SNAP25 Is Associated With Schizophrenia and Major Depressive Disorder in the Han Chinese Population

Qingzhong Wang, PhD; Yanlin Wang, PhD; Weidong Ji, PhD; Guoquan Zhou, PhD; Kuanjun He, PhD; Zhiqiang Li, PhD; Jianhua Chen, PhD; Wenjia Li, PhD; Zujia Wen, PhD; Jiawei Shen, PhD; Yu Qiang, MS; Jue Ji, BS; Yujiong Wang, PhD; Yongyong Shi, PhD; Qizhong Yi, MD, PhD; and Yonggang Wang, PhD

ABSTRACT

Objective: Synaptosomal-associated protein of 25 kDa (SNAP25) is a member of the soluble N-ethylmaleimide-sensitive factor attachment receptor (SNARE) protein complex, which plays essential roles in the modulation of different voltage-gated calcium channels and neurotransmitter release. Many previous studies have reported the SNAP25 gene to be significantly associated with attention-deficit/hyperactivity disorder (ADHD). Recently, shared genetic variants have been demonstrated in 5 major psychiatric disorders, including schizophrenia, major depressive disorder, bipolar disorder, autism spectrum disorders, and ADHD. However, no compelling, convincing evidence has suggested an association between SNAP25 and schizophrenia or major depressive disorder. Thus, we investigated the association between SNAP25 and both schizophrenia and major depressive disorder in the Han Chinese population.

Method: We performed a large-scale case-control study to test the association between SNAP25 and 2 major mental disorders, schizophrenia (DSM-IV criteria) and major depressive disorder (DSM-IV criteria), in the Han Chinese population. Seven single-nucleotide polymorphisms (SNPs) were genotyped in 1,330 schizophrenia patients, 1,045 major depressive disorder patients, and 1,520 healthy controls of Han Chinese origin.

Results: Two SNPs, rs3787283 and rs3746544, were found to be associated with both schizophrenia (rs3746544, adjusted \( P = .00257 \)) and major depressive disorder (rs3746544, adjusted \( P = .0485 \); rs3787283, adjusted \( P = .00387 \)) in this study. The AG haplotype consisting of rs3787283 and rs3746544 was also significantly associated with both schizophrenia and major depressive disorder (schizophrenia: adjusted \( P = .0126 \); major depressive disorder: adjusted \( P = .000580 \)). Additionally, we carried out a meta-analysis of the current data and published association results and further confirmed the association between rs3746544 and schizophrenia (\( P_{\text{meta}} = .002 \), OR\(_{\text{meta}} = 1.213 \) [95% CI, 1.077–1.367]).

Conclusions: Our results indicated that SNPs in SNAP25 represented a common risk factor of both schizophrenia and major depressive disorder in the Han Chinese population.

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Mental disorders are caused by a combination of biological, psychological, and environmental factors. These mental diseases have been recognized as leading causes of morbidity, and they require extensive long-term medical and social care. Schizophrenia and major depressive disorder are 2 of the most common mental disorders. Schizophrenia is a severe mental disorder with a lifetime risk of approximately 1% and is characterized by hallucinations, delusions, and cognitive deficits, with a heritability estimated at up to 80%. Major depressive disorder includes a distinct change in mood and is characterized by sadness or irritability and is accompanied by at least several psychophysiological changes. Previous studies comparing the concordance rates of major depressive disorder between monozygotic and dizygotic twins have suggested a heritability of approximately 37%.

Recent applications of genome-wide association studies (GWAS) and next generation sequencing have discovered rare copy number variants and common single-nucleotide polymorphisms (SNPs) that are associated with the risk of psychiatric disorders. Furthermore, these studies have shown an overlap between the genetic variant that is susceptible to different diseases. To examine the shared genetic etiology, Lee et al. collected GWAS data from the Psychiatric Genomics Consortium and applied univariate and bivariate methods to 5 disorders—schizophrenia, bipolar disorder, major depressive disorder, autism spectrum disorders, and attention-deficit/hyperactivity disorder (ADHD). These researchers reported that the values of SNP-based heritability are reasonably robust and were significantly greater than 0 for all 5 disorders. They also found that the genetic risk variants were substantially shared between schizophrenia and bipolar disorder (high genetic mean ± standard error correlation, 0.68 ± 0.04), bipolar disorder and major depressive disorder (moderate genetic correlation, 0.43 ± 0.06), schizophrenia and major depressive disorder (moderate genetic correlation, 0.47 ± 0.06), and ADHD and major depressive disorder (moderate genetic correlation, 0.32 ± 0.07); and they found a low genetic correlation exists between schizophrenia and autism spectrum disorders (0.68 ± 0.04). In The Lancet, the Psychiatric Genomics Consortium performed a meta-analysis of the GWAS data for 33,332 cases and 27,888 controls, which were distributed among the 5 major psychiatric disorders in Psychiatric Genomics Consortium (major depressive disorder, bipolar disorder, schizophrenia, autism spectrum disorders, and ADHD). In that study, they reported SNPs at 4 loci in regions on chromosomes 3p21 and 10q24 and SNPs in 2 L-type
voltage-gated calcium-channel subunits, CACNA1C and CACNB2, which exceeded the threshold of genome-wide significance ( downward of 5 × 10^−8). Their results provided evidence that genetic variation in calcium channel signaling can increase the risk of these 5 neuropsychiatric disorders.9

SNAP25 is an integral part of the SNARE complex, which enables synaptic vesicle exocytosis in conjunction with syntaxin and synaptobrevin.10 Multiple studies have revealed that the level of SNAP25 mRNA or protein expression was altered in specific brain regions of patients with schizophrenia, which provides supportive evidence for the potential importance of SNAP25 and synaptic-mediated signal pathway in the etiology of schizophrenia.11–15 Until recently, several groups have analyzed the association between SNAP25 and schizophrenia. For example, Carroll et al16 investigated 38 tagging SNPs that span the SNAP25 locus in UK schizophrenic cases. They found that several independent SNPs showed nominal significance, and rs3787283 was the most significant SNP associated with schizophrenia (P = .006, OR = 1.25). They also found that the strongest associated SNP of schizophrenia in SNAP25 was also associated with ADHD with the opposite risk allele.16 In addition, Fanous et al17 genotyped 18 haplotype-tagging SNPs within the SNAP25 gene in a sample of 270 Irish high-density families and performed an association study in an independent sample set with 657 cases and 411 controls. They observed robust association in both single marker and haplotype-based analyses between SNAP25 and schizophrenia in an Irish family.17 Moreover, a Japanese research group18 conducted a 2-stage genetic association analysis of SNAP25 with schizophrenia. In the first-stage screening, they detected only 1 SNP (rs12626080) and a haplotype (rs363014 and rs12626080) in SNAP25, with nominal significance in 377 cases and 377 controls. However, they could not replicate these nominally significant SNPs and haplotypes in the second-stage analysis. Taken together, these association studies provided clues of SNAP25’s important role in the etiology of schizophrenia; however, due to an insufficient sample size, there were no compelling reports of a positive association between SNAP25 and schizophrenia and major depressive disorder.

To investigate whether SNAP25 is associated with mental diseases in the Han Chinese population, we genotyped 7 SNPs (rs363039, rs363050, rs362549, rs362998, rs363006, rs3787283, rs3746544) within SNAP25 in 1,330 schizophrenia patients, 1,045 major depressive disorder patients, and 1,520 healthy controls of Han Chinese origin.19

Subjects
Our sample sets consisted of 1,330 schizophrenia patients (805 male and 525 female; mean ± SD age = 36.4 ± 8.96 years), 1,045 major depression patients (729 male and 316 female; mean ± SD age = 34.4 ± 12.1 years), and 1,520 healthy controls (774 male and 746 female; mean ± SD age = 30.6 ± 11.4 years). All subjects were of Han Chinese origin. The patients were interviewed by 2 independent psychiatrists and diagnosed strictly according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Healthy controls were randomly selected from the Han Chinese general population, and they resided in the same area as the patient group. All volunteers were interviewed by 2 psychiatrists to rule out control subjects with a family history of mental illness. We also obtained written informed consent from all participants. Our study was reviewed and approved by the local ethics committee of Human Genetics Resources.

Selection and Genotyping of SNPs
We used the University of California-Santa Cruz (UCSC) human genome browser (http://genome.ucsc.edu/) and Haploview 4.1 software19 to select tag SNPs within the SNAP25 gene in the Hapmap Han Chinese in Beijing, China + Japanese in Tokyo, Japan (CHB + JPT) population (Release 21). Single nucleotide polymorphisms with a reported minor allele frequency below 0.03 were not considered in the analysis. In addition, 7 tag SNPs were selected for genotyping. These tag SNPs can capture 93% of common SNPs information with r^2 > 0.5 (analyzed using tagger server online software, http://www.broadinstitute.org/mpg/tagger/server.html). Among the 7 SNPs, rs3746544 and rs3787283 were reported to be positive by Carroll et al.16 The other 5 SNPs were randomly chosen according to different blocks. The structure of the SNAP25 gene and the location of the 7 selected tag SNPs are shown in Figure 1. All SNPs were genotyped using TaqMan SNP Genotyping Assays on Fluidigm EP1 platform. All probes were designed and synthesized by Applied Biosystems (Foster City, California). All 7 SNPs had a genotype call rate > 93%.

Sample Preparation
Genomic DNA was extracted from peripheral blood using the Quick Gene DNA whole blood kit (Fugifilm, Tokyo, Japan). Isolated DNA from each sample was used for SNP genotyping with TaqMan chemistry (Applied Biosystems, Foster City, California) and Fluidigm dynamic array chips (Fluidigm Corporation; San Francisco, California).

Statistical Analysis
We calculated Hardy-Weinberg equilibrium, allelic association, genotypic association, and odds ratio (OR) using SHEsis software (http://analysis.bio-x.cn).20,21 Hardy-Weinberg equilibrium was determined using the χ² test for goodness of fit. Linkage disequilibrium estimation and haplotype analyses were performed on Haploview 4.1.19

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We corrected the \( P \) values of genotypes and alleles using Bonferroni correction in which the \( P \) values obtained were multiplied by the number of SNPs, and Bonferroni correction for haplotype analysis was multiplied by the haplotype numbers. The global \( P \) value of haplotype analysis was calculated using the omnibus \( \chi^2 \) test. All tests were 2-tailed and statistical significance was established at \( P < .05 \).

**Meta-Analysis**

For the meta-analysis, we searched PubMed using keywords rs3746544 or MnlI (rs3746544) and schizophrenia. All the case-control studies between rs3746544 and schizophrenia, up to February 2014, were included in the analysis. A \( \chi^2 \)-based \( Q \) statistic test was performed to assess the heterogeneity. If the result of the heterogeneity test was \( P > .05 \), the fixed-effects model (Mantel-Haenszel methods) was used to pool ORs; otherwise, the random-effects model was chosen. The significance of the pooled ORs was determined by the \( Z \) test. Meta-analytic procedures were carried out using Comprehensive Meta-Analysis v.2.0 (Biostat Inc; Englewood, New Jersey; http://www.meta-analysis.com/index.php).

**RESULTS**

Genotype distributions of all SNPs were in Hardy-Weinberg equilibrium in healthy controls. The allele and genotype frequencies of 7 SNPs in all samples are listed in Table 1. The results of haplotype analysis are shown in Table 2. Pairwise linkage disequilibrium analysis of the 7 SNPs is shown in Figure 2. In addition, we identified 2 haplotype blocks, where 1 block contained 3 SNPs (rs362549 and rs362998 and rs363006) and another block contained 2 SNPs (rs3787283 and rs3746544) (Figure 2).

For schizophrenia, we found that rs3746544 was significantly associated with schizophrenia in the \( \chi^2 \) test (allele: \( \chi^2_1 = 12.705, P = .000368, OR = 1.277 \) [95% CI, 1.16–1.46]; genotype: \( \chi^2_2 = 15.126, P = .000525 \)). After Bonferroni correction, rs3746544 was still significant in the allele and genotype distribution (\( P_{\text{allele}} = .00257, P_{\text{genotype}} = .00368 \)). Haplotype analysis revealed that the \( P \) value for the A-G haplotype consisting of rs3746544 and rs3787283 was .0284 and the corrected global \( P \) value was .0126.

For major depressive disorder, we found that rs3787283 and rs3746544 were significant in both allele and genotype distribution in the \( \chi^2 \) test (rs3787283: [allele] \( \chi^2_1 = 11.943, P = .000553; [\text{genotype}] \chi^2_2 = 11.796, P = .002764, OR = 0.8017 \) [95% CI, 0.71–0.91]; rs3746544: [allele] \( \chi^2_1 = 7.295, P = .00694; [\text{genotype}] \chi^2_2 = 8.476, P = .0145, OR = 1.213 \) [95% CI, 1.054–1.396]). After Bonferroni correction, the allele of rs3787283 and rs3746544 still remained significant (rs3787283, allele: \( P_{\text{corrected}} = .00387; \) rs3746544, allele: \( P_{\text{corrected}} = .0485 \)). Haplotype analysis revealed that rs3746544 and rs3787283 were significant between major depressive disorder patients and healthy controls (global \( P = .000580 \), after correction) (Table 2).

Including our current data and published results, we analyzed 5,293 subjects in total in a meta-analysis of rs3746544, including 2,400 schizophrenia cases and 2,893 healthy controls. In the homogeneity analysis, no significant heterogeneity was detected among 5 individual sample groups (rs3746544: \( \chi^2_4 = 3.270, P = .514 \)). The meta-analysis (\( Z \) score test) of the combined samples was assessed with a fixed-effect model. Combining all samples in the meta-analysis, we found that rs3746544 showed significant association with schizophrenia (\( Z = 3.171, P = .002, OR = 1.213 \); Table 3). The forest plot of the meta-analysis is presented in Figure 3.

**DISCUSSION**

Many studies have demonstrated that alterations of the SNAP25 gene structure, expression, and function can directly contribute to neuropsychiatric and neurologic disorders, including ADHD, epilepsy, autism spectrum disorder, schizophrenia.\(^{22}\) The *coloboma* mutant mouse model contains a neuron-irradiation–induced gene region deletion located on mouse chromosome 2, which includes SNAP25.\(^{23}\) The *coloboma* mutant mice displayed spontaneous hyperactivity, inattention, impulsivity, the symptoms of which are parallel to ADHD.\(^{23}\) Interestingly, the normal phenotype was restored using transgenic SNAP25 in *coloboma* mutant mice.\(^{24}\) The number of linkage studies on...
polymorphisms in the SNAP25 gene locus have revealed its linkage with ADHD.25–27,28 Recent GWAS have confirmed the association of SNAP25 with ADHD.29 However, there has been no additional evidence supporting the association between SNAP25 and schizophrenia until now.

In this study, the main finding was a significant association between rs3746544 within the SNAP25 gene and schizophrenia and major depressive disorder in a Chinese Han population. The data suggested that the SNAP25 gene might be involved in schizophrenia and major depressive disorder susceptibilities, and the data also supported previous reports that schizophrenia and major depressive disorder may overlap in pathogenesis.30 Carroll et al16 have reported that rs3746544 showed a nominal association significance with schizophrenia in a UK population via a mutation screening and genotyping (P = .004, OR = 1.2).16 Feng et al27 reported a significant association between the rs3746544 SNP as well as the haplotype transmission of 2 polymorphic loci and ADHD in 97 nuclear families. Kim and colleagues31 investigated further polymorphisms and a mutation screening and genotyping (P = .004, OR = 1.2).16

### Table 1. Allele and Genotype Association Analysis of 7 SNPs in SNAP25

<table>
<thead>
<tr>
<th>SNP ID</th>
<th>Allele Frequency</th>
<th>OR (95% CI)</th>
<th>Allelic P Value</th>
<th>Genotype Frequency</th>
<th>Genotypic P Value</th>
<th>H-W Value</th>
<th>Call Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs363039</td>
<td>A</td>
<td>0.510</td>
<td>0.922 (0.817–0.039)</td>
<td>.601</td>
<td>0.265</td>
<td>0.489</td>
<td>0.246</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>0.490</td>
<td>0.922 (0.817–0.039)</td>
<td>.601</td>
<td>0.265</td>
<td>0.489</td>
<td>0.246</td>
</tr>
<tr>
<td></td>
<td>Schizophrenia</td>
<td>.277</td>
<td>0.507 (0.216)</td>
<td>.582</td>
<td>.941</td>
<td>.582</td>
<td>.941</td>
</tr>
<tr>
<td></td>
<td>MDD</td>
<td>.281</td>
<td>0.514 (0.205)</td>
<td>.824</td>
<td>.288</td>
<td>.824</td>
<td>.288</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>.277</td>
<td>0.507 (0.216)</td>
<td>.582</td>
<td>.941</td>
<td>.582</td>
<td>.941</td>
</tr>
</tbody>
</table>

### Table 2. Haplotype Association Results for SNAP25 in Case-Control Samples

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Schizophrenia</th>
<th>MDD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(case frequency)</td>
<td>(control frequency)</td>
</tr>
<tr>
<td>rs362549-A-G-A</td>
<td>.153</td>
<td>.139</td>
</tr>
<tr>
<td>rs362998-A-G-G</td>
<td>.419</td>
<td>.446</td>
</tr>
<tr>
<td></td>
<td>G-A-G</td>
<td>.219</td>
</tr>
<tr>
<td>rs378278-A-G</td>
<td>.235</td>
<td>.201</td>
</tr>
<tr>
<td>rs3746544-T-C</td>
<td>.194</td>
<td>.218</td>
</tr>
<tr>
<td></td>
<td>G-G</td>
<td>.044</td>
</tr>
<tr>
<td></td>
<td>G-T</td>
<td>.526</td>
</tr>
</tbody>
</table>

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Abbreviations: H-W = Hardy-Weinberg equilibrium, MDD = major depressive disorder, OR = odds ratio, SNP = single-nucleotide polymorphism.
SNAP25 Association With Schizophrenia and MDD

In this study, we genotyped a large sample set, which ensured that our data would be reliable. Our data demonstrated that only rs3746544 was significantly associated with schizophrenia ($P = .00257$, after correction). The meta-analysis $P$ value for rs3746544, based on combining the results from this study and published results, was .002, suggesting robust association of rs3746544 with schizophrenia, further supporting the hypothesis that SNAP25 might be potential susceptibility genes for schizophrenia. We reported that rs3746544, which is located in the 3′ untranslated region (3′UTR) of the SNAP25 gene, affected the binding of microRNAs (mirSNPs). mirSNPs are a novel class of functional SNPs, which are located either in the gene of the microRNA or in the target mRNA. MirSNPs can alter the interaction between a microRNA and large genes to modulate homeostatic protein levels, resulting in phenotypical changes, such as diseases. To predict rs3746544 polymorphism effects on microRNA binding splicing, we employed mirSNPs finder software (http://www.bioguo.org/miRNASNP/), which enabled the investigation of the predicted target gain and loss due to SNPs in microRNA seed regions or in target mRNA 3′UTRs. We found that hsa-mir-3617 and SNAP25 produced miRNA/SNP target duplexes if the rs3746544 allele was T (Figure 4). Previous studies have demonstrated a decrease of SNAP25 expression in the hippocampus of schizophrenia patients. We speculated that the aberrant expression in schizophrenia may be caused by hsa-mir-3617 silencing of SNAP25 expression via the generation of microRNA binding sites. However, further functional studies are required to authenticate the role of hsa-mir-3617 and the T allele of rs3746544 in schizophrenia.

We also found that rs3787283 was significantly associated with major depressive disorder ($P = .00387$, after correction). Kim et al. observed that rs3787283 was most significantly associated with ADHD via family-based association test analysis ($P = .002$). They also observed that ADHD with comorbid major depressive disorder may enhance the association observed with SNAP25 among subphenotypes of ADHD. However, to the best of our knowledge, no previous study has investigated the potential involvement of major depressive disorder susceptibility. Thus, we speculated that potential functional mutations near this marker should be explored and then tested for their association with major depressive disorder.

In the analysis of haplotypes, significant associations with schizophrenia and major depressive disorder were also found in haplotypes of rs3787283-rs3746544, which covered the large part of the tested region. According to the study, the haplotype linkage disequilibrium test has a higher power and is more robust than the corresponding single-marker linkage disequilibrium tests; our results suggested that the rs3787283-rs3746544 might encompass the susceptibility disorder, but not with a late-onset subgroup. Taken together, these data indicated that the risk loci within SNAP25 region might contribute to the genetics risk shared by different psychiatric disorders.
variants for schizophrenia and major depressive disorder.\textsuperscript{36,37} This result was consistent with a report by Carroll et al,\textsuperscript{16} in which they found strong linkage disequilibrium between rs3787283 and rs3746544 within SNAP25, which was associated with schizophrenia in the United Kingdom.

Taken together, our results indicate that SNPs and haplotype within the SNAP25 gene were significantly associated with schizophrenia and major depressive disorder in the Han Chinese population. Further studies using a larger sample size are suggested to validate our findings.

**Author affiliations:** Department of Psychiatry, the First Teaching Hospital of Xinjiang Medical University, Urumqi (Drs Q. Wang, Shi, and Yi); Bio-X Institutes, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders (Ministry of Education) (Drs Q. Wang, He, Z. Li, Chen, W. Li, Wen, Shen, and Shi and Mss Qiang and Ji); Institute of Social Cognitive and Behavioral Sciences (Drs Q. Wang, He, Z. Li, Chen, Shi, and Yunggang Wang); Prenatal Diagnosis Center, International Peace Maternity and Child Health Hospital (Dr Yunggang Wang); Institute of Neuropsychiatric Science and Systems Biological Medicine (Dr Shi); and Department of Neurology, Renji Hospital, School of Medicine (Dr Yunggang Wang), Shanghai Jiao Tong University; Key Laboratory of Molecular Medicine, Ministry of Education, Department of Biochemistry and Molecular Biology, Institutes of Biomedical Sciences, Shanghai Medical College, Fudan University, (Dr Yulin Wang); Shanghai Changning Mental Health Center (Drs Ji and Shi); Shanghai Changning Beixinjing Street Community Health Service Center (Dr Zhou); Shanghai Institute of Mental Health (Dr Chen), Shanghai; and Key Laboratory of Ministry of Education for Conservation and Utilization of Special eBiological Resources in the Western, and College of Life Science, Ningxia University, Yinchuan, Ningxia (Dr Yujiong Wang), P.R. China.

**Author contributions:** Drs Q. Wang, Yulin Wang, Ji, and Zhou contributed equally to this work. The 3 primary investigators for this study, Drs Shi (shiyongyoung@gmail.com), Yi (13079911689@126.com), and Yunggang Wang (w100yg@163.com), all contributed equally and should be considered as authors to have responsibility for this article. Actual contributions of each author are listed as follows—study concept and design: Drs Shi, Yi, and Q. Wang; analysis and interpretation of data: Drs Ji, Zhou, Z. Li, Wen, Shen, and Qiang and Ma Ji; drafting of the manuscript: Drs Q. Wang, Yulin Wang, and Ji; critical revision of the manuscript: Drs Shi, Yi, and Yunggang Wang; statistical analysis: Drs Yulin Wang, He, Chen, W. Li, and Yujiong Wang; obtaining of funding: Drs Shi and Yi; and study supervision: Dr Shi.

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**Figure 3. Forest Plot of Meta-Analysis for rs3746544 [G] (risk allele)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio</th>
<th>Upper Limit</th>
<th>Lower Limit</th>
<th>Z Value</th>
<th>P Value</th>
<th>Odds Ratio and 95% CI</th>
<th>Relative Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musil et al,\textsuperscript{38} 2008</td>
<td>0.869</td>
<td>1.287</td>
<td>0.586</td>
<td>−0.702</td>
<td>.483</td>
<td></td>
<td>9.19</td>
</tr>
<tr>
<td>Golimbet et al,\textsuperscript{39} 2010</td>
<td>1.275</td>
<td>2.355</td>
<td>0.690</td>
<td>0.776</td>
<td>.438</td>
<td></td>
<td>3.78</td>
</tr>
<tr>
<td>Lochman et al,\textsuperscript{40} 2013</td>
<td>1.146</td>
<td>1.728</td>
<td>0.760</td>
<td>0.650</td>
<td>.515</td>
<td></td>
<td>8.44</td>
</tr>
<tr>
<td>Carroll et al,\textsuperscript{16} 2009</td>
<td>1.251</td>
<td>1.565</td>
<td>1.000</td>
<td>1.960</td>
<td>.050</td>
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<td>28.40</td>
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<tr>
<td>Current study</td>
<td>1.274</td>
<td>1.508</td>
<td>1.077</td>
<td>2.823</td>
<td>.005</td>
<td></td>
<td>50.19</td>
</tr>
<tr>
<td>Total</td>
<td>1.213</td>
<td>1.367</td>
<td>1.077</td>
<td>3.171</td>
<td>.002</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Decreased Risk Increased Risk

**Figure 4. The Allele of rs3746544 Gain miRNA/SNP Target Duplexes**

<table>
<thead>
<tr>
<th>SNP in gene</th>
<th>miRNA</th>
<th>SNP location and Target site on UTR</th>
<th>Energy change (kcal/mol)</th>
<th>miRNA/SNP-target duplexes</th>
<th>Effect by SNP on 3’UTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNAP25; rs3746544 (G/J)</td>
<td>hsa-miR-3617</td>
<td>239 222-245 Wild: 0.00 SNP: −20.80</td>
<td>ggguAGAAAGUUGA-UACAGAa5’</td>
<td>miRNA: 3’gguAGAAAGUUGA-UACAGAa5’</td>
<td>\</td>
</tr>
<tr>
<td>hsa-miR-3617</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>gain</td>
</tr>
</tbody>
</table>

Abbreviation: OR = odds ratio.

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**Table 3. Meta-Analysis of 5 Population-Based Association Studies Between Schizophrenia and rs3746544**

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Population</th>
<th>Cases, n</th>
<th>Controls, n</th>
<th>A-Allele Frequencies</th>
<th>P Value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musil et al,\textsuperscript{38} 2008</td>
<td>Caucasian</td>
<td>162</td>
<td>312</td>
<td>0.360</td>
<td>0.390</td>
<td>.483</td>
</tr>
<tr>
<td>Golimbet et al,\textsuperscript{39} 2010</td>
<td>Caucasian</td>
<td>66</td>
<td>136</td>
<td>0.378</td>
<td>0.324</td>
<td>.438</td>
</tr>
<tr>
<td>Lochman et al,\textsuperscript{40} 2013</td>
<td>Czech</td>
<td>192</td>
<td>213</td>
<td>0.360</td>
<td>0.330</td>
<td>.515</td>
</tr>
<tr>
<td>Carroll et al,\textsuperscript{16} 2009</td>
<td>UK</td>
<td>650</td>
<td>712</td>
<td>0.370</td>
<td>0.320</td>
<td>.050</td>
</tr>
<tr>
<td>Current study</td>
<td>Chinese</td>
<td>1,330</td>
<td>1,520</td>
<td>0.281</td>
<td>0.235</td>
<td>.005</td>
</tr>
</tbody>
</table>

Total | 2,400 | 2,893 | 0.320 | 0.284 | .002 | 1.213 (1.077–1.367) |

\textsuperscript{a}Heterogeneity analysis: $\chi^2 = 3.270$, $P = .514$, $I^2 = 0.000$.

Abbreviation: OR = odds ratio.
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