Table 1 Loci selected for follow-up analysis

			Combined UK samples					Replication 1		Replication 1+2		Meta SZ			
			Cases $n = 642$ Controls $n = 2,937$					Cases $n = 1,664$ Controls $n = 3,541$		Cases $n = 6,666$ Controls $n = 9,897$		Cases $n = 7,308$ Controls $n = 12,834$			
Chr./Mb	SNP	Risk allele	SZ	CON	ATT(P)	Adj(P)	OR	CMH(P)	OR	CMH(P)	OR	CMH(P)	Meta-Adj	OR	Locus
2/185.5	rs1344706	T	0.66	0.59	7.08×10^{-7}	1.83×10^{-6}	1.38	0.026	1.09	9.25×10^{-5}	1.09	1.61×10^{-7}	1.95×10^{-7}	1.12	*ZNF804A*
11/29.1	rs1602565	C	0.15	0.11	7.81×10^{-6}	1.70×10^{-5}	1.49	0.005	1.19	3.22×10^{-4}	1.12	2.99×10^{-6}	3.02×10^{-6}	1.16	Intergenic
16/13.0	rs7192086	T	0.30	0.24	3.32×10^{-5}	6.52×10^{-5}	1.33	0.018	1.11	5.10×10^{-4}	1.09	6.08×10^{-6}	1.34×10^{-5}	1.12	Intergenic
11/132.1	rs3016384	C	0.56	0.49	5.82×10^{-5}	1.10×10^{-4}	1.29	0.012	1.10	0.016	1.05	5.63×10^{-4}	1.11×10^{-4}	1.08	*OPCML*
16/52.2	rs9922369	A	0.05	0.03	8.05×10^{-7}	2.05×10^{-6}	2.06	0.015	1.31	0.029	1.14	4.54×10^{-4}	5.01×10^{-6}	1.24	*RPGRIP1L*
12/116.2	rs6490121	G	0.40	0.34	4.33×10^{-6}	9.82×10^{-6}	1.33	0.044	1.08	0.992	1.00	0.109	5.51×10^{-3}	1.04	*NOS1*
2/144.3	rs2890738	A	0.41	0.33	4.96×10^{-9}	1.83×10^{-8}	1.44	0.249	1.03	–	–	–	–	–	Intergenic
3/134.5	rs7624858	A	0.44	0.37	1.15×10^{-4}	2.07×10^{-4}	1.27	0.113	1.06	–	–	–	–	–	*TMEM108*
5/138.5	rs17131938	A	0.07	0.04	2.94×10^{-4}	4.94×10^{-4}	1.64	0.091	0.81	–	–	–	–	–	*SIL1*
10/5.6	rs4750519	T	0.48	0.41	1.07×10^{-4}	1.93×10^{-4}	1.27	0.612	0.98	–	–	–	–	–	Intergenic
15/94.0	rs8031294	T	0.51	0.42	2.29×10^{-5}	4.62×10^{-5}	1.30	0.311	1.02	–	–	–	–	–	Intergenic
18/9.0	rs1893146	A	0.16	0.11	5.40×10^{-7}	1.42×10^{-6}	1.55	0.102	0.89	–	–	–	–	–	Intergenic

SZ and CON; allele frequency in schizophrenia and controls. ATT(P), trend test P value; Adj(P), genomic control adjusted P value; CMH(P), Cochran-Mantel-Haenszel P value; Meta-Adj, genomic control adjusted meta-analysis P value.

The full replication dataset (replication samples 1 + 2; **Table 1**) provided strong independent support for schizophrenia susceptibility variants at 2q32.1 in *ZNF804A* ($P = 9.25 \times 10^{-5}$) and at intergenic regions on 11p14.1 at 29.1 Mb ($P = 3.22 \times 10^{-4}$) and 16p13.12 at ~13 Mb ($P = 5.10 \times 10^{-4}$). Two additional loci, one within the *RPGRIP1L* locus on 16q12.2 at 52.2 Mb and one within *OPCML* at 11q25 (132.1 Mb), remained nominally significant.

The distribution of replication P values is highly unlikely ($P = 9 \times 10^{-8}$) to have occurred by chance, indicating that the GWA threshold $P < 10^{-5}$ enriched for true associations. However, that analysis does not allow any single locus to be assessed in the context of a potential genome-wide study of all samples, nor does it allow for future follow up of lower-order signals. Thus, we combined the data across all samples (**Table 1**), and found that the *ZNF804A* locus ($P = 1.61 \times 10^{-7}$) surpassed the $P < 5 \times 10^{-7}$ benchmark corresponding to strong evidence for association, whereas the regions on chromosomes 11 (29.1 Mb) and 16 (13.0 Mb) showed moderately strong evidence (**Table 1**).

There is evidence that schizophrenia and bipolar disorder have some risk factors in common[9]. Thus, as a secondary analysis, we added genotypes from the bipolar cases ($n = 1,865$) from the WTCCC study to the UK schizophrenia cases to create a large UK psychosis sample for inclusion in the meta-analysis. (See **Table 2**; note that the controls for the schizophrenia and bipolar cases are shared, so the individual associations are not independent. In the meta-analysis, the controls were used only once.) We did not find any evidence for shared risk for most of the loci, but for *ZNF804A*, the evidence was substantially stronger ($P = 9.96 \times 10^{-9}$), suggesting that alleles in the vicinity of *ZNF804A* influence risk to a broader psychosis phenotype. When we combined the data from the WTCCC phenotypes other than bipolar disorder in the meta-analysis with the UK schizophrenia sample, the evidence for association did not strengthen, suggesting that the effect observed from addition of bipolar samples was not simply a consequence of comparing a larger sample with the WTCCC controls.

Our samples included individuals from China and Japan as well as Ashkenazi Jews and outbred Europeans; therefore, the meta-analysis may have been influenced by heterogeneity. In the full replication sample, five of the six loci tested yielded no evidence for heterogeneity (Breslow-Day $P_{min} = 0.10$), and removal of any individual replication sample did not markedly alter the effect size (**Supplementary Table 3** online). The exception was rs9922369, which was monomorphic in Japan and China and had a significantly higher ($P = 8 \times 10^{-10}$

Table 2 Combined schizophrenia and bipolar analysis

						UK SZ		UK BP		Meta SZ + BP	
			Allele freq.			Cases $n = 642$, Controls $n = 2,937$		Cases $n = 1,865$, Controls $n = 2,937$		Cases $n = 9,173$, Controls $n = 12,834$	
Chr./Mb	SNP	Risk allele	SZ	BP	CON	ATT(P)	OR	ATT(P)	OR	CMH(P)	OR
2/185.5	rs1344706	T	0.66	0.62	0.59	7.08×10^{-7}	1.38	4.07×10^{-4}	1.16	9.96×10^{-9}	1.12
11/29.1	rs1602565	C	0.15	0.12	0.11	7.81×10^{-6}	1.49	0.055	1.14	4.26×10^{-6}	1.15
12/116.2	rs6490121	G	0.40	0.35	0.34	4.33×10^{-6}	1.33	0.168	1.06	0.124	1.03
16/52.2	rs9922369	A	0.05	0.03	0.03	8.05×10^{-7}	2.06	0.261	1.15	0.002	1.20
16/13.0	rs7192086	T	0.30	0.25	0.24	3.32×10^{-5}	1.33	0.206	1.06	2.56×10^{-5}	1.10
11/132.1	rs3016384	C	0.56	0.51	0.49	5.82×10^{-5}	1.29	0.057	1.08	4.43×10^{-4}	1.07

SZ, schizophrenia; BP, bipolar; CON, control; ATT(P), trend test P value; meta SZ+BP, meta-analysis for all schizophrenia and bipolar samples reported in this study; CMH(P), Cochran-Mantel-Haenszel P value.

-6×10^{-35}) minor allele frequency in Ashkenazi controls than in any of the European controls. Within the outbred European group alone (discovery plus replication), there was no evidence for heterogeneity at rs9922369 (Breslow-Day $P = 0.75$) and support for association was stronger (OR 1.39, $P = 4.7 \times 10^{-6}$) than in the unrestricted meta-analysis. The results of association analyses for each individual sample are given in **Supplementary Table 3**.

We also applied an imputation approach[10] using a frequentist additive model. The imputed and array data for the loci for which we have nominally significant independent support in the follow up samples are given in **Supplementary Figure 3a–e** online. Imputation did not provide clearly superior additional evidence for association. We observed a secondary region of high statistical significance with the imputed data near *ZNF804A* (**Supplementary Fig. 3a**), but this was not supported by array SNPs or by haplotype analysis based on array SNPs ($P_{min} = 0.01$); provisionally, we assume this to be a false positive.

Genome-wide imputation revealed two additional loci where one or more SNP showed association at $P < 10^{-5}$: chromosome 10 at 17.0 Mb (rs11594134, $P = 2.76 \times 10^{-8}$) and chromosome 15 at 60.4 Mb (rs464356, $P = 4.77 \times 10^{-6}$) (**Supplementary Fig. 3f,g**).

ZNF804A maps to chromosome 2 at 185.1–185.5 Mb (**Supplementary Fig. 3a**). The array association signal was restricted to *ZNF804A*, suggesting that this is the most likely schizophrenia susceptibility gene in the region. The encoded protein is uncharacterized and has no known function, but it contains predicted zinc ion and DNA binding domains, suggesting that it may have a possible role as a regulator of gene expression. Further discussion of the other loci with strong independent support in the replication samples ($P < 0.0005$) is provided in the **Supplementary Note**, but we note that none implicate clear functional candidates on the basis of current understanding of pathophysiology. The identification of risk alleles and genetic mechanisms should therefore provide new insights into schizophrenia pathogenesis.

Our study demonstrates that despite the lack of biological validating criteria for diagnosis, schizophrenia is amenable to the same genetic approaches as other common disorders, and like most other disorders, the effect sizes are small (**Table 1**). Assuming that our UK case-control sample has no unique characteristics that enhance our ability to detect risk loci, our findings strongly suggest that further GWA analyses of larger samples will identify many additional specific genetic risk factors with the potential to shed light into the pathophysiology of one of the most enigmatic major causes of human morbidity. Collection and analysis of large enough samples to provide convincing association signals should now be a priority.

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

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AUTHOR CONTRIBUTIONS

M.C.O'D., M.J.O., and N.C. directed this study and the collection of the UK sample. M.C.O'D. and M.J.O. took primary responsibility for drafting the manuscript assisted by N.N. and H.W. Collaborative scientific direction, replication sample collections, diagnoses and construction of case-control material were led by A.C., M.G., and D.W.M. (Ireland), D.R. (Munich, Germany), W.M., M.R., M.M.N., S.C., J.S. and P.P. (Bonn, Germany), G.K. (Bulgaria), L.H. and G.F. (China); N.I. (Japan) and S.S. and A.D. (Israel). J.L.M., C.C.A.S. and H.-T.L. were responsible for procedures related to calling Affymetrix genotypes. Replication genotyping was performed and analyzed by N.N., H.W., T.P., L.C., L.G. and S.D. (Cardiff); C.V. and P.Hoffmann (Bonn); Y.S. (China); S.S. (Israel); and M.I. (Japan). I.N. developed the database for the GWA project in which the data were stored, the primary analyses were performed and the results visualized. V.M. and P.Holmans supervised the association statistics to which N.N. additionally contributed. M.H. and N.C. were responsible for most of the quality control procedures. Additional scientific coordination of clinical sample collection and diagnosis was performed by S.Z., E.M.Q., A.M.H., H.-J.M., I.G. and T.G.S. All authors discussed the results and approved the manuscript.

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1. Cardno, A.G. & Gottesman, I.I. *Am. J. Med. Genet.* **97**, 12–17 (2000).
2. Risch, N. *Am. J. Hum. Genet.* **46**, 222–228 (1990).
3. Ross, C.A. *et al. Neuron* **52**, 139–153 (2006).
4. The Wellcome Trust Case Control Consortium. *Nature* **447**, 661–678 (2007).
5. Rioux, J.D. *et al. Nat. Genet.* **39**, 596–604 (2007).
6. Zeggini, E. *et al. Science* **316**, 1336–1341 (2007).
7. Frayling, T.M. *et al. Science* **316**, 889–894 (2007).
8. Devlin, B. & Roeder, K. *Biometrics* **55**, 997–1004 (1999).
9. Craddock, N. *et al. J. Med. Genet.* **42**, 193–204 (2005).
10. Marchini, J. *et al. Nat. Genet.* **39**, 906–913 (2007).

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