表1　対象のプロフィール

	広汎性発達障害群	統合失調症群	F value	t value	df	P value
年齢	26.88±6.47	28.06±6.48	.002	−.519	30	.608
性別（Male %）	75.00	68.75	.582	.382	30	.705
教育年数	14.19±1.87	13.69±1.96	.216	.739	30	.466
GAF	61.25±9.04	63.13±9.98	.687	−.557	30	.582
抗精神病薬服用量*1	100.0±156.0	945.4±717.1	19.4	−4.608	16.416	<.001**
罹病期間	N.A	7.00±4.78				
AQ-J*2	37.19±4.46	N.A				
PANSS*3						
陽性尺度	N.A	13.00±4.13				
陰性尺度	N.A	14.38±4.05				
総合精神病理尺度	N.A	26.69±3.82				

**P<0.001
*1：クロルプロマジン換算（mg/日）
*2：自閉性スペクトル指数日本版（Autism-Spectrum Quotient Japanese Version）
*3：Positive and Negative Syndrome Scale

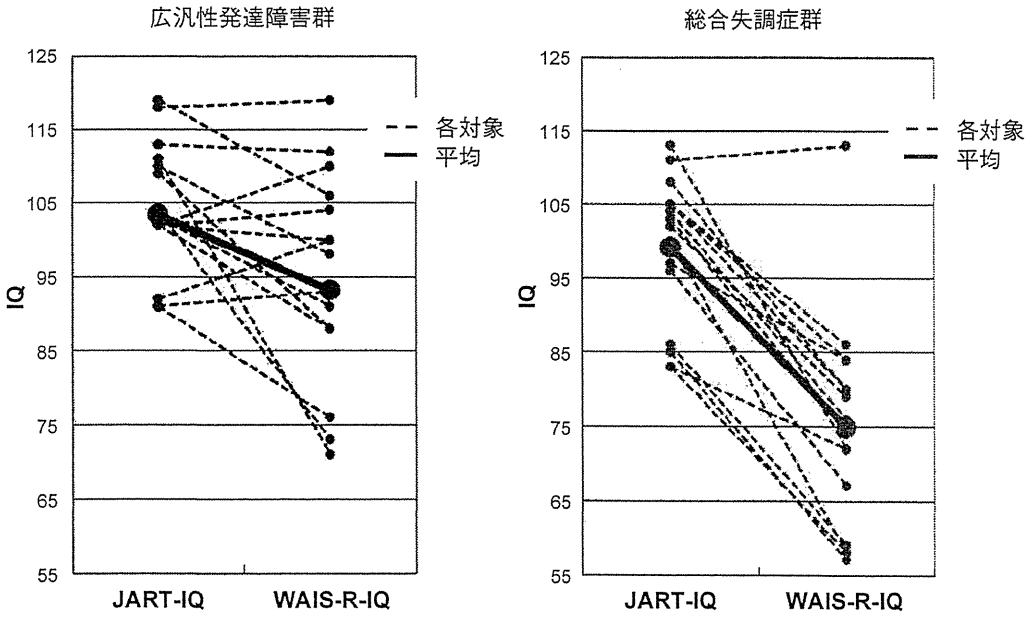

図1　広汎性発達障害群と統合失調症群における JART・WAIS-R 両検査の IQ

くの精神科医療機関において有用であると考える．また，この研究では統合失調症群において抗精神病薬の服薬量と WAIS-R-IQ との間に相関はなく，PDD 群でも抗精神病薬の服薬の有無と WAIS-R-IQ と JART-IQ の変化に違いはなかったため，この研究において抗精神病薬の服薬の影響は少ないものと考えられた．臨床的には，既に服薬をしていることもあるため，この点も日常臨床で活用しやすいのではないかと考える．

この研究は，対象数も少なく，統合失調症と PDD の比較のみである．今後は，対象数を増やし，健常対照と PDD の比較なども行い，JART-IQ と WAIS-R-IQ の差にも着目しながら鑑別ではなく PDD の補助診断ツールとしての有用性も

検討していきたいと考えている．

4．まとめ

補助診断ツールを利用し，横断的にも縦断的にも情報を補完しながら成人のPDDを診断する必要性がある．わが国の現状としては，AQ-J，PARS，WAISなどを用いることが多いようであるが，今後はPDDの診断面接法が広く使用されることが望まれる．

また，WAISとJARTを組み合わせたPDDの補助診断の可能性についても言及した．

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Value of Ancillary Testing in the Diagnosis of Pervasive Developmental Disorder in Adults

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Recently, there has been increasing interest in adults with pervasive developmental disorder (PDD) who seek general psychiatric services for various psychiatric problems. The diagnosis of PDD requires the careful collection of information about the patient's developmental history. A structured diagnostic interview is useful and should be performed, but has limitations now. The clinical value of the measurement of the Wechsler Adult Intelligence Scale, the Autism-Spectrum Quotient Japanese Version, and the Pervasive Developmental Disorders Autism Society Japan Rating Scale was demonstrated by a questionnaire survey that the authors conducted in 2010. These additional tests are useful if interpreted with caution. For example, a discrepancy between the performance intelligence quotient (IQ) and the verbal IQ in the Wechsler Adult Intelligence Scale does not by itself diagnose PDD.

We examined whether the Japanese version of the National Adult Reading Test (Japanese Adult Reading Test; JART), a valid scale for evaluating pre-morbid IQ in patients with schizophrenia, and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) are useful for discriminating between PDD and schizophrenia. Sixteen patients with adult PDD and 16 patients with schizophrenia matched for age, education and sex participated in this study. In addition, the two groups were matched for JART and the Global Assessment of Functioning scores. All subjects were scored on the JART and WAIS-R after giving informed consent for the study. The result was that significant diagnosis-by-IQ examination interactions were found ($F\ [1, 30]=10.049$, $P=0.003$). Also, the WAIS-R scores of the PDD group were higher than those of the schizophrenia group ($P=0.002$) when the two groups were matched for JART. In conclusion, the comparison of IQ in the PDD group and in the schizophrenia group by JART and WAIS-R might be an easy and useful method for helping

to discriminate between PDD and schizophrenia. In addition, the difference in IQ scores measured by JART and by WAIS-R may be helpful in diagnosing PDD.

The diagnosis of PDD in adults may be assisted by the use of these additional tests.

<Authors' abstract>

<**Key words**: pervasive developmental disorder, Wechsler Adult Intelligence Scale, Autism-Spectrum Quotient Japanese Version, Pervasive Developmental Disorders Autism Society Japan Rating Scale, Japanese Adult Reading Test>

Genome-Wide Association Study of Schizophrenia in a Japanese Population

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Background: Genome-wide association studies have detected a small number of weak but strongly supported schizophrenia risk alleles. Moreover, a substantial polygenic component to the disorder consisting of a large number of such alleles has been reported by the International Schizophrenia Consortium.

Method: We report a Japanese genome-wide association study of schizophrenia comprising 575 cases and 564 controls. We attempted to replicate 97 markers, representing a nonredundant panel of markers derived mainly from the top 150 findings, in up to three data sets totaling 1990 cases and 5389 controls. We then attempted to replicate the observation of a polygenic component to the disorder in the Japanese and to determine whether this overlaps that seen in UK populations.

Results: Single-locus analysis did not reveal genome-wide support for any locus in the genome-wide association study sample (best $p = 6.2 \times 10^{-6}$) or in the complete data set in which the best supported locus was *SULT6B1* (rs11895771: $p = 3.7 \times 10^{-5}$ in the meta-analysis). Of loci previously supported by genome-wide association studies, we obtained in the Japanese support for *NOTCH4* (rs2071287: $p_{meta} = 5.1 \times 10^{-5}$). Using the approach reported by the International Schizophrenia Consortium, we replicated the observation of a polygenic component to schizophrenia within the Japanese population ($p = .005$). Our trans Japan–UK analysis of schizophrenia also revealed a significant correlation (best $p = 7.0 \times 10^{-5}$) in the polygenic component across populations.

Conclusions: These results indicate a shared polygenic risk of schizophrenia between Japanese and Caucasian samples, although we did not detect unequivocal evidence for a novel susceptibility gene for schizophrenia.

Key Words: Genome-wide association study, *NOTCH4*, polygenic component, schizophrenia, *SULT6B1*

Epidemiologic studies show that genetic factors account for more than 80% of the population variance in susceptibility for schizophrenia; however, as with virtually all other relatively common disorders, it has historically proven difficult to identify the specific genetic variants involved (1).

The application of genome-wide association technology to large case–control samples of mainly European ancestry has recently implicated a number of risk loci for which the evidence is strong. These include loci defined by single nucleotide polymorphisms (SNPs) in which the effects are weak (odds ratios [ORs] 1.1–1.25) among which the strongest supported loci are *zinc finger protein 804 A* (*ZNF804A*) (2–5), a broad region including the major histocompatibility complex (MHC) on chromosome 6p21.3–22.1 (6–8), *neurogranin* (*NRGN*), and *transcription factor 4* (*TCF4*) (8).

Although the robust support for a number of recently implicated loci represents something of a break from the past inconsistencies, little of the genetic variance of schizophrenia can be explained by the loci identified thus far. One explanation for this is that much of the risk is conferred by common but weak genetic effects that require larger samples. Another explanation is that most of the risk cannot be readily detected by genome-wide association studies (GWAS), the missing genetic component being conferred by mutations that exert substantial individual effects that are rare or even unique to individual pedigrees.

Although the relative contributions of these classes of variant awaits empiric resolution, the GWAS of the International Schizophrenia Consortium (ISC) provided strong support for a substantial polygenic contribution (at least 30%) to the population risk of schizophrenia, much of which is conferred by common alleles with small effect sizes (6,9,10). The basic principle of their analysis was that in the presence of a substantial common polygenic component, although most of the individual genetic effects will not be

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detectable in current sample sizes, the sum of many such effects across multiple SNPs might differ between cases and controls. After discounting the influence of various potential sources of bias, the authors concluded that the findings were best explained by the existence of an important polygenic component to the disorder comprising a large number of common alleles, although some contribution from low-frequency alleles was not excluded or deemed unlikely (6).

There were two additional striking findings in the ISC article (6). The first was that those alleles selected as "risk" alleles for schizophrenia were also enriched in people with bipolar disorder, supporting the hypothesis of shared genetic susceptibility between these disorders (11,12). The second was that sets of "risk" alleles defined from white individuals of European origin were better at predicting affected status in other white European subjects than they were in African Americans, although an attenuated effect was seen in an African American sample. This may be attributable to differences in allele frequencies and linkage disequilibrium between Europeans and African Americans, although genetic heterogeneity remains a possibility. In this article describing a study that sought novel susceptibility variants, we report the first GWAS for schizophrenia in a Japanese sample. Although the Japanese population is considered relatively homogeneous (13), GWAS studies in other populations strongly suggest that our study of 575 cases and 564 controls is underpowered to detect any findings at genome-wide levels of significance. Thus, we attempted to enhance power by following up the top 150 of the most strongly supported SNPs from the GWAS in an independent sample of 1511 cases and 1517 controls drawn from the Japanese population as well as 479 cases and 2938 controls from the United Kingdom (2). We also sought to examine whether the Japanese population shares with Europeans a polygenic component for schizophrenia and bipolar disorder using schizophrenia and bipolar case–control samples from the United Kingdom that have been previously subjected to GWAS (2,14). Because it is unlikely that stratification effects would bias the allele distributions en masse in samples ascertained in Japan in the same direction as in a European sample, confirmation of a shared polygenic effect argues strongly against the idea that residual uncontrolled stratification is responsible for the effect. Moreover, because rare alleles of large effect are expected to reflect an ongoing process of new mutation (to compensate for their removal by selection), the existence of transcontinental effects also argue against the idea that rare alleles alone can drive this effect, it being unlikely that relatively new variants would be carried on the same ancestral haplotypes in both populations.

Methods and Materials

Participants

We selected 575 patients with schizophrenia (43.5 ± 14.8 years) and 564 healthy controls (44.0 ± 14.4 years) for genome-wide association analysis (our screening GWAS: [JPN_GWAS]). All subjects were unrelated, living in the Tokai area of the mainland of Japan, and self-identified as Japanese. The details of the sample and copy number variation analysis of this GWAS data set have been reported previously (15), and see also Supplement 1.

For follow-up studies, we used an independent Japanese sample comprising 1511 cases (aged 45.9 ± 14.0 years) and 1517 controls (aged 46.0 ± 14.6 years) diagnosed and ascertained in the same way as the GWAS data set. These samples were recruited from three areas on the Japanese mainland, comprising the Kansai and Chugoku areas in addition to the Tokai area. To enhance the sample in the replication analysis, data were added from 934 Japanese controls genotyped by Illumina550 (Illumina, San Diego, California) as part of the Japanese Single Nucleotide Polymorphisms (JSNP) project (http://snp.ims.u-tokyo.ac.jp/index.html). If SNP data were available in the JSNP sample, we merged the two sample sets to form a final Japanese replication sample (we refer this as "Rep_JPN") comprising 1511 cases and 2451 controls (SNPs genotyped in both samples can be seen in Table S1 in Supplement 2).

We additionally included data from a UK schizophrenia GWAS data set of 479 cases and 2938 controls genotyped using the Affymetrix 500K array (Santa Clara, California), details of which have been reported before (2,14).

For the polygenic component analysis, we also included the Wellcome Trust Case-Control Consortium (WTCCC) bipolar disorder data set of 1868 cases and 2938 shared controls, details of which are reported elsewhere (2,14).

After complete description of the study to the subjects, written informed consent was obtained. This study was approved by the ethics committees of each university participating in this project.

GWAS and Quality Control

Genotyping was performed using the Affymetrix Genome-Wide Human SNP Array 5.0 according to the manufacturer's protocol. After applying several quality control (QC) criteria (e.g., call rate ≥ 95%, autosomal chromosomes, Hardy–Weinberg equilibrium (HWE) ≥ .0001 and minor allele frequency [MAF] ≥ 5%; Supplement 1), the final GWAS consisted of 1108 samples (560 cases and 548 controls) and 297,645 SNPs (MAF ≥ 5%).

Q-Q plots were generated on the basis of allele-wise analysis of SNPs that passed QC (Supplement 1), and our observed value of λ is consistent with those generally reported in well-matched samples ($\lambda = 1.065$ and $\lambda_{1000} = 1.117$).

Follow-Up Genotyping

Follow-up genotyping in our independent Japanese case–control sample was performed by Sequenom (San Diego, California) using the Sequenom iPLEX Gold System. Markers that could not be assayed on this platform were genotyped using a TaqMan assay (Applied Biosystems, Foster City, California).

Candidate SNPs were selected for replication as follows. First, the top 200 SNPs were identified (corresponding to $p \sim < 5 \times 10^{-4}$). Highly correlated markers based on $r^2 > .9$ to a more significant marker within 100 kb (r^2 was based on HapMap information [release Number 24, October 2008] and our own GWAS from controls) were then removed. From this list, we included the following: 1) SNPs with $p < 5 \times 10^{-5}$ ($n = 15$ after 11 redundant SNPs removed. Total number = 26. Of these, two SNPs failed for primer design. 2) Under the premise that in GWAS analysis, power favors more common alleles and that the enrichment for true associations is greater in this category of alleles (6), SNPs with MAF ≥ 10% surpassing a more relaxed threshold ($P < \sim 3.5 \times 10^{-4}$) were selected, corresponding to the top 150 SNPs ($n = 76$ after 12 low MAF SNPs and 36 redundant SNPs removed. This resulted in a total of 124. Of these, 5 SNPs failed primer design. We additionally included 13 SNPs that ranked from 151st to 200th on the grounds that they could be included in the Sequenom panels of markers without compromising the design of the higher-priority SNPs. Consequently, 97 SNPs were genotyped in the replication sample, of which 5 did not pass QC on the basis of genotype call rate (> .95) and HWE ($p > .001$). All genotype calls were confirmed by visual inspection of cluster plots.

SNP-Based Association Analysis

Consistent with most other GWAS, our study is based upon allele-wise association analysis which assumes an additive model.

Genomic control adjusted p values were also calculated based upon median chi-square statistics. This was performed using PLINK v1.07 (16).

Combined analysis across data sets (Meta_JPN: JPN_GWAS + Rep_JPN, Meta_ALL: JPN_GWAS + Rep_JPN + UK schizophrenia) were conducted using the Cochran–Mantel Haenszel (CMH) approach conditioned by sample as implemented in PLINK v. 1.07.

Polygenic Component Analysis

Discovery (for selecting "score alleles" based on association statistics) and targeting (for calculation of polygenic score) samples are summarized in Table S2 in Supplement 1. Briefly, we examined five discovery and target pairs:

1. Japanese: A set of 280 cases and 274 controls were selected for discovery, and the results were tested in an additional set of 280 cases and 274 controls. The discovery/target samples were selected at random (on the basis of random number generation) from the Japanese GWAS data set. This procedure was repeated 1000 times to ensure the results of this analysis were representative of random divisions of the data set.

2, 3. Each of the UK schizophrenia (479 schizophrenia and 2938 controls) (2) and bipolar (1868 cases and 2938 controls) (14) samples were used separately as a discovery data set to generate lists of "risk" alleles that were tested in the full Japanese GWAS sample.

4, 5. The full Japanese GWAS sample was used as a discovery data set to generate lists of "risk" alleles that were tested in the UK schizophrenia and bipolar data sets.

For the UK data sets, we used the QC criteria applied in the primary manuscripts (2,14) in which SNPs that deviated from HWE ($p < 1 \times 10^{-5}$ in cases or .001 in control) and had a low call rate (< 97%) were excluded. Note that the criteria for HWE exclusion in the UK data set is slightly different from that in the Japanese GWAS. The precise choice of HWE filter is arbitrary, but we note that both data sets criteria are on the more stringent side of customary practice.

Following the ISC (6), we reduced the set of SNPs by removing SNPs that are in linkage disequilibrium (LD) using the same criteria applied by the ISC (r^2 threshold at .25, window size 200 SNPs). In the tests of the split Japanese data set, we used LD-pruned SNPs selected on the basis of the metrics in the full set of Japanese controls. For all comparisons between Japanese and European data sets, we pruned SNPs sequentially first on the basis of the LD metrics in the discovery data set and second on those in the target data set. Polygenic score was calculated by weighting scores for "risk" alleles by the logOR observed in the discovery data set according to the method used by the ISC (6).

Nominally associated alleles were selected on the basis of the genomic-control adjusted p value in the allele-wise association analysis from the discovery samples at the following liberal significance thresholds (P_T) ($P_T < .5$, $P_T < .4$, $P_T < .3$, $P_T < .2$ and $P_T < .1$). The polygenic score was calculated using PLINK v. 1.07. Nagaelkerke's pseudo R^2 (a measure of variance explained by a particular factor) was calculated by logistic regression analysis using *R* (http://www.r-project.org) with covariation for "nonmissing SNPs" according to the ISC study (6).

Results

Single Marker Association Analysis

A summary plot of the GWAS (MAF ≥ 5%) is presented in Figure S1 in Supplement 1. We did not observe any associations at a widely used approximate benchmark for genome-wide significance ($p = 7.2 \times 10^{-8}$) (17). The strongest associations were observed at rs12218361, which maps to chromosome 10 at 126.06 Mb and is 3′ of *ornithine aminotransferase* (*OAT*, $p_{allele} = 6.2 \times 10^{-6}$, two-tailed), and rs11895771, which maps to chromosome 2 at 37.27 Mb within *sulfotransferase family, cytosolic, 6 B, member1* (*SULT6B1*, $p_{allele} = 8.0 \times 10^{-6}$, two-tailed). The most significant 200 markers are given in Table S1 in Supplement 2.

We genotyped 97 LD-pruned SNPs mainly from the top 150 GWAS findings in an independent Japanese replication sample (1511 cases and 1517 controls). For 22 of these, it was possible to expand the control sample size using data from the Japanese population based on the public database (JSNP). Data for 81 SNPs were also available in the UK data set (Affymetrix 500 K chip) and were included in the association analysis. On the basis of the replication sample from Japanese (Rep_JPN) alone, rs9880957 showed the most significant association ($p = 2.8 \times 10^{-3}$, two-tailed, OR = 1.2), but the associated allele was not the same as in the GWAS. Additionally, we undertook set-based analysis (using PLINK) to investigate whether there was an excess of association signals for these top GWAS findings in the replication data set that surpassed nominal p thresholds (e.g., $p < .1$, .05, .01, .001) in the Rep_JPN and UK data sets (10,000 permutation without lambda correction for all SNPs that passed the p threshold). However, no significant enrichment was observed (data not shown). That finding is compatible with the polygenic analysis we describe subsequently and with the now widely accepted hypothesis that common alleles that might be detectable in principle by GWAS exert effects that are too weak to be substantially enriched for associations that surpassed the threshold we specified for follow-up.

In the CMH analysis of the complete Japanese sample (Meta_JPN: JPN_GWAS + Rep_JPN), the best p was found at rs1011131 in LOC392288 ($p = 1.2 \times 10^{-4}$, two-tailed), which is weaker than in the initial GWAS ($p = 2.5 \times 10^{-5}$, two-tailed). Further expanding the sample size by including UK samples (Meta-ALL: JPN_GWAS + Rep–JPN + UK schizophrenia) did not provide convincing support for any locus (Table S1 in Supplement 2). The strongest association signal in Meta_ALL was rs11895771 ($p = 3.7 \times 10^{-5}$, two-tailed) in *SULT6B1*, which had been ranked second in the screening GWAS (Table 1).

Excluding *ZNF804A* (the Japanese data for which were included in the paper by O'Donovan *et al.*) (2), we additionally tested regions containing schizophrenia candidate loci supported by genome-wide significant associations in previous GWAS data sets (6–8). Specifically, we focused on three regions: the MHC region (Chr6 25 ~ 33 Mb), *NRGN*, and *TCF4*. In this analysis, we first imputed ungenotyped SNPs in these regions (boundaries ± 1 Mb) for fine mapping (the imputation method is presented in Supplement 1). None of the specific SNPs at these loci that have been reported by others (6–8) as genome-wide significant were imputable in our Japanese GWAS sample (Figures S2–S4 in Supplement 1). However, interestingly, we did observe a strong, fairly well circumscribed association signal on chromosome 6 in the region of *NOTCH4* (Figure S2 in Supplement 1). Furthermore, genetic association within *NOTCH4* has been reported (18) in another Japanese study (non-overlapping with the present sample) at rs2071287 (Figure S2 in Supplement 1), which is in complete LD ($D' = 1$, $r^2 = .56$) with rs2071286, the best SNP tested in our GWAS data. Because that previously supported SNP (rs2071287) is also associated in our GWAS ($p = 2.1 \times 10^{-3}$), we then followed up this SNP in the Rep_JPN sample; rs2071287 was again significantly associated ($P_{allele} = .018$, two-tailed, Figure S5 in Supplement 1; note: we could not impute this SNP with high confidence in the UK schizophrenia

Table 1. Top Single Nucleotide Polymorphisms Based on GWAS and Meta-Analysis

CHR	SNP	BP	Closest Gene	Meta_ALL (JPN_GWAS+Rep_JPN+UK_SCZ)							Meta_JPN (JPN_GWAS+Rep_JPN)				JPN_GWAS		Rep_JPN		UK_SCZ	
				A1	MAF	A2	P_{CMH}	OR[a]	L95	U95	P_{CMH}	OR[a]	L95	U95	P_{allele}	OR[a]	P_{allele}	OR[a]	P_{allele}	OR[a]
2	rs11895771	37266439	*SULT6B1*	T	.49	G	3.7×10^{-5}	.84	.77	.91	4.1×10^{-4}	.84	.76	.92	8.0×10^{-6}	.64	.14	.92	.033	.84
7	rs1011131	19474460	*LOC392288*	G	.07	C	1.2×10^{-4}	1.30	1.14	1.48	1.2×10^{-4}	1.31	1.14	1.50	2.5×10^{-5}	1.78	.054	1.17	.63	1.14
14	rs1176970	40505514	*LOC644919*	G	.15	C	1.4×10^{-4}	1.22	1.10	1.35	3.0×10^{-4}	1.27	1.12	1.44	3.2×10^{-4}	1.58	.041	1.17	.14	1.14
1	rs4908274	103162502	*COL11A1*	A	.28	T	3.1×10^{-4}	1.20	1.09	1.32	3.1×10^{-4}	1.20	1.09	1.32	1.1×10^{-4}	1.45	.067	1.12	NA	NA
6	rs2294424	11860537	*C6orf105*	T	.41	C	5.0×10^{-4}	1.15	1.06	1.24	5.0×10^{-4}	1.17	1.28	1.07	1.2×10^{-4}	1.40	.081	1.1	.41	1.08
2	rs13010889	40617519		A	.15	C	.0011	.85	.77	.94	.0016	.85	.77	.94	8.7×10^{-5}	.67	.17	.92	.40	.84
2	rs17026152	40611159		A	.26	G	.0012	.85	.77	.94	.0012	.85	.77	.94	1.3×10^{-4}	.69	.15	.92	NA	NA
6	rs2787566	101985455	*GRIK2*	A	.04	G	.0014	1.34	1.12	1.61	.0014	1.39	1.1	1.7	2.8×10^{-4}	2.03	.15	1.19	.49	1.16
6	rs2071286	32287874	*NOTCH4*	T	.19	C	.0014[b]	.87	.79	.95	.0049[b]	.86	.78	.96	3.3×10^{-4}	.68	.23[b]	.93	.13	.87
8	rs17462248	29426926		G	.2	T	.0017	1.16	1.06	1.27	.020	1.14	1.0	1.3	2.1×10^{-4}	1.52	.60	1.04	.030	1.2

p values were calculated on the basis of the allele-wise test (two-tailed).
A1, minor allele based on whole sample; A2, major allele based on whole sample; BP, base position; CHR, chromosome(hg18); GWAS, genome-wide association study JPN_GWAS: our screening GWAS; L95, lower bound of 95% confidence interval for OR; MAF, minor allele frequency based on whole sample; NA, not analyzed; OR, odds ratio; SNP, single nucleotide polymorphism; U95, upper bound of 95% confidence interval for odds ratio, UK-SCZ: UK schizophrenia.
[a]OR was calculated on the basis of A1 in Meta-ALL as reference.
[b]Controls from Japanese SNPs (JSNP) were merged into the replication sample.

data set because of the high missing rate of 12%). Next we conducted a meta-analysis based on Meta_JPN (imputed data from JPN_GWAS was down-weighted using PROPER-INFO from SNPTEST by METAL: http://www.sph.umich.edu/csg/abecasis/metal/) and the sample of Tochigi (18). This provided fairly strong evidence for association ($P_{meta} = 5.1 \times 10^{-5}$, two-tailed, Figure S5 in Supplement 1).

Polygenic Component Analysis

p values and pseudo-R^2 statistics (Nagaelkerke's R^2) for the analysis based on the split Japanese sample are presented in Figure 1 and in Table S3 in Supplement 1. The polygenic scores in the target data were higher in the cases than the controls and, in most cases, significantly so. As in the ISC study, the evidence became stronger and the pseudo-R^2 improved at more liberal P_T values. The most significant correlation was found at $P_T < .5$ ($p = .005$). In this condition, the pseudo-R^2 was slightly lower ($R^2 = .021$) compared with the ISC study (6) in which $R^2 \leq .032$ were observed in the Caucasian samples (Figure 1), although we note that the ISC study used information from a greater number of SNPs, with the larger sample available to that group allowing the inclusion of SNPs with MAF as low as 2%.

The results of the analysis based on discovery in the UK schizophrenia data set and targeting the JPN_GWAS are shown in Figure 2 (Table S3 in Supplement 1). Again, as with the ISC data, the signal and predictive power improved at the more liberal thresholds, with only the most relaxed threshold (corresponding to the optimal threshold from the ISC study) attaining significance ($p = .029$). However, the analysis using the WTCCC bipolar sample for discovery and the Japanese as the target did not reveal significant support for shared risk across disorders (Figure 2 and Table S3 in Supplement 1).

Following are the results of the analyses based on discovery in the JPN_GWAS and testing in the UK schizophrenia and bipolar data sets. Alleles trained in this direction were highly significant, but weakly predictive, of schizophrenia status in the UK sample ($p_{min} = 7.0 \times 10^{-5}$) than those analyses based on training in the UK data sets. Again, no significant effect was observed for bipolar disorder. In the schizophrenia analysis, we observed no clear relationship

Figure 1. Polygenic component analysis for the pair within screening genome-wide association studies samples. $p_T = p$ threshold. Pseudo R^2 and *p* values represent the mean and median values, respectively, from 1000 random divisions of the data set. Error bars represent the 95% confidence intervals for R^2 from those repeat analyses. Bold numbers represent significant *p* values (< .05).

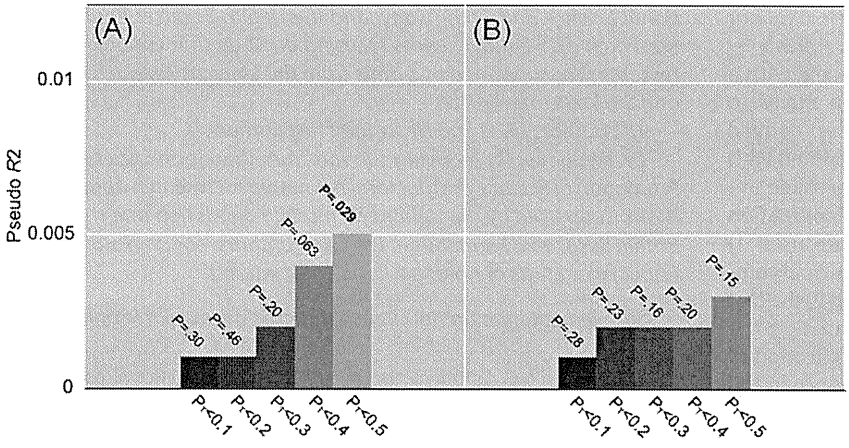

Figure 2. Polygenic component analysis for the pairs of Wellcome Trust Case-Control Consortium (WTCCC) data sets/screening genome-wide association studies (GWAS). **(A)** UK schizophrenia/screening GWAS discovery/target pair. **(B)** WTCCC bipolar/screening GWAS discovery/target pair. $p_T = p$ threshold. Bold numbers represent significant p values (< .05).

between the test allele significance threshold (P_T) and either the statistical support or the pseudo-R^2 (Figure 3 and Table S3 in Supplement 1).

Discussion

In this study, we did not detect unequivocal evidence for a novel susceptibility gene for schizophrenia, although our results do provide weak support for association between *SULT6B1* and schizophrenia, and our analyses of previously implicated regions and candidate genes provide support for the hypothesis that previous findings at the MHC region of chromosome 6 may point to *NOTCH4*. The absence of association at genome-wide levels of significance is not surprising given the relatively small size of our GWAS. Recent large-scale GWAS of schizophrenia suggest that the effect sizes of common risk alleles are small (ORs < 1.25). Power analysis suggests that our GWAS has only .18% power under an additive model to detect at $\alpha = 7.2 \times 10^{-8}$, a susceptibility variant with an allele frequency of .3 conferring an OR of 1.25. Clearly, with power like this, it would be extremely unlikely that any one locus would be detected at strong levels of support; however, in the presence of a thousand or more loci as has been suggested (6), the power to detect at least one of these would be considerably greater, albeit the subsequent power to replicate that specific locus would once again be low.

Despite the obvious power limitations, two findings are worthy of comment. The most strongly associated individual SNP was rs11895771 at *SULT6B1* (Meta-ALL $p = 3.7 \times 10^{-5}$). *SULT6B1* is a member of one of the subfamilies of cytosolic sulfotransferases (SULT) that catalyze the sulfonation of xenobiotics, hormones, and neurotransmitters, including 17β-estradiol and corticosterone (19), functions that are at least plausibly related to schizophrenia (20–22), and brain function (23–25) more widely.

The second locus of interest was *NOTCH4*. *NOTCH4* has been reported to be associated with schizophrenia in a small UK sample (26) (not overlapping with the present sample), but replication data from candidate gene studies have not been strongly supportive. However, a recent synthesis of GWASs as well as a large number of additional subjects reported a genome-wide significant association at rs3131296 (8), which is located within *NOTCH4* (Figure S2 in Supplement 1), although the extensive LD across the MHC region makes pinpointing the source of that signal to a specific gene impossible. It is therefore of interest in our evaluation of the MHC region that the signal clearly maximized to the *NOTCH4* region (Figure S2 in Supplement 1), lending support to the hypothesis that this may be the relevant susceptibility gene in the region. We are unable to evaluate the specific SNP (rs3131296) reported in the SGENE study for the Japanese population because of the failure of imputation. In the Japanese population, the MAF of rs3131296 differs considerably from that in Europeans (MAF = 10% and 2.3% for CEU and JPT populations, respectively, in HapMap Phase 3 data, 13% reported in SGENE), which means the ability of this marker to tag a common functional variant is likely to differ significantly between populations. Given the evidence for association observed in our study and the prior genetic evidence for *NOTCH4*, this locus warrants further detailed analysis in larger and more ethnically diverse samples.

This study provides the first independent (of the samples used by the ISC) replication of the polygenic score analysis reported by

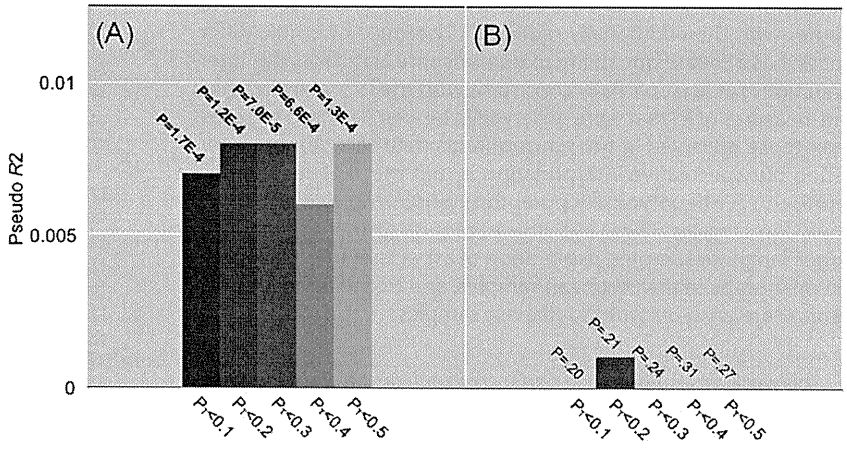

Figure 3. Polygenic component analysis for the pairs of the screening genome-wide association studies (GWAS)/ Wellcome Trust Case-Control Consortium (WTCCC) data sets. **(A)** Screening GWAS/UK schizophrenia discovery/ target pair. **(B)** Screening GWAS/ WTCCC bipolar discovery/target pair. $p_T = p$ threshold. Bold numbers represent significant p values (< .05).

the ISC (6). Although our sample is low powered (power is .6 for our full sample and .56 for half of the sample to detect at an alpha level of .5, a weak genetic effect [OR 1.1] conferred by an allele with a frequency of .3), the set of "risk" alleles (in quotation marks to emphasize that most are not likely to be true risk alleles) derived from half of the Japanese sample was significantly correlated with affection status in the other half of the samples. One possible important confounding factor to consider is an effect of population stratification. To check for this as a possible effect, we used 1) principal components analysis–adjusted (the first 10 principal components) discovery statistics for the selection of SNPs and 2) the first 10 principal component vectors as covariates in calculating the polygenic score in the target sample. However, the application of either or both of these did not lead to a material difference in the results (Table S4 in Supplement 1), indicating that stratification is not likely to explain our replication of the ISC findings.

Our Japan–UK analyses also suggests this effect is unlikely to be due to stratification (this was also convincingly argued in the ISC study) because the Japanese and UK schizophrenia samples are ascertained directionally for the same stratification biases and because the UK schizophrenia sample, but not the UK bipolar sample, would be unlikely to be stratified in that manner. Instead, those data point to a shared genetic component to schizophrenia susceptibility across major ethnic groups, as predicted by an effect driven by common "risk" alleles rather than rare alleles, although not excluding an effect of rare alleles, which are much more likely to reside on different haplotype backgrounds in different populations. However, there is also evidence for population differences in risk. Thus, the analyses restricted to the Japanese population showed much higher maximal estimates for R^2 (.021) compared with the analyses of schizophrenia between populations ($R^2 = .005 \sim .008$) and was more similar to the estimates of R^2 when the analyses were performed within European populations (6). The ISC also undertook one cross-population analysis, between Caucasian and African Americans. As in our study, R^2 was much lower between the ethnic groups (.004) than within the European populations. These results suggest that although at least some "risk" alleles are shared across populations, there are also differences in those "risk" alleles or at least in the extent to which they are tagged by markers at the density currently provided by the arrays we have studied. At a practical level, this means that failures to replicate findings across ethnic groups, even with respect to common alleles, should be treated with considerable caution.

One intriguing finding was our failure to find evidence that "risk" alleles for bipolar disorder in the European sample predict risk of schizophrenia in the Japanese sample (or vice versa). One likely explanation is that there is only a partial overlap between "risk" alleles for schizophrenia and bipolar disorder and that this, together with the additionally reduced R^2 because of ethnic differences, has affected our ability to demonstrate an effect. This interpretation is at least partially consistent with the ISC study in which the measures of R^2 that were observed in bipolar data sets were less than those observed in the schizophrenia data sets. A more interesting but speculative interpretation is that the Japanese sample represents a phenotypically purer form of schizophrenia than the European samples. These hypotheses require further evaluation in larger Japanese samples, exploration of aspects of the schizophrenia phenotype in the European samples, and transdiagnostic polygenic score analyses within Japanese samples.

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Supplementary material cited in this article is available online.

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