

## **RGS4 Polymorphisms Associated With Variability of Cognitive Performance in a Family-Based Schizophrenia Sample**

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**Polymorphisms of the gene encoding the regulator of G protein signaling, subtype 4 (*RGS4*), may be associated with schizophrenia. Among first-episode schizophrenia patients, they are also associated with dorsolateral prefrontal cortex (DLPFC) volume. The DLPFC is a key region that regulates heritable cognitive functions implicated in schizophrenia pathogenesis. To further understand the relationship of *RGS4* variants to schizophrenia, we examined their associations with cognitive functions among schizophrenia patients and their relatives. We analyzed 31 multiplex, multigenerational Caucasian families with schizophrenia recruited on the basis of 2 affected first-degree relatives. All participants underwent a computerized neurocognitive battery that evaluates accuracy and speed (response time) of performance on abstraction/mental flexibility; attention; verbal, spatial, and face memory; and spatial ability. “Tag” single-nucleotide polymorphisms (SNPs) representing common polymorphisms were genotyped. Measured genotype analyses accounting for family relationships were performed using Sequential Oligogenic Linkage Analysis Routines. SNPs rs10917670 (“SNP1”) and rs951439 (“SNP7”) were associated with face memory speed ( $P = .0003$ ) at a significance level that survived Bonferroni correction ( $P = .039$ ). The same SNPs have earlier been reported to be associated with schizophrenia. There also were uncorrected associations with rs10917670 (“SNP1”) and rs951439 (“SNP7”) on face memory efficiency ( $P = .03$ ) and verbal memory efficiency ( $P = 0.02$ ), rs28757217 on abstraction/mental flexibility speed ( $P = .02$ ) and verbal memory efficiency ( $P = .03$ ), SNP18 (rs2661319) on spatial memory accuracy**

**( $P = 0.02$ ) and face memory speed ( $P = .03$ ). *RGS4* polymorphisms are associated with variations in cognitive functions and contribute a small but statistically significant proportion of variance in a family-based sample.**

*Key words:* schizophrenia/genetics/cognition/memory

### **Introduction**

The regulator of G protein signaling, subtype 4 (*RGS4*), has been implicated in the etiology and pathogenesis of schizophrenia. *RGS4* is localized to chromosome 1q23.3 in close proximity to a region that showed linkage to schizophrenia in a meta-analysis.<sup>1</sup> Convergent evidence from microarray studies,<sup>2</sup> genetic association studies,<sup>3–8</sup> as well as imaging studies on first-episode, antipsychotic-naïve schizophrenia subjects<sup>9</sup> and healthy subjects<sup>10</sup> also implicate certain *RGS4* variations in the etiology of schizophrenia. On the other hand, some studies on *RGS4* polymorphisms<sup>11,12</sup> have not yielded significant associations. A meta-analysis of 13 studies<sup>13</sup> observed an association of *RGS4* variants with schizophrenia, whereas 2 meta-analyses<sup>14,15</sup> involving smaller subsets of the samples used in the initial meta-analysis did not show an association. Subsequently, an association study involving a comprehensive list of common *RGS4* polymorphisms has been published. It suggests that *RGS4* haplotypes associated with schizophrenia may have promoter activity in vitro, providing a possible functional basis for the genetic associations.<sup>3</sup> The association of some *RGS4* variants with baseline symptom severity and treatment response suggests clinical significance of these variations.<sup>16</sup>

*RGS4* negatively regulates the G protein activation by accelerating the hydrolysis of guanosine triphosphate from  $G\alpha$  to produce guanosine diphosphate and  $P_i$  at the G protein-coupled receptors. This reaction shortens the duration of signal transduction of many neurotransmitters of interest to schizophrenia, such as dopamine, glutamate, serotonin, and  $\gamma$ -aminobutyric acid (GABA). Although it is known that *RGS4* participates in neuronal signal transduction, the precise mechanisms by which *RGS4* variations may confer risk for schizophrenia are unclear.

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A potentially useful approach to clarify such mechanisms is to examine the association of *RGS4* variants with putative intermediate phenotypes of schizophrenia. Cognitive deficits have been consistently demonstrated among individuals with schizophrenia and their first-degree relatives. A meta-analysis of cognitive deficits in schizophrenia found that intelligence, memory, language, executive function, and attention were impaired in patients compared with healthy controls.<sup>17</sup> Some cognitive measures have been suggested as “endophenotypes” or intermediate phenotypes, ie, heritable variables that occur proximal to the clinical syndrome in the chain of pathogenic events.<sup>18</sup> Although there are questions regarding the effect size of genetic variations on endophenotypes relative to the clinical syndrome, they are useful markers to investigate the pathways linking the genotype and the phenotype. Significant heritability of cognitive domains among healthy individuals<sup>19–21</sup> and among schizophrenia patients<sup>22,23</sup> has been documented in several studies. These domains include working memory, accuracy of verbal memory, face memory, spatial processing and emotion identification, and speed of attention and abstraction. Some of these cognitive functions are regulated by the dorsolateral prefrontal cortex (DLPFC), eg, working memory<sup>24</sup> and executive function.<sup>25</sup> Our group has reported an association between decreased volume of the DLPFC among first-episode, antipsychotic-naïve schizophrenia patients and specific *RGS4* polymorphisms.<sup>9</sup> These observations were replicated and extended by a subsequent study.<sup>10</sup> Therefore, a systematic examination of association of *RGS4* variants with cognitive performance could provide insight into the impact of underlying candidate gene variations and provide clues to elucidate the molecular pathways associated with such variations.

Variations in schizophrenia susceptibility genes have been associated with cognitive deficits frequently observed in schizophrenia. An exonic polymorphism (rs4380) on the catechol-*O*-methyltransferase gene (*COMT*) has been associated with executive subprocesses of working memory.<sup>26</sup> This polymorphism leads to the substitution of valine by methionine in the COMT enzyme that results in altered metabolism of synaptic dopamine. Similarly, dysbindin (*dystrobrevin binding protein; DTNBP1*) and disrupted in schizophrenia-1 (*DISC1*) have also been associated with variations in cognitive functions in schizophrenia. A 6-SNP haplotype (CTCTAC) of *DTNBP1* has been observed to correlate with cognitive decline in schizophrenia.<sup>27</sup> *DISC1* variations were associated with performance in verbal working memory and rapid visual search.<sup>28</sup> While these studies have examined the variance contributed by specific variants of a susceptibility gene, none have been comprehensively interrogated for the common polymorphisms at those genes.

We hypothesized that the *RGS4* polymorphisms contribute to the variability of cognitive functions in schizo-

phrenia in line with suggested links between *RGS4* variants and different aspects of schizophrenia pathology outlined above. In this study, we used the quantitative trait approach among multiplex, multigenerational families comprising schizophrenia probands. We reasoned that the quantitative approach among related individuals may enhance the prospects of detecting associations. Thus, we examined the association of common polymorphisms of *RGS4* with variability in cognitive functions in such families and estimated the proportion of variance in selected cognitive functions attributable to polymorphisms in or near *RGS4*.

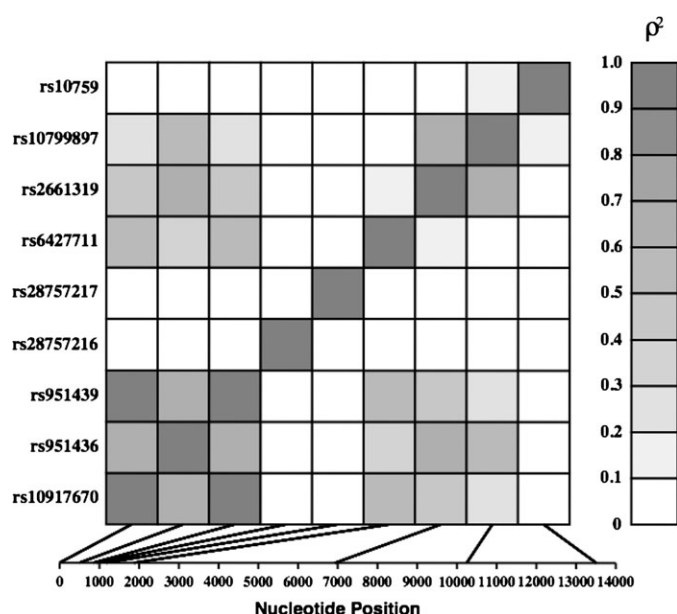
## Methods

### *Clinical Evaluation*

The sample consisted of European Americans from 37 multiplex, multigenerational families, recruited at 2 sites. Details of clinical evaluation are given in our previous publication.<sup>23</sup> Briefly, the Diagnostic Interview for Genetic Studies (version 2.0), the Family Interview for Genetic Studies, and medical records review were used for the psychiatric evaluation. Trained interviewers with established reliability conducted interviews under the supervision of the investigators. Two investigators blind to the subject group reviewed each case independently and provided *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) multiaxial lifetime diagnoses. Consensus diagnosis was reached in diagnostic meetings attended by board-certified psychiatrists/psychologists. Complex cases were discussed between the 2 ascertainment sites. At each site, interrater reliability among investigators and interviewers was tested at regular intervals using videotaped interviews and bi-monthly joint interviews. Kappa values > 0.8 were maintained. After fully explaining the study procedures, we obtained informed consent from all subjects.

### *Genetic Analysis*

Genomic DNA was collected from all consenting subjects. Based on sequencing, linkage disequilibrium (LD) analysis, and our previous observations, we selected 9 representative “tag” SNPs at a correlation threshold of  $r^2 < 0.80$  between loci. In addition, we included the 4 SNPs that were found to be associated with schizophrenia in our previous report.<sup>29</sup> The final list of genotyped SNPs were rs10917670 (“SNP1”), rs951436 (“SNP4”), rs951439 (“SNP7”), rs28757216 (“SNP8”), rs28757217 (“SNP9”), rs6427711, rs2661319 (“SNP18”), rs10799897, and rs10759. The SNPs were genotyped using the SNaPshot assay (SNaPshot, ABI Biosystems Inc, Carlsbad, CA)<sup>30</sup> and were read independently by 2 investigators. To assure quality control, positive controls (determined by sequencing) were included in all assays. No discrepancies were detected between the positive controls across assays.



**Fig. 1.** Linkage Disequilibrium Structure of Regulator of G Protein Signaling, Subtype 4, in the Multiplex, Multigenerational Families.

All SNPs could be genotyped reliably except for SNP4 (rs951436). Therefore, this SNP was not included in the statistical analyses. Two common risk haplotypes have been reported by us and others,<sup>29</sup> namely A-T-A-A and G-G-G-G on SNPs 1, 4, 7, and 18, respectively. SNP4 could not be genotyped reliably in this sample; we encountered failures in the assay in a substantial proportion of subjects.

SNP1 (rs10917670) and SNP4 (rs951436) are in virtually complete LD with SNP 7 (rs951439) and SNP 18 (rs2661319), respectively (figure 1). Therefore, haplotypes were constructed using SNP7 and SNP18 only.

### Neuropsychological Methods

A computerized neurocognitive battery (CNB)<sup>31,32</sup> validated in both subjects with schizophrenia and healthy comparison subjects was used. The CNB includes a training module and automated scoring with direct data downloading. It evaluates 8 domains: abstraction and mental flexibility, spatial memory, attention, spatial processing, verbal memory, sensorimotor dexterity, face memory, emotion processing.

Two performance indices were calculated for each domain: accuracy and speed. In addition, we derived the efficiency of performance in each domain as a ratio between the accuracy and response time (speed). A brief description of each of these tests is given in table 1. Details regarding the test administration and a description of individual tests are provided in our earlier publication.<sup>23</sup>

### Statistical Analyses

Variance component-based quantitative trait analyses were conducted using Sequential Oligogenic Linkage Analysis Routines (SOLAR).<sup>33</sup> SNP genotypes were coded as 0 for heterozygotes, -1 for one homozygote, and 1 for the other homozygote, and maximum likelihood

**Table 1.** Neuropsychological Tests and Cognitive Variables Measured<sup>31,32</sup>

Cognitive Domain	Test	Description
Abstraction and mental flexibility	Penn Conditional Exclusion Test	Four objects are presented at a time, subject selects the object that does not belong with the other 3 based on a sorting principle, sorting principle changes, and the feedback guides further performance
Attention	Penn Continuous Performance Test	Subject responds to a set of vertical and horizontal lines in 7-segment displays represent a digit; uses the continuous performance test paradigm
Verbal memory	Penn Word Memory Test	Twenty target words are presented followed by forced-choice recognition of these words when mixed with 20 distracters. Words are matched for frequency, length, concreteness, and imageability
Face memory	Penn Face Memory Test	Twenty black and white pictures of faces of neutral emotional expression and 40 foils are presented. Immediate and delayed forced-choice recognition of faces
Spatial memory	Visual Object Learning Test	Twenty euclidean shapes are presented followed by immediate and delayed recognition when these shapes are presented along with 40 distracters
Spatial processing	Judgment of Line Orientation	Two lines at an angle are shown, and subjects are asked to identify the corresponding lines in a simultaneously presented array of lines
Emotion processing	Emotion Intensity Discrimination Test	A 40-item test where 2 faces of same emotion are presented. Subject is asked to pick the one with more intense emotion expression
Sensorimotor dexterity	—	Subject is shown squares that progressively get smaller on the computer monitor and asked to click on the squares

<sup>a</sup>Total number of true positive responses and median reaction times are the performance measures.

**Table 2.** Demographic Characteristics of the Study Sample

Demographic Variable	Study Group		Statistics
	Schizophrenia	Relatives	
<i>N</i>	45	282	$\chi^2 = 4.38, df = 1, P = .036$
Sex (male:female)	27:18	122:160	
Age, mean (SD)	45.58 (11.88)	44.40 (18.99)	$t = 0.56, P = .58$
Education, mean (SD)	12.09 (2.30)	12.68 (2.36)	$t = 1.56, P = .12$
Parental education, mean (SD)	11.51 (4.65)	11.07 (3.86)	$t = 0.68, P = .5$

methods, implemented in SOLAR, were used to test whether the trait mean varies by genotype. A model in which a regression parameter for the SNP is estimated was compared with a model in which the parameter is fixed at 0 for a simple 1 *df* likelihood ratio test. Differences in trait value by *RGS4* genotype were assessed with a fixed-effects model, while accounting for nonindependence of family members by modeling covariance among related individuals. Age and sex were included as covariates. The multivariate *t* distribution was used in all analyses because the neurocognitive scores showed significant kurtosis. Heritability for each trait was estimated using maximum likelihood variance component-based methods, implemented in SOLAR, and whether heritability was significantly different from 0 was assessed using a likelihood ratio test. We, first, examined the efficiency of cognitive performance in each domain and then the accuracy and speed measures separately.

LD was estimated as  $\rho^2$  values using unrelated members of the sample (figure 1). In order to examine the haplotype associations, haplotypes were estimated using Simwalk2.<sup>34</sup> These haplotypes were binned such that haplotypes A-A and G-G were considered high risk and haplotypes A-G and G-A low risk, consistent with earlier publications.<sup>3,13,29</sup> We tested for a difference in mean trait values by number of high-risk haplotypes carried. Nominal significance of  $P < .05$  (uncorrected) is reported for most comparisons. Where feasible, corrections for multiple testing were made. The corrections accounted for the number of SNPs and the number of cognitive traits tested.

## Results

The mean age of the sample was  $44.56 \pm 18.16$  years (range 11–85 years). About 46% were males, and 54% were females. Average family size was  $10.51 \pm 8.46$  members per family with a range of 3–32. Table 2 shows the demographic variables of the study sample. The genotypes and complete neuropsychological data together were available for all subjects on 7 SNPs. The genotypes for 2 SNPs (rs951436 and rs10759) were not available for all subjects; therefore, these 2 SNPs were not included in

the analyses. Complete data were available for 327 individuals from 31 families for 7 SNPs (rs10917670 [“SNP1”], rs951439 [“SNP7”], rs28757216 [“SNP8”], rs28757217 [“SNP9”], rs6427711, rs2661319 [“SNP18”], rs10799897).

Among the cognitive functions examined, variability in face memory efficiency and speed, verbal memory efficiency, spatial memory accuracy, and abstraction and mental flexibility speed were associated with *RGS4* polymorphisms. Subjects with schizophrenia who comprised less than 16% of the total sample were included in the analyses. We did not include sensorimotor dexterity in this study because it was not found to be significantly different between the patients and comparison subjects and was not heritable in our previous study on the same dataset.<sup>23</sup> Similarly, verbal memory speed and efficiency and accuracy on abstraction and mental flexibility were not heritable in our samples; therefore, these measures were not included in the analyses.<sup>23</sup>

Among the SNPs examined, SNPs rs10917670 (‘‘SNP1’’), rs951439 (‘‘SNP7’’), rs28757217 (‘‘SNP9’’), rs6427711 and rs2661319 (‘‘SNP18’’) showed nominally significant associations with variability in cognitive functions. Table 3 shows significant associations between the SNPs and the cognitive domains. SNPs rs10917670 (‘‘SNP1’’) and rs951439 (‘‘SNP7’’) were significantly associated with face memory speed ( $P = .0003$ ). The associations with face memory speed survived Bonferroni correction ( $P = .039$ ) (19 traits with 7 markers, total tests 133). Whereas the efficiency measures showed nominally significant associations with these SNPs, the accuracy measures did not. Mean trait values for face memory speed for probands, first-degree relatives, and other relatives were similar across the genotypes of these 2 SNPs (rs10917670 [‘‘SNP1’’] and rs951439 [‘‘SNP7’’]), as expected (CC  $0.81 \pm 0.46$ , CT  $0.60 \pm 1.09$ , and TT  $0.60 \pm 0.88$  for probands; CC  $0.34 \pm 0.87$ , CT  $0.55 \pm 1.13$ , and TT  $0.88 \pm 0.99$  for first-degree relatives; and CC  $0.49 \pm 1.46$ , CT  $0.51 \pm 1.05$ , and TT  $0.61 \pm 1.02$  for second- and third-degree relatives). We also reanalyzed our data based on the ascertainment status, which was based on another affected first-degree relative of the proband. We observed that the face memory speed remained significant ( $P = .01$ ).

**Table 3.** Association of ‘Tag’ SNPs With Cognitive Functions

‘Tag’ SNP	Cognitive Measure	Significance Values for Cognitive Measures		
		Efficiency	Accuracy	Speed
rs10917670 (SNP1)	Face memory	.03	.14	.0003 <sup>a</sup>
	Verbal memory	.02	.09	<sup>b</sup>
rs951439 (SNP7)	Face memory	.03	.14 (NS)	.0003 <sup>a</sup>
	Verbal memory	.02	.09	<sup>b</sup>
rs28757217 (SNP9)	Abstraction/mental flexibility	<sup>b</sup>	<sup>b</sup>	.02
	Verbal memory	.03	.14 (NS)	<sup>b</sup>
rs6427711	Face memory	0.27 (NS)	0.59 (NS)	.005
rs2661319 (SNP18)	Face memory	0.11 (NS)	0.29 (NS)	.03
	Spatial memory	.06	.02	.92 (NS)

*Note:* Traits that showed significant heritability in our previous report (Gur et al<sup>23</sup>) were examined. Note that SNP1 and SNP7 show identical results because the SNPs are in complete linkage disequilibrium. SNP, single-nucleotide polymorphism; NS, not significant.

<sup>a</sup>Survived Bonferroni correction for multiple testing.

<sup>b</sup>These measures were not included in the analysis because these measures were not significantly heritable in our report.

Besides, rs6427711 was nominally associated with face memory speed ( $P = .005$ ). The efficiency of verbal memory showed nominal associations with SNPs rs10917670 (“SNP1”) ( $P = .02$ ), rs951439 (“SNP7”) ( $P = .02$ ), and rs28757217 (“SNP9”) ( $P = .03$ ). Furthermore, rs28757217 (“SNP9”) was also associated with the speed of abstraction/mental flexibility ( $P = .02$ ). We observed similar association with spatial memory accuracy ( $P = .02$ ) for rs2661319 (“SNP18”). These associations did not survive Bonferroni correction for multiple tests.

Haplotype frequencies in this sample were as follows: A-A 35%, G-G 41%, G-A 15%, and A-G 9%. Face memory speed and accuracy were not significantly associated with any haplotype. Verbal memory efficiency and accuracy were negatively correlated with the number of risk haplotypes carried ( $P = .005$  for efficiency and  $.015$  for accuracy). Other cognitive traits did not show significant associations.

We estimated the variance contributed by the associated SNPs to heritability of the traits. After accounting for the effects of age and sex, SNPs 1 and 7 explained an estimated 3.5% of the residual trait variance for face memory speed and 1.4% for face memory accuracy and verbal memory scores. Because SNPs 1 and 7 are in complete LD,<sup>3</sup> the trait variance may be the joint effect of these SNPs or of an unknown functional variant with which these SNPs may be in LD.

## Discussion

We have evaluated a comprehensive set of common *RGS4* polymorphisms in moderately sized, multiplex, multigenerational families with schizophrenia for their associations with selected domains of cognitive function that are heritable and known to be impaired among patients and unaffected relatives. The SNPs included

those previously reported to be associated with schizophrenia<sup>3,4,13</sup> and prefrontal structure and function.<sup>9,10</sup> Using an efficient computerized battery, the accuracy, speed, and efficiency of performance were estimated. Two *RGS4* variants, denoted SNP1 and SNP7, are involved in most of the associations in this study, which include the speed (response time) for face memory, along with suggestive associations for the efficiency of face memory and verbal memory. The findings are notable because these SNPs are also associated with schizophrenia,<sup>3,4,13</sup> and SNP1 showed suggestive associations with the DLPFC volume in a previous study.<sup>9</sup> Because SNP1 (rs10917670) and SNP7 (rs951439) are in complete LD ( $r^2 = 1.0$ ) in this sample (figure 1), identical associations with cognitive performance scores for these SNPs provides internal validation for our observations. A previous study also showed that these 2 SNPs are in strong LD ( $r^2 = 0.96$ ).<sup>3</sup>

Individual SNPs appear to be associated with either accuracy or speed of cognitive traits such as face and verbal memory. It is difficult to say whether the differences reflect LD or whether, as the haplotype analyses suggest, these cognitive traits are influenced by different functional variants in the region. At the individual SNP level, the variants affecting the face memory appear to be in LD with rs951439 (SNP7) alone, whereas verbal memory measures may be affected by putative functional variant(s) in LD with the haplotype comprising rs951439 (“SNP7”) and rs2661319 (“SNP18”). Similarly, the associations of rs6427711 and rs2661319 (SNP18) with face memory may be explained by the LD between these 2 SNPs and SNPs1/7 ( $r^2$  between rs6427711 and SNPs1/7 is 0.53,  $r^2$  between rs2661319 and SNPs1/7 is 0.50).

At present, molecular mechanisms to explain the associations are unknown, but studies such as ours may help elucidate the chain of events leading from *RGS4* variants, through structural changes in certain regions of the brain

and cognitive function, and possibly culminating in the diagnostic entity. The order of the events in our model is speculative at present. For example, it is uncertain if and how the cognitive variations are linked with gray matter volume, though prior studies have suggested associations between these variables.<sup>35</sup> When such relationships are observed, the nature of association between brain structure and cognitive domain is complex.<sup>36</sup> However, functional imaging studies could provide further clues; a recent imaging study showed that rs951436 (“SNP18”) of *RGS4* was associated with blood oxygen level-dependent responses in the frontotemporal and frontoparietal networks during a working memory (n-back) task performance.<sup>10</sup> It is unclear whether such relationships would hold for facial memory, too. Furthermore, the specificity of the association of *RGS4* variations with facial memory requires replication and validation with imaging and electrophysiological studies.

The expression of *RGS4* messenger RNA (mRNA) and protein in the brain is region specific.<sup>37</sup> For example, the prefrontal and some of the medial temporal regions express *RGS4* more densely. Mirnics *et al.*<sup>2</sup> reported underexpression of *RGS4* in the neocortical regions, including the prefrontal cortex among schizophrenia patients. The associated SNPs in the present study contribute to haplotypes that may alter transcription.<sup>3</sup> If prior *in vitro* results mirror an effect of these SNPs on mRNA levels *in vivo*, the associated *RGS4* polymorphisms could impact signal transduction at dopamine, glutamate, serotonin, or some GABA neurons. Abnormalities in these neurotransmitters have been associated with cognitive variations.<sup>38,39</sup> It is unclear whether such relationships would hold for facial memory, too. Furthermore, the specificity of the association of *RGS4* variations with facial memory requires replication and validation with imaging and electrophysiological studies.

The domains of memory and executive functions that showed significant associations in this study have been consistently reported to be impaired among patients with schizophrenia.<sup>17</sup> Previous studies have demonstrated that memory and executive functions are the central components of higher order information processing<sup>40</sup> that may be one of the core deficits observed in schizophrenia. Face and verbal working memory deficits have been consistently identified in patients with schizophrenia and their relatives.<sup>41</sup> For this reason, it is important to investigate the variance contributed by a putative schizophrenia susceptibility gene to variations in cognitive domains. Such efforts could assist in delineating the pathway between these cognitive traits and genetic variations.

The variance contributed to the heritability of cognitive variations by the *RGS4* SNP that is relatively (approximately 3.5%) consistent with a multifactorial causation for these traits. This is a lower bound, and the exact variance depends on the strength of the LD

between the associated SNP and the presumably ungenotyped functional variant(s). Though Bonferroni corrections may be overly conservative, corrections based on effective number of markers did not alter our findings. Replicate studies using adequately powered samples to examine genome-wide associations are needed to not only replicate the present findings with *RGS4* but also account for the rest of the trait variance attributable to genetic factors.

A comprehensive LD map of common SNPs at *RGS4* is now available.<sup>3</sup> We selected the “tag” SNPs for the current studies, based on the LD patterns among Caucasians<sup>3</sup> and in our earlier reported association study among schizophrenia patients.<sup>29</sup> However, reliable genotype data could not be obtained for 2 SNPs in the present sample (rs951436, aka “SNP4”) and rs10759. Of these, rs951436 is in strong LD with rs2661319 (aka SNP18,  $r^2 = 0.88$ ),<sup>3</sup> so rs2661319 was a suitable surrogate for rs951436 using our chosen correlation threshold for tag SNPs and the loss of information is probably not substantial. On the other hand, rs10759 is not in significant LD with any of the other SNPs assayed here. This SNP is localized to the 3′ untranslated region (3′ UTR), and its function is unknown. It was not associated with schizophrenia in our prior analyses.<sup>3</sup>

In summary, polymorphisms of *RGS4* reported to be associated with schizophrenia were also found to be associated with selected heritable cognitive measures known to be impaired among schizophrenia patients. Our results show that the *RGS4* variations were associated with the speed (response time) and accuracy of memory and executive functions. Such findings can help build a model for pathogenesis linking genetic variation, cognitive traits, and the diagnosis. To investigate this model further, multimodal imaging studies on an extended sample are planned. Replication and further molecular analyses of the associations are also warranted.

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