Evidence of AS3MT^{d2d3}-Associated Variants within 10q24.32–33 in the Genetic Risk of Major Affective Disorders

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Keywords

10q24.32–33 · AS3MT^{d2d3} · Schizophrenia · Major affective disorders

Abstract

Genome-wide association studies suggest that 10q24.32–33 is a risk region for schizophrenia (SCZ). Considering the substantial genetic overlap between SCZ and major affective disorders, we would like to investigate whether the 10q24.32–33 region confers risk of affective disorders. We chose three SCZ genome-wide significant SNPs (rs7914558, rs7085104, and rs11191580) in 10q24.32–33 and collected the statistical data from European and Asian populations to perform systematic meta-analyses, which finally included up to 26,413 cases with affective disorders and 24,849 controls. Meta-analyses showed that all SNPs were nominally associated with major affective disorders. Considering the a priori evidence that these SNPs were associated with the expression of AS3MT^{d2d3} isoform in the human brain, our data confirms the potential involvement of AS3MT^{d2d3} in the genetic risk of major affective disorders.

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Introduction

The association between psychotic and affective illnesses has been an area of debate in psychiatry. Within the family members of a proband with schizophrenia (SCZ), there is an increased risk (above the level in the general population) of both bipolar disorder (BPD) and major depressive disorder (MDD) [1, 2]. More recently, a population-based cohort study reported that the prevalence of either SCZ or BPD was higher in family members of an index proband regardless of their diagnosis [3], and some genome-wide association studies (GWAS) also suggested shared genetic risk between SCZ and affective disorders (BPD and MDD) [4, 5].

Chromosome 10q24.32–33 is one of the most significant genomic regions for SCZ [6–8]. In 2011, rs7914558 and rs11191580 in 10q24.32–33 were significantly associated with SCZ in the GWAS by the Psychiatric Genomics Consortium (PGC1) in populations of European descent [7], and the association became stronger in the later European GWAS meta-analysis (PGC1+SWE) with an increased sample size [6]. In this PGC1+SWE GWAS [6], rs7085104 was the most significant variant among the 10q24.32–33 region. Rs7085104 is in moderate to strong linkage disequilibrium with rs7914558

($r^2 = 0.69$ in Europeans and $r^2 = 0.74$ in Asians; Fig. 1), although it is in low linkage disequilibrium with rs11191580 ($r^2 = 0.17$ in Europeans and $r^2 = 0.32$ in Asians; Fig. 1). In our previous study, we showed that rs7914558 and rs11191580 were also strongly associated with SCZ in Asian samples [9].

In searching for the molecular mechanisms underlying the genetic risk of SCZ in 10q24.32–33, Li et al. [10] found that the risk allele of rs7085104 was strongly associated with an increased expression of a human-specific AS3MT transcript (AS3MT^{d2d3}), which lacks exon 2 and 3 compared with its full-length form. Rs7914558 and rs11191580 were also associated with AS3MT^{d2d3} expression, although less significant than rs7085104 (supplementary data in the study by Li et al. [10]).

Considering the genetic overlap between SCZ and major affective disorders, it is compelling to investigate whether the SCZ risk variants in 10q24.32–33 also confer susceptibility to major affective disorders. Therefore, we systematically collected data from the literature to perform meta-analytic associations of the three SNPs in up to 51,262 subjects from diverse ethnic groups, and we found that these SCZ genetic risk variants at 10q24.32–33 were also nominally associated with major affective disorders.

Methods

Search Strategy

The search strategy was designed to identify all sources of published data in the literature. Electronic searches without language or date restriction were carried out in PubMed (1966–present), Web of Science (1899–present) and Embase (1974–present).

Fig. 1. Linkage disequilibrium relationship of the included SNPs in Europeans and Asians.

Fig. 2. Literature search flow chart.

Table 1. Characteristics of included samples in this meta-analysis

	Data source				
	Ruderfer et al. [5], 2014	Saito et al. [11], 2014	Grigoriou-Serbanescu et al. [13], 2015	PGC Cross-Disorder Group [4], 2013	CONVERGE Consortium [12], 2015
Phenotype	BPD	BPD	BPD	MDD	MDD
Diagnostic criteria	DSM-IV, DSM-IIR, RDC	DSM-IV	DSM-IV	DSM-IV	DSM-IV
Cases, <i>n</i>	10,410	1,012	461	9,227	5,303
Controls, <i>n</i>	10,700	993	436	7,383	5,337
Genotyping method	Multiple	Sequenom iPLEX	Illumina	Multiple	Illumina Hi-Seq
<i>rs7914558</i>					
<i>p</i> value	0.0198	0.387	0.300	0.00245	0.255
OR	1.051	1.060	1.100	1.074	1.036
95% CI	1.008–1.096	0.931–1.206	0.918–1.317	1.026–1.125	0.981–1.095
<i>rs7085104</i>					
<i>p</i> value	0.00571	N/A	N/A	0.00198	0.0861
OR	1.063	N/A	N/A	1.078	1.054
95% CI	1.018–1.110	N/A	N/A	1.028–1.130	0.998–1.113
<i>rs11191580</i>					
<i>p</i> value	0.0120	0.391	0.240	0.0220	0.0231
OR	1.098	1.064	1.244	1.098	1.075
95% CI	1.021–1.181	0.918–1.232	0.913–1.695	1.013–1.190	1.012–1.143

BPD, bipolar disorder; MDD, major depressive disorder; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; DSM-IIR, Diagnostic and Statistical Manual of Mental Disorders, second edition, revised; RDC, Research Diagnostic Criteria; OR, odds ratio; CI, confidence interval; N/A, not available.

Search terms containing “10q24.32–33,” “rs7085104,” “rs7914558,” or “rs11191580,” and the terms “bipolar,” “depression,” and “GWAS” were used in all databases to identify relevant studies, along with a representative search strategy used for the PubMed query. Once these publications had been collected, their bibliographies were then searched for additional references. All articles identified through the searching process were evaluated based on the title and abstract. Clearly irrelevant studies were excluded from further consideration. The remaining articles received a full-text review. The last search was undertaken on August 21, 2016.

Eligibility Criteria

The studies eligible for the meta-analysis satisfy the following criteria: (1) case-control or family-based studies were included; (2) eligible studies should have case status defined with having a diagnosis of BPD or MDD according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) or related measurements; (3) studies included should have no overlap with each other.

Data Extraction

The data from each study were extracted using a standardized data extraction form. Descriptive information extracted contained

(1) basic information with the name of the first author and year of publication, (2) methodology including study design, sample size, and definition of case status, and (3) sample characteristics such as collection area and ethnicity.

Statistical Analysis

We used odds ratio (OR) and standard error from each individual study to estimate heterogeneity between samples and to calculate the pooled OR and 95% confidence interval (CI) in the combined samples. To combine the results from individual samples, we first used Cochran's (*Q*) χ^2 test to calculate the heterogeneity between studies. This test is a weighted sum of the squares of deviations of individual OR estimates from the overall estimate. If $p_Q < 0.10$, the heterogeneity was considered statistically significant. In the presence of heterogeneity among individual studies, we used random effects models to combine the samples and to calculate the OR and the corresponding 95% CIs; for homogeneous studies, a fixed-effect model was used. The meta-analyses were performed using the classical inverse variance weighted methods in RevMan, version 5.3.5 (<http://tech.cochrane.org/revman/download>). The pooled ORs and the 95% CIs were graphically presented using a forest plot. Each study and its weight were represented by a square with the corresponding size in the plot.

Fig. 3. Forest plot of meta-analysis for the included SNPs with major affective disorders: rs7914558 (a), rs7085104 (b), and rs11191580 (c). The results for BPD samples are marked in dark gray, and results for MDD samples are marked in light gray.

Results

Literature Search and Eligible Studies

A flow chart illustrating the literature search and selection process is presented in Figure 2. The initial literature search identified 45 references. We removed 29 references with obviously irrelevant titles and reviewed the abstracts of the remaining 16 studies. This process left 14 potentially eligible studies. The full texts of the 14 publications were screened to examine their eligibilities based on the inclusion criteria. Among them, 9 studies were excluded because of the overlapped samples and lack of analyses of the SNPs of interest (rs7914558, rs7085104, and rs11191580). Therefore, a total of 5 studies with independent samples were considered eligible for the present meta-analysis [4, 5, 11–13]. Characteristics of the 5 included samples are listed in Table 1. Overall, the meta-analysis provided 11,883 BPD cases, 14,530 MDD cases, and 24,849 controls, and this sample size yielded >90%

power to detect a significant association ($p < 0.05$) for any of the three SNPs assuming a commonly observed OR (1.10) in psychiatric genetic studies.

Meta-Analysis of rs7914558 with Major Affective Disorders

A total of 3 BPD and 2 MDD studies were included to perform meta-analysis of rs7914558 [4, 5, 11–13]. Due to the fact that no significant heterogeneity between samples was observed ($p = 0.875$, $I^2 = 0$), a classical fixed effect model was adopted to combine the individual samples. For BPD, our results showed that rs7914558 was nominally associated with the disease in a total of 11,883 patients and 12,129 normal controls ($p = 0.0081$, OR = 1.054). For MDD, we found that rs7914558 was also nominally associated with the illness in a total of 14,530 patients and 12,720 normal controls ($p = 0.0017$, OR = 1.074). We then merged BPD and MDD cases as a single phenotype, namely “major affective disorders.” In this

analysis, the association for rs7914558 was strengthened in a total of 26,413 cases and 24,849 controls ($p = 4.15 \times 10^{-5}$, OR = 1.056). The forest plot of the meta-analysis between rs7914558 and major affective disorders is presented in Figure 3a.

Meta-Analysis of rs7085104 with Major Affective Disorders

Rs7085104 was analyzed in three studies [4, 5, 12]. We adopted a classical fixed effect model to combine the individual samples given no significant heterogeneity was observed ($p = 0.819$, $I^2 = 0$). An overall analysis showed that rs7085104 was strongly associated with major affective disorders in a total of 24,940 patients and 23,420 normal controls ($p = 6.39 \times 10^{-6}$, OR = 1.066), which was in the same direction of allelic effects with a priori SCZ analysis [6]. The forest plot of the meta-analysis between rs7085104 and major affective disorders is presented in Figure 3b.

Meta-Analysis of rs11191580 with Major Affective Disorders

A total of three BPD and two MDD studies were included to perform meta-analysis of rs11191580 [4, 5, 11–13]. A classical fixed effect model was adopted to combine the individual samples since no significant heterogeneity was observed ($p = 0.900$, $I^2 = 0$). For BPD, rs11191580 showed nominal association in a total of 11,883 patients and 12,129 controls ($p = 0.0043$, OR = 1.097). For MDD, this SNP was also associated with the illness in a total of 14,530 patients and 12,720 normal controls ($p = 0.0012$, OR = 1.084). When we merged BPD and MDD samples, the association was further strengthened in a total of 26,413 cases and 24,849 controls ($p = 1.62 \times 10^{-5}$, OR = 1.089). The forest plot of the meta-analysis between rs11191580 and major affective disorders is presented in Figure 3c.

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Discussion

Chromosome 10q24.32–33 is one of the most significant loci for SCZ in world populations [6–9, 14, 15]. In searching for the molecular mechanisms underlying the risk of psychiatric disorders conferred by 10q24.32–33 region, Li et al. [10] previously found that the risk SNPs (e.g., rs7085104) were significantly associated with the expression of AS3MT^{d2d3}, a truncated isoform of AS3MT. Intriguingly, the expression of AS3MT^{d2d3} was also significantly increased in patients with MDD than healthy controls [10]. AS3MT^{d2d3} expression is also higher in patients with BPD [10], but such increase did not achieve statistical significance, which is likely due to limited sample size.

In sum, the present study confirms that 10q24.32–33 is a susceptibility locus for major affective disorders. These results also suggest the involvement of AS3MT^{d2d3} in the risk of major affective disorders.

Acknowledgement

The authors are deeply grateful for the authors of previous studies who shared the genotype data. This work was supported by CAS Pioneer Hundred Talents Program (to M.L.).

Statement of Ethics

The study was approved by the internal review board of Kunming Institute of Zoology, Chinese Academy of Sciences.

Disclosure Statement

The authors declare no conflict of interest.

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