Schizophrenia Research 142 (2012) 200–205

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Meta-analysis and brain imaging data support the involvement of *VRK2* (rs2312147) in schizophrenia susceptibility

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ARTICLE INFO

Article history:
Received 11 April 2012
Received in revised form 27 August 2012
Accepted 7 October 2012
Available online 25 October 2012

Keywords:
VRK2
Schizophrenia
Asian populations
MRI
Brain imaging analysis

ABSTRACT

Recent genome-wide association studies have reported a set of schizophrenia susceptibility genes, but many of them await further replications in additional samples. Here we analyzed 5 genome-wide supported variants in a Han Chinese sample, and the variant rs2312147 at *VRK2* showed significant association, which was confirmed in the meta-analysis combining multiple Asian and European samples ($P = 3.17 \times 10^{-4}$, $N = 7498$). Rs2312147 is also associated with brain structure in healthy subjects, including the total brain volume and the white matter volume. Gene expression analyses indicated an up-regulation of *VRK2* in schizophrenia patients. Our data provide further evidence for the contribution of *VRK2* to schizophrenia.

1. Introduction

Schizophrenia (SCZ) is a complex neuropsychiatric disorder with high heritability. Recently, by utilizing genome-wide association studies (GWASs) and large-scale meta-analyses, researchers have reported a set of common sequence variations conferring significant risk of SCZ in Europeans (Purcell et al., 2009; Shi et al., 2009; Stefansson et al., 2009; Williams et al., 2010; Rietschel et al., 2011; Ripke et al., 2011; Steinberg et al., 2011). However, when tested in multiple populations, some of the genome-wide risk polymorphisms can be successfully replicated, such as *TCF4* rs9960767 and *Notch4* rs3131296 (Ikeda et al., 2010; Li et al., 2010), but some variants cannot, e.g., *ZNF804A* rs1344706 and *NRGN* rs12807809 (Li et al., 2010, 2011, 2012), suggesting that the initial findings from the GWASs need to be tested in independent samples, especially in samples with different ethnic backgrounds (detailed information about the genome wide significant risk variants and the data of replications are listed in Table S1).

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http://dx.doi.org/10.1016/j.schres.2012.10.008

In 2011, researchers from Europe and the U.S. reported several novel risk SNPs for SCZ on *MIR137*, *CSMD1* and *NT5C2* in a meta-analysis combining multiple GWAS datasets (Ripke et al., 2011). Another research group reported additional novel risk loci on *AMBRA1* using a smaller GWAS (Rietschel et al., 2011). Meanwhile, Steinberg et al. (2011) reported genome-wide significant association of another novel risk SNP rs2312147 at *VRK2* and they also confirmed the associations of *TCF4* and *NRGN* as well as SNPs at the major histocompatibility complex (MHC) region in a meta-analysis using the largest SCZ samples so far (N > 60,000). But all these newly identified risk SNPs have only been reported in Europeans and have not been replicated by independent groups in different ethnic populations (Table S1). Additionally, two recent GWASs in Chinese did not find these loci surviving genome-wide significance in their studies (Shi et al., 2011; Yue et al., 2011). Therefore, in light of these findings, we sought to test these novel genome-wide significant SNPs in independent Asian and European samples.

2. Materials and methods

We recruited 4 independent SCZ case–control samples (from Yuxi, Kunming, Singapore and Japan) with a total of 6565 Asian subjects and a SCZ case–control sample (CBDB/NIMH) with 933 European subjects (Table 1). There is no overlap among these studied samples and most of them have been described previously and no obvious population stratifications were observed (Huffaker et al., 2009; Ikeda et al., 2010; Li et al., 2011, 2012). We also obtained the data from a recent GWAS by the SCZ group of Psychiatric Genetic Consortium (PGC) with 21,856 European subjects (Ripke et al., 2011). The Yuxi sample (Han Chinese) from China was used in the initial screening of the candidate SNPs and the other SCZ samples were used for further replication analysis, and the genotyping methods for each sample are shown in Table 1. In order to test the genetic overlap between schizophrenia and other mental disorders, we conducted meta-analyses of the SCZ-risk SNP (rs2312147) in bipolar disorder (BPD) and major depressive disorder (MDD) samples respectively. For BPD, a recent GWAS (PGC BPD GWAS) (Sklar et al., 2011) and three individual BPD samples from Germany and Australia were used (Cichon et al., 2011) (N = 18,788). For MDD, two German GWAS samples were used (N = 4305) (Rietschel et al., 2010; Kohli et al., 2011) (sample information was shown in Table S2). Additionally, we measured the mRNA expression of *VRK2* in the blood cells of 20 SCZ patients and 18 healthy controls (refer to Supplemental Material for experimental details). This study was approved by the internal review board of Kunming Institute of Zoology, Chinese Academy of Sciences.

We also recruited 286 healthy subjects (Han Chinese, 177 females and 109 males, mean age 35.4 ± 12.5 years) to perform the brain imaging analysis. All volunteers were free from mental disorders, drug abuse, alcohol dependence, or brain injury. Structural magnetic resonance imaging data were acquired using a Philips MRI scanner (Achieva Release 3.2.1.0) operating at 3 T (Repetition Time = 7.38 ms, Echo Time = 3.42 ms, flip angle = 8, voxel dimensions $1.04 \times 1.04 \times 1.80$ mm^3, slice thickness = 1.2 mm). The total brain volume, the gray matter volume and the white matter volume were determined using standard voxel-based morphometry protocol employing unified segmentation in Statistical Parametric Mapping-5.

Among these newly identified risk SNPs in Europeans (Table S1), a total of 5 SNPs were selected as our candidates based on the following selection criteria. Firstly, the distances of the identified genome-wide supported variants and the nearest genes should be less than 100 kb so that the variants can be assigned to the nearest genes confidently, thus rs17662626 (*PCGEM1*) and rs7004633 (*MMP16*) were excluded from the present study (Table S1). Secondly, the minor allele frequency (MAF) of the risk SNPs should not be smaller than 5% in our Han Chinese sample. Both rs1625579 (*MIR137*) and rs11819868 (*AMBRA1*) have a MAF smaller than 5%, which were confirmed by sequencing 100 randomly selected Chinese individuals for our sample (data not shown), and therefore were dropped from further analysis. Thirdly, those risk SNPs on the previously identified risk genes such as *TCF4* and *NRGN*, which have been already studied in Han Chinese (Li et al., 2010), were not included. Finally, we also selected a novel risk SNP rs2021722 in *TRIM26* at the MHC region, a chromosome region consistently reported associated with SCZ (Purcell et al., 2009; Shi et al., 2009; Stefansson et al., 2009; Ripke et al., 2011). Collectively, a total of 5 SNPs from the 5 newly reported risk genes (*VRK2* rs2312147, *CSMD1* rs10503253, *CNNM2* rs7914558, *NT5C2* rs11191580 and *TRIM26* rs2021722) were selected for genotyping in our sample, and the risk SNP was tested in the replication samples.

3. Results

Among the 5 SNPs tested in the Yuxi sample, rs2312147 at the *VRK2* gene was associated with SCZ (P = 0.0036, Table 1; P = 0.018 after multiple test correction), and the other 4 SNPs were not significant (Table 2), therefore rs2312147 was selected for further replication analyses. As shown in Table 1, rs2312147 was strongly associated with SCZ in the combined Asian samples ($P = 4.24 \times 10^{-4}$, N = 6565), and the significance was strengthened when we combined the Asian and European samples together ($P = 2.21 \times 10^{-8}$, N = 29,354). It should be noted that there was partial overlap between the studied PGC SCZ samples and the samples previously used by Steinberg et al. (2011). When we removed the PGC SCZ samples from the meta-analyses, rs2312147 was still significant ($P = 3.17 \times 10^{-4}$, N = 7498). Of note, the imputation data for rs2312147 from the two recent GWASs in Chinese are not available, therefore cannot be evaluated in this study (Shi et al., 2009; Yue et al., 2011).

There has been accumulating evidence, including clinical, epidemiological and genetic studies suggesting substantial overlap of risk

Table 1
Association results of rs2312147 [C] with schizophrenia in samples of Asian and European ancestries.

Sample	Ethnicity	Sample description	N cases/N controls	Genotyping platform	Frequency		P-value	OR	95%CI	Test of heterogeneity
					Cases	Controls				
Yuxi	Chinese	Li et al. (2011)	547/755	SNaPShot	0.7367	0.6821	0.0036	1.28	1.08–1.52	/
Kunming	Chinese	Li et al. (2011)	495/1768	SNaPShot	0.7374	0.6875	0.0025	1.28	1.09–1.50	/
Singapore	Chinese	Supplemental data	885/976	Illumina 1M	0.6763	0.6701	0.72	1.03	0.90–1.18	/
Japan	Japanese	Ikeda et al. (2010)	575/564	Affymetrix 5.0	0.7299	0.7125	0.36	1.09	0.91–1.31	/
Asian combined	/	/	2502/4063	/	0.7140	0.6857	$\mathbf{4.24 \times 10^{-4}}$	1.16	1.07–1.26	0.10
CBDB/NIMH	European American	Huffaker et al. (2009)	543/390	Illumina 550	0.6344	0.6128	0.36	1.09	0.91–1.33	/
PGC SCZ GWAS	European ancestry	Ripke et al. (2011)	9394/12,462	Multiple	/	/	1.21×10^{-5}	1.10	/	/
All samples	/	/	12,439/16,915	/	/	/	$\mathbf{2.21 \times 10^{-8}}$	1.11	/	0.20
All samples excluding PGC	/	/	3045/4453	/	0.6835	0.6684	$\mathbf{3.17 \times 10^{-4}}$	1.14	1.07–1.24	0.18

Abbreviation: OR, odds ratio; CI, confidence interval.
Significant p-values ($p<0.05$) were marked in bold. Association analyses were firstly conducted in each sample, and meta-analysis was performed using the Mantel–Haenszel test with PLINK in the combined samples with the fixed-effects model (Purcell et al., 2007).

Table 2
The non-significant results of SNP associations with schizophrenia in Yuxi sample.

Gene ID	SNP ID	Chromosome	Allele	Frequencies		P-value	OR (95%CI)	OR reported in European GWAS
				SZ	CON			
TRIM26	rs2021722	6p21.3–p22.1	C	0.8718	0.8894	0.17	0.85 (0.66–1.07)	1.15 (1.11–1.19)
CSMD1	rs10503253	8p23.2	T	0.3663	0.3450	0.26	1.10 (0.93–1.29)	1.11 (1.07–1.15)
CNNM2	rs7914558	10q24.32	A	0.5754	0.5801	0.81	0.98 (0.84–1.15)	1.10 (1.07–1.13)
NT5C2	rs11191580	10q24.33	T	0.7345	0.7040	0.088	1.16 (0.98–1.38)	1.15 (1.10–1.20)

Abbreviation: OR, odds ratio; CI, confidence interval.

factors and genetic components between SCZ and BPD (Lichtenstein et al., 2009; Purcell et al., 2009). Thus, we further analyzed rs2312147 in the European BPD samples, and rs2312147 showed a trend of association with BPD though not significant (P = 0.07, Table 3). Additionally, to further study the role of rs2312147 in other mental disorders, we also tested the association of rs2312147 with MDD in Europeans, but it was not significant (P = 0.56, Table 3).

We also conducted an association analysis of rs2312147 with brain structure in a sample including 286 healthy subjects. The results showed that rs2312147 was significantly associated with the total brain volume (P = 0.01, Fig. 1-a) and the white matter volume (P = 0.008, Fig. 1-b), and the significance of the gray matter volume was marginal (P = 0.09, Fig. 1-c). In all scenarios, the individuals carrying the risk allele (C) of rs2312147 tend to have smaller volumes. These data add further support for the involvement of *VRK2* in SCZ susceptibility and also imply its potential role in brain development.

Rs2312147 is located ~50 kb upstream of *VRK2*, so we compared *VRK2* gene mRNA expression in the blood cells between 20 SCZ patients and 18 healthy controls (refer to supplemental material for experimental details), and the results showed that the expression of *VRK2* was up-regulated in patients compared with controls (P = 0.0147, Fig. 1-d). Since SCZ is a disorder almost exclusively originating from defects in brain function, we subsequently obtained the results from the SMRI Online Genomics Database (https://www.stanleygenomics.org) and found that the expression of *VRK2* was relatively higher in the brains of SCZ patients than normal controls though it did not achieve statistical significance (Fig. S1).

However, the gene expression–SNP correlation analyses showed that rs2312147 itself was not associated with *VRK2* expression in our blood sample (Fig. S2). To exclude the possibly false negative results caused by the limited sample size, we also examined six existing databases of genome-wide gene expression analyses using post mortem brains (2 databases) (Heinzen et al., 2008; Colantuoni et al., 2011) and lymphoblastic cells (4 databases) (Heinzen et al., 2008; Dimas et al., 2009; Nica et al., 2011; Stranger et al., 2012). Still, no association of rs2312147 with *VRK2* expression was observed (Table S3 and Figs. S3–S6).

4. Discussion

VRK2, a gene coding for a serine/threonine kinase of the casein kinase I group, is located on human chromosome 2p16.1. In 2009, by conducting a GWAS, Stefansson et al. (2009) reported several risk polymorphisms conferring risk of SCZ in 47,536 European subjects, and rs2312147, located about 50 kb upstream of *VRK2*, was identified as a risk SNP ($P = 3 \times 10^{-7}$) though it did not achieve genome-wide significance. In 2011, Steinberg et al. (2011) confirmed the association of rs2312147 with SCZ in a combined sample (N = 60,742, $P = 1.9 \times 10^{-9}$). However, these studies were both conducted in Europeans and the associations in other ethnic populations were still unknown. Here we report significant association of rs2312147 with SCZ in Asian populations, and our expression analyses provided additional evidence for the involvement of *VRK2* schizophrenia susceptibility, implying that *VRK2* is probably a common risk gene for SCZ in populations worldwide. Additionally, rs2312147 also showed a trend of association with BPD, suggesting that this polymorphism might be involved in major psychosis, but this needs to be tested in future studies.

It has been shown that there is a reduction of brain volume and total gray matter volume as well as total white matter volume in SCZ patients compared with normal controls (Rimol et al., 2010), and significant effects of SCZ risk genes on brain structure variations in healthy subjects have been reported (Kempton et al., 2009). We demonstrated that rs2312147 was significantly associated with the total brain volume and the white matter volume, and this is consistent with the previous studies (Kempton et al., 2009). These data added further support to the hypothesis that schizophrenia susceptibility genes may play pivotal roles in brain development.

The non-significant associations in our replications of the other 4 risk SNPs (rs2021722, rs11191580, rs10503253 and rs7914558) indicated the difficulties of replicating GWAS findings across different ethnic populations. However, it should be noted that, though not significant, the estimated odds ratios of rs11191580 [T] and rs10503253 [A] reached 1.16 and 1.10 respectively, which were similar with the GWAS findings (1.15 and 1.11) (Ripke et al., 2011), and the

Table 3
Association of rs2312147 with bipolar disorder and major depressive disorder in samples of European ancestry.

	Sample	N cases/N controls	Allele	Frequencies		P-value	OR	95%CI
				CASE	CON			
Bipolar disorder	Germany II	488/861	C	0.6066	0.6127	0.80	0.98	0.83–1.16
	Australia	330/1811	C	0.6045	0.6201	0.43	0.93	0.79–1.11
	Germany III	181/527	C	0.6492	0.6148	0.0085	1.53	1.11–2.10
	PGC BPD GWAS	7481/9250	C	/	/	0.065	1.05	/
	All BPD samples	8480/12,449	C	/	/	0.07	1.04	/
Major depressive disorder	Germany (Bonn)	597/1295	C	0.6047	0.6054	0.97	1.00	0.87–1.15
	Germany (Munich)	1553/860	C	0.6233	0.6116	0.42	1.05	0.93–1.19
	All MDD samples	2150/2155	C	/	/	0.56	1.03	/

Abbreviation: OR, odds ratio; CI, confidence interval.
No significant heterogeneity was detected in the combined BPD or MDD samples (P = 0.051 and 0.58), and the meta-analysis was assessed using the Mantel–Haenszel method under fixed-effects model.

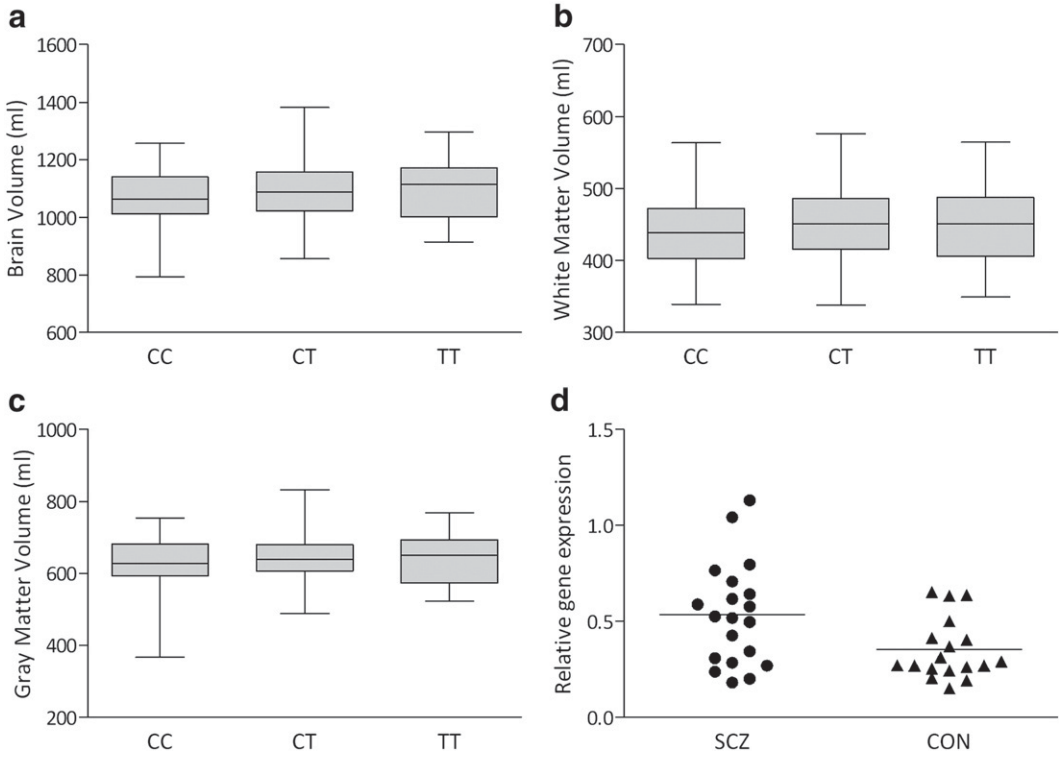

Fig. 1. a. Mean total brain volume in carriers of genotypes CC, CT, and TT of rs2312147. The P-value was calculated using the logistic regression model with age and gender as covariates. b. Mean total white matter volume in carriers of genotypes CC, CT, and TT of rs2312147. The P-value was calculated using the logistic regression model with age and gender as covariates. c. Mean total gray matter volume in carriers of genotypes CC, CT, and TT of rs2312147. The P-value was calculated using the logistic regression model with age and gender as covariates. d. Comparison of *VRK2* expression in SCZ patients and healthy controls (CON) using the Student t-test (2-tailed) with SPSS16.0.

non-significant results in our samples are probably due to the reduced power of our limited sample size. In contrast, the odds ratios of rs2021722 [G] and rs7914558 [A] in our samples were highly different from the GWAS results (Table 2) (Ripke et al., 2011), suggesting potential between-population heterogeneity at these two loci.

In summary, our genetic screening and meta-analysis in Asian and European samples successfully replicated the association of *VRK2* with SCZ, which was further supported by the observed up-regulation of *VRK2* mRNA expression in SCZ patients and the significant association of *VRK2* with brain structure variations in healthy subjects. Hence, *VRK2* is likely a common risk gene for SCZ in world populations. However, since the risk SNP rs2312147 did not show significant influence on *VRK2* mRNA expression, whether it is the causal variant is yet to be dissected.

Role of funding source

This work was supported by grants from the National 973 project of China (grant number, 2011CBA00401), the National Natural Science Foundation of China (31237068), the National Medical Research Council Translational and Clinical Research Flagship Program (grant number, NMRC/TCR/003/2008), the German Federal Ministry of Education and Research (BMBF), within the context of the National Genome Research Network (NGFN), and the Integrated Genome Research Network (IG) MooDS (grant 01GS08144 to S.C, grant 01GS08147 to M.R.). Recruitment of the Australian BDP sample was supported by the Australian NHMRC program (grant number 510135).

Contributors

Authors ML, YW and BS designed the study. Authors ML, YW, XBZ, MI, NI, XJL, MR, FZ, BMM, SC, DRW, MM, TGS, NGM, PBM, PRS and JJL generated the experimental data. Authors ML and BS analyzed all data and wrote the paper. Authors SAC and JL provided the patient samples. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors have no conflicts of interest to declare.

Acknowledgment

We are grateful to all the voluntary donors of DNA samples in this study. We acknowledge the National Research Foundation Singapore and the Agency for Science, Technology and Research for data sharing. We thank Hui Zhang and Richard Straub for technical assistances in genotyping.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2012.10.008.

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