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Genome-wide association study identifies five new schizophrenia loci

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Note: Supplementary information is available on the Nature Genetics website.

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COMPETING FINANCIAL INTERESTS

The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturegenetics/.

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The Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium[1]

Abstract

We examined the role of common genetic variation in schizophrenia in a genome-wide association study of substantial size: a stage 1 discovery sample of 21,856 individuals of European ancestry and a stage 2 replication sample of 29,839 independent subjects. The combined stage 1 and 2 analysis yielded genome-wide significant associations with schizophrenia for seven loci, five of which are new (1p21.3, 2q32.3, 8p23.2, 8q21.3 and 10q24.32-q24.33) and two of which have been previously implicated (6p21.32-p22.1 and 18q21.2). The strongest new finding ($P = 1.6 \times 10^{-11}$) was with rs1625579 within an intron of a putative primary transcript for *MIR137* (microRNA 137), a known regulator of neuronal development. Four other schizophrenia loci achieving genome-wide significance contain predicted targets of *MIR137*, suggesting *MIR137*-mediated dysregulation as a previously unknown etiologic mechanism in schizophrenia. In a joint analysis with a bipolar disorder sample (16,374 affected individuals and 14,044 controls), three loci reached genome-wide significance: *CACNA1C* (rs4765905, $P = 7.0 \times 10^{-9}$), *ANK3* (rs10994359, $P = 2.5 \times 10^{-8}$) and the *ITIH3-ITIH4* region (rs2239547, $P = 7.8 \times 10^{-9}$).

In stage 1, we conducted a mega-analysis combining genome-wide assocation study (GWAS) data from 17 separate studies (with a total of 9,394 cases and 12,462 controls; Table 1 and Supplementary Tables 1,2). We imputed allelic dosages for 1,252,901 autosomal SNPs (Table 1, Supplementary Table 3 and Supplementary Note) using HapMap3 as the reference panel[1]. We tested for association using logistic regression of imputed dosages with sample identifiers and three principal components as covariates to minimize inflation in significance testing caused by population stratification. The quantile-quantile plot (Supplementary Fig. 1) deviated from the null distribution with a population stratification inflation factor of $\lambda = 1.23$. However, λ_{1000}, a metric that standardizes the degree of inflation by sample size, was only 1.02, similar to that observed in other GWAS meta-analyses[2,3]. This deviation persisted despite comprehensive quality control and inclusion of up to 20 principal components (Supplementary Fig. 1). Thus, we interpret this deviation as indicative of a large number of weakly associated SNPs consistent with polygenic inheritance[4]. We also examined 298 ancestry-informative markers (AIMs) that reflect European-ancestry population substructure[5]. Unadjusted analyses showed greater inflation in the test statistics than we saw for all markers (AIMs $\lambda = 2.26$ compared to all markers $\lambda = 1.56$). After inclusion of principal components, the distributions of the test statistics did not differ between AIMs ($\lambda = 1.18$) and all markers ($\lambda = 1.23$), a result inconsistent with population stratification explaining the residual deviation seen in Supplementary Figure 1. Moreover, the results of a meta-analysis using summary results generated using study specific principal components (Supplementary Note) were highly correlated with those from the mega-analysis (Pearson correlation = 0.94, with a similar $\lambda = 1.20$; Supplementary Fig. 2). Of the ten SNPs in Table 2, four increased and six decreased in significance, suggesting that the most extreme values did not result from systematic inflation artifacts. Therefore, our primary analysis used unadjusted *P* values (nevertheless, see Table 2 for stage 1 *P* values adjusted for λ (ref. 6).

In stage 1 (Table 2, Supplementary Table 4 and Supplementary Figs. 3 and 4), 136 associations reached genome-wide significance ($P < 5 \times 10^{-8}$)[7]. The majority of these associations ($N = 129$) mapped to 5.5 Mb in the extended major histocompatibility complex (MHC, 6p21.32-p22.1), a region of high linkage disequilibrium (LD) previously implicated in schizophrenia in a subset of the samples used here[4,8,9]. The other stage 1 regions included new regions (10q24.33 and 8q21.3) and previously reported regions (18q21.2 at *TCF4* (encoding transcription factor 4) and 11q24.2 (ref. 8)). The signal at 11q24.2 is ~0.85 Mb

from *NRGN* (encoding neurogranin) and is uncorrelated with the previously associated variant near this gene[8].

In Table 2 and Supplementary Table 4, we denote regions of association by the most significant marker. Associated SNPs with $r^2 \geq 0.2$ in HapMap3 (CEU+TSI populations) were not considered independent. However, we noticed instances where multiple SNPs within 250 kb of each other yielded evidence for association ($P < 10^{-5}$) despite weak LD ($r^2 < 0.2$) between them. For regions with $P < 10^{-6}$, we performed a conditional analysis using as covariates the dosages of the strongest associated SNP, principal components 1–4 and 6 and study indicator. We observed multiple statistically independent signals at the MHC. Although a number of SNPs within the MHC were potentially independent per HapMap r^2 values, only rs9272105 withstood formal conditional analysis, showing $P = 1.8 \times 10^{-6}$ conditional on association to the best SNP, rs2021722 (stage 1 $P = 4.3 \times 10^{-11}$, inter-SNP distance = 2.4 Mb, $r^2 = 0.01$ in HapMap). Excluding the MHC region, we identified six regions with at least one SNP associated at $P < 10^{-5}$ and a second SNP with a conditionally independent $P < 10^{-3}$ (Supplementary Table 5). We performed 100 simulations after permuting case-control status randomly within each study. In contrast to the six regions in the real dataset, we never observed more than a single region with co-localized statistically independent signals in any simulated genome-wide scan, indicating our observation is highly unlikely to have occurred by chance.

Noteworthy co-localizing independent signals occurred at three regions (Supplementary Table 5): one region with a genome-wide significant association at 10q24.32-q24.33 (Table 2), a second region that nearly met this threshold at *MAD1L1* (encoding mitotic arrest deficient-like 1; rs10226475, $P = 5.06 \times 10^{-8}$; Supplementary Table 4) and a third region at *CACNA1C* (encoding calcium channel, voltage-dependent, L type, α 1C subunit), the latter of which has previously been associated with bipolar disorder[10] and other psychiatric phenotypes including schizophrenia[11]. The conditionally independent signal at *CACNA1C* was more significant than any observation made in 100 permutations of the entire experiment (both conditional $P < 10^{-5}$) and supports *CACNA1C* in schizophrenia after genome-wide correction ($P < 0.01$), even without considering these prior reports.

In stage 2, we evaluated in 29,839 independent subjects (8,442 cases and 21,397 controls) the most significant SNPs ($N = 81$) in each LD region where at least one SNP had surpassed $P < 2 \times 10^{-5}$ (Supplementary Table 6) in the mega-analysis. Of 22 SNPs from the MHC, 5 surpassed the genome-wide significant threshold in stages 1 and 2 combined (minimum $P = 2.2 \times 10^{-12}$ at rs2021722; Supplementary Table 6). Excluding the MHC region, a sign test for consistency between stages 1 and 2 was highly significant ($P < 10^{-6}$), with the same direction of effect as observed stage 1 also being observed in stage 2 for 49 of 59 SNPs. A Fisher's combined test revealed the distribution of stage 2 *P* values was unlikely to have occurred by chance ($P < 10^{-15}$). We also performed a transmission analysis using the family based Multicenter Pedigree replication sample in conjunction with a GWAS of 622 parent-offspring schizophrenia trios from Bulgaria[12], and the stage 1 associated allele was over-transmitted to cases for 44 of the 59 SNPs (one-sided $P = 1.0 \times 10^{-4}$). Thus, the stage 2 replication results are highly consistent with the stage 1 discovery results.

In the combined dataset (stages 1 and 2), five new (1p21.3, 2q32.3, 8p23.2, 8q21.3 and 10q24.32-q24.33) and two previously reported (6p21.32-p22.1 and 18q21.2) loci met genome-wide significance (Figs. 1,2, Table 2, Supplementary Tables 6,7 and Supplementary Fig. 4). After adjusting for λ (ref. 6), four loci (1p21.3, 6p21.32-p22.1, 10q24.32-q24.33 and 18q21.2) remained significant at $P \leq 5 \times 10^{-8}$. For the primary analyses (unadjusted for λ), the strongest new association was at 1p21.3 (rs1625579; $P = 1.6 \times 10^{-11}$), which is over 100 kb from any RefSeq protein-coding gene but is within intron 3 of AK094607, which

contains the primary transcript for *MIR137* (ref. 13). The next best locus, 10q24.32 (Supplementary Table 5 and Supplementary Fig. 5), has independent associations 130 kb apart at rs7914558 ($P = 1.8 \times 10^{-9}$) and rs11191580 ($P = 1.1 \times 10^{-8}$), implicating a 0.5-Mb region containing multiple genes (Supplementary Fig. 5). The third best locus, rs7004633 ($P = 2.8 \times 10^{-8}$) on 8q21.3, is 400 kb from the nearest gene (*MMP16*, encoding matrix metallopeptidase 16). The fourth best locus, rs10503253 ($P = 4.4 \times 10^{-8}$) at 8p23.2, is in an intron of *CSMD1* (encoding CUB and Sushi multiple domains 1). Finally, rs17662626 ($P = 4.7 \times 10^{-8}$) at 2q32.3 is intergenic, mapping 300 kb from a non-coding RNA, *PCGEM1* (prostate-specific transcript 1)[14].

MIR137 has been implicated in regulating adult neurogenesis[15,16] and neuronal maturation[17], mechanisms through which variation at this locus could contribute to brain development abnormalities in schizophrenia. Of relevance, two independent schizophrenia imaging studies found *MIR137* to be one of three microRNAs with targets significantly enriched for association[18]. In stage 1, SNPs in or near 301 high-confidence predicted *MIR137* targets (with a TargetScan[19] probability of conserved targeting ≥0.9) were enriched for association compared with genes matched for size and marker density: 17 predicted *MIR137* targets (Supplementary Table 8) had at least one SNP with $P < 10^{-4}$, which is more than twice as many as the control gene sets ($P < 0.01$). Excluding the MHC and *MIR137*, of the nine loci with genome-wide significant support either in stage 1 or in the combined set (six loci, 2q32.3, 8p23.2, 8q21.3, 10q24.32-q24.33, 11q24.2 and 18q21.2; Table 2 and Supplementary Tables 6,7) or in a joint analysis with bipolar disorder (three genes, *CACNA1C*, *ANK3* and *ITIH3-ITIH4*, described below), four genes (*TCF4*, *CACNA1C*, *CSMD1* and *C10orf26*) have predicted *MIR137* target sites according to analyses using three different prediction programs (TargetScan[19], PicTar[20] and miRanda[21]). *In vitro* overexpression and locked nucleic acid–mediated knockdown of *MIR137* in neuronal cell line N2a leads to changes in expression levels of TCF4 protein, strongly supporting the prediction that *TCF4* is a target of *MIR137* (L.-H. Tsai, personal communication). Our observations suggest *MIR137*-mediated dysregulation as a new etiologic mechanism in schizophrenia.

The International Schizophrenia Consortium (ISC) reported evidence for a polygenic contribution to schizophrenia[4]. An independent family based study confirmed these results, greatly minimizing the possibility of population stratification artifact[12]. We reevaluated the polygenic model, dividing stage 1 samples into independent training and testing sets (Supplementary Note). The training set had 15,429 subjects (over twice the size of the ISC training set), and the testing set consisted of 6,428 individuals independent of the ISC report. The proportion of variance (Nagelkerke's r^2) explained in the testing set increased from 3% in the ISC to around 6% here (Supplementary Table 9 and Supplementary Fig. 6). This estimate is much lower than the true total variation in liability that is tagged by all SNPs because SNP effects are estimated with error[3,4,22–25]. The polygenic model appears to explain a substantial fraction of the heritability of schizophrenia[4], as has been shown for other complex traits[3,26–28]. Some of these additional risk loci are likely contained near the most highly significant results of our stage 1 analysis. Supporting this hypothesis, of the top loci that did not reach genome-wide significance in the combined stage 1 and 2 analysis, a sign test ($P < 10^{-4}$) and a Fisher's combined test ($P < 10^{-5}$) both showed an excess of same-direction allelic association (41 of 51 non-MHC SNPs) in the discovery and replication datasets.

Clinical, epidemiological and genetic findings suggest shared risk factors between bipolar disorder and schizophrenia[29]. In stage 1, three genes with strong support had prior genome-wide significant associations with bipolar disorder: *CACNA1C*, the region containing *ITIH3-ITIH4* (encoding inter-α (globulin) inhibitors H3 and H4) and *ANK3* (encoding ankyrin 3,

node of Ranvier (ankyrin G))[10,11,30] (Supplementary Table 10). We performed a joint analysis with the Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium (PGC) for bipolar disorder applying identical analytical methods. After removing duplicate subjects, we analyzed 16,374 cases with schizophrenia, schizoaffective disorder or bipolar disorder and 14,044 controls. Support for shared susceptibility was strengthened (Supplementary Table 11) at *CACNA1C* (rs4765905, $P = 7.0 \times 10^{-9}$), *ANK3* (rs10994359, $P = 2.5 \times 10^{-8}$) and the *ITIH3-ITIH4* region (rs2239547, $P = 7.8 \times 10^{-9}$), each of which reached genome-wide significance. A coding variant in *ITIH4* (p.Pro698Thr; rs4687657) is in perfect LD with the most associated SNP. Although we included all subjects from an earlier report[10], the increased support found with additional independent cases ($N = 11,987$) and controls ($N = 7,835$) provides further evidence for shared risk effects of schizophrenia and bipolar disorder.

The risk variants implicated here confer small risks (odds ratios ~1.10), but the polygenic analysis shows many more susceptibility variants with effects for which our sample is underpowered (Supplementary Table 12). At every stage where samples were added, we found an increase in the number of genome-wide significant loci and enhancement of signals at *CACNA1C, ANK3* and *ITIH3-ITIH4* when schizophrenia and bipolar disorder were jointly analyzed. Thus, gains in power offset any penalty for increased heterogeneity.

In summary, we report seven genome-wide significant schizophrenia associations (five of which are new) in a two-stage analysis of 51,695 individuals. We also report loci that confer susceptibility to both bipolar disorder and schizophrenia. The association near *MIR137*, associations in multiple predicted *MIR137* targets and the known role of *MIR137* in neuronal maturation and function together suggest an intriguing new insight into the pathogenesis of schizophrenia.

URLs

PLINK, http://pngu.mgh.harvard.edu/~purcell/plink/; Haploview, http://www.broadinstitute.org/scientific-community/science/programs/medical-and-population-genetics/haploview/haploview.

METHODS

Methods and any associated references are available in the online version of the paper at http://www.nature.com/naturegenetics/.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

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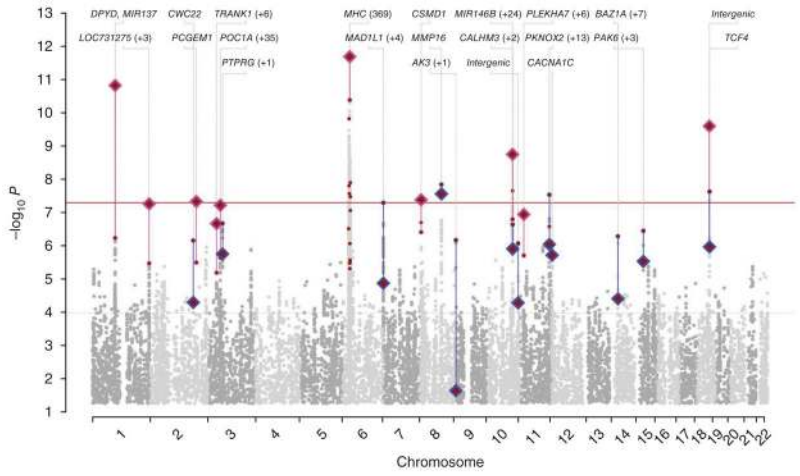

Figure 1.

Manhattan plot for stages 1 and 2. Standard $-\log_{10} P$ plot of the study results. For the stage 1 results, 16 regions with one or more SNP achieving $P < 10^{-6}$ are highlighted in color and labeled with the name of the nearest gene. SNPs selected for stage 2 replication are highlighted, with the resulting combined P value after replication (that is, after incorporation of stage 2 results) indicated by the large diamonds. Blue highlighting indicates SNPs that were less significantly associated after replication, and pink highlighting indicates SNPs that were more significantly associated after replication.

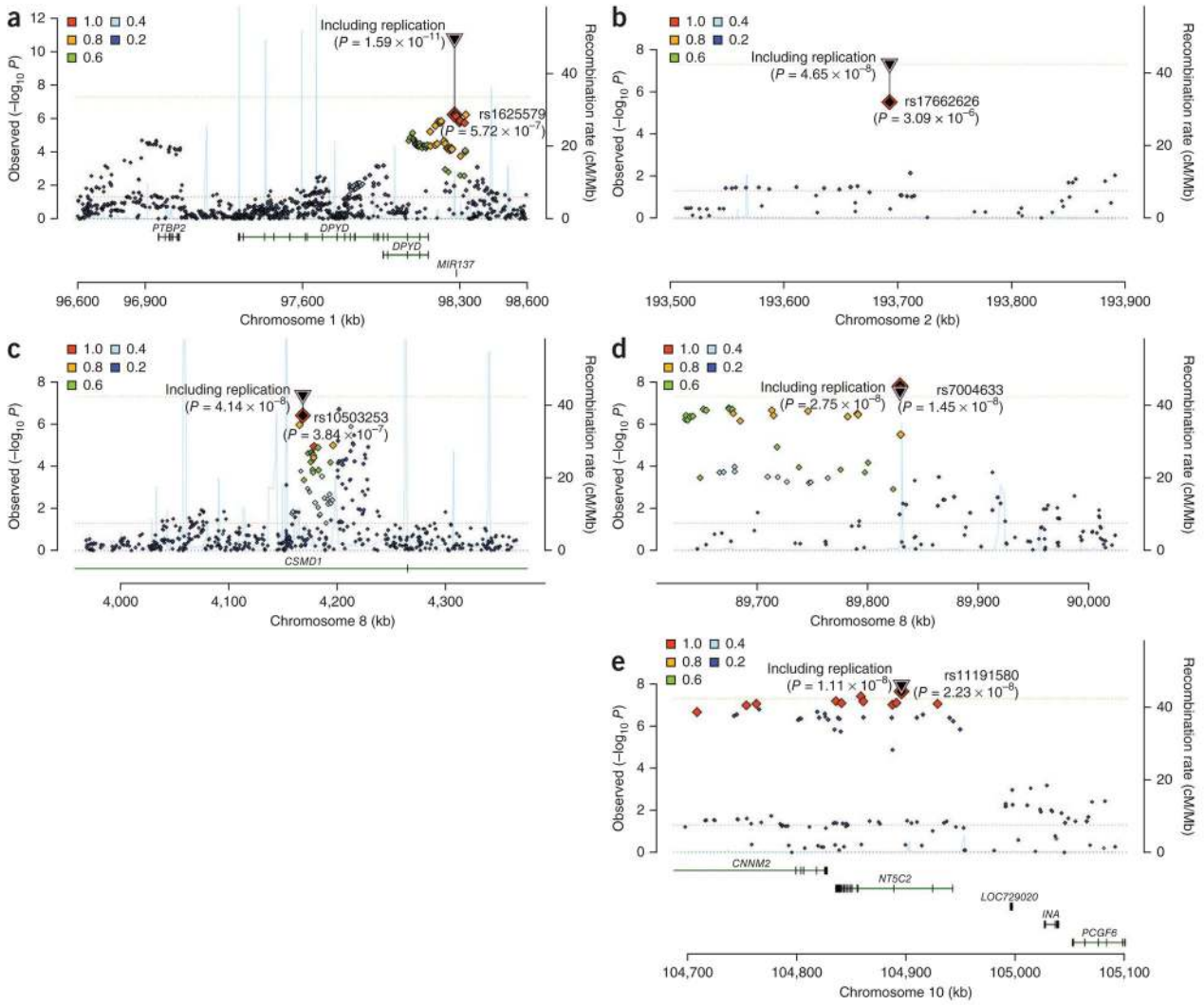

Figure 2.

Regional association plots for five new schizophrenia loci. Regional *P* value plots for each of the five new schizophrenia loci: 1p21.3, 2q32.3, 8p23.2, 8q21.3 and 10q24.32-q24.33. Each plot shows the most associated SNP (key SNP) and its genomic region from the first column of Table 2: stage 1 scan results for each SNP ± 200 kb to the key SNP are shown. On the *x* axis is the genomic position, and on the *y* axis is $-\log_{10} P$. Larger SNP symbols indicate higher LD (based on HapMap 3 data) to the key SNP than smaller SNP symbols. Color coding (from red to blue) denotes LD information; see also the legend within the plot.

Table 1

Study design and samples

			Cases included by sex				Controls included by sex			
Collection	**Country**	**Platform**	**Male**	**Female**	**Unknown**	**Total**	**Male**	**Female**	**Unknown**	**Total**
Cardiff UK	UK	Affymetrix 500K	320	152	0	472	1,442	1,492	0	2,934
CATIE	United States	Affymetrix 500K; Perlegen 164K	308	94	0	402	161	46	0	207
ISC-Aberdeen	UK	Affymetrix 5.0	536	184	0	720	447	251	0	698
ISC-Cardiff	Bulgaria	Affymetrix 6.0	270	257	0	527	291	318	0	609
ISC-Dublin	Ireland	Affymetrix 6.0	188	82	0	270	258	602	0	860
ISC-Edinburgh	UK	Affymetrix 6.0	267	101	0	368	146	138	0	284
ISC-London	UK	Affymetrix 5.0; Affymetrix 500K	369	149	0	518	207	284	0	491
ISC-Portugal	Portugal	Affymetrix 5.0	213	133	0	346	80	135	0	215
ISC-SW1	Sweden	Affymetrix 5.0	93	75	0	168	82	85	0	167
ISC-SW2	Sweden	Affymetrix 6.0	231	159	0	390	116	113	0	229
MGS	United States, Australia	Affymetrix 6.0	1,863	816	0	2,679	1,140	1,344	0	2,484
SGENE-Bonn	Germany	Illumina 550K	238	236	0	474	664	640	0	1,304
SGENE-Copenhagen	Denmark	Illumina Human 610-Quad	280	202	0	482	268	189	0	457
SGENE-Munich	Germany	Illumina 300K	279	155	0	434	167	184	0	351
SGENE-TOP3	Norway	Affymetrix 6.0	132	116	0	248	176	175	0	351
SGENE-UCLA	The Netherlands	Illumina 550K	529	175	0	704	310	321	–	631
Zucker Hillside	United States	Affymetrix 500K	128	64	0	192	92	98	0	190
Grand totals for the GWAs			**6,244**	**3,150**	**0**	**9,394**	**6,047**	**6,415**	**–**	**12,462**
Multicenter Pedigree	Europe, United States, Australia	Illumina Human 610-Quad	n.a.	n.a.	0	583	0	0	0	0
SGENE-Aarhus	Denmark	Illumina Human 610-Quad	477	399	0	876	477	397	0	874
SGENE-Aarhus	Denmark	Centaurus	114	102	1	217	176	317	0	493
SGENE-Belgium	Belgium	Centaurus; Illumina 370K	326	184	0	510	149	192	0	341
SGENE-Copenhagen	Denmark	Centaurus	264	198	0	462	499	375	0	874
SGENE-Iceland	Iceland	Illumina 300K	346	185	0	531	5,802	5,813	0	11,615
SGENE-England	UK	Illumina 300K	71	22	0	93	48	40	0	88
SGENE-Helsinki	Finland	Illumina 300K	112	70	0	59	122	75	0	147
SGENE-Kuusamo	Finland	Illumina 300K				123				50

			Cases included by sex				Controls included by sex			
Collection	**Country**	**Platform**	**Male**	**Female**	**Unknown**	**Total**	**Male**	**Female**	**Unknown**	**Total**
SGENE-Hungary	Hungary	Centaurus	105	136	0	241	89	125	0	214
SGENE-Italy	Italy	Illumina 300K	48	36	0	84	50	39	0	89
SGENE-Munich	Germany	Illumina 300K	280	186	0	163	887	912	0	185
SGENE-Munich	Germany	Centaurus				303				1,614
SGENE-Russia	Russia	Centaurus	132	343	0	475	178	290	0	468
SGENE-Sweden	Sweden	Centaurus	158	94	0	252	178	109	0	287
SW3	Sweden	Affymetrix 6.0	327	212	0	539	457	448	0	905
SW4	Sweden	Affymetrix 6.0	656	407	0	1,063	605	568	0	1,173
UQ and ASRB	Australia	SequenomMassArray	347	190	21	558	487	455	15	957
ISGC and WTCCC2	Ireland	Affymetrix 6.0	968	342	0	1,310	245	778	0	1,023
Grand totals for the replication follow up			**4,731**	**3,106**	**22**	**8,442**	**10,449**	**10,933**	**15**	**21,397**

Stage 1 describes the 17 samples that provided full GWAS genotyping data, and stage 2 describes the 19 studies that provided results for the top SNPs identified in the combined analysis of stage 1 studies. Stage 2 replication SGENE-Belgium had four cases missing sex information. Stage 2 replication SGENE-Aarhus (focused genotyping sample) had one case missing sex information. Stage 2 replication-University of Queensland had 21 cases and 15 controls missing sex information. Sex information for the two stage 2 replication SGENE-Munich samples are combined. Sex information for the two stage 2 replication SGENE-Finnish (Helsinki and Kuusamo) samples are combined to enable that these two samples are located adjacent to each other in the table (rather than alphabetically). Multicenter Pedigree was a family sample, and so case sex counts are not applicable (n.a). SGENE, Schizophrenia Genetics Consortium; ISC, International Schizophrenia Consortium; TOP3, Thematic Organized Psychoses Research 3; UCLA, University of California at Los Angeles; SW1, Sweden 1; SW2, Sweden 2; WTCCC, Wellcome Trust case Control Consortium; for the Multicenter Pedigree study, the number of cases indicates the number of families; CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness; MGS, Molecular Genetics of Schizophrenia; UQ, University of Queensland; ASRB, Australian Schizophrenia Research Bank; ISGC, Irish Schizophrenia Genomics Consortium.

Table 2

Top genome-wide association results for schizophrenia

SNP	Chr.	Mb	Alleles	Frequency	*P* (GC-adjusted *P*)	OR (95% CI)	Consistency of direction	Gene	Distance (kb)
					5.72×10^{-7} (6.52×10^{-6})	1.14 (1.08–1.19)			
rs1625579	1p21.3[a]	98.3	TG	0.80	**2.65×10^{-6}** (n.a.)	1.11 (1.07–1.16)	+−++++−+	*MIR137*	Intragenic
					1.59×10^{-11} (6.87×10^{-10})	1.12 (1.09–1.16)			
					3.09×10^{-6} (2.60×10^{-5})	1.22 (1.13–1.30)			
rs17662626	2q32.3[a]	193.7	AG	0.91	**1.70×10^{-3}** (n.a.)	1.16 (1.06–1.27)	+ −+ +++	*PCGEM1*	343
					4.65×10^{-8} (1.25×10^{-6})	1.20 (1.13–1.26)			
					4.30×10^{-11} (2.76×10^{-9})	1.18 (1.13–1.23)			
rs2021722	6p21.3-p22.1	30.3	CT	0.78	**1.55×10^{-3}** (n.a.)	1.10 (1.03–1.17)	+ ++ −++	*TRIM26*	Intragenic
					2.18×10^{-12} (2.88×10^{-10})	1.15 (1.11–1.19)			
					3.84×10^{-7} (4.71×10^{-6})	1.14 (1.09–1.19)			
rs10503253	8p23.2[a]	4.2	AC	0.19	**7.60×10^{-3}** (n.a.)	1.08 (1.01–1.14)	+ ++ +−+	*CSMD1*	Intragenic
					4.14×10^{-8} (8.98×10^{-7})	1.11 (1.07–1.15)			
					1.45×10^{-8} (3.22×10^{-7})	1.16 (1.11–1.21)			
rs7004633	8q21.3[a]	89.8	GA	0.18	**0.011** (n.a.)	1.05 (1.01–1.10)	++−+++−+	*MMP16*	421
					2.75×10^{-8} (7.03×10^{-7})	1.10 (1.07–1.14)			
					1.58×10^{-7} (2.27×10^{-6})	1.11 (1.07–1.15)			
rs7914558	10q24.32[a]	104.8	GA	0.59	**1.07×10^{-3}** (n.a.)	1.08 (1.03–1.13)	+ ++ +++	*CNNM2*	Intragenic
					1.82×10^{-9} (3.11×10^{-8})	1.10 (1.07–1.13)			
					2.23×10^{-8} (4.58×10^{-7})	1.22 (1.15–1.29)			
rs11191580	10q24.33[a]	104.9	TC	0.91	**5.09×10^{-3}** (n.a.)	1.09 (1.02–1.16)	+++++++	*NT5C2*	Intragenic
					1.11×10^{-8} (3.72×10^{-7})	1.15 (1.10–1.20)			
					2.91×10^{-8} (5.69×10^{-7})	1.20 (1.13–1.26)			
rs548181	11q24.2	125.0	GA	0.88	0.068 (n.a.)	1.04 (0.98–1.11)	+++++−+	*STT3A*	1
					8.87×10^{-7} (1.74×10^{-5})	1.11 (1.07–1.16)			
					1.00×10^{-6} (1.03×10^{-5})	1.10 (1.06–1.14)			
rs12966547	18q21.2	50.9	GA	0.58	**2.29×10^{-5}** (n.a.)	1.08 (1.04–1.12)	+−++++++	*CCDC68*	126
					2.60×10^{-10} (5.99×10^{-9})	1.09 (1.06–1.12)			

SNP	Chr.	Mb	Alleles	Frequency	*P* (GC-adjusted *P*)	OR (95% CI)	Consistency of direction	Gene	Distance (kb)
					2.35×10^{-8} (4.78×10^{-7})	1.40 (1.28–1.52)			
rs17512836	18q21.2	51.3	CT	0.02	0.085 (n.a.)	1.08 (0.96–1.20)	−+++++++	*TCF4*	Intragenic
					1.05×10^{-6} (2.86×10^{-5})	1.23 (1.14–1.31)			

The SNPs listed are those with a stage 1 $P < 5 \times 10^{-8}$ and/or a combined stage 1 and 2 $P < 5 \times 10^{-8}$. These ten independent ($r^2 < 0.2$) SNPs represent eight physically distinct genomic loci, as there are two SNPs listed for two loci (10q24.32-q24.33 and 18q21.2). For the MHC region, only one SNP is listed for clarity. The eight susceptibility loci represent three previously reported and five new loci (Supplementary Table 7). Stage 1 is the discovery GWAS mega-analysis. Stage 2 is the replication sample (single-tailed meta-analysis *P* values are weighted by 1/s.e.), and because the *P* values are single tailed, some 95% confidence intervals contain 1 (if $0.10 < P < 0.05$). Combined values include stages 1 and 2 (two-tailed meta-analysis *P* values are weighted by 1/s.e.). For each SNP, *P* values and odds ratios are listed for stage 1 (top), stage 2 (middle) and combined stage 1 and 2 analysis (bottom) with the genomic control (GC)-adjusted values bracketed (n.a., not applicable for stage 2). Alleles are listed with the stage 1 risk allele first; the frequency (in stage 1 controls) and odds ratio (OR) refer to the stage 1 risk allele. Bolded *P* values indicate $P < 5 \times 10^{-8}$, except for in the stage 2 data, where bolded values indicate $P < 0.05$. The directions of association in eight replication samples are represented by + if the associations are in the same direction, − if they are in opposite directions and a blank space if the data are not available. Mb is the base position based on hg18. Cytogenetic bands are listed for each SNP, though because only one of multiple MHC SNPs are listed, a band range is given in that instance. The nearest gene (or microRNA) is listed, with the distance (kb) from the gene (or if the SNP is intragenic) noted. None of these SNPs showed a significant test for hetereogeneity among the samples. Chr., chromosome.

[a] New finding.