by Varying PGC2 *P*-Value Thresholds

PGC2 *P*-value threshold	Number of markers showing same direction (%) of effect in Epi Gen AJ SZ dataset	Binomial *P*-value (sign-test)
$P < 1 \times 10^{-4}$	1125/1698 (66.3%)	$P < 2.2 \times 10^{-16}$
$P < 1 \times 10^{-5}$	468/729 (64.2%)	$P = 7.89 \times 10^{-15}$
$P < 1 \times 10^{-6}$	226/320 (70.6%)	$P = 5.4 \times 10^{-14}$
$P < 1 \times 10^{-7}$	124/165 (75.2%)	$P = 3.4 \times 10^{-11}$
$P < 1 \times 10^{-8}$	72/90 (80.0%)	$P = 4.0 \times 10^{-9}$

TABLE III. Newly Identified Genome-Wide Significant ($P < 5 \times 10^{-8}$) loci in the Meta-Analysis of the Epi Gen AJ SZ and PGC2 GWAS

				Meta-analysis		Epi Gen AJ SZ GWAS		PGC 2 GWAS		
Marker	Chr	Location (hg19)	Risk allele	OR	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	Nearest gene(s)
rs10425465	19	33897934	T	1.07	3.17×10^{-8}	1.22 (1.17–1.28)	0.07	1.07 (1.07–1.07)	8.27×10^{-8}	*PEPD, CEBPG*
rs12474906	2	28033538	A	1.07	3.92×10^{-8}	1.19 (1.15–1.24)	0.11	1.07 (1.07–1.07)	1.01×10^{-7}	*BRE, GPN1, MIR4263, MRPL33, RBKS, SLC4A1AP, SUPT7L*
rs73191547	8	10033425	A	0.94	3.92×10^{-8}	0.83 (0.86–0.80)	0.10	0.94 (0.94–0.94)	9.05×10^{-8}	*LINC00599, MIR124-1, MIR597, MSRA, TNKS*
rs7601312	2	229320093	A	0.94	4.15×10^{-8}	0.92 (0.93–0.91)	0.34	0.94 (0.95–0.94)	6.43×10^{-8}	
rs9330316	2	110284236	A	1.06	4.68×10^{-8}	1.11 (1.09–1.13)	0.28	1.06 (1.06–1.07)	7.69×10^{-8}	*SEPT10, SOWAHC*
rs28730912	3	161779956	T	1.07	4.79×10^{-8}	1.04 (1.03–1.05)	0.66	1.07 (1.07–1.07)	5.09×10^{-8}	

The association results have been clumped (500 kb and $R^2 > 0.2$) to represent approximately independent loci. Genes shown are those within the clumped region.

Figure 5. As can be seen in Table III, the association with these new loci was driven primarily by the PGC2 results, which were just below genome-wide significance in the PGC2 study.

Polygenic Analyses

To test for a polygenic contribution, we performed polygenic scoring using the publically available pruned markers from the PGC2 meta-analysis of SCZ [Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014]. We selected common markers between the PGC2 training set and the high quality imputed GWAS (INFO >0.6) markers of the Epi Gen AJ SZ sample. After adjusting for 5 ancestry principal components, we found strong evidence for an association of the polygenic scores and case-control status in the Epi Gen AJ SZ sample across all training set *P*-value thresholds, with association *P*-values $\leq 3 \times 10^{-12}$ and pseudo-R^2 values between 3.1–9.7% (Fig. 1). As a complimentary approach to detect the polygenic burden of schizophrenia in the Epi Gen AJ SZ sample, we also calculated a genome-wide SNP-based heritability estimate of schizophrenia and found robust evidence for common variant heritability of schizophrenia assuming a disorder prevalence rate of 1% ($h^2_{SNP} = 0.39$; SE = 0.12, $P = 0.00046$).

Gene Based, Gene-set, and eQTL Analyses

To further explore the results of the AJ-specific meta-analysis meta-analysis, we performed a number of secondary analyses of the AJ specific meta-analysis results. First, we performed a gene-based association analysis using VEGAS2 (results shown in supplementary Table 5). The best gene-based association was found in *COMT*, with a *P*-value of 3×10^{-6}, which was just below the Bonferroni threshold for multiple testing ($P < 2.1 \times 10^{-6}$). Two other genes within the chromosome 22q11.2 deletion region (*TRMT2A*, *ARVCF*, and *DGCR8*) were also among the top gene-based findings, although with association *P*-values in the 10^{-5} range. Second, we used DEPICT to test for the over-representation of gene sets and pathways among markers with *P*-value $<1 \times 10^{-4}$ in the AJ specific meta-analysis. The strongest gene-set associations were found in a number of protein-protein interaction networks (see Supplementary Table 6), but no finding was significant after correction for multiple testing (all false discovery rates $\geq$0.2). Finally, we also explored whether the top findings from the AJ specific meta-analysis (Table I) and the newly identified genome-wide significant loci from the Epi Gen AJ SZ PGC2 (Table III) were associated with brain eQTLs from the braineac database [Ramasamy et al., 2014]. We did not find any strictly defined eQTLs in the top loci of the AJ specific analysis, but found eQTLs in two loci from Table III, which shows the newly identified genome-wide loci from the Epi Gen AJ SZ and PGC2 analyses. In particular, we found local eQTLs for LINC00599 with a SNP (rs12544798) in LD ($r^2 = 0.55$) with the chromosome 8 index marker (rs73191547), and for *ZNF512* with a marker (rs8731) in moderate LD ($r^2 = 0.44$) with the index marker rs7601312 on chromosome 2.

Clinical Subphenotypes

Detailed clinical phenotyping of the Epi Gen AJ SZ sample has previously led to the identification of nine familial clinical factors

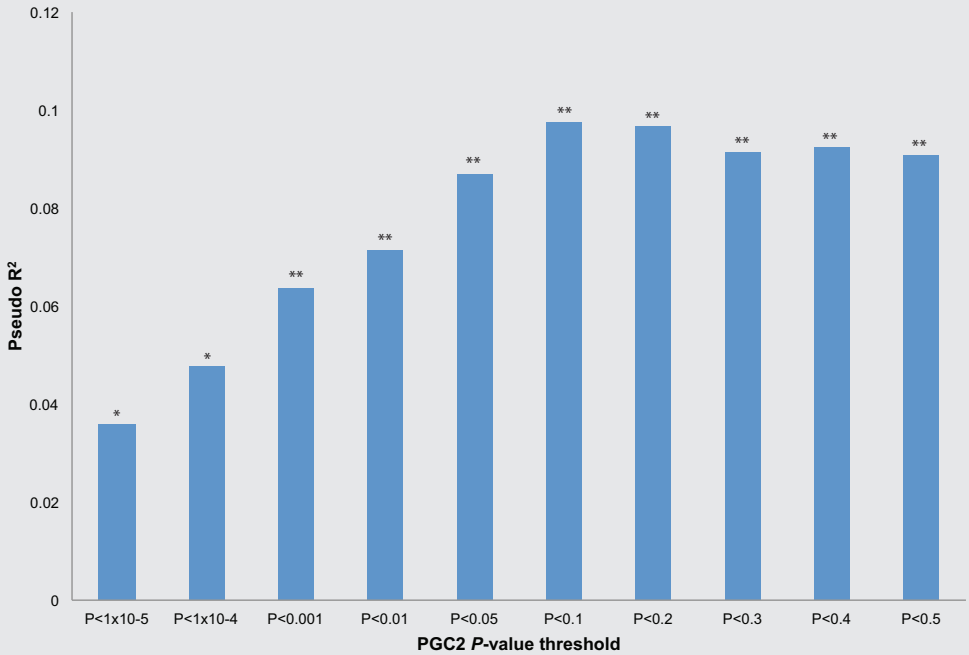

FIG. 1. Proportion of the variance accounted for (pseudo-R^2) in the Epi Gen AJ SZ AJ sample using pruned summary results from the PGC2 discovery dataset. **Association *P*-value $\leq 3 \times 10^{-12}$.

[McGrath et al., 2009]. To further characterize the genome-wide significant loci from the PGC2 analyses, we tested whether the 102 out of 108 genome-wide significant markers from the PGC2 study present in the Epi Gen AJ SZ imputed dataset showed specific associations with the nine phenotypic factors in a case only analysis. These loci were tested across the 9 clinical factors using linear regression, but no marker met significance criteria ($P < 5.4 \times 10^{-5}$) after adjusting for the 918 tests (summary QQ plot show in supplementary figure 6b). We also investigated whether the polygenic risk scores derived from PGC2 showed an association with any of the 9 clinical factors. We selected the PGC2 training set *P*-value threshold that was associated with the higher pseudo-R^2 in the primary case-control analysis ($P < 0.1$, $R^2 = 0.10$ in the Epi Gen AJ SZ case control analysis) and tested for association with phenotypic factors. We found a nominal association between the schizophrenia polygenic scores and both the negative symptom ($P = 0.039$) and the prodromal factor ($P = 0.040$), but neither association survived correction for the 9 factors tested (corrected $P < 0.0056$).

DISCUSSION

In this study we initially performed a GWAS of a U.S. AJ schizophrenia case-control sample and found strong evidence for common polygenic inheritance, but no genome-wide significant findings. We subsequently performed a meta-analysis with a recently published Israeli AJ case-control sample, representing an AJ specific meta-analysis of 1,505 cases and 2,184 controls. Although several genes with prior evidence of association, including the HLA region, *CNTN4*, *IMMP2L*, and *GRIN2A*, showed association *P*-values in the10^{-5} to 10^{-6} range, this meta-analysis also did not yield genome-wide significant findings, suggesting that common variation in the AJ is likely to increase the risk of schizophrenia primarily through a polygenic manner, being comprised of many associations of modest effects. We performed a further meta-analysis of the Epi Gen AJ SZ sample with summary data from a recently reported PGC2 SCZ GWAS and found strong evidence of replication of the top PGC2 SNPs (sign test $P \leq 4.0 \times 10^{-9}$), as well as a initial genome-wide significant evidence for six loci that were just below genome-wide significance in the original PGC2 study.

Consistent with prior GWAS in psychiatric and other complex disorders, the effect sizes of the most significant associations in the meta-analysis of AJ samples were modest and not sufficiently large to reach genome-wide significance. Although our combined sample had sufficient power to identify most common alleles with an odds ratio $\geq$1.4 [Purcell et al., 2003], the strongest findings from common variants in the AJ specific meta-analysis had ORs in the 1.2–1.35 range. While the HUGR sample had initially shown a strong association on 4q26 with an OR of 1.41, we found no evidence for a similar association in the Epi Gen AJ SZ sample, suggesting that the initial strength of the association may have been due to a "winner's curse," or that the two AJ samples are not be directly comparable.

Among the top findings of the AJ specific meta-analysis, several have prior evidence of association with psychiatric illness. The strongest associated marker (rs41297816) was found in *TBX1*, within a linkage disequilibrium block that includes *GNB1L*. Both genes are located in the 22q11.2 deletion syndrome region, which represents one of the most strongly associated copy-number variants with schizophrenia [Jonas et al., 2014]. Notably, haploinsufficiency in either of these two genes has been found to be causally associated with reduced pre-pulse inhibition in a murine model of schizophrenia [Paylor et al., 2006]. Moreover, the AJ specific analysis also provided suggestive evidence for association (*P*-values in the 10^{-6} range) to a marker in *COMT*, which is also found in the 22q11.2 deletion region. Neither of these markers reached genome-wide significance in our meta-analysis with the PGC2 sample, although the marker in TBX1 (rs41297816) did show some evidence of association ($P = 0.00046$) in the PGC2 study. Intriguingly, the gene-based analyses also showed some evidence of association with genes in the 22q11.2 deletion region, with four such genes (*COMT*, *TRMT2A*, *ARVCF*, *DGCR8*) having gene based association *P*-values $<5 \times 10^{-5}$.

The AJ specific analysis also provided evidence for association to several loci that were recently identified as genome-wide significant by the PGC2 study. These loci include a number of promising susceptibility genes, including contactin 4 (*CNTN4*), a neuronal cell adhesion molecule previously linked to rare cases of autism [Zuko et al., 2013], the glutamate receptor protein GRIN2A, and the mitochondrial protein IMMP2L.

Although these specific associations in the AJ specific meta-analysis require further replication, the evidence for an increased polygenic burden was robust, suggesting that, at least for common variants, the genetic architecture of schizophrenia in the AJ population may be similar to that of other Caucasians populations. The extent of the polygenic association was found to be greatest at a threshold between $P < 0.05$ and $P < 0.1$ (pseudo-$R^2 \approx 10\%$), which is similar to the magnitude found in the original PGC2 study. Based on this consistency, we performed a meta-analysis with the PGC2 summary results and found 6 novel genome-wide significant loci. Given the much larger sample size of the PGC2 study, this meta-analysis was largely driven by the results of the PGC2 study, with the new genome-wide significant loci having consistent but quite modest evidence for association the Epi Gen AJ SZ sample. Four of the six novel loci highlight regions with a number of potential susceptibility genes (Supplementary Figure 5), perhaps the most notable being the Peptidase D gene (*PEPD*), which encodes for prolidase, an enzyme involved in the recycling of proline residues from larger imidopetides [Kitchener and Grunden, 2012]. Intriguingly, recessive mutations in *PEPD* are associated with a rare prolidase deficiency syndrome with variable developmental delay and cognitive deficits [Falik-Zaccai et al., 2010]. Additional studies will be necessary to replicate these initial associations and to begin the process of identifying causal associations.

A strength of the samples ascertained by the Epi Gen AJ SZ Program is the detailed, rigorous phenotyping that has been applied to the collection of all its samples from its inception. In prior work, we have found that most of the phenotypic variables with consensus diagnoses could be reduced to nine clinical factors [McGrath et al., 2009]. In this study, we explored whether the PGC2 findings with genome-wide significance criteria present in the Epi Gen AJ SZ sample were associated with any of the clinical

factors, but failed to find evidence for a specific subphenotype association after correction for multiple testing. We also sought to evaluate whether polygenic scores derived from PGC2 were associated with any of the clinical factors, but again found no evidence of an association. Since the power in a polygenic analysis derives largely from the size of the training set [Wray et al., 2014], these results suggest that the PGC2 based polygenic scores are broadly associated with many facets of the schizophrenia phenotype, which likely reflect the wide diversity of phenotypes collated by the PGC2 consortium.

The results of this study should be interpreted in light of several important limitations. First, although we initially hypothesized that certain common variants would be more penetrant in a more homogeneous population such as the AJ, the results suggest that our modest sample size was insufficient to detect genome-wide significant findings using the AJ samples alone. Second, in attempting to limit genotyping errors prior to imputation, we chose strict QC parameters that may have excessively removed markers and thereby limited the overall power of the study. Although this was important to reduce the overall type I error for this specific study, this will likely be less important as the Epi Gen AJ SZ sample becomes integrated in larger meta-analyses, where individual study specific errors have less potential to make an overall impact. Thirdly, the results of our meta-analyses were not corrected for genomic inflation, which was primarily seen in the PGC2 results. However, the degree of inflation seen in the PGC2 study has been found to be consistent with the effects of polygenic inheritance rather than population stratification [Bulik-Sullivan et al., 2015] Finally, our analysis focused exclusively on common variants, which may not leverage the advantage of population isolates such as the Ashkenazi population, where rare and more penetrant variants can be an order of magnitude more prevalent compared with outbred populations [Zuk et al., 2014]. As the human genetics field moves increasingly towards whole genome and whole exome sequencing, the value of populations such as the AJ to map complex phenotypes like schizophrenia will soon be empirically tested.

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