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·Original Article·

The schizophrenia/bipolar disorder candidate gene *GNB1L* is regulated in human temporal cortex by a *cis*-acting element located within the 3'-region

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ABSTRACT

22q11.2 deletion syndrome (DS) is a complex developmental disorder with a high incidence of psychiatric illnesses, including schizophrenia and mood disorders. Recent studies have identified *Guanine Nucleotide Binding Protein (G protein) Beta Polypeptide 1-Like* (*GNB1L*), located within the 1.5 Mbp 22q11.2 DS critical region, as a candidate liability gene for schizophrenia and bipolar disorder. In this study, we used mRNA expression measurements in Han Chinese postmortem temporal cortex and linkage disequilibrium (LD) analysis to show that *GNB1L* is regulated by a *cis*-acting genetic variant within the 3'-region of the gene. Significantly, this variant is located within an LD block that contains all of the common SNPs previously shown to associate with schizophrenia and bipolar disorder in Han Chinese and Caucasian populations. Contrary to our expectations, re-analysis of previously published case-control study data in light of our mRNA expression results implies that the *GNB1L* high-expression allele is the risk allele for schizophrenia and bipolar disorder in the Han Chinese population.

Keywords: *GNB1L*; schizophrenia; linkage disequilibrium; eQTLs; *cis*-regulatory variants

INTRODUCTION

Hemizygous deletion of 1.5 or 3 Mbp DNA within the 22q11.2 locus produces a complex spectrum of deficits, including facial, palatal, and conotruncal malformations, endocrine and immune deficiencies, and behavioral and cognitive abnormalities of variable severity[1, 2]. In addition, individuals with 22q11.2 deletions frequently suffer from psychiatric disorders, including schizophrenia[3-6] and bipolar spectrum disorders (bipolar I and II and schizoaffective disorders)[7-10]. The strong association of schizophrenia with 22q11.2 deletions has stimulated the search for genes within the deleted regions that contribute more widely to non-syndromic autism and schizophrenia.

The 3 Mbp deletion region at 22q11.2 contains ~60 genes and the 1.5 Mbp deletion region ~28 genes[11]. Because individuals carrying the 1.5 Mbp deletion collectively display most of the deficits observed in carriers of the longer deletion, the chromosomal segment affected by this deletion is inferred to comprise a critical

region for 22q11.2 DS[12]. It is proposed that deletions of dose-sensitive genes within the critical region produce developmental deficits *via* haploinsufficiency.

Among the many genes in the critical region, *GNB1L* has been linked to schizophrenia in two independent case-control studies[13, 14]. An additional study did not find statistically significant associations between *GNB1L* SNPs and schizophrenia in Japanese case-control samples, but did find evidence for low *GNB1L* mRNA expression in prefrontal cortex (Brodmann area 9) from schizophrenia patients[15].

The study by Williams and colleagues[14] identified two SNPs (rs5746832 and rs2269726) located within the 3'-region of *GNB1L* for which there was excess homozygosity in male schizophrenia patients. The study by Li and colleagues[13] identified 5 SNPs (rs5746832, rs5748427, rs5748432, rs2269726, and rs748806) also located within the 3'-region of *GNB1L* that are associated with schizophrenia and/or bipolar disorder in the Han Chinese (Shanghai) population. By contrast, a study by Ma and colleagues[16] failed to detect an association between three SNPs in the neighboring *TBX1* gene and schizophrenia in a Han Chinese-based case-control study. A summary of the results of Williams *et al*., Li *et al*., and Ma *et al.* is provided in Fig. S1.

GNB1L encodes a 327 amino-acid protein of unknown function[17]. Bioinformatics-based analysis of the amino-acid sequence of GNB1L protein predicts six WD40 motifs, homologous in structure (but not amino-acid sequence) to WD40 repeats found in the beta subunit of the human guanine nucleotide binding protein[17, 18].

GNB1L mRNA is ubiquitously expressed, with especially high levels in skeletal muscle, spleen, thymus, and testes[17]. The major mRNA transcript detected in northern blots is 1.4 to 1.5 kb in length. Expression is low in adult brain, but has higher levels in embryonic human and mouse brain[17, 19]. *GNB1L* knockout is lethal in early embryogenesis. Homozygous deletion of this gene causes reduced prepulse inhibition in adult mice[20], a phenotype associated with several psychiatric disorders, including schizophrenia[21]. These studies suggest that *GNB1L* haploinsufficiency caused by 22q11.2 DS may contribute to the pathology of schizophrenia.

In the present study, we used expression quantitative trait locus (eQTL) mapping and linkage disequilibrium (LD) analysis to further investigate the *GNB1L* SNPs previously shown to associate with schizophrenia.

MATERIALS AND METHODS

Brain Samples

Frozen sections of anterior temporal cortex from 36 Han Chinese individuals were obtained from the Chinese Brain Bank Center (CBBC; South-Central University for Nationalities, Wuhan, China). Written consent for tissue donation was given by relatives (on file at CBBC). The use of human autopsy tissue is not considered to be human-subject research and is internal review board-exempt under the NIH guidelines. A description of the demographics of the set of brain tissues, including gender, age, RNA integrity number (RIN), and cause of death, where available, is provided in Table S1.

Isolation of Genomic DNA, Total RNA, and cDNA Synthesis

Isolation of genomic (g) DNA and total RNA and preparation of cDNA were carried out as previously described[22]. Briefly, ~30 mg frozen brain tissue from each individual was used for gDNA isolation using QIAamp® Mini kits (Qiagen, Valencia, CA). About 100 mg of frozen tissue from each brain sample was used for isolation of total RNA. The frozen tissue was extracted with TRIzol® reagent (Invitrogen, Carlsbad, CA) followed by DNase I treatment (New England Biolabs, Ipswich, MA) and RNA purification using Qiagen RNeasy® Mini kits. The quantity of gDNA and total RNA was determined spectrophotometrically using a Nanodrop® spectrophotometer (Thermo Inc, Waltham, MA). The quality of isolated RNA was assessed by measuring RINs using Agilent® 2100 and software provided by the company. cDNA was generated from 5 μg total RNA in 20 μL reaction mixes using SuperScript® III First Strand kits (Invitrogen) and stored at −20°C until use. All procedures were conducted according to the instructions of the manufacturers.

Real-time PCR Quantification of *GNB1L* mRNA Expression

GNB1L mRNA levels in samples of anterior temporal cortex from the 36 Han Chinese individuals in our collection were quantified by real-time PCR using a Mastercycler®

ep Realplex Thermal Cycler (Eppendorf, Hamburg, Germany) and Thunderbird SYBR® qPCR Mix (Toyobo, Osaka, Japan) to detect PCR products. mRNA levels in each sample were normalized to the mRNA expression levels of three house-keeping genes: *glyceraldehyde-3-phosphate dehydrogenase* (*GAPDH*), *cytochrome c-1* (*CYC1*), and *β-actin* (*ACTB*). Correlations of expression among the three house-keeping genes were quantified by linear regression (Fig. S2). Primers were designed using Oligo 6.0 (National Biosciences Inc., Plymouth, MN) and synthesized by Sangon Biotech (Shanghai, China): *GNB1L*, 5'-CGGCTATGAGGATGGATCG-3' (forward) and 5'-CTGGGAGTCAAAGTCAAGGTC-3' (reverse); *GAPDH*, 5'-TCAAGATCATCAGCAATGCC-3' (forward) and 5'-TGTGGTCATGAGTCCTTCCA-3' (reverse); *CYC1*, 5'-GAGCACGACCATCGAAAACG-3' (forward) and 5'-CGATATGCCAGCTTCCGACT-3' (reverse); *ACTB*, 5'-GAAGGTGACAGCAGTCGGTT-3' (forward) and 5'-GGGACTTCCTGTAACAACGCA-3' (reverse). Normalized mRNA expression (in ΔC_t units) was calculated by subtracting the cycle threshold (C_t) for the target gene from the geometric mean C_t of the three house-keeping genes: $\Delta C_{t(GNB1L)} = [C_{t(GAPDH)}\ C_{t(CYC1)}\ C_{t(ACTB)}]^{1/3} - C_{t(GNB1L)}$.

GNB1L mRNA Expression in European Brain Samples

Array expression data of "BrainCloud"[23] (Gene Expression Omnibus (GEO) Accession Number GSE30272) and "Four Brain Region"[24] (GEO Accession Number GSE15745) were downloaded from the GEO website (http://www.ncbi.nlm.nih.gov/geo/).

Genotyping and Imputation

Whole-genome genotyping of the 36 samples (~1.14 × 10^6 genotypes/sample) was carried out using Illumina HumanOmni1-Quad arrays (Illumina, San Diego, CA) by Genesky Biotech (Shanghai, China) following the directions supplied by the manufacturer. Quality control using the PLINK[25] (http://pngu.mgh.harvard.edu/~purcell/plink/) toolset consisted of eliminating SNPs with minor allele frequencies <0.05 and those with a genotype missing rate >5% and yielded ~700,000 genotypes per sample. SNPs of interest were examined *post hoc* for violation of Hardy-Weinberg equilibrium (*P* <0.05). Genotype data for "Four Brain Regions" (dbGAP Study Accession: phs000249.v1.p1) and "BrainCloud" (dbGAP Study Accession: phs000417.v1.p1) were obtained from dbGAP (http://www.ncbi.nlm.nih.gov/gap) and cleaned using the same quality control criteria.

To enable comparison of eQTLs in different studies, we imputed genotypes for *GNB1L* region SNPs into our Han Chinese genotype data and the "Four Brain Regions" and "Braincloud" databases using IMPUTE2[26, 27] with the assistance of SHAPEIT2[28] and GTOOL (http://www.well.ox.ac.uk/~cfreeman/software/gwas/gtool.html) with genotype data from the 1000 Genomes Project (Phase 1, Integrated Variant Set) as the reference. All imputed SNPs met the quality control criteria described above.

Expression Quantitative Trait Locus Analysis

Prior to eQTL analysis, *GNB1L* mRNA expression data from the Han Chinese samples (in C_t units), "BrainCloud", and "Four Brain Regions" array studies were adjusted for available biological and methodological covariates using linear regression in SPSS (Version 20.0). Values for biological (age and gender) and methodological (RIN) covariates for each of the 36 Han Chinese samples are listed in Table S1. Covariate values for individual samples for the "Braincloud" study were obtained from the GEO website and those for "Four Brain Regions" study from Supplementary Files in Gibbs *et al.*[24].

The residuals from the regression were retained as "adjusted *GNB1L* expression values" and used as a quantitative phenotype for linear regression analysis of correlation between mRNA expression and SNP genotype using the *--assoc* command within PLINK (see Section 11. "Association, Quantitative traits" in the Plink documentation). The empirical linear regression *P*-value for the correlation between *GNB1L* mRNA expression and the genotype for each SNP was determined by 10,000 random permutations of expression level values *versus* fixed genotypes. SNPs with permutation *P*-values <0.05 were identified as eQTLs for *GNB1L*.

Linkage Disequilibrium Analysis

The LD structure of human chromosome 22 in the neighborhood of *GNB1L* based upon genotype data for all studies was generated using Haploview[29] (version 4.2: http://www.broadinstitute.org/scientific-community/science/programs/medical-and-population-genetics/haploview/haploview). We used the proxy search option of SNAP

software (http://www.broadinstitute.org/mpg/snap/ldsearch.php/) to find pairwise LD constants for SNPs in the 1000 Genome project CEU (Utah residents with ancestry from northern and western Europe) and CHB/JPT (Han Chinese Beijing/Japanese in Tokyo) populations.

RESULTS

Identification of eQTLs in the *GNB1L* Region That Correlate with *GNB1L* mRNA Expression in Temporal Cortex from Han Chinese

To identify *cis*-eQTLs for *GNB1L* mRNA expression, we measured relative *GNB1L* mRNA levels in anterior temporal cortex samples from 36 Han Chinese and looked for correlations with genotypes for common SNPs within a ~134 kb region of chromosome 22 containing *GNB1L* and *TBX1* (Chr22: 19730592-19864252, GRCh37.3/hg19). In total, 44 genotyped and 28 imputed SNPs were examined. Linear regression analysis identified 8 SNPs with nominally significant correlations (permutation P <0.05; not corrected for multiple testing) between mRNA expression and SNP genotype (Fig. 1). P-values and coefficients of determination (R^2) for these SNPs are listed in Table 1.

The *C*-allele of rs2269726 (C>T) and the *G*-allele of rs11704083 (A>G) were identified as high-expression alleles for each SNP (Fig. 2). Inspection of the LD structure of these SNPs (Fig. 1 and Table S2) revealed that 7 SNPs located within the 3'-region of *GNB1L* (rs5993830, rs5748427, rs5748432, rs2269726, rs880194, rs748806, and rs3788301) were in moderate-to-strong LD (D' >0.8, r^2

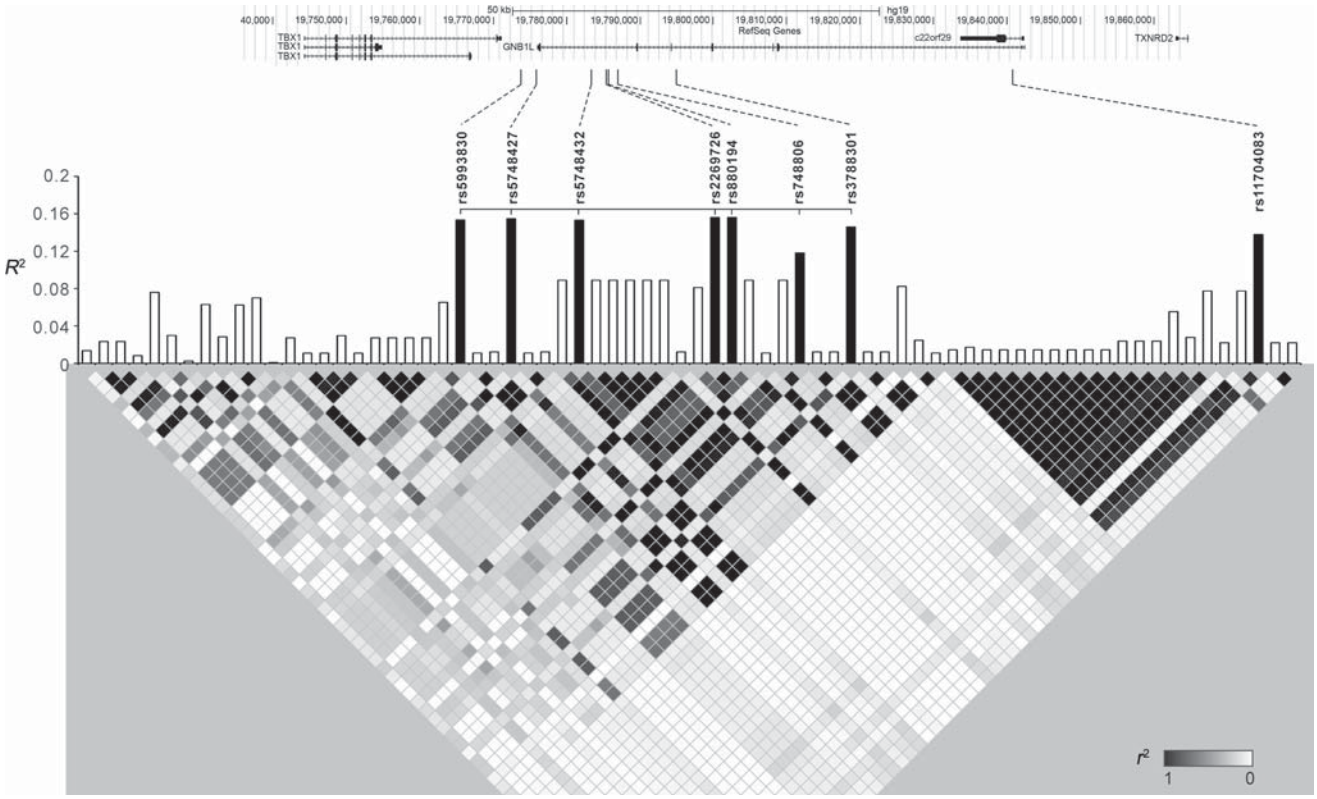

Fig. 1. SNPs in the *GNB1L* region showing correlations between genotype and *GNB1L* mRNA expression in temporal cortex from 36 Han Chinese. Top: Exon/intron structures for primary *TBX1* and *GNB1L* mRNA transcripts. Dashed lines indicate the locations of the 8 SNPs that correlate with *GNB1L* mRNA expression. Middle: Plot of coefficients of determination (R^2) from linear regression analysis of correlations between *GNB1L* mRNA expression and genotype for a set of genotyped and imputed SNPs in the set of 36 brain samples. Eight SNPs with nominally significant correlations with *GNB1L* mRNA expression analyzed by linear regression are plotted using solid bars. Bottom: LD plot showing values of the LD constant r^2 based on genotype data for 72 SNPs in the 36 Han Chinese individuals generated using Haploview.

Table 1. *GNB1L* SNPs that correlate with *GNB1L* mRNA expression in temporal cortex from Han Chinese

SNP	Position*	MAF** (major > minor alleles)	Linear regression			Origin
			R^2	*P*-value	Permutation *P*-value***	
rs5993830	19773308	0.400 (C>T)	0.154	0.0199	0.0206	Imputed
rs5748427	19775287	0.403 (G>A)	0.155	0.0177	0.0182	Genotyped
rs5748432	19783362	0.371 (G>A)	0.153	0.0201	0.0196	Imputed
rs2269726	19785006	0.375 (C>T)	0.156	0.0171	0.0163	Genotyped
rs880194	19785329	0.375 (C>T)	0.156	0.0171	0.0163	Genotyped
rs748806	19787736	0.471 (T>C)	0.118	0.0431	0.0415	Imputed
rs3788301	19795191	0.386 (G>C)	0.146	0.0235	0.0241	Imputed
rs11704083	19840413	0.403 (A>G)	0.138	0.0258	0.0248	Genotyped

*Chromosome 22 (Genome Build 37.3/HG19, reference assembly).

**MAF, minor allele frequency; based on genotype data from the set of brain samples from 36 Han Chinese.

***Permutation of mRNA expression levels was performed 10 000 times for each SNP.

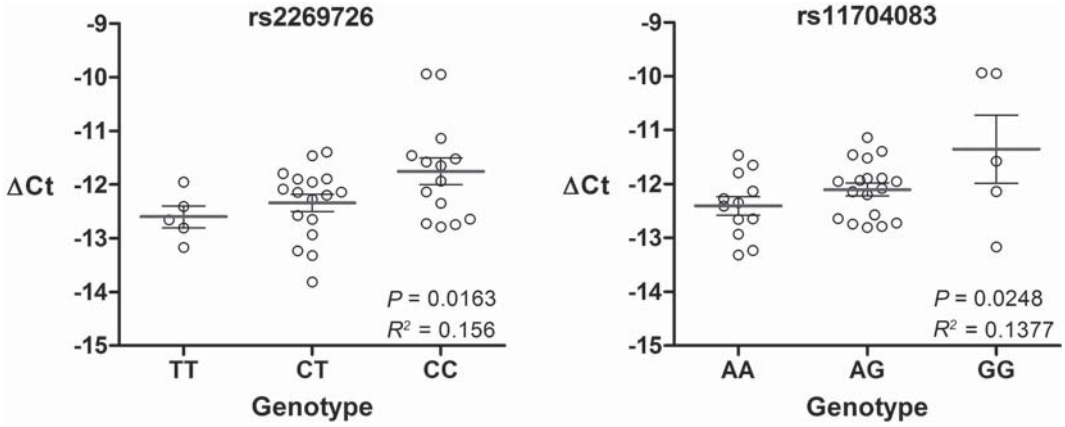

Fig. 2. Identification of high- and low-expression alleles for the 3'-region SNP rs2269726 and the 5'-region SNP rs11704083. Scatterplots show normalized *GNB1L* mRNA expression (in ΔC_t units) for 36 Han Chinese brain samples stratified according to genotype. Each dot represents one individual and the horizontal bars show the mean and standard error of the mean. Linear regression R^2 and *P*-value (10 000 permutations) for *GNB1L* mRNA expression *versus* genotype are listed. High expression alleles for rs2269726 and rs11704083 are the *C*-allele and the *G*-allele, respectively.

>0.53), while the 5'-region SNP rs11704083 was less tightly linked to the other SNPs (D' <0.4, r^2 <0.07).

Because these 7 SNPs had similar properties, we chose rs2269726, which has the highest R^2 and lowest *P* value for correlation with *GNB1L* mRNA expression, as the "index" SNP to represent the 3'-region LD block. Stepwise linear regression analysis showed that the 5'-region SNP rs11704983 combined with rs2269726 to produce a higher R^2 (0.251, P = 0.008), while the other 3'-region SNPs did not further increase the R^2 significantly. These results are consistent with the hypothesis that *GNB1L* mRNA expression in temporal cortex is controlled by at least two

independent *cis*-regulatory variants, one linked to SNPs in the 3'-region LD block and another linked to rs11704083.

GNB1L eQTLs in Caucasian Brain Samples

Currently, genome-wide genotype and mRNA expression data from two brain eGWAS studies are publicly available: the "BrainCloud" study[23] and the "Four Brain Regions (4BrainR)" study[24], both of which include a large number of samples from Caucasian individuals. To determine if correlations between *GNB1L* mRNA expression and SNP genotype are similar in Han Chinese and Caucasian brain samples, we downloaded individual-level genotype and expression data and searched for eQTLs in Caucasian individuals using the methods described above. To facilitate comparisons, we selected a subset of 44 SNPs that were genotyped or reliably imputed in all three studies. Only SNPs within the 3'-region LD block correlated with *GNB1L* expression in all three studies (Fig. 3). Although the 5'-region SNP rs11704083 also correlated with expression in most assays (except for the "4BrainR-PONS" and "BrainCloud" samples), the *P*-values were larger and the coefficients of determination smaller than SNPs in the Caucasian samples and our Han Chinese samples (Table S3).

In contrast to the results obtained with the Han Chinese brain samples, step-wise linear regression analysis of *GNB1L* mRNA expression in the Caucasian samples showed that rs11704083 did not significantly increase R^2 when combined with 3'-region SNPs (data not shown). These results suggest that either rs11704083 is an eQTL for *GNB1L* mRNA expression in the Han Chinese population only, or the observed correlation is a false-positive due to the relatively small number of Han Chinese brain samples analyzed. On the other hand, the finding that the 3'-region SNPs correlated with *GNB1L* mRNA expression in both the Han Chinese and Caucasian samples provides strong support for the existence of one or more *cis*-regulatory elements for *GNB1L* within the 3'-region LD block.

SNPs Tightly Linked to the Index SNP rs2269726 Correlate with Schizophrenia and/or Bipolar Disorder in Han Chinese and Caucasian Populations

Finally, we examined the relationship between linkage to rs2269726 and association with schizophrenia and/or bipolar disorder in Han Chinese and Caucasian case-control studies. We chose r^2 as the measure of linkage, since it more accurately correlated with *GNB1L* mRNA expression than D' or the midpoint of the 95% confidence interval for D' (data not shown). Estimates of r^2 in Chinese and European populations were based on genotype data obtained by the 1000 Genomes project for the "CHB/JPT" and "CEU" populations, respectively.

Only *GNB1L* SNPs with r^2 >0.649 with respect to rs2269726 associated with schizophrenia and/or bipolar disorder in Chinese[13] or European-based[14] case-control studies (Fig. 4). Because neither of these studies genotyped rs11704083 or any SNPs linked to it, we do not know its possible contribution to the risk of schizophrenia/bipolar disorder. Taken together, these observations strongly support the hypothesis that one or more regulatory variants that are tightly linked to rs2269726 contribute to schizophrenia and bipolar disorder.

Contrary to our expectations, the rs2269726 high-expression *C*-allele, rather than the low-expression *T*-allele, was identified as the schizophrenia risk allele in the Han Chinese case-control studies. The high-expression alleles of the rs2269726-linked SNPs rs5748427 (*G*), rs5748432 (*G*), and rs748806 (*T*) were also identified as schizophrenia risk alleles in the Han Chinese case-control study (Table 2, Fig. S3).

DISCUSSION

The results of this study confirm and extend the finding of Li and colleagues[13], who showed that *GNB1L* 3'-region SNPs associate with schizophrenia and bipolar disorder in the Han Chinese population. Specifically, we showed that each of the SNPs that correlated with schizophrenia and/or bipolar disorder in the study of Li and colleagues also correlates with *GNB1L* mRNA expression in both Han Chinese temporal cortex and Caucasian temporal and prefrontal cortex.

Because hemizygous deletion of a 1.5 Mbp segment of 22q11.2 containing *GNB1L* is strongly associated with schizophrenia and mood disorders, we had hypothesized that low expression of *GNB1L* mRNA in brain would also associate with schizophrenia and bipolar disorder. Surprisingly, however, re-analysis of the results of the Li *et al*. case-control association data in light of our mRNA

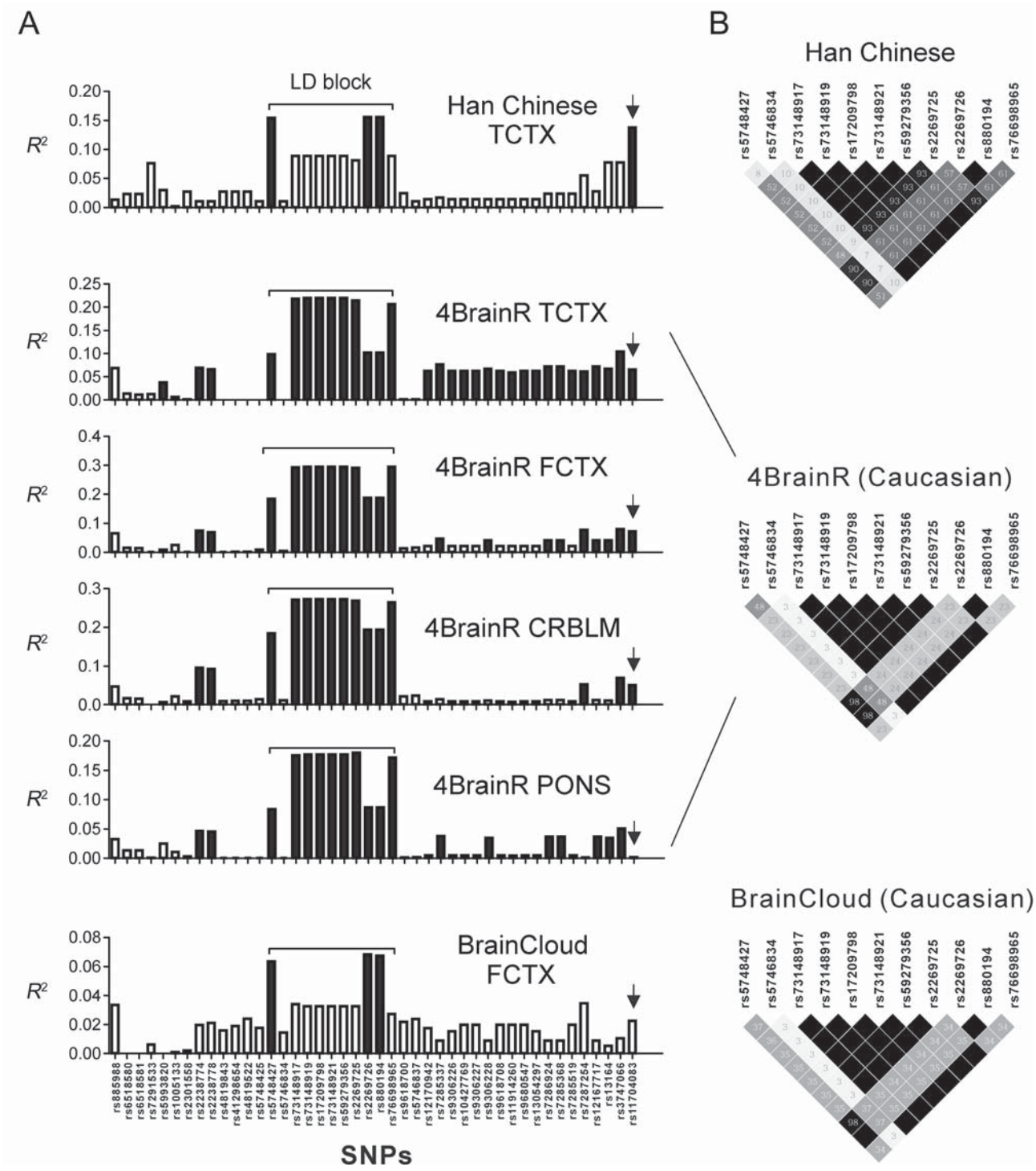

Fig. 3. SNPs located in the 3'-region LD block consistently correlate with *GNB1L* expression in Han Chinese and Caucasian brain eQTL studies. (A) Linear regression R^2 values for Han Chinese, "BrainCloud"[23], and "Four Brain Region"[24]. Solid bars indicate SNPs with nominally significant correlations with *GNB1L* mRNA expression. (B) Structure of 3'-region LD block generated using SNP genotypes for individuals in the indicated studies. Numbers within the small boxes within each plot are pairwise LD (r^2) values. TCTX, temporal cortex; FCTX, prefrontal cortex; CRBLM, cerebellum.

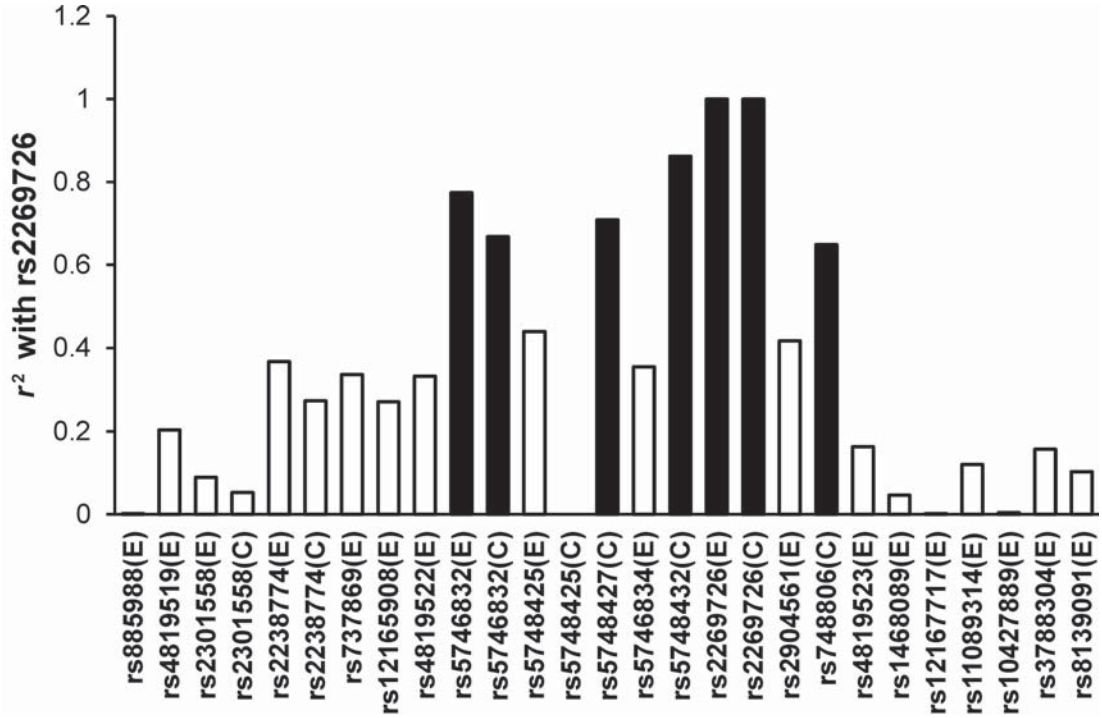

Fig. 4. Degree of linkage to rs2269726 predicts association with schizophrenia and/or bipolar disorder in Chinese and European samples for *GNB1L* SNPs. Values of LD constants (r^2) between rs2269726 and the listed SNPs estimated from data provided from the 1000 Genomes Project for CHB/JPT (C) or CEU (E) populations were obtained using the SNAP proxy SNP search program (Broad Institute, Cambridge, MA). SNPs that associate with schizophrenia are plotted as solid bars.

Table 2. Correspondence of the high-expression and risk alleles of *GNB1L* SNPs

Studies	Population	Tissue/Disease	Alleles	SNP				
				rs5746832	rs5748427	rs5748432	rs2269726	rs748806
This study	Han Chinese	Temporal cortex	High-expression	-	G	G	C	T
4BrainR [24]	Caucasian	Temporal cortex	alleles	A	G	G	C	T
	Caucasian	Prefrontal cortex		A	G	G	C	T
Braincloud [23]	Caucasian	Prefrontal cortex		A	G	-	C	-
Li *et al*.[13]	Han Chinese	SCZ	Risk alleles	-	G	G	C	T
	Han Chinese	BP		A	G	A	C	T

(-), not determined; 4BrainR, "Four Brain Region"; SCZ, schizophrenia; BP, bipolar disorder.

expression results implies that the *GNB1L* high-expression allele is the risk variant for these disorders in the Han Chinese population. This is the first report that high expression of a gene in the 22q11.2 DS critical region is associated with schizophrenia.

As noted above, an earlier study by Williams and colleagues[14] identified two SNPs in the 3'-region of *GNB1L*, rs5746832 and rs2269726, that associated with schizophrenia in two European population-based case-control studies (UK and Germany). The details of these associations differ from that reported for the Chinese population, in that associations were not found at the

allele-level, but rather as an excess of homozygosity for the above SNPs in males only. Based on our expression results, an association of homozygosity with schizophrenia can be interpreted as association with either high- or low-expression.

It should be mentioned that in the study by Williams and colleagues, both rs5746832 and rs2269726 were found to deviate significantly from Hardy-Weinberg equilibrium among male cases, but not male controls or female cases or controls. No evidence was found for duplicate samples or closely-related individuals among the male schizophrenia cases, suggesting that the excess homozygosity is related to the schizophrenia phenotype.

By contrast, no significant deviation from Hardy-Weinberg equilibrium or association with schizophrenia was found for rs5746832 or rs2269726 in a third European population (Bulgaria)-based case-control study. We also failed to find a statistically significant association between alleles or homozygous/heterozygous genotypes for rs2269726 in a large USA-based Caucasian case-control study (1189 cases/949 controls)[30] (data not shown). The interpretation of these divergent results is difficult, but we suggest that the contribution of *GNB1L* to schizophrenia may be stronger in specific populations.

In this study, we also identified a *GNB1L* 5'-region SNP, rs11704083, that correlated with *GNB1L* expression in 36 Han Chinese samples. This result, however, was not replicated in the two Caucasian population-based brain expression studies, "Braincloud"[23] and "Four Brain Regions"[24]. Although these results suggested that rs11704083 is a Han Chinese-specific eQTL, we are inclined to consider rs11704083 to be a false-positive correlation, since other SNPs within the 5'-region LD block did not show a significant correlation with *GNB1L* mRNA expression (see Fig. 1). By contrast, the finding that correlations between mRNA expression and genotypes were replicated in four independent studies strongly supports the conclusion that the 3'-region *GNB1L* SNPs are true eQTLs for this gene.

The fact that the same cluster of *GNB1L* 3'-region SNPs correlated with *GNB1L* mRNA expression in four different brain regions (Fig. 3), with the same alleles identified as the high-expression alleles in each region (Fig. S3), suggests that anterior temporal cortex is a suitable surrogate for other brain regions, such as the dorsolateral prefrontal cortex, which are more directly implicated in the etiology of schizophrenia.

In summary, we used measurements of mRNA expression in temporal cortex and linkage disequilibrium analysis to show that *GNB1L* is regulated by at least one *cis*-acting variant located within the 3'-region of the gene. In addition, we found that SNPs previously shown to associate with schizophrenia in Chinese and European case-control studies all share the property of being strongly linked to rs2269726. Finally, the high-expression allele of each of these SNPs was identified as the risk allele for schizophrenia and bipolar disorder in the Chinese population.

SUPPLEMENTAL DATA

Supplemental data include three tables and three figures, and can be found online at http://www.neurosci.cn/epData.asp?id=185.

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