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Comparative genetic architectures of schizophrenia in East Asian and European populations

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Schizophrenia is a debilitating psychiatric disorder with approximately 1% lifetime risk globally. Large-scale schizophrenia genetic studies have reported primarily on European ancestry samples, potentially missing important biological insights. Here, we report the largest study to date of East Asian participants (22,778 schizophrenia cases and 35,362 controls), identifying 21 genome-wide-significant associations in 19 genetic loci. Common genetic variants that confer risk for schizophrenia have highly similar effects between East Asian and European ancestries (genetic correlation = 0.98 ± 0.03), indicating that the genetic basis of schizophrenia and its biology are broadly shared across populations. A fixed-effect meta-analysis including individuals from East Asian and European ancestries identified 208 significant associations in 176 genetic loci (53 novel). Trans-ancestry fine-mapping reduced the sets of candidate causal variants in 44 loci. Polygenic risk scores had reduced performance when transferred across ancestries, highlighting the importance of including sufficient samples of major ancestral groups to ensure their generalizability across populations.

Schizophrenia is an often-disabling psychiatric disorder that occurs worldwide with a lifetime risk of about 1% (ref. [1]). It is well established that genetic factors contribute to the susceptibility of schizophrenia. Recently, 145 genetic loci were associated with schizophrenia in samples of primarily European ancestry[2,3] (EUR), but this still represents the tip of the iceberg with respect to common variant liability to the disorder: the highly polygenic nature of common variation underlying this disorder predicts that there are hundreds more loci to be discovered[4].

Most genetic studies of schizophrenia have been performed in EUR samples, with relatively few studies in other populations[5–8]. This is a substantial deficiency for multiple reasons, particularly as it greatly limits the discovery of biological clues about schizophrenia. For some causal variants, ancestry-related heterogeneity yields varying allele frequency and linkage disequilibrium (LD) patterns such that associations that can be detected in one population may not be readily detected in others. Examples include a nonsense variant in *TBC1D4*, which confers muscle insulin resistance and increases risk for type 2 diabetes, which is common in Greenland but rare or absent in other populations[9], several Asian-specific coding variants that influence blood lipids[10], a variant highly protective against alcoholism that is common in Asian populations but uncommon elsewhere[11], and two loci associated with major depression[12] that are more common in Chinese populations than in EUR samples[12,13] (rs12415800: 45 versus 2%; rs35936514: 28 versus 6%).

Even if alleles have similar frequencies across populations, the effects of alleles on risk might be specific to certain populations if there are prominent but local contributions of clinical heterogeneity or gene–environment or gene–gene interactions. In addition, there have been debates about differences in prevalence, symptomatology, etiology, outcome and course of illness across geographical regions[14–19]. Understanding the genetic architecture of schizophrenia across populations provides insights into whether any differences represent etiologic heterogeneity on the illness.

Finally, polygenic risk score (PRS) prediction is emerging as a useful tool for studying the effects of genetic liability, identifying

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more homogeneous phenotypes, and stratifying patients. However, previous studies have shown that prediction accuracy decays with increasing genetic divergence between the risk allele discovery and target datasets[20,21]. The risk predicted, measured as R^2 (coefficient of determination), was only 45% as accurate in East Asians (EAS) compared with in EUR individuals when computed from genome-wide association studies (GWASs) of Europeans[22]. These differences can be explained by ancestry-related differences in allele frequencies, LD and other factors[22]. Importantly, the applicability of training data from EUR studies to those of non-EUR ancestry has not been fully assessed, leaving uncertainty as to the biological relevance of discoveries made in EUR samples for non-Europeans[21].

Results

Schizophrenia genetic associations in East Asian (EAS) populations. This study combined multiple samples from individuals with schizophrenia across EAS to systematically examine the genetic architecture of schizophrenia in individuals of EAS ancestry. We compiled 22,778 schizophrenia cases and 35,362 controls from 20 sample collections from East Asia (Supplementary Table 1). Individual-level genotypes were available from 16 sample collections (Supplementary Table 1), on which we performed quality control, imputation and association tests (Methods and Supplementary Table 2). Two sample collections (TAI-1 and TAI-2) were trio-based, and pseudo-controls were used. Four sample collections made available summary statistics for 22,000–31,000 selected variants (Methods) that had been analyzed in published studies[7,8]. Compared with the latest study using only Chinese individuals[8], our study had about twice the sample size, and was much more diverse.

We used a two-stage study design (Supplementary Table 1a). Stage 1 included 13 sample collections for which we had individual genotype data (13,305 cases and 16,244 controls after quality control). Stage 2 incorporated the remaining seven sample collections: full genotype data from three sample collections that arrived after the stage 1 data freeze, and summary statistics (for selected variants) from four sample collections (Supplementary Table 1). Meta-analyses across stage 1 samples and across all EAS samples were conducted using a fixed-effect model with inverse-variance weighting. QQ plots (Extended Data Fig. 1) showed no inflation of test statistics (indicating that ancestry effects had been well controlled), with the genomic inflation factor (λ_{gc}) = 1.14, the genomic inflation factor scaled for an equivalent study of 1,000 cases and 1,000 controls ($\lambda_{1,000}$) = 1.01 and an LD score regression[23] (LDSC) intercept of 1.0145 ± 0.011 using stage 1 samples.

Combining stages 1 and 2, we found 21 genome-wide-significant associations at 19 loci (Table 1, Fig. 1, Supplementary Table 3 and Supplementary Datasets 1 and 2)—an additional 14 associations compared with the most recent schizophrenia genetic study of Chinese ancestry[8]. Most associations were characterized by marked differences in allele frequencies between the EAS and EUR samples: for 15 of 21 loci, the index variants had higher minor allele frequencies (MAFs) in EAS than EUR. The higher allele frequency potentially confers better power to detect associations in EAS. For example, we identified a locus (Supplementary Dataset 1) with the top association (rs374528934) having strong evidence in EAS ($P = 5 \times 10^{-11}$) but not in EUR using the stage 1 samples. rs374528934 has a MAF of 45% in EAS but only 0.7% in EUR. No other variant in this locus is significantly associated with schizophrenia in EUR. This locus contains *CACNA2D2* (encoding the calcium channel α2δ-2 subunit associated with childhood epilepsy[24,25], and to which the anticonvulsant medication gabapentin binds), suggesting a path for further therapeutic investigation[25]. This finding also adds new evidence to the calcium signaling pathway suggested to be implicated in psychiatric disorders[26,27].

Genetic effects are consistent across populations. For causal variants, heterogeneity of genetic effects across populations could arise from clinical heterogeneity, differences in pathophysiology, environmental differences that change the genetic effects (gene–environment interaction) or interaction with other genetic factors that may differ in frequency across populations (gene–gene interaction). Heterogeneity in estimating genetic effect sizes may also be a consequence of differential correlation across genetic markers in a region, when investigating variants that are tagging the causal variant but do not exert any influence on the trait in question. Such heterogeneity does not reflect biological differences, but is rather statistical in nature. While it is assumed that biological pathways underlying complex human disorders are generally consistent across populations, genetic heterogeneity has been observed in other genetically complex disorders[28]. The large EAS sample allowed us to systematically explore the heterogeneity of genetic effects influencing liability to schizophrenia across two major world populations.

Using LDSC[23] and common variants (MAF > 5%) outside of the major histocompatibility complex (MHC) region, we found that the single-nucleotide polymorphism (SNP) heritability of schizophrenia is very similar in EAS (0.23 ± 0.03) and EUR (0.24 ± 0.02) (Methods and Extended Data Fig. 2a). Using the same set of variants, we found that the genetic correlation (r_g) for schizophrenia between EAS and EUR was indistinguishable from 1 ($r_g = 0.98 \pm 0.03$) (using POPCORN[29]—a method designed for cross-ancestry comparisons). This finding indicates that the common variant genetic architecture of schizophrenia outside of the MHC region is highly consistent across EAS and EUR samples.

Genetic correlations between schizophrenia and 11 other psychiatric disorders and behavior traits also showed no significant differences when estimated within EUR and across EAS–EUR (Extended Data Fig. 2b). In agreement with recent reports[30–33], we observed significant positive genetic correlations for schizophrenia with bipolar disorder, major depressive disorder, anorexia nervosa, neuroticism, autism spectrum disorder and educational attainment. We observed significant negative correlations with general intelligence, fluid intelligence score, prospective memory and subjective well-being.

We used partitioned LDSC[23] to look for heritability enrichment in diverse functional genomic annotations defined and used in previous publications[34,35] (Methods and Extended Data Fig. 2c,d). Using EAS stage 1 samples, we observed significant enrichment (after Bonferroni correction) in regions conserved across 29 mammals (as described in Lindblad-Toh et al.[36]; 'Conserved LindbladToh'). No other annotations were significantly enriched, and there were no significant differences between EUR-only and EAS-only enrichments ($P = 0.16$, two-sided paired t-test).

We identified gene sets that are enriched for schizophrenia genetic associations using MAGMA[37] and gene set definitions from a recent schizophrenia exome sequencing study[38] (Methods). Despite large differences in sample size and genetic background, the gene sets implicated in EAS and EUR samples were highly consistent: we observed no significant differences between gene set ranks using the EAS samples and gene set ranks using the EUR samples ($P = 0.72$, two-sided Wilcoxon test). In addition, nine of the top ten gene sets identified using the EAS samples were also among the top ten gene sets identified using the EUR samples (Extended Data Fig. 3).

A study of EUR individuals suggested that common schizophrenia alleles are under strong background selection[3]. We performed two analyses and found that the natural selection signatures, including positive and background selections, are consistent in schizophrenia-associated loci across EAS and EUR populations. First, we compared the signatures in the top 100 associated loci in EAS with those in EUR. Among the selection signatures we calculated (Methods), none showed a significant difference across populations (Extended Data Fig. 4a; $P > 0.05$ for all panels, two-sided

Table 1 | Genome-wide-significant loci in the EAS populations

				Stage 1		Stage 2		Combined	
SNP	Chromosome	BP	AL	*P*	OR	*P*	OR	*P*	OR
rs4660761	1	44440146	A/G	3.6×10^{-6}	0.91	3.53×10^{-4}	0.92	5.08×10^{-9}	0.91
rs848293	2	58382490	A/G	3.7×10^{-10}	0.90	3.10×10^{-9}	0.87	9.87×10^{-18}	0.89
rs17592552	2	201176071	T/C	8.4×10^{-10}	0.86	2.68×10^{-5}	0.89	1.50×10^{-13}	0.88
rs2073499	3	50374293	A/G	1.1×10^{-9}	0.89	2.14×10^{-5}	0.91	1.33×10^{-13}	0.90
rs76442143	3	51043599	T/C	6.9×10^{-9}	1.14	1.03×10^{-2}	1.08	6.40×10^{-10}	1.12
rs10935182	3	136137422	A/G	1.3×10^{-6}	0.90	1.33×10^{-4}	0.90	7.08×10^{-10}	0.90
rs4856763	3	161831675	A/G	3.9×10^{-6}	0.92	8.54×10^{-6}	0.91	1.73×10^{-10}	0.92
rs13096176	3	180752138	T/C	3.1×10^{-7}	0.88	2.21×10^{-3}	0.90	3.35×10^{-9}	0.89
rs6832165	4	24270210	C/G	3.7×10^{-8}	1.12	3.70×10^{-1}	1.08	2.79×10^{-8}	1.12
rs13142920	4	176728614	A/C	9.5×10^{-5}	0.93	5.85×10^{-6}	0.89	4.85×10^{-9}	0.92
rs4479913	6	165075210	A/G	3.6×10^{-7}	1.13	9.98×10^{-5}	1.12	1.53×10^{-10}	1.12
rs320696	7	137047137	A/C	5.5×10^{-8}	0.90	1.07×10^{-2}	0.93	2.81×10^{-9}	0.91
rs11986274	8	38259481	T/C	5.1×10^{-4}	1.07	2.73×10^{-6}	1.11	1.44×10^{-8}	1.08
rs2612614	8	65310836	A/G	2.2×10^{-8}	1.14	4.51×10^{-2}	1.06	1.62×10^{-8}	1.11
rs4147157	10	104536360	A/G	6.6×10^{-10}	0.90	3.87×10^{-7}	0.89	1.32×10^{-15}	0.89
rs10861879	12	108609634	A/G	4.8×10^{-7}	1.09	5.00×10^{-3}	1.07	1.18×10^{-8}	1.08
rs1984658	12	123483426	A/G	5.1×10^{-11}	0.89	2.14×10^{-4}	0.92	8.62×10^{-14}	0.90
rs9567393	13	32763757	A/G	3.5×10^{-8}	1.11	4.37×10^{-3}	1.07	1.13×10^{-9}	1.09
rs9890128	17	1273646	T/C	3.5×10^{-8}	0.90	2.44×10^{-2}	0.91	2.61×10^{-9}	0.90
rs11665111	18	77622996	T/C	5.2×10^{-6}	1.08	6.89×10^{-4}	1.09	1.46×10^{-8}	1.09
rs55642704	18	77688124	T/C	1.1×10^{-6}	1.09	7.11×10^{-6}	1.10	3.76×10^{-11}	1.09

For EAS stage 1, $n=13{,}305$ cases and $n=16{,}244$ controls. For EAS stages 1 and 2, $n=22{,}778$ cases and $n=35{,}362$ controls. Fixed-effect inverse-variance meta-analysis was utilized to generate the *P* values. AL, reference and non-reference alleles; BP, genomic position in HG19; OR, odds ratio.

t-test). Next, we asked whether the population differentiation drives schizophrenia variants to have different effects in different populations. Using 295 autosomal variants that are genome-wide significant in EAS, EUR or combined EAS and EUR samples, we did not observe a correlation ($R^2=0.003$; Extended Data Fig. 4b) between the population differentiation (measured by fixation index (F_{ST})) and the heterogeneity of the effect size (measured by $-\log_{10}$[*P* value] from the heterogeneity test across EAS and EUR).

As a further test, we examined whether the effect size estimates from EUR differed from those from EAS. We performed a heterogeneity test (Cochran's *Q*) for the most significant variants in the 108 published schizophrenia-associated loci[2]. Among them, seven variants showed significant heterogeneity after Bonferroni correction (Supplementary Table 4). Postulating that this might in part be driven by the inflation of EUR estimates as a result of the winner's curse, we applied a correction for the winner's curse[39], after which none of the variants showed evidence for significant heterogeneity, and the *P* values from the heterogeneity test followed a uniform distribution ($P=0.10$; two-tailed Kolmogorov–Smirnov test).

Lastly, we evaluated the heterogeneity of schizophrenia genetic effects within EAS samples. None of the EAS associations showed significant heterogeneity across EAS samples (Supplementary Table 3). Using their principal components, we further grouped the samples into Northeast Asian, Southeast Asian and Indonesian subpopulations (Methods). We then performed a heterogeneity test (Cochran's *Q*) and found no significant heterogeneity among the three subpopulations (Extended Data Fig. 5).

Schizophrenia genetic associations from the meta-analysis of EAS and EUR. As the genetic effects observed in EAS are largely consistent with those observed in EUR, we performed a meta-analysis including the EUR and EAS samples (stages 1 and 2), using a fixed-effect model with inverse-variance weighting[40]. The EUR + EAS samples in this analysis ($n=56{,}418$ cases and $n=78{,}818$ controls) included all samples of EUR ancestry ($n=33{,}640$ cases and $n=43{,}456$ controls) from a previous publication[2], with the exclusion of three samples of EAS ancestry and the deCODE samples ($n=1{,}513$ cases and $n=66{,}236$ controls), for which only summary statistics for selected variants were available. The three EAS samples (IMH-1, HNK-1 and JPN-1) excluded from the EUR samples were included in our EAS stage 1.

We identified 208 independent variants (both in EAS and EUR) associated with schizophrenia across 176 genetic loci (Fig. 2 and Supplementary Tables 5 and 6), among which 53 loci were novel (not reported in refs. [2,3,7,8]). Of the 108 schizophrenia-associated loci reported in the previous EUR study[2], 89 remained significant in this study (Supplementary Table 4). Using simulations with a correction for winner's curse[39], we found that this was consistent with an expected overestimation of the effect sizes due to the winner's curse in the previous study, rather than implying that the 19 loci no longer significant in this study were false positives (Supplementary Note). In addition, the deCODE samples ($n=1{,}513$ cases and $n=66{,}236$ controls) were not included in the present study, causing the power for loci that had low MAF in EAS to drop.

Population diversity improves fine-mapping. Causal variants in complex genetic disorders are defined as those that mechanistically contribute to the disorders, but this does not imply that the variant in isolation is likely to result in the disorder[41,42]. Due to LD, disease-associated loci from GWASs usually implicate genomic regions

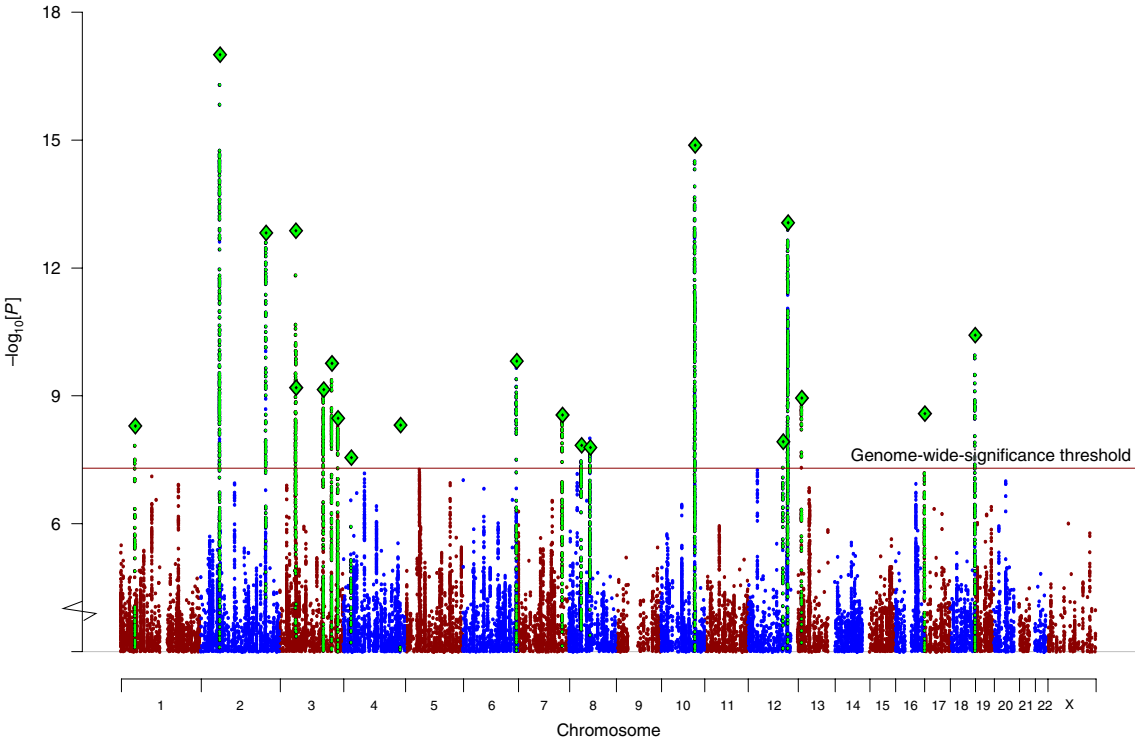

Fig. 1 | Genetic associations in EAS populations. Manhattan plot for schizophrenia genetic associations using EAS samples (stages 1 and 2; $n = 22{,}778$ cases; $n = 35{,}362$ controls). Red and blue dots refer to variants within odd and even chromosomes, respectively. Green dots refer to variants within genome-wide-significant loci. Diamonds represent index variants within genome-wide-significant loci. The genome-wide-significance threshold ($P < 5 \times 10^{-8}$) is represented as the horizontal red line.

containing many associated variants. A number of approaches allow for the associated variants to be refined to a smaller set of the most plausible (or credible) candidate causal variants[43–46]. Loci implicated in psychiatric disorders usually have small effect sizes, and as a result have generally poor performance using such approaches[2,3].

Diversity in genetic background across populations can be used to improve fine-mapping resolution[47]. Here, we demonstrate that resolution can be improved by exploiting differences in the patterns of LD between causal (directly associated) and non-causal (indirectly associated through LD) variants. Based on the premise that genetic effects are highly consistent across populations, the causal variants will have consistent effects across populations, whereas non-causal variants can have inconsistent effects due to population-specific LD patterns. We therefore expect causal variants to have greater statistical significance and less heterogeneity in the trans-ancestry meta-analysis compared with other alleles that are indirectly associated via LD (Extended Data Fig. 6). Using an algorithm based on this expectation (Methods), we fine-mapped 59 schizophrenia associations that reached genome-wide significance in the EUR and EAS stage 1 combined meta-analysis, had a MAF > 0.01 in both EAS and EUR, and for which we had >95% coverage of common variants (MAF > 1%) with imputation INFO > 0.6 (Supplementary Table 7). The MHC region was excluded from the fine-mapping analysis due to its long-range LD. EAS stage 2 samples were excluded because not all had full genome coverage, which confounds the fine-mapping outcome (Methods).

The results from this EAS and EUR trans-ancestry approach improved on those using only EUR, with 44 out of 59 loci mapped to a smaller number of candidate causal variants (Supplementary Table 7). For example, a locus on chromosome 1 (238.8–239.4 megabases (Mb)), which initially contained seven potentially causal variants based on a published fine-mapping method[43] and EUR samples only, was resolved to a single variant (rs11587347) with 97.6% probability (Fig. 3a). This variant showed strong association in both populations, while the other six variants were equally associated in EUR but not in EAS (Fig. 3b,c). Over all of the associations, the median size of the 95% credible set, defined as the minimum list of variants that were >95% likely to contain the causal variant, dropped from 49 to 30, and the number of associations mapped to ≤5 variants increased from two to seven (Fig. 3d). The number of associations mapped to a single variant with >50% probability increased from five to eight, and median size of the genomic regions the associations mapped decreased from 154 to 94 kilobases (kb).

Transferability of genetics across populations. For genome-wide-significant loci that individually explain >0.05% of the variance in schizophrenia liability in either ancestry, we compared the variance explained across EAS and EUR. Variance was approximated as $2f(1-f)\log[\mathrm{OR}]^2/(\pi^2/3)$ (ref. [48]) (Extended Data Fig. 7), where f represents the prevalence of the risk allele. Although these variants most often have comparable odds ratios across populations, their allele frequencies can differ. The variance explained when combining the effect size (odds ratio) and prevalence of the risk allele (f) can be regarded as an approximate measure of the importance of a causal variant in a population. In our analysis, most of the trans-ancestry differences in variance are explained by allele frequency differences. One of the implications of this observation, as suggested in recent studies[21,49,50], is that even if the risk alleles and effect sizes are primarily shared across populations, the disease predictive power of individual alleles, and of composite measures of those risk alleles such as PRS, may not be equivalent across populations.

Here, we evaluate this empirically. We assessed how much variation in schizophrenia risk can be explained in EAS using both EAS stage 1 and EUR training data. Using a standard clumping approach, we first computed PRS using a leave-one-out meta-analysis approach with EAS summary statistics (Methods), which explained ~3% of

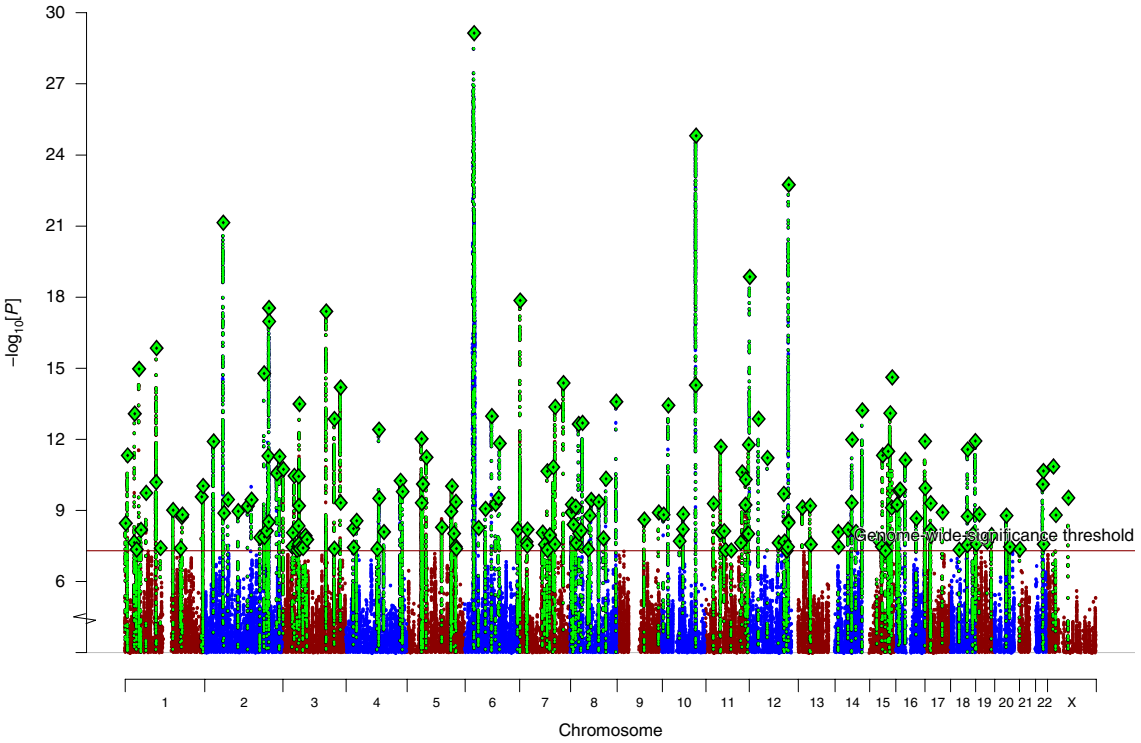

Fig. 2 | Schizophrenia associations in EUR and EAS samples. Manhattan plot for the schizophrenia genetic associations from the EAS (stages 1 and 2) and EUR meta-analysis ($n = 56{,}418$ cases; $n = 78{,}818$ controls). Red and blue dots refer to variantss within odd and even chromosomes, respectively. Green dots refer to variants within genome-wide-significant loci. Diamonds represent index variants within genome-wide-significant loci. Genome-wide-significance threshold ($P < 5 \times 10^{-8}$) is represented as the horizontal red line.

schizophrenia risk using genome-wide variants on the liability scale ($R^2 = 0.029$ at $P = 0.5$). In contrast, when EUR summary statistics were used to calculate PRS in the EAS samples, a maximum of only ~2% of schizophrenia risk was explained ($R^2 = 0.022$ at $P = 0.1$), despite a greater than threefold larger EUR effective sample size (Fig. 4 and Extended Data Fig. 8). The variance explained across various *P* value thresholds provides a proxy for the signal-to-noise ratio, which differs by training population—relative to the EUR training data, variants from the EAS training data with more permissive *P* values improve the EAS prediction accuracy. These results indicate that larger EAS studies will be needed to explain case/control variance similar to that currently explained in EUR individuals. Furthermore, although individual loci typically have the same direction and a similar magnitude across populations, aggregating variants that differentially tag causal loci across populations for genetic risk prediction results in considerable variability in prediction accuracy.

Discussion

To date, most large-scale psychiatric genetics studies have been based on samples of primarily EUR ancestry[6]. To increase global coverage, we compiled the largest non-EUR psychiatric genetics cohort to date and leveraged its size and diversity to provide new insights into the genetic architecture of schizophrenia. This study includes all available major genotyped schizophrenia samples of EAS ancestry, and presents analyses that have not previously been performed with sufficient power in psychiatric genetics. Although the first schizophrenia genetic associations from two much smaller studies of Chinese ancestry[51,52] were not genome-wide significant in the present EAS analysis, several loci from their subsequent better-powered studies[7,8] reached genome-wide significance. Consistent with a study using EUR samples[3], we note that this is consistent with the expected inflation of effect size from small studies, rather than suggesting that loci in previous studies are false positives.

When a single population is used to identify the disease-associated loci, the discovery is skewed towards disease-associated variants that have greater allele frequency in that population (Extended Data Fig. 9). When multiple populations are used, disease-associated variants are equally represented across the allele frequency spectrum in these populations (Extended Data Fig. 9). This shows that including global samples improves the power to find disease associations for which the power varies across populations. In this study, for example, more EUR than EAS samples would be required to detect around half of the new loci, as the MAF is higher in EAS than in EUR in these loci.

For traits such as body mass index and autoimmune diseases, we observed heterogeneity across populations in genetic effects[28,53], which may point to interactions between genetic associations and environmental factors and/or other genetic loci. In contrast, for schizophrenia, we did not find significant heterogeneity across EAS and EUR ancestries. Analyses of genetic heritability, genetic correlation, gene set enrichment and natural selection signatures converge on the conclusion that the schizophrenia biology is substantially shared across EAS and EUR ancestries (with MHC as a potential exception, as is discussed below). The remarkable genetic correlation ($r_g = 0.98$) shows that schizophrenia risk alleles operate consistently across different ethnic and cultural backgrounds—at least across EAS and EUR ancestries. Given that the main putative environmental risk factors (migration, urbanicity and substance misuse) differ across populations, this finding also suggests that any specific genetic liability to schizophrenia acting via these routes is minimal.

We note that a direct comparison of the effect sizes estimated in EAS with those estimated in EUR has reduced accuracy as we do not know the exact schizophrenia causal variants. This is further complicated by inflations in effect size estimates due to the winner's curse, which are of different magnitudes due to the sample size.

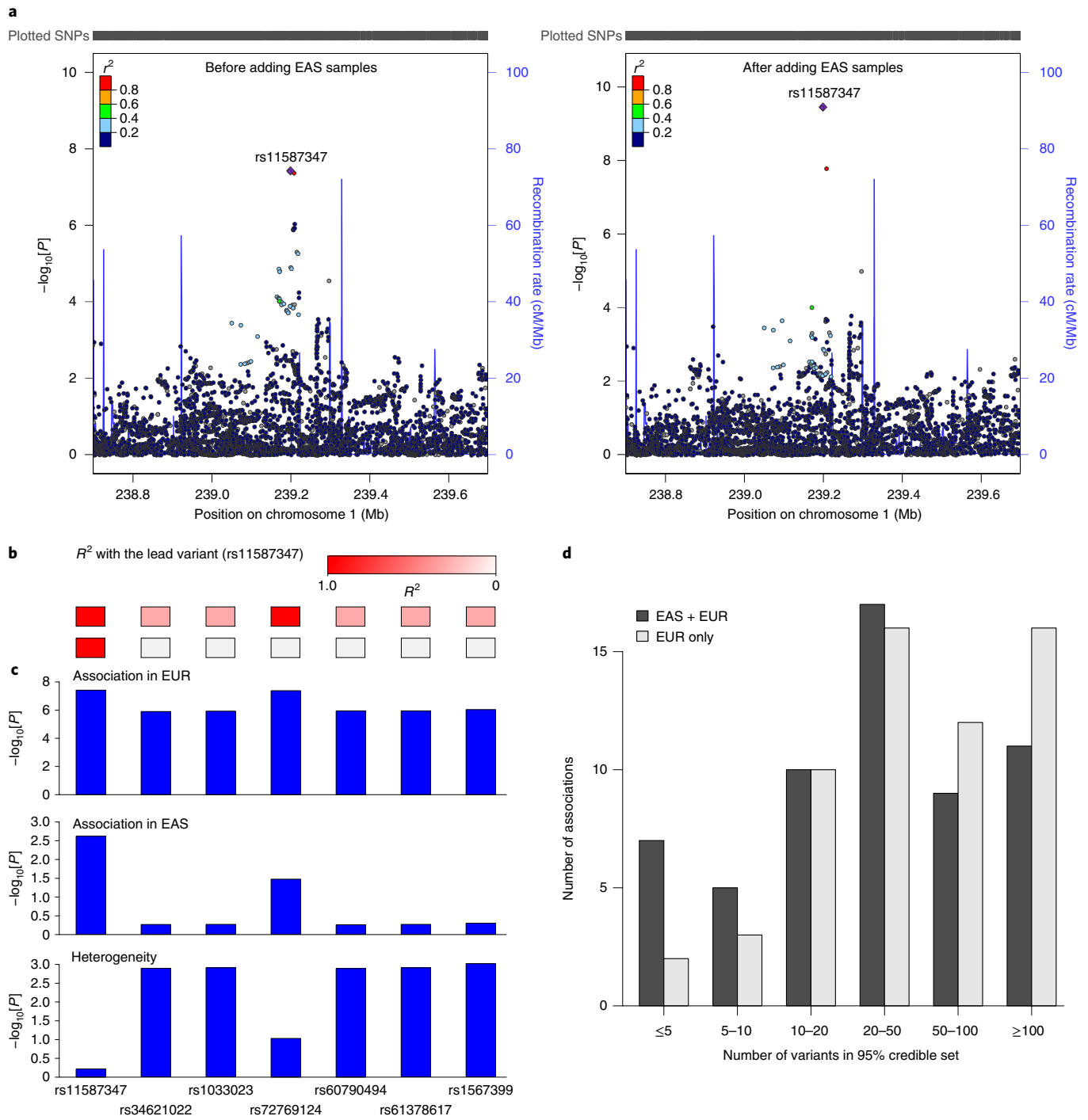

Fig. 3 | Trans-ethnic fine-mapping improves resolution. a, An association was mapped to a single variant (rs11587347) after adding EAS samples and using the trans-ancestry fine-mapping approach. Regional association plots were generated using http://locuszoom.org/ and LD from 1000 Genomes Project Phase 3 EUR subjects. Left, EUR-only samples. Right, Meta-analysis of EUR and EAS samples. **b**, LD with the lead variant (rs11587347). **c**, The lead variant (rs11587347) has strong association significance in both populations, and low heterogeneity across populations. In **a**–**c**, for EAS stage 1, $n = 13{,}305$ cases and $n = 16{,}244$ controls, and for EUR, $n = 33{,}640$ cases and $n = 43{,}456$ controls. **d**, Number of variants in the 95% credible set using the trans-ancestry (EAS + EUR) and published fine-mapping approaches (EUR only).

Increasing the sample size, especially in those of non-EUR ancestries, will reduce the bias and enable a better isolation of causal variants, leading to a more precise comparison of the genetic effect size across populations.

The MHC hosts the strongest schizophrenia association in EUR[54]. In this study, we did not find a significant schizophrenia association in MHC in EAS. An earlier EUR study[55] mapped the MHC associations to a set of variants (in LD) at both distal ends of the extended MHC (lead variant: rs13194504) and the complement component 4 (C4). None of these associations was significant in EAS in this study, which is consistent with previous studies of Chinese ancestry[7,8,51,52]. However, this does not necessarily

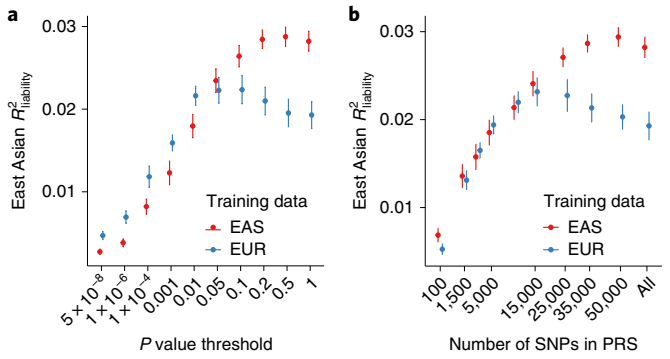

Fig. 4 | Genetic risk prediction accuracy in EAS from EAS or EUR training data. PRSs were computed with GWAS summary statistics from EAS and EUR populations as training sets. EAS risk alleles and weights were computed with a leave-one-out meta-analysis approach across the 13 stage 1 samples. Error bars indicate 95% confidence intervals. The LD panel for clumping is from the EUR and EAS 1000 Genomes Phase 3 samples. **a**, Case/control variance explained in EAS samples by variants from EAS and EUR training data with a *P* value more significant than the threshold. **b**, Case/control variance explained by the *n* most significant independent variants. In **a** and **b**, for EAS stage 1, $n=13{,}305$ cases and $n=16{,}244$ controls, and for EUR, $n=33{,}640$ cases and $n=43{,}456$ controls.

suggest population heterogeneity in their pathophysiological effect, as we attribute the disappearance of MHC signals partially to low frequencies. rs13194504 has a MAF < 1% in EAS, compared with 9% in EUR, and the C4-BS allele is extremely uncommon in samples from China and Korea[56,57]. Another reason may be the EUR-specific LD. In EUR, multiple protective alleles that contribute to the MHC associations are all on the same haplotype across about 6 Mb, due to an extremely long and EUR-specific haplotype that generates LD patterns at a 5-Mb scale. This may also be the reason that association signals span so many megabases of genome, and the aggregate association signal (at variants that are in partial LD to multiple signals) is stronger than the signals at the individual associations.

Two recent studies using much smaller samples with individuals of Chinese ancestry[7,8] reported variants in MHC significantly associated with schizophrenia (rs115070292 and rs111782145, respectively). The two studies did not replicate each other's findings, as the reported risk alleles were in very weak LD ($r^2=0.07$), nor did they replicate the EUR study[55], because the risk alleles were not in LD with the EUR MHC associations. rs115070292, from Yu et al.[7], is more frequent in EAS (12%) than in EUR (2%), with $P=10^{-9}$ using 4,384 cases and 5,770 controls of Chinese ancestry. This variant was not significantly associated in our study ($P=0.44$), even though some samples from the earlier study were included in the current study (BJM-1; 1,312 cases and 1,987 controls). The odds ratio estimated from these shared samples marginally differs from that estimated using all EAS samples ($P=0.018$), and this association showed marginally significant heterogeneity across all EAS samples ($P=0.039$). Similarly, we did not replicate the association at rs111782145 from Li et al.[8] ($P=0.47$) despite sample overlap (2,555 cases and 3,952 controls).

The lack of replication across all of these studies reflects the complexity of the MHC region and the limited power for the MHC signals in EAS. As shown in previous studies of complex disorders, it is still possible that when sample size increases for the EAS, genome-wide association within the MHC region could emerge. A study designed for the MHC region, such as in ref. [55], will be necessary to delineate the contribution of MHC to schizophrenia in EAS individuals.

Genetic associations usually implicate a large genomic region; thus, it can be challenging to map their molecular functions. We designed a novel algorithm to leverage the population diversity to fine-map schizophrenia associations to precise sets of variants. Using this algorithm, we reduced the number of candidate variants associated with schizophrenia and facilitated the functional interpretation of these associations. Our algorithm only maps the primary association signals in a locus because the power to fine-map signals beyond that, especially in the EAS samples, is still limited at the current sample size for schizophrenia. We also made an assumption that there is only one causal variant driving the primary association signal. In the scenario that there is a haplotypic effect driven by multiple variants in strong LD, our approach will split the posterior probability among these variants. We expect the causal variants to have non-trivial probability so that they will still be reported in the credible set for future studies. Imputation quality plays a key role in fine-mapping, as the power to map the causal variant decreases if it is poorly imputed. We restricted our study to genetic associations that have a MAF > 1% in both EAS and EUR populations to ensure the imputation quality. For these associations, we found no major change in the size of the credible sets when the EUR samples were imputed using the more powerful Haplotype Reference Consortium panel[58]. However, the Haplotype Reference Consortium reference panel, with its much larger sample size and better characterization of low frequency and rare variants, could improve fine-mapping resolution for variants with a MAF ≤ 1%[59].

Finally, this large-scale EAS sample allowed us to empirically evaluate the congruence of the genetic basis of schizophrenia between EAS and EUR. Despite a cross-population common variant genetic correlation being highly consistent, we found that polygenic risk models trained in one population have reduced performance in the other population due to different allele frequency distributions and LD structures. This highlights the importance of including all major ancestral groups in genomic studies, both as a strategy to improve the power to find disease associations, and to ensure that the findings have maximum relevance for all populations.

Online content

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Methods

Overview of samples. *EAS samples.* Full genome. Genome-wide genotype data were obtained from 16 samples from East Asia (Supplementary Table 1). Two of these samples (TAI-1 and TAI-2) had parent–offspring trios and were processed as case/pseudo-controls. The *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition)[60] was used for diagnosing all schizophrenia cases in these samples, except for the trios (TAI-1 and TAI-2), for which the *Diagnostic Interview for Genetic Studies*[61] was used. All samples were processed according to the quality control procedures reported in ref. [2], with details reported in the following sections. After quality control, genotypes were phased and imputed against the 1000 Genomes Project Phase 3 reference panel[6]. Principal component analysis (PCA) was conducted across samples via imputed best-guess genotypes to identify and remove overlapping samples across datasets, cryptic related samples and population outliers. Eight principal components that were associated with case-control status were included in univariate logistic regression as covariates to control for the population stratification in each sample.

Selected variants. Summary statistics were obtained for a set of variants from four EAS samples (BJM-2, BJM-3, BJM-4 and BIX-5) that had been analyzed in published studies[7,8]. The summary statistics included odds ratios, standard errors, reference and tested alleles for variants that had $P < 10^{-5}$ in either stage 1 or the meta-analysis combining stage 1 and EUR samples. Between 22,156 and 31,626 variants were available after the exclusion of strand-ambiguous[62] variants (Supplementary Table 2).

EUR samples. Genotypes for EUR schizophrenia patients and controls were obtained from the Psychiatric Genomics Consortium, as reported in ref. [2]. All samples of EUR ancestry were included in this study except for the deCODE samples (1,513 cases and 66,236 controls). We also note that three sample collections of EAS ancestry reported in ref. [2] (IMH-1, HNK-1 and JPN-1) were not included in the EUR samples in our analysis, but were included in the EAS samples. The same procedures used in processing EAS samples were applied to the EUR samples.

EAS subpopulations. To investigate the heterogeneity of schizophrenia genetics effects within EAS, we grouped the samples based on their principal components. Other than Indonesians (UWA-1), who fall into their own subpopulation, samples were grouped into the Northeast Asian subpopulation if their average principal component 2 score was significantly greater than 0 (BIX-2, BJM-1, XJU-1, JPN-1 and KOR-1) and into the Southeast Asian subpopulation if their average principal component 2 score was significantly less than 0 (TAI-1, TAI-2, IMH-1, IMH-2, HNK-1 and BIX-3). The remaining samples (UMC-1, SIX-1, BIX-1 and BIX-4) were not included in the subpopulations. The heterogeneity test (Cochran's *Q*) across subpopulations (calculated pairwise and across all) was conducted using RICOPILI[63].

Quality control. Quality control procedures were carried out as part of the RICOPILI pipeline[63] with the following steps and parameters: (1) excluding variants with a call rate below 95%; (2) excluding subjects with a call rate below 98%; (3) excluding monomorphic variants; (4) excluding subjects with an inbred coefficient above 0.2 and below −0.2; (5) excluding subjects with a mismatch in their reported sex and chromosome X imputed sex; (6) excluding variants with missing rate differences >2% between cases and controls; (7) subsequent to step 6, excluding variants with a call rate <98%; and (8) excluding variants in violation of Hardy–Weinberg equilibrium ($P < 10^{-6}$ for controls or $P < 10^{-10}$ for cases). The numbers of variants or subjects removed in each step are reported in Supplementary Table 2.

Phasing and imputation. All datasets were phased using SHAPEIT[64] and IMPUTE2 (ref. [65]) using regular steps and parameters. Additional processing for trios (TAI-1 and TAI-2) was carried out such that case/pseudo-controls were identified and imputed. All samples were imputed to the 1000 Genomes Project Phase 3 reference panel[66] (2,504 subjects, including 504 EAS subjects). Imputation procedures resulted in dosage files and best-guess genotypes in PLINK[67] binary format. Dosage files were used for subsequent association analysis, while best-guess genotypes were used in the PCA and PRS analyses.

Sample overlaps, population outliers and population stratification. We used EIGENSTRAT[68] to calculate the principal components for all of the samples using the best-guess genotypes from imputation (Extended Data Fig. 10b). We computed the identity-by-descent matrix to identify intra- and inter- dataset sample overlaps. Samples with pi-hat > 0.2 were extracted, followed by a Fisher–Yates shuffle on all samples. The number of times each sample was related to another sample was tracked, and samples that were related to more than 25 samples were removed. When deciding which samples to retain, trios were preferred, followed by cases, and thereafter a random sample for each related pair was removed, resulting in the removal of 704 individuals.

To identify population outliers, *k*-means clustering was conducted using the first 20 principal components from PCA and covariates representing each of the 13 stage 1 samples. Guided by the results of *k*-means clustering and visual inspection of PCA plots, 46 individuals were identified as outliers and were excluded. Further population-level inspection was carried out by merging the 1000 Genomes Project Phase 1 reference samples with stage 1 samples and conducting PCA (Extended Data Fig. 10a). Using similar approaches to those reported above, no further samples were excluded as population outliers.

Eight principal components that were associated with case/control status with $P < 0.2$ were used as covariates for association analysis in each sample (principal components 1, 4, 5, 6, 8, 9, 15 and 19). QQ plots (Extended Data Fig. 1) showed that the population structure was well controlled.

Association analysis and meta-analysis. Association analysis was carried out for each sample using PLINK[67] and genotype dosage from imputation. Only variants with imputation INFO ≥ 0.6 and a MAF ≥ 1% were included in the analysis. We performed logistic regression with principal components identified in the previous subsection as covariates to control for population stratification within each study. Fixed-effect meta-analysis[69], weighted by inverse variance, was then used to combine association results across samples. A meta-analysis for EUR samples was conducted in the same manner. To find independent schizophrenia associations in both EUR and EAS populations (Supplementary Table 6), we performed LD clumping twice using the 1000 Genomes Project Phase 3 EUR and EAS reference panels, respectively (with default parameters in RICOPILI).

Chromosome X analysis. Chromosome X genotypes were processed separately from autosomal variants. Quality control was conducted separately for males and females, using similar quality control parameters as above. Cases and pseudo-controls were built out of the trios. Phasing and imputation were then performed on males and females separately for each sample, followed by logistic regression with the same principal components, and meta-analysis combining samples (same parameters as the autosomal analyses). The results were generated for EAS stage 1 samples and EUR and EAS combined (excluding BIX-1, BIX-2 and BIX-3). EAS stage 2, BIX-1, BIX-2 and BIX-3 samples did not have chromosome X data and were therefore not analyzed.

Genetic correlation and heritability. Schizophrenia heritabilities in the observed scale for samples of EUR and EAS ancestry were estimated from their summary statistics using LDSC[23]. We converted the heritabilities in the observed scale to a liability scale assuming a schizophrenia population prevalence of 1%. The LD scores were pre-computed from the 1000 Genomes Project Phase 3 reference panel in EUR and EAS, respectively (https://github.com/bulik/ldsc). Only autosomal variants with a MAF > 5% in their respective population were included in the analysis, and variants in the MHC region were not included due to the long-range LD.

We computed the genetic correlations between schizophrenia and other traits within EUR and across EUR and EAS. EUR and EAS (stage 1 only) summary statistics for autosomal variants from this study were used as schizophrenia genetic association inputs for their respective populations. The traits tested included schizophrenia[2], bipolar[70], major depression[71], anorexia nervosa[72], neuroticism and subjective well-being[73], autism spectrum disorder ('GWAS - 2015' release; available at http://www.med.unc.edu/pgc), attention deficit hyperactivity disorder ('European Ancestry GWAS'; available at http://www.med.unc.edu/pgc)[74], educational attainment[30], general intelligence[75], fluid intelligence score and prospective memory result (using individuals from UK Biobank; http://www.nealelab.is/uk-biobank). Only variants with a MAF > 5% were available and included. Variants in the MHC region were excluded from the analysis. Genetic correlations within EUR were computed using LDSC with LD scores pre-computed on the 1000 Genomes Project Phase 3 reference panel (503 EUR subjects). Genetic correlations across EUR and EAS were computed using POPCORN[29]. POPCORN uses a Bayesian approach that assumes that genotypes are drawn separately from each population and effect sizes follow the infinitesimal model. Genetic correlations in POPCORN were computed in the 'genetic effect' mode, which estimates the correlation based on the LD covariance scores and effect sizes from summary statistics.

Partitioned heritability. Partitioned LDSC[34] was conducted to look for heritability enrichment in diverse annotations using EAS (stage 1) and EUR autosomal variants (summary statistics), respectively. LD scores for each annotation were computed using a combination of PLINK[67] and LDSC[23], using the 1000 Genomes Project EAS and EUR subjects, respectively. We used baseline annotations[34] and additional annotations including chromatin accessibility in the brain dorsolateral prefrontal cortex, as determined via assay for transposase-accessible chromatin using sequencing peaks (Bryois et al.[35]; 'ATAC Bryois'), conserved regions (Lindblad-Toh et al.[36]; 'Conserved LindbladToh') located via the assay for transposase-accessible chromatin using sequencing peaks[35], and introgressed regions from Neanderthals[76] ('Neanderthal Vernot'). Variants can be included in multiple annotations. Multi-allelic variants were removed.

Gene set analysis. We performed gene- and gene set-based tests using MAGMA[37]. Genome-wide summary statistics for autosomal variants from EAS, EUR and EAS + EUR meta-analyses were used in this analysis. Variant-to-gene annotation

was performed using RefSeq NCBI37.3 with a window of 5 kb upstream and 1.5 kb downstream. LD was taken from the 1000 Genomes Project EAS, EUR and EUR + EAS panels, respectively. The gene-based *P* values were computed by *F*-test and multivariate linear modeling, and competitive tests were used for gene set analysis. A total of 70 gene sets were selected and tested in this study (Supplementary Table 8), including those from the Molecular Signatures Database[77], those related to psychiatric diseases[38,78,79] and those from gwaspipeline (https://github.com/freeseek/gwaspipeline/blob/master/makegenes.sh). Gene sets were ranked for EUR, EAS and EAS + EUR analyses, respectively. The top-ranking gene sets were compared across analyses to identify common schizophrenia pathways. Additionally, Wilcoxon signed-rank tests were conducted to compare the ranking of gene sets between the EUR and EAS datasets.

Natural selection analysis. We used the Han Chinese in Beijing (CHB) and Utah residents with ancestry from northern and western Europe (CEU) panels from the 1000 Genomes Project Phase 3 to investigate the natural selection signatures in schizophrenia-associated loci for the EAS and EUR populations, respectively. We used the following selection signatures, with their sensitivity to timeframes discussed in ref. [3].

Integrated haplotype score (iHS). The iHS captures the haplotype homozygosity at a given variant. We calculated iHS using the R rehh package[80]. Genetic distance between variants was determined using the HapMap phase II genetic map. Ancestral and derived alleles were obtained from the 1000 Genome project, which inferred the ancestral state using six primates on the Enredo–Pecan–Ortheus pipeline. Only biallelic variants that with a MAF ≥ 5% were included in the analysis.

Cross-population extended haplotype homozygosity (XPEHH). XPEHH[81] detects variants under selection in one population but not the other. We used CEU as the reference panel when calculating XPEHH for CHB, and vice versa.

F_{ST}. F_{ST} measures the population differentiation due to genetic structure. We estimated F_{ST} using the Weir and Cockerham approach[82], which is robust to sample-size effects.

Absolute derived allele frequency difference (|ΔDAF|). |ΔDAF| measures population differentiation between CHB and CEU populations.

Composite of multiple signals (CMS). CMS[83–86] combines iHS, XPEHH, F_{ST} and |ΔDAF|. As a result, CMS potentially has better power to detect the selection signature. For each variant, CMS $= \prod_{i=1}^{n} p_i$, in which p_i is the rank of the variant using method *i*, sorted by increasing *P* values, divided by the total number of variants.

B statistic. The B statistic measures the background selection. We calculated the B statistic as in ref. [85].

Trans-ethnicity fine-mapping. For a disease-associated genetic locus, fine-mapping defines a 'credible set' of variants that contains the causal variant with certain probability (for example, 99% or 95%). Bayesian fine-mapping approaches[2,43,87,88] have been widely used for studies of a single ancestry. Here, we extended a Bayesian fine-mapping approach[87] (defining credible sets; Methods) to studies of more than one ancestry. Intuitively, the extension was achieved through a prior calculated from the heterogeneity across ancestries, such that variants with different odds ratios across populations have a smaller prior probability to be the causal variant.

As in several previous studies[2,87], we restricted our fine-mapping analysis to the primary association signal in each locus. This was done by taking *P* variants that were in LD with the lead variant (the variant with the most significant *P* value), with $r^2 > 0.1$ in EUR or EAS. Assume that *D* represents the data including the genotype matrix *X* for the *P* variants and disease *Y* for *N* individuals, and β represents a collection of model parameters. We define the model, denoted by *A*, as the causal status for the *P* variants in locus $\mathbf{A} \equiv \{a_j\}$, in which a_j is the causal status for variant *j*. $a_j = 1$ if the variant *j* is causal, and $a_j = 0$ if it is not. For the primary association signal and under the presumption that the causal variant is the same across all ancestries, one and only one of the *P* variants is causal: $\sum_j a_j = 1$. For convenience, we define A_j as the model in which only variant *j* is causal, and A_0 as the model in which no variant is causal (the null model). The probability of model A_j (where variant *j* is the only causal variant in the locus), given the data (*D*), can be calculated using Bayes' rule:

$$\Pr(A_j|D) = \Pr(D|A_j)\frac{\Pr(A_j)}{\Pr(D)}$$

With the steepest descent approximation, the assumption of a flat prior on the model parameters (β), and the assumption of one causal variant per locus (equation (2) in ref. [87]), $\Pr(A_j|D)$ can be approximated as:

$$\Pr(A_j|D) \approx \Pr\left(D|A_j, \hat{\beta}_j\right) N^{-1/2} \frac{\Pr(A_j)}{\Pr(D)} \quad (1)$$

in which *N* is the sample size. We denote χ_j^2 as the χ^2 test statistic for variant *j*, which can be calculated from the *P* value from the meta-analysis combining the EAS and EUR samples. Using equation (3) in ref. [87], we have:

$$\Pr\left(D|A_j, \hat{\beta}_j\right) \approx \exp\left(\frac{\chi_j^2}{2}\right) \Pr\left(D|A_0, \hat{\beta}_0\right) \quad (2)$$

$\Pr(A_j)$ is the prior probability that variant *j* is causal. We have shown that schizophrenia causal variants have consistent genetic effects across populations. Therefore, we model the prior probability as a function of the heterogeneity measured in I^2:

$$\Pr(A_j) = 1 - I_j^2 \quad (3)$$

Using equations (2) and (3), $\Pr(A_j|D)$ in equation (1) can be calculated as:

$$\Pr(A_j|D) \approx \exp\left(\frac{\chi_j^2}{2}\right)\left(1 - I_j^2\right)\frac{N^{-1/2}}{\Pr(D)}\Pr\left(D|A_0, \hat{\beta}_0\right)$$

We only use stage 1 samples in fine-mapping, so the variants have the same sample size (assuming all variants have good imputation quality). Therefore, $N^{-1/2}$, $\Pr(D)$ and $\Pr\left(D|A_0, \hat{\beta}_0\right)$ can be regarded as constants:

$$\Pr(A_j|D) \propto \exp\left(\frac{\chi_j^2}{2}\right)\left(1 - I_j^2\right)$$

The normalized causal probability for variant *j* is then:

$$P(A_j) = \Pr(A_j|D) / \sum_k \Pr(A_k|D)$$

And the 95% credible set of variants is defined as the smallest set of variants, *S*, such that:

$$\sum_{A_j \in S} P(A_j) \geq 95\%$$

PRS analysis. We constructed PRSs using a pruning and thresholding approach in EAS individuals with training summary statistics from either EUR or EAS individuals. For EUR, we used summary statistics from all EUR individuals in this study, whereas for EAS, we used a leave-one-out meta-analysis approach across the 13 EAS stage 1 sample collections to build the PRS.

For the EUR training data, we extracted EUR individuals (FIN, GBR, CEU, IBS and TSI) from the 1000 Genomes Project[66] Phase 3 as an LD reference panel to greedily clump variants. For the EAS LD reference panel, we created two panels: (1) an analogous EAS panel (CDX, CHB, CHS, JPT and KHV) from the 1000 Genome Project[66] Phase 3 (Fig. 4 and Extended Data Fig. 8c,d); and (2) an LD panel from best-guess genotypes from each cohort in the study (Extended Data Fig. 8a,b,e,f). For both the EAS and EUR prediction sets, we filtered to variants with MAF > 1% in each respective population, and removed indels and strand-ambiguous variants. We subset each list of variants to those in the summary statistics with an imputation INFO > 0.9. We then selected approximately independent loci at varying *P* value thresholds or top-ranking *n* variants using an LD threshold of $r^2 \leq 0.1$ in a window of 500 kb in PLINK[67] with the --clump flag. We treated the MHC with additional caution to minimize overfitting by selecting only the most significant variant in this region. To profile variants, we multiplied the log[odds ratio] for selected variants by genotype dosages, and summed these values across the genome in PLINK[67] using the --score flag for each of the 13 EAS stage 1 samples. We assessed case/control variance explained by computing Nagelkerke's R^2 and a liability-scale pseudo-R^2, as in Lee et al.[89], by comparing a full model with the PRS and ten principal components with a model excluding the PRS. The results of PRS were presented in two ways. First, we selected SNPs based on GWAS *P* value thresholds (that is, 5×10^{-8}, 1×10^{-6}, 1×10^{-4}, 0.001, 0.01, 0.05, 0.1, 0.2, 0.5 and 1) and *P* value ranks. Second, top-ranked SNPs that existed between both EUR and EAS summary statistics were selected based on the SNP rank thresholds (that is, the top 100, 1,500, 5,000, 15,000, 25,000, 35,000 and 50,000, and all).

Ethics. The study protocols were approved by the institutional review board at each center involved with recruitment. Informed consent and permission to share the data were obtained from all subjects, in compliance with the guidelines specified by the recruiting center's institutional review board. Samples recruited in mainland China were processed and analyzed in a Chinese server to comply with the Interim Measures for the Administration of Human Genetic Resources (a regulation from the Ministry of Science and Technology of the People's Republic of China). We set up the computer codes on the Chinese server so that analyses performed on these samples were exactly the same as other samples. Summary statistics from these Chinese samples, with no individual-level data, were then shared and combined with the rest of the EAS samples.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

Genome-wide summary statistics relating to the EAS samples, EUR samples ($n = 49$) and all samples combined (that is, EAS and EUR) can be downloaded from https://www.med.unc.edu/pgc/. Individual-level genotype data for EAS samples are available on request from the contact authors (Supplementary Note). Alternatively, requests can be made to the Psychiatric Genomics Consortium. In this case, access to individual-level genotypes from samples recruited outside of mainland China will go through the Psychiatric Genomics Consortium's fast-track approval system. Access to individual-level genotypes from samples recruited within mainland China has to be approved by the individual Chinese contact authors (Supplementary Note), and are subject to the policies and approvals from the Human Genetic Resource Administration, Ministry of Science and Technology of the People's Republic of China. Individual-level genotypes from samples recruited within mainland China are stored and kept in a server physically located in mainland China. Analyses were performed on these samples using the same computer codes as those used for other EAS and EUR samples, which are available in the 'Code availability' section.

Code availability

Computer code relating to this study includes: RICOPILI (quality control, PCA, pre-phasing, imputation, association test and meta-analysis; https://github.com/Nealelab/ricopili/wiki); The following code is embedded within RICOPILI (EIGENSTRAT; https://github.com/DReichLab/EIG/tree/master/EIGENSTRAT; SHAPEIT, https://mathgen.stats.ox.ac.uk/genetics_software/shapeit/shapeit.html; EAGLE, https://github.com/poruloh/Eagle; IMPUTE, https://mathgen.stats.ox.ac.uk/impute/impute_v2.html; Minimac, https://genome.sph.umich.edu/wiki/Minimac); POPCORN (trans-ancestry genetic correlation; https://github.com/brielin/Popcorn); LDSC (heritability, partitioned heritability and within-ancestry genetic correlation; https://github.com/bulik/ldsc); MAGMA (pathway analysis; https://ctg.cncr.nl/software/magma); fine-mapping (fine-mapping and PAINTOR; https://github.com/hailianghuang/FM-summary and https://github.com/gkichaev/PAINTOR_V3.0, respectively); rehh (selection; https://cran.r-project.org/web/packages/rehh/index.html); B score (background selection; http://www.phrap.org/othersoftware.html); and PRS analyses (https://github.com/armartin/pgc_scz_asia).

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Author contributions

M.L. and H.H. performed the genotype quality control and PCA. M.L. and C.-Y.C. performed the association analysis. M.L. and B.C.B. performed the heritability and genetic correlation. Xixian Ma, C.-Y.C. and S.X. investigated the effects of natural selection. J.B. investigated the effects of partitioned heritability. Z.L., M.L. and H.G. performed the gene set analysis. A.R.M., C.-Y.C. and R.L. calculated the PRSs. H.H. performed the fine-mapping. P.H. performed the replication analysis. Data acquisition, generation, quality control and analysis were performed by: M.L., J. Lee and J. Liu (IMH-1 and IMH-2); P. Sham (HNK-1); A.T., Y.K., M.K., M.I. and N.I. (JPN-1); Z.L., L.H. and Y.S. (BIX-1, BIX-3 and BIX-5); W.Z., L.H., S.Q., F.Z. and Xiancang Ma (XJU-1 and BIX-4); L.G., H.M., Z.X., P. Sklar, X.Y., R.S.K. and the Genetic REsearch on schizophreniA neTwork-China and Netherlands (UMC-1 and SIX-1); B.B., A.K., D.B.W., S.G.S. and the Indonesia Schizophrenia Consortium (UWA-1); H.Y., D.Z. and W.Y. (BJM-1, BJM-2, BJM-3 and BJM-4); C.-M.L., W.J.C., S.F., S.J.G., H.-G.H., S.A.M., B.M.N. and M.T. (TAI-1 and TAI-2); S.-W.K. and K.S.H. (KOR-1); and the Schizophrenia Working Group of the Psychiatric Genomics Consortium (EUR samples). M.L., C.-Y.C., S.G.S., M.C.O'D., M.J.D. and H.H. drafted the primary manuscript, with major contributions from A.R.M., S.J.G., B.B., S.P., B.J.M., K.S.H., M.T., J. Lee, W.Y., H.-G.H., J.B., S.R. and P.F.S. H.H., Y.S., R.S.K., X.C.M., J. Liu., M.T., W.Y., S.G.S., K.S.H., N.I., P. Sham, S.Q., B.M.N., M.J.D., M.C.O'D., S.R., P. Sklar, L.H. and S.E.H. conceived, designed, supervised and implemented the project. All authors reviewed and approved the final draft.

Competing interests

B.M.N. is a member of the Deep Genomics Scientific Advisory Board. He also serves as a consultant for the Camp4 Therapeutics Corporation, Takeda Pharmaceutical and Biogen. M.J.D. is a founder of Maze Therapeutics. The remaining authors declare no competing interests.

Additional information

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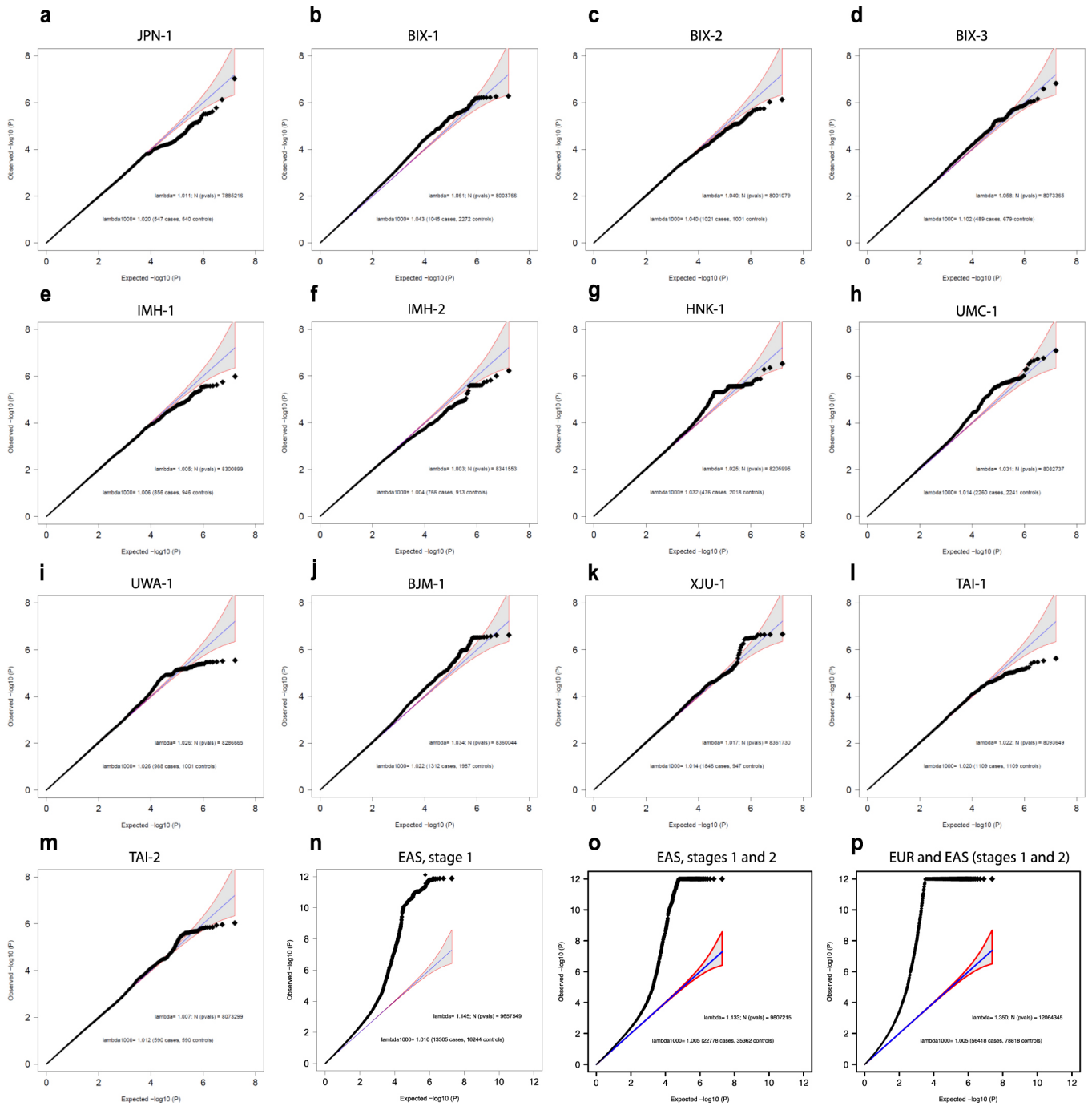
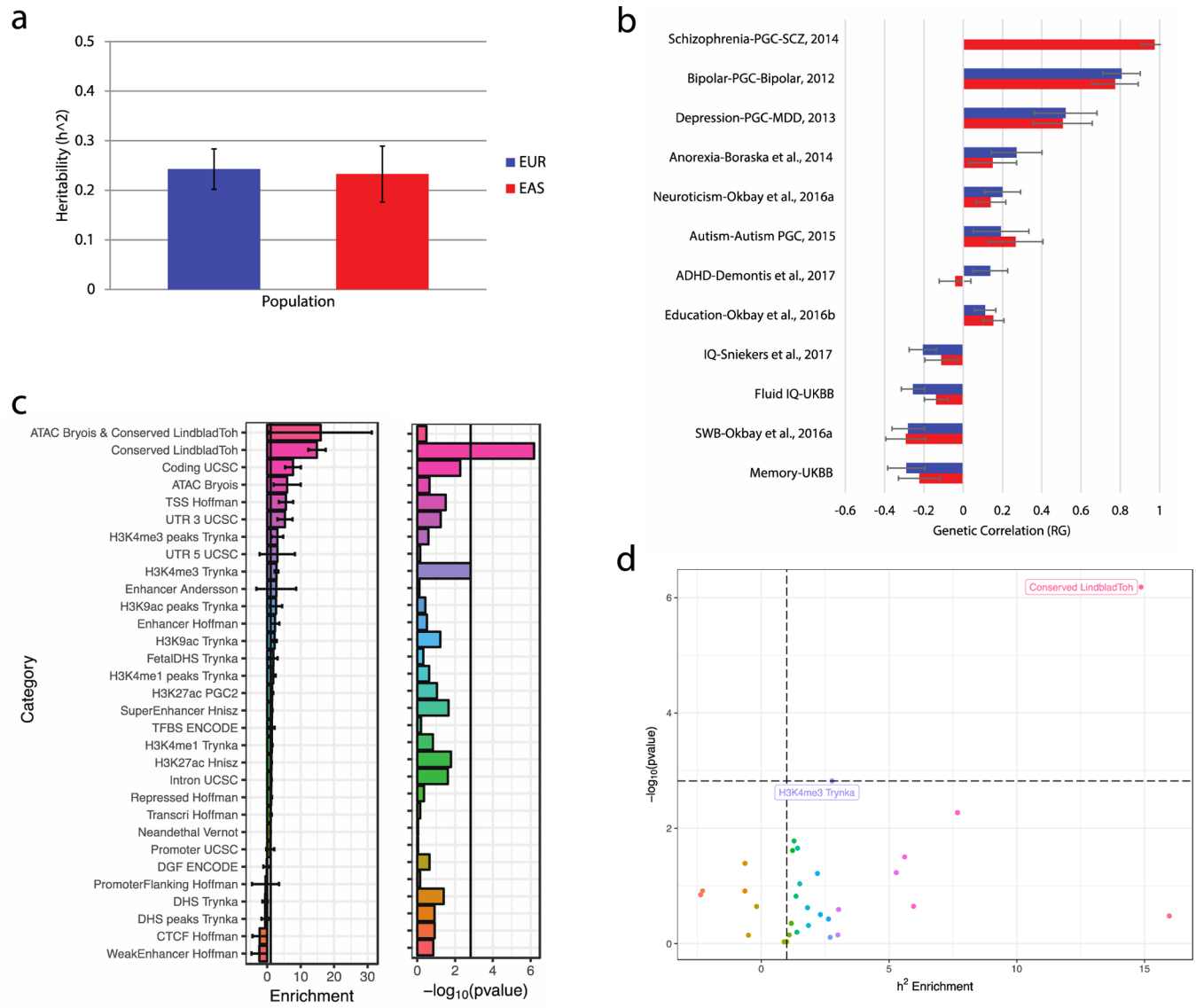
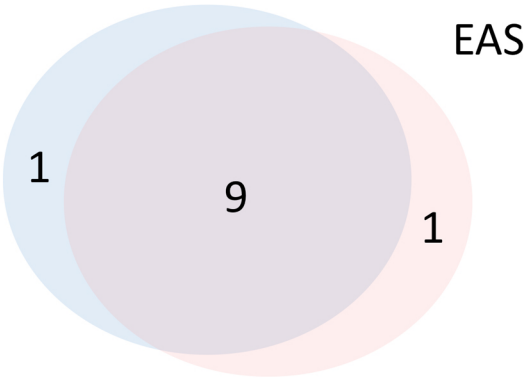


Extended Data Fig. 1 | Quantile-quantile (QQ) plots. a-p, QQ plots for two-tailed logistic regression in each EAS stage 1 sample (**a-m**) and fixed effect inverse variance meta-analyses including all EAS stage 1 samples (**n**), stages 1 and 2 samples (**o**), and all EUR and EAS (stages 1 and 2) samples (**p**). Blue line indicates the expected null distribution, and the shaded area indicates the 95% confidence interval of the null distribution. Legend: "lambda" = genomic inflation factor; "lambda1000" = genomic inflation factor for an equivalent study of 1,000 cases and 1,000 controls; "N(pvals)" = number of variants used in the plot. Autosomal variants that have minor allele frequency ≥ 1% and INFO ≥ 0.6 from imputation were included. Observed *P*-values were capped at 10^{-12} for visualization purposes.



Extended Data Fig. 2 | Heritability and genetic correlation. a, Heritability (h^2) for the EAS stage 1 ($n = 13,305$ cases; 16,244 controls) and EUR samples ($n = 33,640$ cases; 43,456 controls). Sample description applies to **b-d**. Error bars indicate the 95% confidence interval. **b**, Genetic correlation between schizophrenia and other traits within EUR (blue) and across EAS and EUR (red). Error bars indicate the 95% confidence interval. **c**, Enrichment and its corresponding significance for heritability partitioned based on various annotations. Error bars indicate the 95% confidence interval. **d**, Scatterplot showing the enrichment versus the significance for heritability partitioned based on various annotations. More details are available in Methods.

a

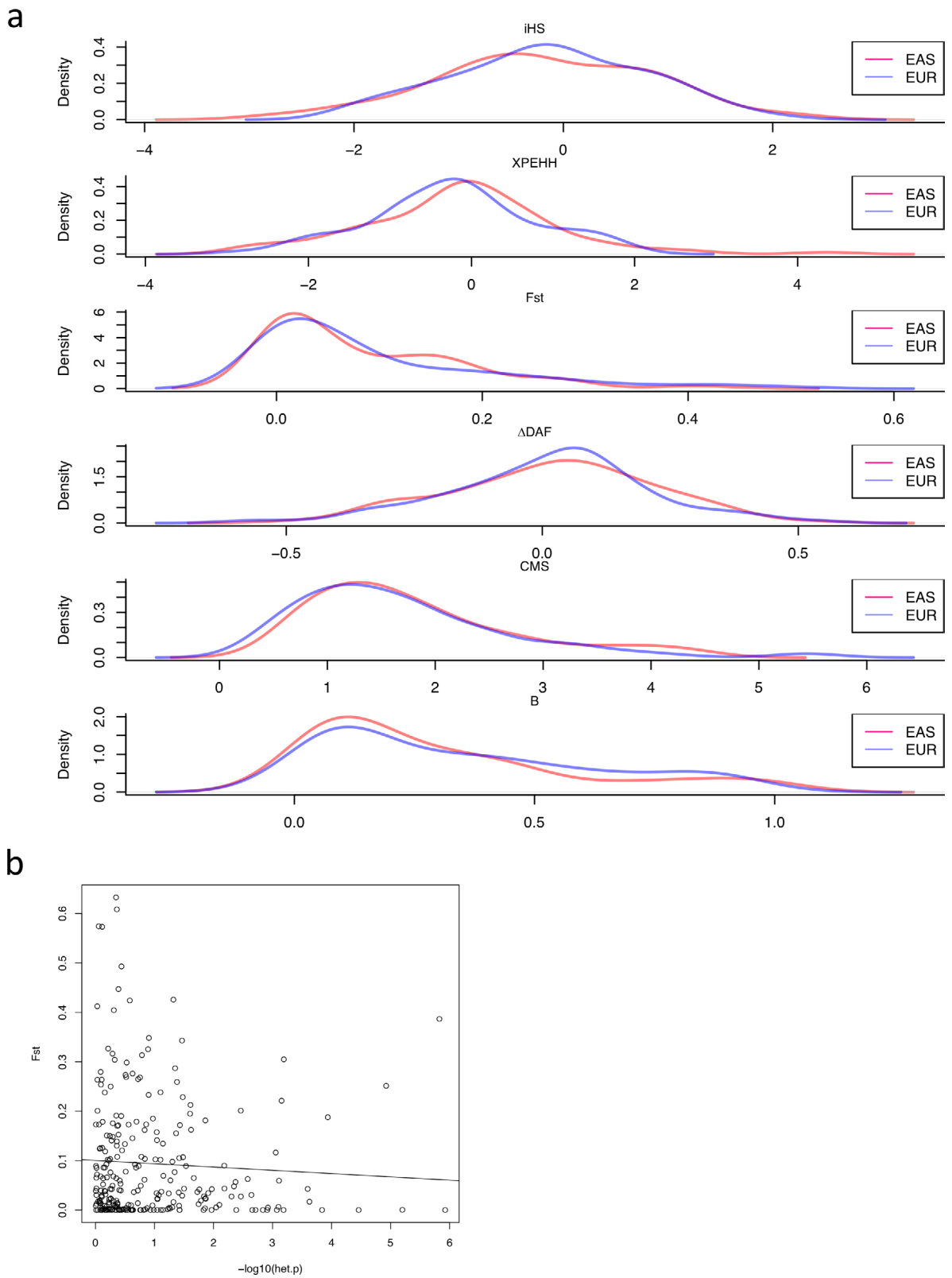


b

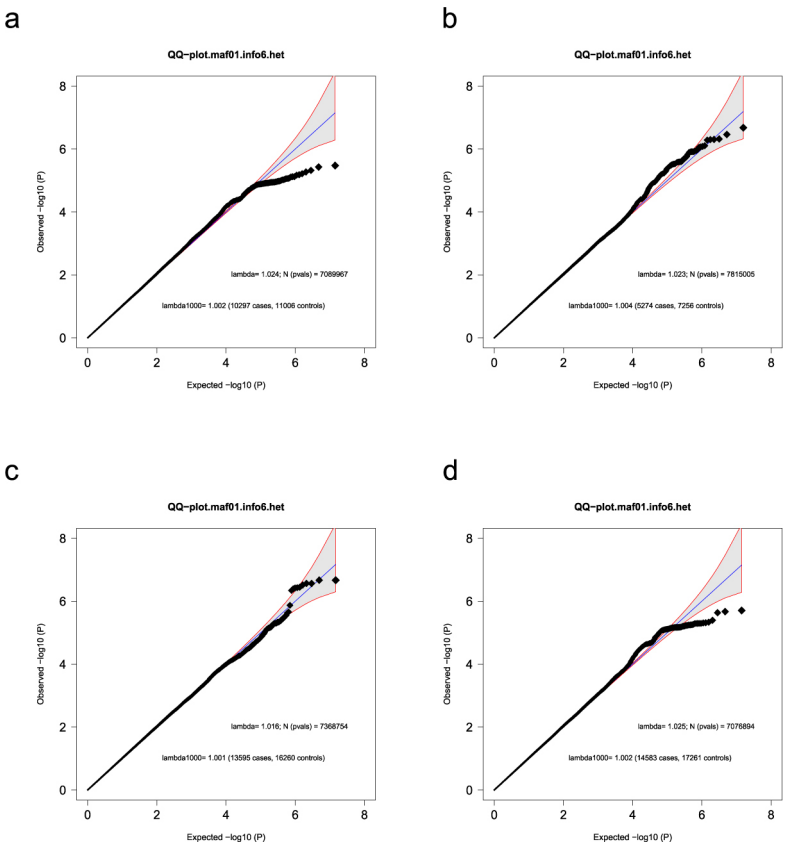
Top 10 EUR and EAS Pathways

			EAS+EUR	EUR	EAS
EAS ∩ EUR	9	PGC_SCZ_P10-4	101.39	112.54	6.05
		RBFOX1_RBFOX3	19.13	14.48	4.87
		POTENTIALLY_SYNAPTIC_ALL	17.20	11.90	4.44
		PLI09	14.60	11.75	3.96
		RBFOX2	14.09	12.45	3.37
		CHD8_HNSC	12.02	11.06	3.83
		FMRP	13.58	10.45	2.52
		CELF4	10.58	7.13	2.87
		CHD8_HNSC+HUMAN_BRAIN	7.44	6.83	2.32
EUR	1	CONSTRAINED	6.88	7.68	1.01
EAS	1	MIR-137	3.47	2.62	2.31

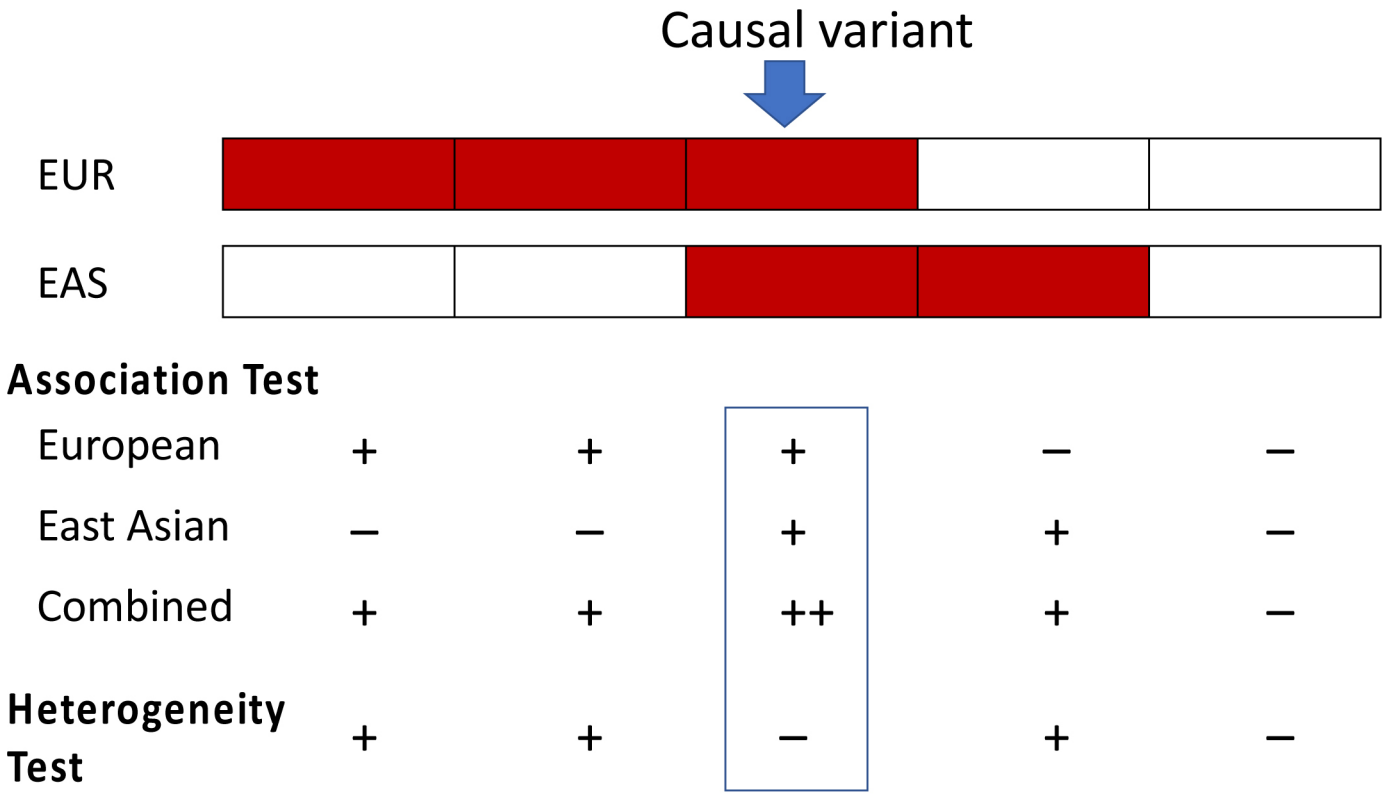
Extended Data Fig. 3 | Gene-sets implicated by schizophrenia genetic associations. a, Overlap of implicated gene-sets across EAS stage 1 ($n = 13,305$ cases; 16,244 controls) and EUR samples ($n = 33,640$ cases; 43,456 controls). **b**, List of the top 10 gene-sets implicated in the EAS and EUR samples and their MAGMA Gene-Set Analysis *P*-values in -$\log_{10}$ scale. Descriptions of the gene-sets are available in Supplementary Table 8.



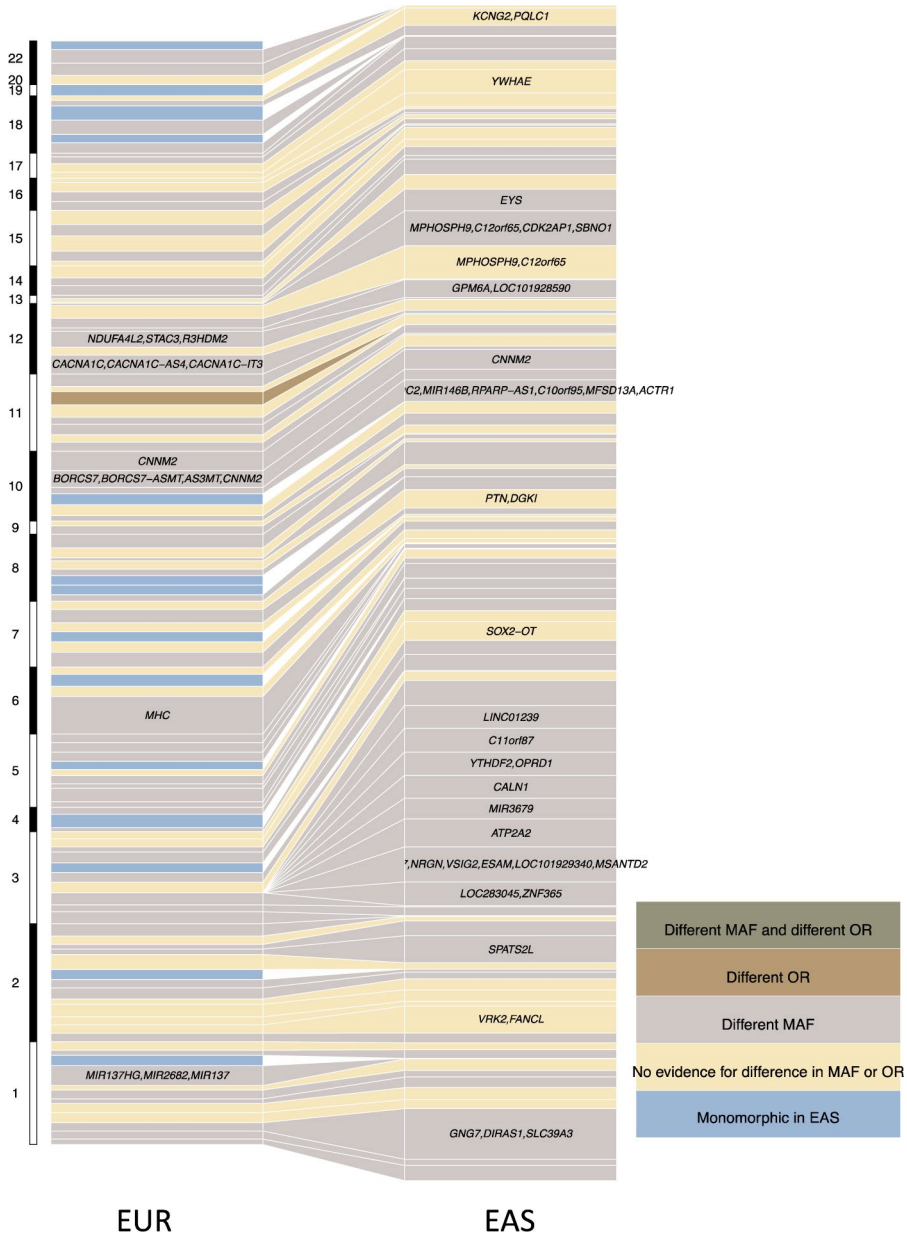
Extended Data Fig. 4 | Natural selection signals in EAS and EUR. a, Distributions of natural selection signals in the top 100 schizophrenia associations in EAS (red) and EUR (blue). **b**, Scatterplot of *Fst* versus the heterogeneity of effect size for schizophrenia associations. More details are available in Methods.



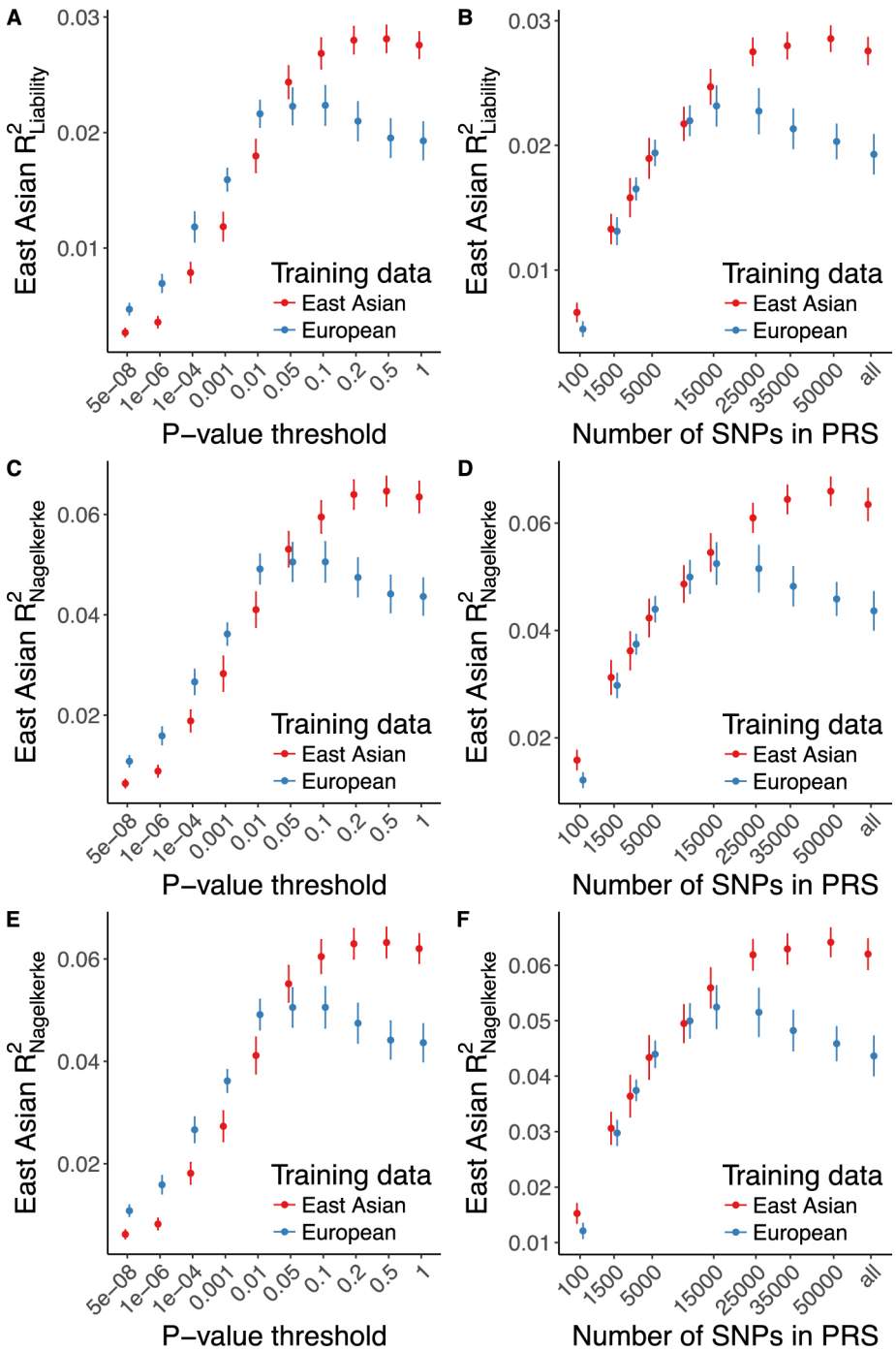
Extended Data Fig. 5 | Quantile-quantile (QQ) plots for heterogeneity within EAS. a, Heterogeneity QQ-plot across Northeast Asian and Indonesian samples. **b**, Heterogeneity across Southeast Asian and Indonesian samples. **c**, Heterogeneity QQ-plot across Northeast Asian and Southeast Asian samples. **d**, Heterogeneity QQ-plots across all three subpopulations. Cochran Q-test used to compute heterogeneity effects (**a-d**).



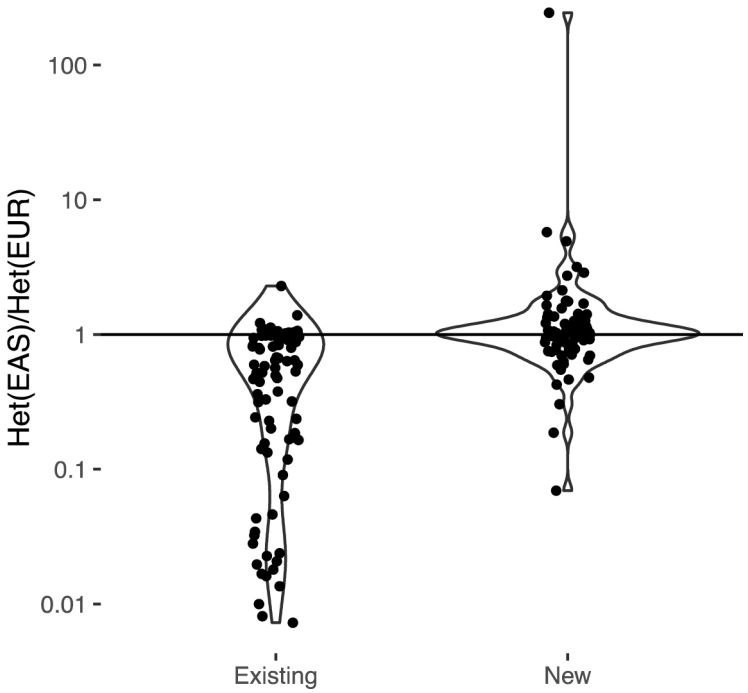
Extended Data Fig. 6 | Trans-ethnicity fine-mapping. Illustration of the fine-mapping method.



Extended Data Fig. 7 | Variance explained for schizophrenia associations across EUR and EAS samples. Genome-wide significant associations that have variance explained greater than 0.05% in either EAS or EUR samples were plotted. One locus can host multiple independent associations. Different MAF is defined as $Fst > 0.01$, and different OR is defined as heterogeneity test P-value < 0.05 after Bonferroni correction. Nearest genes to the associations were used as labels for associations when the text space is available, with the exception that the MHC locus was labeled as "MHC".



Extended Data Fig. 8 | Genetic risk prediction accuracy in EAS from EAS or EUR training data. As in Fig. 4, PRS shows case/control variance explained with EUR and EAS samples using a leave-one-out meta-analysis approach for the EAS samples. Error bars indicate the 95% confidence intervals. **a,b**, Liability-scale variance explained when LD panel for clumping is from EUR 1000 Genomes Phase 3 samples and best-guess genotypes are from each EAS cohort. **c,d**, Nagelkerke's R^2 for EAS prediction accuracy when LD panel for clumping is from EUR and EAS 1000 Genomes Phase 3 samples. **e,f**, Nagelkerke's R^2 for EAS prediction accuracy when LD panel for clumping is from EUR 1000 Genomes Phase 3 samples and best-guess genotypes are from each EAS cohort. **a-f**, EAS stage 1 (n = 13,305 cases; 16,244 controls) and EUR samples (n = 33,640 cases; 43,456 controls).



Extended Data Fig. 9 | Ratio of the heterozygote rate in EAS to that in EUR for existing and new loci. Het(EAS) and Het(EUR), calculated as $2f(1-f)$, are the heterozygote rates for a variant in EAS and EUR respectively, in which f is the variant allele frequency in EAS or EUR. Power to identify genetic associations increases with the expected non-centrality parameter for the association, which is proportional to the heterozygote rate. Therefore, we use the ratio of the heterozygote rate in EAS to that in EUR as a measure of the relative power to identify genetic association of the same effect size in the two populations. A ratio greater than 1 means that EAS samples have more power to identify the association and vice versa. Existing loci are those that are genome-wide significant in the previous study of European ancestry[2], and new loci are those that are genome-wide significant just in this study combining EAS and EUR samples. Sample sizes utilized were EAS stage 1 (n = 13,305 cases; 16,244 controls) and EUR samples (n = 33,640 cases; 43,456 controls).

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n/a	Confirmed	
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☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
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☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☐	☒	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
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☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No other direct software used for data collection. Genome Studio v1.9.4 used for extracting Plink binary genotype files.
Data analysis	Computer code used in this manuscript: RICOPILI (quality control, principal component analysis, pre-phasing, imputation, association test and meta-analysis) https://github.com/Nealelab/ricopili/wiki; embedded within RICOPILI (Eigenstrat https://github.com/DReichLab/EIG/tree/master/EIGENSTRAT; SHAPEIT https://mathgen.stats.ox.ac.uk/genetics_software/shapeit/shapeit.html; EAGLE https://github.com/poruloh/Eagle; IMPUTE https://mathgen.stats.ox.ac.uk/impute/impute_v2.html; Minimac https://genome.sph.umich.edu/wiki/Minimac); POPCORN (trans-ancestry genetic correlation): https://github.com/brielin/Popcorn; LDSC (heritability, partitioned heritability and within-ancestry genetic correlation): https://github.com/bulik/ldsc; MAGMA (pathway analysis): https://ctg.cncr.nl/software/magma; Fine-mapping (Fine-mapping and PAINTOR): https://github.com/hailianghuang/FM-summary, https://github.com/gkichaev/PAINTOR_V3.0; REHH (selection): https://cran.r-project.org/web/packages/rehh/index.html; B score (background selection): http://www.phrap.org/othersoftware.html; PRS analyses: https://github.com/armartin/pgc_scz_asia

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Genome-wide summary statistics from EAS samples, EUR samples ("49 EUR samples") and all samples (EAS and EUR combined) in this study can be downloaded from https://www.med.unc.edu/pgc/results-and-downloads/. Individual-level genotype data for EAS samples are available upon request to contact authors

(Supplementary Information). Alternately, requests can be made to the Psychiatric Genomics Consortium (PGC). In this case, access to individual-level genotypes from samples recruited outside of mainland China will go through the PGC "fast-track" approval. Access to individual-level genotypes from samples recruited within mainland China has to be approved by the individual Chinese contact authors (Supplementary Information), and are subject to the policies and approvals from the Human Genetic Resource Administration, Ministry of Science and Technology of the People's Republic of China. Individual-level genotypes from samples recruited within mainland China have been stored and kept in a server physically located in mainland China. Analyses were performed on these samples using the same computer codes as those used for other EAS and EUR samples, which are available in the Code availability section.

Field-specific reporting

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Previous studies of European individuals suggest that a sample size of over 100,000 individuals may be needed to saturate the power of schizophrenia genetic loci discovery. We have not reached this sample size but have included all major East Asian samples that are available date in the current study.
Data exclusions	We used standard quality control procedures for genome-wide association studies. Quality control procedures were carried out as part of the RICOPILI pipeline (https://sites.google.com/a/broadinstitute.org/ricopili/home; Lam et al., 2019) with the following steps and parameters: 1) Excluding variants with call rate below 95%; 2) Excluding subjects with call rate below 98%; 3) Excluding monomorphic variants; 4) Excluding subjects with inbred coefficient above 0.2 and below -0.2; 5) Excluding subjects with mismatch in reported gender and chromosome X computed gender; 6) Excluding variants with missing rate differences greater than 2% between cases and controls; 7) Subsequent to step 6, exclude variants with call rate below 98%; and 8) Exclude variants in violation of Hardy-Weinberg equilibrium (P < 10-6 for controls or P < 10-10 for cases). Numbers of variants or subjects removed in each step were reported in Supplementary Table 2. Additionally, We used Eigenstrat66 to calculate the principal components for all the samples using the best guess genotypes from imputation (Supplementary Figure 9b). We computed the identity-by-descent matrix to identify intra- and inter- dataset sample overlaps. Samples with pi-hat > 0.2 were extracted, followed by Fisher-Yates shuffle on all samples. The number of times with which each sample was related to another sample was tracked and samples that were related to more than 25 samples were removed. When deciding which samples to retain, trio were preferred, followed by cases, and thereafter a random sample for each related pair was removed, 704 individuals were removed. To identify population outliers, k-means clustering was conducted using the first 20 PCs from PCA and covariates representing each of the 13 Stage 1 samples. Guided by results of k-means clustering and visual inspection of PCA plots, 46 individuals were identified as outliers and were excluded. These steps are considered standard procedures to retain high quality samples fro the data-analysis.
Replication	The current study employs a two-stage study. Stage 2 serves the purpose replication.
Randomization	No randomization was conducted. The current study is a large-scale genetics study. Randomness is achieved from the nature of how alleles are relatively distributed in the population. Alleles are randomly passed from parent to offspring during meiosis, hence the nature of these types of studies tend to be shielded from extraneous confounds of standard epidemiological studies.
Blinding	No blinding was carried out. The nature of the study is in of itself blind to study recruiters. No one would beforehand know the genotype make up of the cases and controls recruited in the current study.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	The following samples were used in this study: EAS samples, full-genome: genome-wide genotype data was obtained from 16 samples from East Asia (Supplementary Table 1). Two of these samples (TAI-1 and TAI-2) had parents off-spring trios and were processed as case/pseudo-controls. DSM-IV was used for diagnosing all schizophrenia cases in these samples except for the trios (TAI-1 and TAI-2), for which DIGS was used. EAS samples, selected variants: summary statistics was obtained for a set of variants from four EAS samples (BJM-2, BJM-3, BJM-4, BIX-5) which had been analyzed in published studies7,8. The summary statistics included odds ratio, standard error, reference and tested alleles for variants that have P<10-5 in either Stage 1 or the meta-analysis combining Stage 1 and EUR samples. Between 22,156 and 31,626 variants were available after the exclusion of strand ambiguous60 variants (Supplementary Table 2). EUR samples: Genotypes for EUR schizophrenia patients and controls were obtained from the Psychiatric Genomics Consortium as reported in ref 2. All samples of EUR ancestry were included in this study except for the deCODE samples (1,513 cases and 66,236 controls). We also like to note that three samples of EAS ancestry reported in this publication were not included in the EUR samples in our analysis but were included in the EAS samples (IMH-1, HNK-1 and JPN-1). The same procedures used in processing EAS samples were applied to the EUR samples.
Recruitment	East Asian Ancestry Cohorts: Stage 1 Discovery and Stage 2 Replication Sample: IMH-1, HNK-1 and JPN-1 Type: Case-Control Contact: IMH-1: Liu, Jianjun (liuj3@gis.a-star.edu.sg) and Lee, Jimmy (jimmy_lee@imh.com.sg); HNK-1: Sham, Pak (pcsham@hku.hk); JPN-1: Iwata, Nakao (nakao@fujita-hu.ac.jp) Description: These samples were included in a previous publication1. Description of these samples can be found on Page 11 of the Supplementary Information in the publication ("East Asian ancestry, case-control design" subsection). Mapping between the study identifiers: IMH-1=scz_tcr1_asn; HNK-1=scz_hok2_asn; JPN-1=scz_jpn1_asn. Sample: IMH-2 Type: Case-Control Contact: Liu, Jianjun (liuj3@gis.a-star.edu.sg) and Lee, Jimmy (jimmy_lee@imh.com.sg) Description: Subjects were part of the Singapore Translational and Clinical Research in Psychosis (STCRP) Study, and comprised of cases and healthy controls of Chinese ancestry. Schizophrenia cases were recruited from the Institute of Mental Health, Singapore. Diagnosis of schizophrenia was made using the Structured Clinical Interview for DSM-IV, Research Version, Patient Edition (SCID-I/P) by trained raters. And healthy controls were screened using the DSM-IV, Research Version, Non-Patient Edition (SCID-N/P). All participants gave consent according to IRB/DSRB guidelines prior to participating. Sample: BIX-1, BIX-2, BIX-3 and BIX-5 Type: Case-Control Contact: Shi, Yongyong (shiyongyong@gmail.com) Description: BIX1, BIX2 and BIX3: Participants in the schizophrenia group were in-patients or out-patients who were recruited from various mental health centres. The patients were interviewed by two independent psychiatrists and were diagnosed according to the DSM-IV criteria, and had two-year histories of the disorder. All met the following two criteria: preoccupation with one or more delusions and frequent auditory hallucinations. However, none of the following symptoms were prominent: disorganised speech, disorganised or catatonic behaviour, or flat or inappropriate affect. All healthy controls were randomly selected from Chinese Han volunteers (from hospitals and a community survey) who were asked to reply to a written invitation to evaluate their medical histories. Potential lists of controls were screened for suitable volunteers by excluding individuals with major mental illnesses. The study had been previously reported2. BIX5: Case were schizophrenia patients according to DSM-IV criteria, and controls were volunteers with no psychiatric history. All the cases and controls were of Han Chinese ancestry, and recruited in the mainland of China. Further details for ascertainment, inclusion/exclusion criteria, and other information have been previously described3,4. Approval was obtained from the Ethics Committee of Human Genetic Resources at the Bio-X Institutes of Shanghai Jiao Tong University, in accordance with the tenets of the Declaration of Helsinki, and all participants provided written, informed consent. The genotyping was conducted at Bio-X Institutes at Shanghai Jiao Tong University, and details were provided in previous publication3. Sample: XJU-1 and BIX-4 Type: Case-Control Contact: Qin, Shengying (chinsir@sjtu.edu.cn) Description: XJU-1: Schizophrenia patients were recruited from the inpatients in nine clinical centers in Shaan Xi Province, China, including 1) Department of Psychiatry of the First Affiliated Hospital of Xi'an Jiaotong University (TFAHXJTU) and Mental Health Centers of 2) Baoji City, 3) Xianyang City, 4) Weinan City, 5) Hanzhong City, 6) Huayin City, 7)Yulin City, 8)Yanan City. Healthy controls were recruited from native residents of communities and villages in the city that each clinical center located in. Two professional psychiatrists interviewed all participants and evaluated their mental status according to DSM-IV criteria using SCID and/or Mini-International Neuropsychiatric Interview. The present study was approved by the Medical Ethics Committee of TFAHXJTU. All subjects participated voluntarily and signed written informed consent prior to the enrollment. BIX-4: Subjects were recruited from the Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine between August 2015 and August 2017. Patients were diagnosed by at least two experienced psychiatrists according to the DSM-IV based on structured Clinical Interview for DSM-IV Axis 1 Disorders (SCID-1). Healthy controls were selected from the general public of Chinese population in Shanghai. The control subjects were also excluded with major mental illness and matched with patients in terms of age and gender. All the subjects were Han Chinese in origin. The study was approved by the Ethical Committee of Human Genetic Resources in Shanghai. All subjects or their guardians understood the procedure and gave written informed

consent, according to the Declaration of Helsinki.

Sample: UMC-1 and SIX-1
Type: Case-Control
Contact: Kahn, Rene (rene.kahn@mssm.edu) and Yu, Xin (yuxin@bjmu.edu.cn)
Description: Funded by the Division of Neuroscience of the University Medical Center in Utrecht (UMC, Utrecht), a collaborative genetic study was developed between UMC Utrecht and Peking University Institute of Mental Health (PKUIMH). The goal of the study was to identify susceptibility genes that contribute to the development of schizophrenia and related disorders. Subjects were recruited from thirteen major cities across mainland China. All patients were interviewed with Structured Clinical Interview for DSM-IV axis I Disorder (SCID–I) by extensively trained Chinese psychiatrists and researchers involved in the study. All included patients fulfilled DSM-IV criteria for schizophrenia. The SCID interviews were tape-recorded and randomly checked by senior psychiatrists not involved in the recruitment of interviewing. Healthy controls were matched with patients in terms of age, gender, and geographic information, and educational level, ethnic and economic background and were free of a history of psychiatric illness based on GHQ-20 and SCL-90. Regular inter-rater reliability sessions and onsite check-ups were conducted to secure the long-term research quality. This study was approved by the institutional review boards of the participating hospitals, including that at UMC Utrecht. Written informed consent was obtained from all subjects after complete description of the study and its procedures.

Sample: UWA-1
Type: Case-Control
Contact: Schwab, Sibylle (schwab@uow.edu.au)
Description: Patients with schizophrenia admitted consecutively to psychiatric hospitals in the greater Jakarta area were informed about the study and were asked to sign the Informed Consent document for participation in interviews, blood withdrawal and subsequent genetic studies. The study was approved by the institutional review board of the University of Indonesia and by local Ethics Committees. Clinical consensus diagnosis of schizophrenia was made by psychiatrists according to the DSM-IV criteria. Non-psychiatric controls were recruited from students and staff of the University of Indonesia, Jakarta, and from the participating hospitals. Details of the study were previously reported5.

Sample: BJM-1, BJM-2, BJM-3 and BJM-4
Type: Case-Control
Contact: Yue, Weihua (puh60380@bjmu.edu.cn)
Description: All samples in BJM1 and BJM3 are of Northern Han Chinese origin, all participants in BJM2 are from northern China; and all participants in BJM4 are from a southern Han Chinese population. Consensus diagnoses were made by at least two experience psychiatrists according to the criteria for schizophrenia from DSM-IV. None of the subjects had sever medical complications or other psychiatric disorders. All healthy control individuals were clinically determined to be free of psychiatric disorders or family history of such disorders. The study was approved by the institutional review board of each hospital and written consent was obtained from all participants. Further information can be found in a previous publication6, with the following mapping between cohorts: BJM1 = GWAS3, BJM2 = GWAS1, BJM3 = GWAS2, and BMJ4 = GWAS4.

Sample: TAI-1 and TAI-2
Type: Trio
Contact: Tsuang, Ming (mtsuang@ucsd.edu) and Hwu, Hai-Gwo (haigohwu@ntu.edu.tw)
Description: Schizophrenia probands and their first-degree relatives were recruited from Schizophrenia Trio Genomic Research in Taiwan (S-TOGET) funded by National Institute of Mental Health. Schizophrenia patients were interviewed with the Diagnostic Interview for Genetic Studies (DIGS), which was designed specifically for family-genetic studies of schizophrenia and bipolar disorder. Research diagnostic assessment was made independently by two board-certified psychiatrists based on integrated clinical information of DIGS interview data and summary note of clinical course, symptom manifestations and social functioning derived from the records of the medical charts according to DSM-IV for schizophrenia. This study was approved by the institutional review boards of the participating hospitals. Written informed consent was obtained from all subjects after complete description. Study details have been reported elsewhere7.

Sample: KOR-1
Type: Case-Control
Contact: Hong, Kyung Sue (hongks@skku.edu)
Description: Patients who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria were recruited from the inpatient unit and outpatient clinic of Samsung Medical Center and Chonnam National University Hospital. South Korea. The healthy subjects consisted of volunteers from the community who were free of any history of clinically significant psychiatric symptoms. Written informed consent was obtained from all subjects after a complete explanation of the study. This study was approved by the institutional review boards of Samsung Medical Center and Chonnam National University Hospital. Details of the study have been previously reported8.

** Note: We have carried out large scale recruitment of case-control samples across these sites. As the majority of these samples are of East Asian descent, we do not foresee potential bias pertaining to our conclusions of the current study - at the genomic level.

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Ethics oversight

Ethics Oversight
The following institutions provided ethics oversight for data reported in the current manuscript:
Domain Specific Review Board (Singapore); University of Hong Kong; Fujita Health University; RIKEN Center for Integrative Medical Sciences; Nagoya University; Osaka University; Niigata University; Bio-X Institutes of Shanghai Jiao Tong University; University Medical Center Utrecht; The University of Western Australia; The University of Indonesia; Peking University Sixth Hospital; National Taiwan University; Samsung Medical Center; Chonnam National University Hospital.

Note that full information on the approval of the study protocol must also be provided in the manuscript.