Association of ARHGAP18 polymorphisms with schizophrenia in the Chinese-Han population

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Abstract

Numerous developmental genes have been linked to schizophrenia (SZ) by case-control and genome-wide association studies, suggesting that neurodevelopmental disturbances are major pathogenic mechanisms. However, no neurodevelopmental deficit has been definitively linked to SZ occurrence, likely due to disease heterogeneity and the differential effects of various gene variants across ethnicities. Hence, it is critical to examine linkages in specific ethnic populations, such as Han Chinese. The newly identified RhoGAP ARHGAP18 is likely involved in neurodevelopment through regulation of RhoA/C. Here we describe four single nucleotide polymorphisms (SNPs) in ARHGAP18 associated with SZ across a cohort of >2000 cases and controls from the Han population. Two SNPs, rs7758025 and rs9483050, displayed significant differences between case and control groups both in genotype (\( P = 0.0002 \) and \( P = 7.54 \times 10^{-6} \)) and allelic frequencies (\( P = 4.36 \times 10^{-5} \) and \( P = 5.98 \times 10^{-7} \)), respectively. The AG haplotype in rs7758025−rs9385502 was strongly associated with the occurrence of SZ (\( P = 0.0012, \ OR = 0.67, \ 95\% \ CI = 0.48–0.93 \)), an association that still held following a 1000-times random permutation test (\( P = 0.022 \)). In an independently collected validation cohort, rs9483050 was the SNP most strongly associated with SZ. In addition, the allelic frequencies of rs12197901 remained associated with SZ in the combined cohort (\( P = 0.021 \)), although not in the validation cohort alone (\( P = 0.251 \)). Collectively, our data suggest the ARHGAP18 may confer vulnerability to SZ in the Chinese Han population, providing additional evidence for the involvement of neurodevelopmental dysfunction in the pathogenesis of schizophrenia.

Introduction

Schizophrenia (SZ) is among the most severe and difficult to treat psychiatric disorders due to variable expression of psychotic symptoms, mood deregulation, and cognitive dysfunction[1].
There is also considerable heterogeneity in disease heritability, implying that SZ arises from a complex interaction of multiple genetic susceptibility factors; thus, there is no unified pathogenic model [2]. Compelling evidence points to disturbances in neurodevelopment during the prenatal and early postnatal periods that impact brain maturation during adolescence and early adulthood, ultimately leading to the delayed emergence of psychiatric symptoms [3]. It is thus believed that different allelic combinations of neurodevelopmental genes (haplotypes) may predispose individuals to SZ and other major psychiatric disorders [4, 5].

Neurodevelopmental abnormalities may result from prenatal immune activation [6], alimentary deficiency [7], and genetic factors. Indeed, multiple genetic factors have been linked to schizophrenia susceptibility [8–10], including genes associated with Rho GTPase signaling pathways [11]. Rho GTPase activating proteins (RhoGAPs) are a large protein family containing approximate 80 members that stimulate GTP hydrolysis, thereby turning the GTP-bound active form of Rho into a inactive GDP-bound form [12, 13]. The Rho family GTPase play a critical role in many aspects of neuronal development, including neurite outgrowth [14, 15], neuronal differentiation [14], axon guidance [15–17], and synaptic formation and maintenance [18,19]. Likewise, many RhoGAP proteins have been linked to neurodevelopmental processes and related disabilities. For example, oligophrenin-1 encodes a RhoGAP involved in X-linked mental retardation [20, 21]. Recently, dysfunction of RhoGAPX-1 and ARHGAP6 has been implicated in a wide range of developmental defects seen in microphthalmia with linear skin defects syndrome[22, 23], while srGAP1, srGAP2, and srGAP3 have been linked to mental retardation, schizophrenia, and seizures [24]. Considering the functional redundancy of many RhoGAP proteins, these findings suggest that additional family members are also involved in pathological conditions related to aberrant neurodevelopment.

ARHGAP18 is a newly identified RhoGAP capable of regulating RhoA and RhoC activities in a cell type-specific context [25, 26]. Although the functions of ARHGAP18 in the central nervous system are presently unknown, recent studies have shown a potential correlation between genetic polymorphisms of ARHGAP18 and the occurrence of schizophrenia. Through the combinatorial use of a genome-wide screening and neuroimaging, single nucleotide polymorphisms (SNPs) within ARHGAP18 were associated with schizophrenia [27, 28]. However, these studies were based on Western populations and not validated in an independent case-control study. Herein, we evaluated the association of ARHGAP18 polymorphisms and schizophrenia in a large Chinese Han population of SZ patients and matched controls.

Materials and methods

Subjects

All participants were recruited from northern Henan Province and had four biological grandparents of Han Chinese ancestry. The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition IV (DSM-IV) (1994) Axis I Disorders was used to exclude individuals with a history of severe medical complications (such as diabetes, cardiovascular disease, hypertension), organic brain diseases, concomitant major psychiatric disorders, and/or substance dependence. The discovery cohort consisted of 528 patients (264 males and 264 females; mean age: 27.32 ± 8.03 years old) and 528 healthy controls matched for sex ratio, age, and ethnicity (264 males and 264 females; mean age: 27.73 ± 8.01 years old). The validation cohort consisted of 860 patients (430 males and 430 females; mean age: 28.34 ± 9.25 years old) and 860 healthy matched controls (430 males and 430 females; mean age: 29.58 ± 7.29 years old). For each patient, the diagnosis of SZ was confirmed by at least two psychiatrists according to the DSM-IV criteria for paranoid SZ. All healthy volunteers were recruited from Xinxiang Medical University, Xinxiang city, and surrounding communities and villages by
posters in Physical Examination Center and hospitals in towns and counties. Any individual with a personal or family history of mental or neurological diseases was excluded. The controls were well matched to the patient group for gender ratio (1:1 for both groups), age ($F = 0.621$, $P = 0.464$), and ethnicity (all unrelated, living in North Henan Province, and with all biological grandparents of Chinese-Han ancestry).

Written informed consent was obtained for all participants. The study was approved by the ethics committee of the Second Affiliated Hospital of Xinxiang Medical University.

**Genotyping**

A peripheral blood sample was drawn from each subject into vacutainer tubes containing the anticoagulant ethylenediaminetetraacetic acid. Genomic DNA was extracted from leukocytes using the RelaxGene Blood DNA System (Tiangen Biotech., Beijing, China). In the discovery stage, the genotypes of 35 SNPs in *ARHGAP18* were evaluated using the Illumina GoldenGate assay on a BeadStation 500G Genotyping System (Illumina, Inc., San Diego, CA, USA) according to the manufacturer’s instructions.

Validation of specific SNPs, including rs9483050, rs7758025, rs12197901, and rs9492347, was performed using the TaqMan genotyping method according to the manufacturer’s protocol, with allelic discrimination and analysis performed on an ABI Prism 7900 Sequence Detection System (Applied Biosystems, Foster City, CA, USA). The ABI Taqman probe sequences are listed in S1 Table. To evaluate the quality of genotyping, 5% of the samples were randomly selected and re-genotyped. The genotyping consistency rate was more than 98%.

**Bioinformatics analyses**

All genotype data were examined for cluster separation using Illumina quality scores generated by the software. Poorly performing SNPs as defined by a GenTrain score $< 0.4$ or a cluster separation score $< 0.6$ were excluded. SNPs were further excluded if controls were not in Hardy—Weinberg equilibrium. As a genotyping quality control, four SNPs were genotyped in duplicate in 100 samples by DNA sequencing.

Genotypes and allele frequencies in SZ and control subjects were compared using the Haploview V4.1 program with Bonferroni correction to exclude type I errors (including from other SNPs in the same GoldenGate 384 assay relevant to a different experimental design). Hardy—Weinberg equilibrium was also evaluated using this program,. The standardized measures of linkage disequilibrium (LD) coefficients ($D^*$), haplotype frequency, haplotype block, and haplotype association were assessed using Haploview V4.1.

Allele and genotype counts were compared by the Pearson chi-square test. A power analysis was performed using the Genetic Power Calculator[29]. Genotyping data (include other SNPs in the same GoldenGate 384 assay relevant to a different experimental design) were analyzed using the Markov chain Monte Carlo algorithm in Structure 2.3 [30] to generate population stratification assignments for all individuals. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated to evaluate the effect of different alleles and haplotypes on SZ risk. The haplotype frequencies were estimated using the expectation maximization (EM) algorithm.

**Results**

We selected a total of thirty-five SNPs in *ARHGAP18* for genotypic distribution analysis in 528 patients with schizophrenia and 528 healthy controls. All SNPs evaluated demonstrated a minor allele frequency greater than 5% in the studied samples. Power analysis revealed that the total sample size ($n = 1056$) had the power (0.86) to detect a small ($r = 0.1–0.23$) effects and the
### Table 1. Genotype and allele frequencies of thirty-two SNPs in the ARHGAP18 gene of schizophrenia patients and controls.

| SNP# | dbSNP ID   | Allele(D/d)a | Patients | Genotype | MAF | Controls | Genotype | MAF | P-value |
|------|-------------|---------------|----------|----------|-----|----------|----------|-----|---------|
|      |             |               | n<sup>b</sup> | HWE(P)  |     | n<sup>b</sup> | HWE(P)  |     |         |
| 1    | rs6569610   | A/T           | 527       | 0.931   | 304 | 0.240 | 527       | 0.109 | 0.246 | 0.524 |
| 2    | rs9492347   | A/G           | 528       | <0.001  | 480 | 0.052 | 528       | 0.821 | 0.066 | 0.011 |
| 3    | rs6923483   | A/G           | 527       | 0.451   | 262 | 0.300 | 527       | 0.646 | 0.275 | 0.456 |
| 4    | rs4895852   | G/A           | 527       | 0.719   | 178 | 0.416 | 527       | 0.908 | 0.445 | 0.371 |
| 5    | rs7758025   | G/A           | 528       | 0.041   | 417 | 0.116 | 528       | 0.213 | 0.065 | 0.0002 |
| 6    | rs9385502   | G/A           | 527       | 0.203   | 277 | 0.268 | 527       | 0.305 | 0.278 | 0.841 |
| 7    | rs9402145   | A/G           | 528       | 0.445   | 390 | 0.138 | 528       | 0.708 | 0.144 | 0.663 |
| 8    | rs3813366   | A/G           | 527       | 0.950   | 139 | 0.486 | 527       | 0.436 | 0.450 | 0.216 |
| 9    | rs1705716   | A/G           | 514       | <0.001  | 383 | 0.163 | 512       | <0.001 | 0.164 | 0.514 |
| 10   | rs9483048   | A/T           | 525       | 0.970   | 207 | 0.372 | 528       | 0.671 | 0.354 | 0.647 |
| 11   | rs1173915   | C/A           | 528       | 0.852   | 359 | 0.176 | 528       | 0.364 | 0.196 | 0.370 |
| 12   | rs9483050   | A/G           | 528       | 0.194   | 379 | 0.157 | 528       | 0.551 | 0.086 | 0.754 |
| 13   | rs12216321  | A/G           | 525       | <0.001  | 429 | 0.114 | 525       | <0.001 | 0.108 | 0.344 |
| 14   | rs13193932  | C/G           | 528       | <0.001  | 97  | 0.449 | 528       | <0.001 | 0.454 | 0.099 |
| 15   | rs12197901  | A/G           | 528       | 0.339   | 364 | 0.173 | 528       | 0.452 | 0.137 | 0.082 |
| 16   | rs9388722   | A/G           | 527       | 0.336   | 158 | 0.462 | 528       | 0.296 | 0.448 | 0.296 |
| 17   | rs10499164  | G/A           | 528       | 0.011   | 456 | 0.075 | 528       | 0.447 | 0.083 | 0.438 |
| 18   | rs9388723   | A/G           | 527       | 0.889   | 288 | 0.260 | 528       | 0.169 | 0.287 | 0.256 |
| 19   | rs765511    | A/G           | 528       | 0.378   | 489 | 0.037 | 526       | 0.924 | 0.046 | 0.433 |
| 20   | rs1202304   | C/A           | 526       | 0.995   | 481 | 0.044 | 528       | 0.224 | 0.050 | 0.393 |
| 21   | rs6928167   | G/A           | 527       | 0.050   | 160 | 0.469 | 528       | 0.427 | 0.447 | 0.445 |
| 22   | rs11968342  | G/C           | 528       | 0.165   | 418 | 0.107 | 527       | 0.863 | 0.119 | 0.413 |
| 23   | rs10872345  | A/G           | 528       | 0.507   | 236 | 0.327 | 528       | 0.325 | 0.304 | 0.503 |
| 24   | rs9398917   | G/A           | 528       | 0.832   | 323 | 0.217 | 528       | 0.385 | 0.185 | 0.153 |
| 25   | rs1476042   | C/A           | 528       | 0.160   | 175 | 0.438 | 528       | 0.524 | 0.402 | 0.097 |
| 26   | rs11962358  | A/G           | 527       | 0.417   | 211 | 0.374 | 527       | 0.783 | 0.400 | 0.432 |
| 27   | rs17467757  | G/A           | 527       | 0.452   | 400 | 0.131 | 528       | 0.481 | 0.132 | 0.998 |
| 28   | rs763132    | A/C           | 527       | 0.783   | 191 | 0.400 | 528       | 0.143 | 0.415 | 0.569 |
| 29   | rs17057659  | G/A           | 527       | 0.408   | 285 | 0.269 | 528       | 0.396 | 0.282 | 0.813 |
| 30   | rs6917887   | G/A           | 527       | 0.924   | 183 | 0.410 | 528       | 0.106 | 0.413 | 0.554 |
| 31   | rs11154495  | C/A           | 527       | 0.274   | 242 | 0.330 | 528       | 0.647 | 0.328 | 0.899 |
| 32   | rs3752536   | G/A           | 521       | 0.052   | 324 | 0.221 | 525       | 0.859 | 0.212 | 0.322 |
| 33   | rs17057685  | C/A           | 528       | 0.323   | 291 | 0.263 | 528       | 0.453 | 0.287 | 0.480 |
| 34   | rs11154496  | G/A           | 528       | 0.425   | 446 | 0.080 | 528       | 0.020 | 0.078 | 0.149 |
| 35   | rs9402163   | C/G           | 527       | 0.231   | 351 | 0.189 | 528       | 0.676 | 0.167 | 0.381 |

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<sup>a</sup> Major/minor allele, major and minor alleles are denoted by D and d, respectively.

<sup>b</sup> Number of samples which are well genotyped.

<sup>c</sup> The significance of bold values is p<0.05.

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The genotype and allelic frequencies of two SNPs, rs7758025 and rs9483050 displayed significant differences between the case and control groups (rs7758025: genotype P = 0.0002;
allele $P = 4.36 \times 10^{-5}$; rs9483050: genotype $P = 7.54 \times 10^{-6}$; allele $P = 5.98 \times 10^{-7}$). In addition, rs9492347 genotype frequency was associated with schizophrenia ($P = 0.011$) as was rs12197901 allelic frequency ($P = 0.022$). The genotypic distribution of these four SNPs did not demonstrate significant deviations from Hardy–Weinberg equilibrium in the control group.

We next performed LD analysis using pairs of SNPs to further analyze the haplotype structure. As shown in Fig 1, Table 2, the LD plot consisted of thirty-five SNPs. Haplotypes GG and GA in the LD block rs7758025–rs9385502 showed minimal difference between the case and control groups ($P = 0.175$ and $P = 0.232$, respectively), while haplotype AG was strongly associated with schizophrenia ($P = 0.0012$, OR = 0.67, 95% CI = 0.48–0.93). These associations

![Fig 1. LD structure and the D' values for the 31 Single Nucleotide Polymorphisms (SNPs).](https://doi.org/10.1371/journal.pone.0175209.g001)

### Table 2. Haplotype analysis among SZ and controls.

| Haplotype* | Haplotype frequenciesb | $\chi^2$ | $P$-valuec | OR (95% CI) |
|------------|------------------------|---------|-----------|------------|
| rs7758025–rs9385502 |                       |         |           |            |
| GG | 666.6(63.1) | 696.4(65.9) | 1.837 | 0.175 | 1.00 |
| GA | 266.4(25.2) | 290.6 (27.5) | 1.429 | 0.232 | 1.06 (0.86–1.30) |
| AG | 106.8(10.1) | 66.0(6.3) | 10.489 | 0.0012(0.022) | 0.67 (0.48–0.93) |
| rs11753915–rs9483050 |                       |         |           |            |
| CA | 716.8(67.9) | 760.6(72.0) | 4.323 | 0.038 | 1.00 |
| AA | 173.2(16.4) | 204.4(19.4) | 3.138 | 0.077 | 1.12 (0.88–1.41) |
| CG | 153.2(14.5) | 88.4(8.4) | 19.628 | $9.6 \times 10^{-6}$ (0.0001) | 0.58 (0.44–0.78) |

*Haplotypes were omitted from analysis if the estimated haplotype probabilities were less than 5%.

b Frequencies are shown in parenthesis (%).

c $P$ values in the parenthesis were analyzed with 1000 random permutations, Global haplotype association $P$-value all <0.0001.

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remained following a 1000-times random permutation test \((P = 0.022)\). Haplotype CG in the LD block rs11753915−rs9483050 was also associated with schizophrenia \((P = 9.6 \times 10^{-6}, \text{OR} = 0.58, 95\% \text{CI} = 0.44−0.78)\) even after Bonferroni correction \((P = 0.0001)\).

We then re-tested the four \(\text{ARHGAP18}\) SNPs associated with schizophrenia in an independent validation cohort of 860 patients and 860 controls. In stage 2, the ample size gets a high power \((0.93)\). As shown in Table 3, both genotype and allelic frequencies of rs7758025 and rs9483050 SNPs displayed strong associations with schizophrenia in the validation cohort. Of note, rs9483050 appeared most strongly associated with the disease state across the two cohorts. In addition, the allelic frequency of rs12197901 remained associated with schizophrenia in the combined analysis \((P = 0.021)\), although not in the validation cohort alone \((P = 0.251)\). The trends observed for the association of rs9492347 with SZ were not confirmed in the validation cohort or combined analysis.

**Discussion**

Herein, we describe associations between \(\text{ARHGAP18}\) polymorphisms and schizophrenia in a Chinese Han population. In stage one, we screened SNPs in \(\text{ARHGAP18}\) from GWAS data, and discovered four SNPs, rs7758025, rs9483050, rs9492347 and rs12197901, associated with schizophrenia. In stage two, we validated our findings in an independent cohort and demonstrated that rs9483050 is strongly associated with schizophrenia. Our data suggest that allelic variation in the \(\text{ARHGAP18}\) gene may confer vulnerability to SZ in the Chinese Han population, providing additional evidence for the involvement of disrupted neurodevelopmental signals in disease pathogenesis.

Although the detailed molecular events during SZ progression remain elusive, it is widely accepted that abnormalities in early brain development caused by inherited genetic variants alter critical developmental and maturational processes, resulting in eventual emergence of disabling psychoses[31–33]. A plethora of genes have polymorphisms associated with SZ [9, 34–38]. Nevertheless, due to complexity of epidemiology, including ethnicity and disease

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**Table 3. SNP association analysis for ARHGAP18 in stage 2 and combined sample set.**

| Stage | dbSNP ID | Allele (D/d)a | n\(^b\) | Patients | Controls | P-value |
|-------|----------|---------------|---------|----------|----------|---------|
|       |          |               |         | Genotype | Genotype |
|       |          |               |         | MAF      | MAF      |
|       |          |               |         | n\(^b\) | HWE(P)   | Genotype | MAF      |
|       |          |               |         |         |          |          |
|       |          |               |         | DD      | DD      |         |         |
|       |          |               |         | Dd      | Dd      |         |         |
|       |          |               |         | dd      | dd      |         |         |

\(a\) Major/minor allele, major and minor alleles are denoted by D and d, respectively.  
\(b\) Number of samples which are well genotyped.

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subtype, our understanding of disease heritability remains limited and it is likely that many more SZ susceptibility genes remain to be identified.

ARHGAP18 (6q22.33) lies within a previously reported SZ candidate region (SCR) identified by Lerer et al [39], in an ethnically homogeneous family-based Arab—Israeli sample [27, 28]. There are 134 genes in this risk region, of which several contain SNPs enriched in sporadic SZ cases, such as dystrobrevin-binding protein 1 (DTNBP1) and laminin alpha-2 (LAMA2). Given the large genomic distance spanned and the difference in localization of linkage peaks, it is possible that this region harbors additional SZ susceptibility genes, one of which may be ARHGAP18. In fact, there are several reports on the involvement of ARHGAP18 SNPs in human diseases, including SZ. Recurrent chromosomal imbalances affecting the ARHGAP18 locus were observed in six of nine patients with neurofibromatosis type 1 [40]. Also, Potkin et al. used brain activation pattern during a working memory task as a quantitative trait to interpret GWAS data and identified ARHGAP18 as a SZ risk gene [27]. Specifically, they found six SNPs within ARHGAP18, rs12664247, rs4509146, rs11154490, rs2051632, rs17469847 and rs10484284, with statistically significant relationships in both the discovery and validation cohorts.

Herein, we used large discovery and validation cohorts to identify the rs9492347, rs7758025, and rs9483050 SNPs of ARHGAP18 as susceptibility loci for SZ. Our results are intriguing in several ways. First, these SNPs were not associated with SZ in GWASs interrogating ARHGAP18, although those studies did not use the sample SNP panel studied here. Also, the number of included samples in our study is much higher than previous studies on ARHGAP18 SNPs. Moreover, our study extends the risk of SZ conferred by ARHGAP18 SNPs from Western populations to the Eastern Han population.

ARHGAP18 encodes one of approximately 80 RhoGAP proteins [12, 13]. As a RhoGAP, ARHGAP18 mainly serves as a molecular switch for controlling the balance between active and inactive Rho proteins to regulate Rho-mediated signaling pathways. Rho GTPases, a protein family composed of 22 members in mammals, are known as important modulators of the actin cytoskeleton influencing neuronal morphology and migration [41, 42]. In addition, Rho GTPases are also reportedly involved in the regulation of growth factor-linked signal pathways.

Among members of the Rho GTPase family, RhoA is the main molecule responding to ARHGAP18 regulation. ARHGAP18-knockdown cells demonstrated impaired cell spreading, premature formation of stress fibers, and sustained activation of RhoA upon cell attachment, resulting in inhibition of cell migration [25, 26]. Although the neurodevelopmental function of ARHGAP18 has not been elucidated, numerous studies have suggested a critical role for RhoA in neurogenesis and maturation [43–46]. Abolishing RhoA activity in the postnatal stage led to major changes in density and absolute number of neurons in the somatosensory cortex [47]. Also, deletion of RhoA from neural progenitor cells in mice resulted in abnormal locomotor behavior [48, 49]. Of note, all three identified SNPs are located in the intron region, which is common for most top hit SZ-associated SNPs revealed by GWASs. The presence of these intronic SNPs may regulate ARHGAP18 mRNA splicing in a trans-acting manner, thereby leading to malfunction of the ARHGAP18–RhoA axis in neurodevelopment.

Conclusion

In summary, our study provides novel data suggesting an association between ARHGAP18 and SZ susceptibility. Replication studies in different ethnic populations, particularly in patients with defined SZ phenotypes, and more samples, are required to confirm the role of ARHGAP18 variants in SZ.
Supporting information
S1 Table. Taqman probe sequences of four SNPs.

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