

# Common variants on chromosome 6p22.1 are associated with schizophrenia

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Schizophrenia, a devastating psychiatric disorder, has a prevalence of 0.5–1%, with high heritability (80–85%) and complex transmission<sup>1</sup>. Recent studies implicate rare, large, high-penetrance copy number variants in some cases<sup>2</sup>, but the genes or biological mechanisms that underlie susceptibility are not known. Here we show that schizophrenia is significantly associated with single nucleotide polymorphisms (SNPs) in the extended major histocompatibility complex region on chromosome 6. We carried out a genome-wide association study of common SNPs in the Molecular Genetics of Schizophrenia (MGS) case-control sample, and then a meta-analysis of data from the MGS, International Schizophrenia Consortium and SGENE data sets. No MGS finding achieved genome-wide statistical significance. In the meta-analysis of European-ancestry subjects (8,008 cases, 19,077 controls), significant association with schizophrenia was observed in a region of linkage disequilibrium on chromosome 6p22.1 ( $P = 9.54 \times 10^{-9}$ ). This region includes a histone gene cluster and several immunity-related genes—possibly implicating aetiological mechanisms involving chromatin modification, transcriptional regulation, autoimmunity and/or infection. These results demonstrate that common schizophrenia susceptibility alleles can be detected. The characterization of these signals will suggest important directions for research on susceptibility mechanisms.

The symptoms and course of schizophrenia are variable, without forming distinct familial subtypes<sup>1</sup>. There are positive (delusions and hallucinations), negative (reduced emotions, speech and interest), and disorganized (disrupted syntax and behaviour) symptoms, as well as mood symptoms in many cases. Onset is typically in adolescence or early adulthood, and rarely in childhood. The course of illness can range from acute episodes with primarily positive symptoms to the more common chronic or relapsing patterns often accompanied by cognitive disability and histories of childhood conduct or developmental disorders.

To search for common schizophrenia susceptibility variants, we carried out a genome-wide association study (GWAS) in cases from three methodologically similar National Institute of Mental Health repository-based studies, and screened controls from the general

population. Cases were included with diagnoses of schizophrenia or (in 10% of cases) schizoaffective disorder, with the schizophrenia syndrome present for at least six months, genotyped with the Affymetrix 6.0 array. Because the frequencies of tag SNPs and disease susceptibility alleles can vary across populations, we carried out a primary analysis of the larger MGS European-ancestry sample (2,681 cases, 2,653 controls), and then further analyses of the African-American sample (1,286 cases, 973 controls) and of both of these samples combined, to test the hypothesis that there are alleles that influence susceptibility in both populations. All association tests were corrected using principal component scores indexing subjects' ancestral origins. Genotypic data were imputed for additional HapMap SNPs in selected regions.

These analyses did not produce genome-wide significant findings at a threshold of  $P < 5 \times 10^{-8}$  (see Supplementary Methods). Table 1 summarizes the best results in the European-ancestry and African-American analyses. The strongest genic findings were in *CENTG2* (also known as AGAP1; chromosome 2q37.2,  $P = 4.59 \times 10^{-7}$ ) in European-ancestry subjects, and in *ERBB4* (2q34,  $P = 2.14 \times 10^{-6}$ ) in African-American subjects. Common variants in *ERBB4* (the strongest signal in African-American subjects) and its ligand neuregulin 1 (*NRG1*) have been reported to be associated with schizophrenia<sup>3</sup>. Further information about results in previously reported schizophrenia candidate genes is provided in Supplementary Results 3 and Supplementary Data 2.

As shown in Supplementary Table 17, power was adequate in the MGS European-ancestry sample to detect very common risk alleles (30–60% frequency, log additive effects) with genotypic relative risks of approximately 1.3, with lower power in the smaller African-American sample. The results indicate that there are few or no single common loci with such large effects on risk. The lack of consistency between the European-ancestry and African-American analyses could be due to low power, but new genome-wide analyses presented in the companion paper by the International Schizophrenia Consortium (ISC)<sup>4</sup> (discussed further later) suggest that although there is substantial overlap between the sets of risk alleles that are detected by GWAS in pairs of European-ancestry samples, much less

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**Table 1 | MGS GWAS results**

SNP	Chromosome/ band	Location (bp)	Odds ratio	P value	Gene(s)	Function/relevance
European-ancestry analysis						
rs13025591	2q37.2	236460082	1.225	$4.59 \times 10^{-7}$	<i>CENTG2</i>	GTPase activator; deletions reported in autism cases <sup>14</sup>
rs16941261	15q25.3	86456524	1.255	$8.10 \times 10^{-7}$	<i>NTRK3</i>	Tyrosine receptor kinase; MAPK signalling
rs10140896	14q31.3	88288291	1.216	$9.49 \times 10^{-7}$	<i>EML5</i>	Microtubule assembly
rs17176973	5p15.2	10864474	1.679	$2.16 \times 10^{-6}$		(50 kb upstream of <i>DAP</i> ; mediates interferon- $\gamma$ -induced cell death)
rs17833407	9p21.3	21738320	0.804	$3.02 \times 10^{-6}$		(54 kb upstream of <i>MTAP</i> ; enzyme involved in polyamine metabolism)
rs1635239	Xp22.33	3242699	0.790	$3.04 \times 10^{-6}$	<i>MXRA5</i>	Cell adhesion protein
rs915071	14q12	31503609	0.834	$3.94 \times 10^{-6}$		(102 kb downstream of <i>NUBPL</i> ; nucleotide binding protein-like)
rs11061935	12p13.33	1684035	0.773	$4.06 \times 10^{-6}$	<i>ADIPOR2</i>	Adiponectin (antidiabetic drug) receptor
rs6809315	3q13.11	107360155	0.828	$7.58 \times 10^{-6}$		
rs1864744	14q31.3	88020759	0.828	$7.59 \times 10^{-6}$	<i>PTPN21</i>	Regulation of cell growth and differentiation
rs1177749	10q23.33	97887981	0.835	$1.29 \times 10^{-5}$	<i>ZNF518</i>	Regulation of transcription
rs17619975	6p22.3	15510731	0.611	$1.49 \times 10^{-5}$	<i>JARID2</i>	Neural tube formation; histone demethylase; adjacent to <i>DTNBP1</i> (candidate gene)
African-American analysis						
rs1851196	2q34	212178865	0.733	$2.14 \times 10^{-6}$	<i>ERBB4</i>	Neuregulin receptor
rs3751954	17q25.3	75368080	0.528	$4.59 \times 10^{-6}$	<i>CBX2</i>	Polycomb protein; histone modifications, maintenance of transcriptional repression
rs10865802	3p24.2	25039902	1.330	$6.73 \times 10^{-6}$		
rs17149424	9q34.13	134523705	1.680	$8.00 \times 10^{-6}$	<i>DDX31</i>	RNA helicase family; embryogenesis
rs2162361	10q23.31	90037689	2.020	$9.19 \times 10^{-6}$	<i>RNLS</i>	Degrades catecholamine (regulation of vascular tone)
rs17149524	9q34.13	134546628	1.642	$9.59 \times 10^{-6}$	<i>GTF3C4</i>	Required for RNA polymerase III function
rs2587562	8q13.3	73153592	1.301	$1.56 \times 10^{-5}$	<i>TRPA1</i>	Cannabinoid receptor (cannabis may $\uparrow$ schizophrenia risk <sup>1</sup> ); pain, sound perception
rs4316112	8p12	32539889	0.564	$1.59 \times 10^{-5}$	<i>NRG1</i>	Neuregulin 1; schizophrenia candidate gene; neuronal development
rs4732838	8p21.1	28098106	0.768	$1.68 \times 10^{-5}$	<i>ELP3</i>	Histone acetyltransferase, RNA polymerase III elongator
rs9927946	16p13.2	8990868	0.718	$1.70 \times 10^{-5}$		(26 kb upstream of <i>UPS7</i> ; ubiquitin fusion protein cleavage; induction of apoptosis)
rs13065441	3q26.2	172478029	0.626	$1.94 \times 10^{-5}$	<i>TNIK</i>	Stress-activated serine/threonine kinase
rs2729993	8p12	34116593	0.687	$2.14 \times 10^{-5}$		

Shown are the top 12 results (excluding duplicates—SNPs in the same genes or regions with less significant results) of the MGS European-ancestry (2,681 cases, 2,653 controls) and African-American (1,286 cases, 973 controls) MGS GWAS analyses. Listed are genes within 10 kb of the SNP and annotated information on possible functional relevance; or (in parentheses), information on genes within 150 kb. The odds ratio is for the tested allele (see Supplementary Data 2). Supplementary Data 1 contains results for all SNPs with  $P < 0.001$ , and full gene names. Results of a further exploratory analysis that combined the two data sets are summarized in Supplementary Results 1, Supplementary Table 18 and Supplementary Data 1.

overlap is seen between European-ancestry and African-American samples. This could be because there are actually major differences between the sets of segregating common disease variants in these two populations, and/or because many risk variants are tagged by different GWAS markers or not adequately tagged by the GWAS array, which has poorer coverage of alleles that are more frequent in African populations. The hypothesis underlying our combined analysis, on the other hand, was that there could also be allelic effects common to these populations.

For many common diseases, common risk alleles with genotypic relative risks in the range of 1.1 to 1.2 have been detected when samples were combined to create much larger data sets<sup>5</sup>. Therefore, we carried out a meta-analysis of European-ancestry data with two other large studies: the ISC (3,322 cases, 3,587 controls) and the SGENE consortium (2,005 cases, 12,837 controls). Note that because the Aberdeen sample was part of both the ISC and SGENE consortia, Aberdeen data were excluded from SGENE association tests for the meta-analysis. To identify the regions containing the strongest findings across the three studies (which used several Affymetrix and Illumina genotyping platforms), each group created a list of the SNPs with the best  $P$  values in its final analysis (for example, those with  $P < 0.001$  in MGS), and provided the other groups with its  $P$  values for the SNPs on their lists, on the basis of the genotyped or imputed data or data for the best proxy based on linkage disequilibrium. On the basis of these initial results, all available data for genotyped SNPs and imputed HapMap II SNPs were then shared for regions of interest, of which four emerged from the European-ancestry data: 1p21.3 (*PTBP2*), 4q33 (*NEK1*), 6p22.1–6p21.31 (extended major histocompatibility complex (MHC) region) and 18q21.2 (*TCF4*). We then combined  $P$  values for all SNPs in each region by appropriately weighting  $Z$  scores for sample size, accounting for the direction of association in each sample.

In the meta-analysis of European-ancestry MGS, ISC and SGENE data sets, seven SNPs on chromosome 6p22.1 yielded genome-wide significant evidence for association. These SNPs span 209 kilobases (kb) and are in strong linkage disequilibrium ( $r^2 > 0.9$ ), with substantial linkage disequilibrium across 1.5 megabases (Mb) (Table 2 and Fig. 1). Because of the strong linkage disequilibrium among these SNPs, it is unclear whether the signal is driven by one or several genes, by intergenic elements, or by longer haplotypes that include susceptibility alleles in many genes. The region includes several types of genes of potential interest. The strongest evidence for association was observed in and near a cluster of histone protein genes, which could be relevant to schizophrenia through their roles in regulation of DNA transcription and repair<sup>6,7</sup> or their direct role in antimicrobial defence<sup>8</sup>. Other genes in the broad region are involved in chromatin structure (*HMGNA4*), transcriptional regulation (*ABT1*, *ZNF322A* and *ZNF184*), immunity (*PRSS16*; the butyrophilins<sup>9</sup>), G-protein-coupled-receptor signalling (*FKSG83*) and in the nuclear pore complex (*POM121L2*), although the functions of many genes in the region (and of intergenic sequence variants) are not well understood.

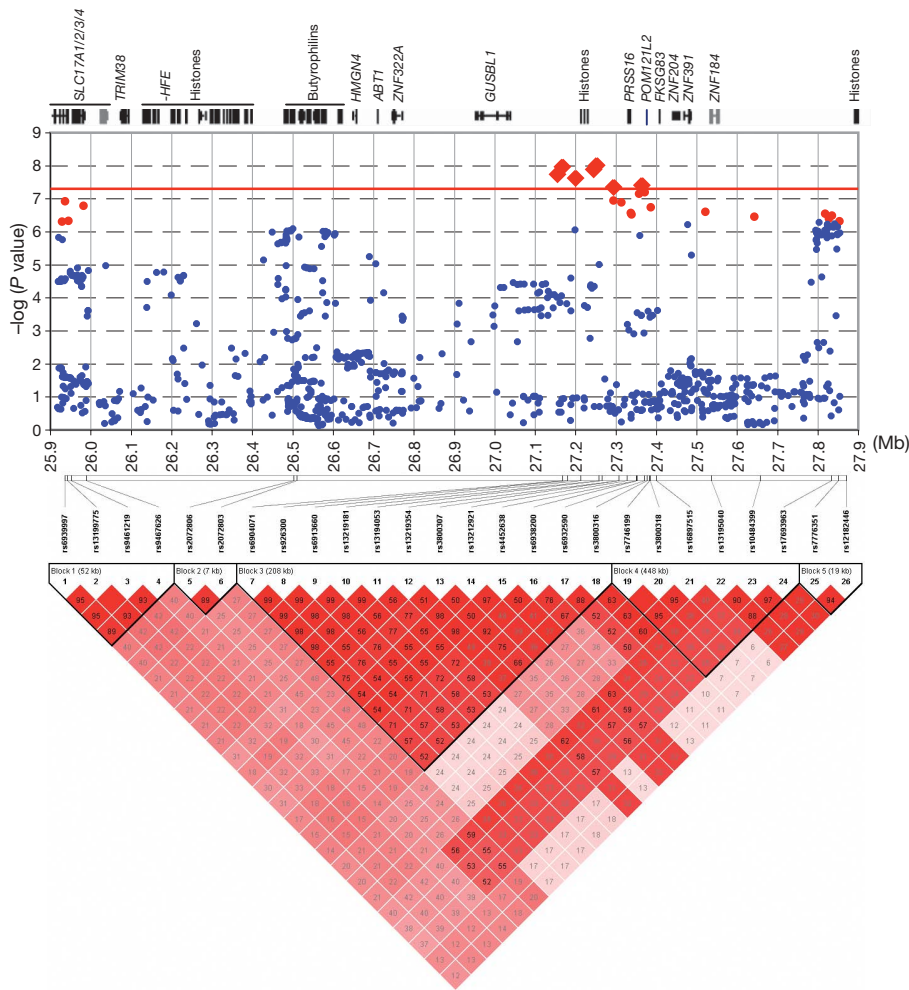
$P$  values of less than  $10^{-7}$  were also observed in the meta-analysis in *HLA-DQA1* ( $P = 6.88 \times 10^{-8}$ , Table 2), suggesting autoimmune mechanisms. This gene is in the class II HLA region, which is not in linkage disequilibrium with 6p22.1 in the MGS sample. We note also that the MGS GWAS (see Supplementary Data 1, European-ancestry results) produced some evidence for association in the *FAM69A-EVT-RPL5* gene cluster, which has been implicated in multiple sclerosis, a DQA-associated autoimmune disorder<sup>10</sup>.

Furthermore, in an analysis reported in the companion paper by the ISC<sup>4</sup>, case-control status in the MGS sample could be predicted with very strong statistical significance on the basis of an aggregate test of large numbers of common alleles, weighted by their odds ratios in the single-SNP association analysis of the ISC sample (see ref. 4 for

**Table 2 | Meta-analysis results in the extended MHC class I and II regions**

rs ID	No.	bp	MGS freqs			P values			Odds ratios			Information			Gene(s) (location)		
			A:1/2	Ctrl	Cases	Comb	MGS	ISC	SGENE	MGS	ISC	SGENE	MGS	ISC		SGENE	Band
rs693997	1	25929203	T/C	0.089	0.080	4.90 × 10 <sup>-7</sup>	1.40 × 10 <sup>-1</sup>	5.66 × 10 <sup>-4</sup>	2.85 × 10 <sup>-4</sup>	0.900	0.785	0.712	0.978	0.851	0.955	6p22.2	SLC17A1 (intr)
rs13199775	2	25936761	T/A	0.087	0.075	1.19 × 10 <sup>-7</sup>	5.12 × 10 <sup>-2</sup>	5.66 × 10 <sup>-4</sup>	2.57 × 10 <sup>-4</sup>	0.869	0.785	0.710	0.999	0.851	0.956	6p22.2	SLC17A1 (intr)
rs9461219	3	25944906	G/C	0.087	0.075	4.72 × 10 <sup>-7</sup>	4.99 × 10 <sup>-2</sup>	2.68 × 10 <sup>-3</sup>	2.52 × 10 <sup>-3</sup>	0.868	0.826	0.710	1.000	1.000	0.956	6p22.2	SLC17A1 (up), SLC17A3 (dwn)
rs9467626	4	25981725	A/C	0.091	0.080	1.65 × 10 <sup>-7</sup>	5.32 × 10 <sup>-2</sup>	7.47 × 10 <sup>-4</sup>	2.68 × 10 <sup>-4</sup>	0.872	0.784	0.710	0.988	0.806	0.959	6p22.2	SLC17A3 (intr)
rs2072806	5	26493072	G/C	0.115	0.097	9.27 × 10 <sup>-7</sup>	5.91 × 10 <sup>-3</sup>	2.80 × 10 <sup>-4</sup>	3.40 × 10 <sup>-2</sup>	0.836	0.814	0.857	0.959	1.000	0.971	6p22.1	BTN3A2 (dwn), BTN2A2 (intr bound), BTN3A1 (up)
rs2072803	6	26500494	C/G	0.115	0.097	8.19 × 10 <sup>-7</sup>	5.53 × 10 <sup>-3</sup>	2.80 × 10 <sup>-4</sup>	3.23 × 10 <sup>-2</sup>	0.835	0.814	0.856	0.960	1.000	0.974	6p22.1	
rs6904071	7	27155235	A/G	0.186	0.166	<b>1.78 × 10<sup>-8</sup></b>	1.21 × 10 <sup>-2</sup>	3.03 × 10 <sup>-4</sup>	3.72 × 10 <sup>-4</sup>	0.879	0.819	0.799	0.987	0.851	0.988	6p22.1	
rs926300	8	27167422	T/A	0.186	0.166	<b>1.06 × 10<sup>-8</sup></b>	1.22 × 10 <sup>-2</sup>	3.03 × 10 <sup>-4</sup>	2.08 × 10 <sup>-4</sup>	0.879	0.819	0.791	0.989	0.851	0.988	6p22.1	
rs6913660	9	27199404	A/C	0.184	0.164	<b>2.36 × 10<sup>-8</sup></b>	1.71 × 10 <sup>-2</sup>	3.03 × 10 <sup>-4</sup>	3.35 × 10 <sup>-4</sup>	0.884	0.819	0.798	0.998	0.851	1.000	6p22.1	HIST1H2AG (up), HIST1H2BJ (dwn)
rs13219181	10	27244204	G/A	0.183	0.163	<b>1.29 × 10<sup>-8</sup></b>	1.47 × 10 <sup>-2</sup>	3.03 × 10 <sup>-4</sup>	2.05 × 10 <sup>-4</sup>	0.881	0.819	0.791	0.983	0.851	0.989	6p22.1	
rs13194053	11	27251862	C/T	0.182	0.162	<b>9.54 × 10<sup>-9</sup></b>	1.45 × 10 <sup>-2</sup>	3.03 × 10 <sup>-4</sup>	1.48 × 10 <sup>-4</sup>	0.880	0.819	0.783	0.977	0.851	0.978	6p22.1	
rs13219354	12	27293643	C/T	0.118	0.102	1.12 × 10 <sup>-7</sup>	3.59 × 10 <sup>-2</sup>	5.11 × 10 <sup>-4</sup>	4.39 × 10 <sup>-4</sup>	0.877	0.823	0.766	0.994	1.000	1.000	6p22.1	
rs3800307	13	27293771	A/T	0.205	0.183	<b>4.35 × 10<sup>-8</sup></b>	1.34 × 10 <sup>-2</sup>	3.35 × 10 <sup>-3</sup>	6.12 × 10 <sup>-5</sup>	0.886	0.880	0.787	1.000	1.000	0.988	6p22.1	
rs13212921	14	27313401	T/C	0.124	0.108	1.28 × 10 <sup>-7</sup>	3.09 × 10 <sup>-2</sup>	5.76 × 10 <sup>-4</sup>	5.53 × 10 <sup>-4</sup>	0.873	0.823	0.770	0.960	0.940	0.968	6p22.1	
rs4452638	15	27337244	A/G	0.117	0.102	2.68 × 10 <sup>-7</sup>	4.51 × 10 <sup>-2</sup>	3.96 × 10 <sup>-4</sup>	1.11 × 10 <sup>-3</sup>	0.882	0.821	0.780	1.000	1.000	0.987	6p22.1	PRSS16 (dwn)
rs6938200	16	27339129	G/A	0.205	0.188	3.02 × 10 <sup>-7</sup>	5.28 × 10 <sup>-2</sup>	2.40 × 10 <sup>-3</sup>	1.51 × 10 <sup>-4</sup>	0.910	0.874	0.801	1.000	0.992	1.000	6p22.1	PRSS16 (dwn)
rs6932590	17	27356910	C/T	0.240	0.215	7.13 × 10 <sup>-8</sup>	3.37 × 10 <sup>-3</sup>	2.23 × 10 <sup>-3</sup>	8.48 × 10 <sup>-4</sup>	0.872	0.877	0.834	0.973	0.933	1.000	6p22.1	
rs3800316	18	27364081	C/A	0.257	0.229	<b>3.81 × 10<sup>-8</sup></b>	7.19 × 10 <sup>-4</sup>	3.51 × 10 <sup>-3</sup>	1.09 × 10 <sup>-3</sup>	0.856	0.886	0.834	0.975	0.956	0.977	6p22.1	
rs7746199	19	27369303	T/C	0.185	0.160	5.03 × 10 <sup>-8</sup>	6.85 × 10 <sup>-4</sup>	8.77 × 10 <sup>-4</sup>	5.70 × 10 <sup>-3</sup>	0.837	0.859	0.839	1.000	1.000	1.000	6p22.1	
rs3800318	20	27371620	T/A	0.180	0.158	6.38 × 10 <sup>-8</sup>	2.80 × 10 <sup>-3</sup>	8.82 × 10 <sup>-3</sup>	2.27 × 10 <sup>-3</sup>	0.855	0.859	0.822	0.998	1.000	0.981	6p22.1	
rs16897515	21	27385999	A/C	0.173	0.154	1.83 × 10 <sup>-7</sup>	1.22 × 10 <sup>-2</sup>	6.40 × 10 <sup>-4</sup>	2.16 × 10 <sup>-3</sup>	0.876	0.853	0.816	1.000	1.000	0.972	6p22.1	POM121L2 (missense) ZNF184 (dwn)
rs13195040	22	27521903	G/A	0.076	0.076	2.50 × 10 <sup>-7</sup>	1.04 × 10 <sup>-1</sup>	3.00 × 10 <sup>-5</sup>	2.82 × 10 <sup>-5</sup>	0.892	0.714	0.768	1.000	1.000	0.983	6p22.1	
rs10484399	23	27642507	G/A	0.091	0.080	3.50 × 10 <sup>-7</sup>	1.09 × 10 <sup>-1</sup>	8.50 × 10 <sup>-3</sup>	8.69 × 10 <sup>-3</sup>	0.895	0.762	0.795	1.000	1.000	1.000	6p22.1	
rs17693963	24	27818144	C/A	0.101	0.085	2.81 × 10 <sup>-7</sup>	2.87 × 10 <sup>-2</sup>	6.00 × 10 <sup>-5</sup>	8.85 × 10 <sup>-5</sup>	0.864	0.781	0.795	1.000	0.993	0.986	6p22.1	
rs776351	25	27834710	T/C	0.255	0.236	3.22 × 10 <sup>-7</sup>	2.83 × 10 <sup>-2</sup>	1.13 × 10 <sup>-4</sup>	6.51 × 10 <sup>-3</sup>	0.905	0.855	0.865	1.000	1.000	1.000	6p22.1	
rs12182446	26	27853717	A/G	0.247	0.227	4.77 × 10 <sup>-7</sup>	2.99 × 10 <sup>-2</sup>	7.17 × 10 <sup>-5</sup>	1.22 × 10 <sup>-2</sup>	0.905	0.850	0.874	0.999	1.000	0.990	6p22.1	
rs9272219		32710247	T/G	0.283	0.263	6.88 × 10 <sup>-8</sup>	1.32 × 10 <sup>-2</sup>	2.24 × 10 <sup>-5</sup>	1.03 × 10 <sup>-5</sup>	0.897	0.847	0.880	1.000	1.000	0.977	6p21.32	HLA-DQA1 (up)
rs9272535		32714734	A/G	0.283	0.263	8.87 × 10 <sup>-8</sup>	1.63 × 10 <sup>-2</sup>	2.47 × 10 <sup>-5</sup>	9.92 × 10 <sup>-5</sup>	0.900	0.848	0.879	1.000	1.000	0.977	6p21.32	HLA-DQA1 (intr)

No. refers to the numbering of SNPs in the linkage disequilibrium diagram in Fig. 1. A1/2, alleles 1 and 2 (minor/major, forward strand); comb, combined analysis (meta-analysis) of the three data sets; ctrl, controls; freqs, minor allele frequencies. For SNP locations (as reported by <http://snpper.chip.org>); dwn, downstream (within 10 kb of transcribed sequence); intr, intron; intr bound, intron-exon boundary; up, upstream (within 10 kb). Shown are data for all SNPs with  $P < 10^{-6}$  in the extended MHC class I and II regions of chromosome 6p, in the meta-analysis of European-ancestry MGS, ISC and SGENE data (see Table 1 and Supplementary Methods). Odds ratios are reported for the minor allele. Genome-wide significant meta-analysis  $P$  values ( $P < 5 \times 10^{-8}$ ) are shown in bold (see Supplementary Methods as regards this threshold). The information content for the SNP for each study is the imputation  $r^2$ , reported by MACH1.0 for MGS, and the PLINK and IMPUTE information measure for ISC and SGENE, respectively. '1,000' indicates an SNP that was genotyped or had a perfect proxy. Genes within 10 kb of a SNP are listed; see Fig. 1 for more details for 6p22.1. See Supplementary Data 1 for further meta-analysis results.



**Figure 1 | Chromosome 6p22.1: genetic association and linkage disequilibrium results in European-ancestry samples.** Genome-wide significant evidence for association ( $P < 5 \times 10^{-8}$ , threshold shown by solid red line, SNPs by large red diamonds) was observed at seven SNPs across 209 kb.  $P$  values are shown for all genotyped and imputed SNPs (25,900,000–27,875,000 bp) for the meta-analysis of European-ancestry MGS, ISC and SGENE samples (8,008 cases, 19,077 controls). Red circles indicate other SNPs with  $P < 5 \times 10^{-7}$ . Not shown are two SNPs in *HLA-DQA1* (6p21.32; lowest  $P = 6.88 \times 10^{-8}$ , 32,710,247 bp; see Supplementary Data 1). Locations are shown for RefSeq genes and *POM121L2*. Pairwise linkage disequilibrium relationships are shown for 26 SNPs with  $P < 10^{-7}$  (except that SNPs 5 and 6 are shown, despite slightly larger  $P$  values, to

details). As expected, results were similar for an analysis with MGS as the discovery sample and ISC as the target (see Supplementary Results 3). As discussed in the ISC paper, the results demonstrate that a substantial proportion of the variance may be explained by many common variants, most of them with small effects that cannot be detected one at a time.

We have identified a region of association of common SNPs with schizophrenia on chromosome 6p22.1. Further research will be required to identify the sequence variation in this region that alters susceptibility, and the mechanisms by which this occurs. The results of this meta-analysis and of the aggregate analysis of multiple alleles reported in the ISC paper strongly suggest that individual common variants have small effects on schizophrenia risk, and that still larger samples may be valuable. The larger goal of research in the field will be to detect and understand the full range of rare and common sequence and structural schizophrenia susceptibility variants. Association findings will advance knowledge of pathophysiological mechanisms, even if they initially explain small proportions of genetic variance. Future advances in the knowledge of gene and protein functions and

illustrate linkage disequilibrium for that segment; and a SNP in strong linkage disequilibrium with SNPs 25 and 26 is omitted). Linkage disequilibrium was computed from MGS European-ancestry genotyped and imputed SNP data. The signal is poorly localized because of strong linkage disequilibrium: of the seven significant SNPs, 7–8 and 9–11 are in nearly perfect linkage disequilibrium; they are in or within ~30–50 kb of a cluster of five histone genes (*HIST1H2BJ*, *HIST1H2AG*, *HIST1H2BK*, *HIST1H4I* and *HIST1H2AH*; 27,208,073–27,223,325 bp). These SNPs are in moderately strong linkage disequilibrium ( $r^2 = 0.52$ – $0.77$ ) with two other significant SNPs 70–140 kb away, upstream of *PRSS16* (SNP 13) or between *PRSS16* and *POM121L2* (SNP 18). See Table 2 and Supplementary Figs 10 and 11 for further details.

interactions should make it possible to dissect the functional sets of pathogenic variants on the basis of previous hypotheses.

## METHODS SUMMARY

Details of MGS subject recruitment and sample characteristics are provided in the Supplementary Methods (section A1). DNA samples were genotyped using the Affymetrix 6.0 array at the Broad Institute. Samples (5.3%) were excluded for high missing data rates, outlier proportions of heterozygous genotypes, incorrect sex or genotypic relatedness to other subjects. SNPs (7% for African-American, 25% for European-ancestry and 27% for combined analyses) were excluded for minor allele frequencies less than 1%, high missing data rates, Hardy–Weinberg deviation (controls), or excessive Mendelian errors (trios), discordant genotypes (duplicate samples) or large allele frequency differences among DNA plates. Principal component scores reflecting continental and within-Europe ancestries of each subject were computed and outliers were excluded. Genomic control  $\lambda$  values for autosomes after quality control procedures were 1.042 for African-American and 1.087 for the larger European-ancestry and combined analyses.

For MGS, association of single SNPs to schizophrenia was tested by logistic regression (trend test) using PLINK<sup>11</sup>, separately for European-ancestry, African-American and combined data sets, correcting for principal component scores that reflected

geographical gradients or that differed between cases and controls, and for sex for chromosome X and pseudoautosomal SNPs. Genotypic data were imputed for 192 regions surrounding the best findings, and for further regions selected for meta-analysis<sup>12</sup>. Detailed results are available in Supplementary Data 1 and 2, and complete results are available from dbGAP ([www.ncbi.nlm.nih.gov/sites/entrez?db=gap](http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap)).

Meta-analysis of the MGS, ISC and SGENE data sets was carried out by combining *P* values for all SNPs (in the selected regions) for which genotyped or imputed data were available for all data sets, with weights computed from case-control sample sizes. See the companion papers for details of the ISC and SGENE analyses<sup>4,13</sup>.

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