Schizophrenia Bulletin vol. 32 no. 2 pp. 203–208, 2006
doi:10.1093/schbul/sbj058
Advance Access publication on February 9, 2006

Can RGS4 Polymorphisms Be Viewed as Credible Risk Factors for Schizophrenia? A Critical Review of the Evidence

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There has been a recent explosion in the list of putative susceptibility genes for schizophrenia (SZ). These genes have been identified on the basis of presumed pathogenesis, linkage, and genetic association studies. While several promising candidates have arisen, identification of a conclusive genetic risk factor has remained elusive. The proof would be most compelling if it stemmed from all three of these domains. In this review, we consider such evidence in relation to the regulator of G-protein signaling 4 (RGS4), a gene localized to chromosome 1q23. Disorder-specific changes in RGS4 mRNA levels have been observed in post-mortem brain samples; linkage has been reported at chromosome 1q23; and several association studies have concluded that significant associations exist. The latter are supported by a recently conducted meta-analysis. Thus, there is suggestive evidence in each of these domains implicating a role for *RGS4* in SZ susceptibility. However, analogous to other promising susceptibility candidates, the nature of the genetic association, the precise polymorphism(s) conferring risk, and the functional implications of sequence variation at this gene are unclear. We review the published data and place them in the context of suggested criteria for establishing a candidate gene as a credible susceptibility factor for disorders with non-Mendelian patterns of inheritance.

Key words: schizophrenia/genetic risk/RGS4/polymorphisms/association/linkage

Introduction

Following path-breaking family, twin, and adoption studies, it was established that a significant inherited predisposition to schizophrenia (SZ) exists.[1] The precise number and identity of the genetic risk factors for SZ is unknown, though the past two decades have witnessed an explosion of increasingly sophisticated studies. During the past five years, a number of putative genetic risk factors for schizophrenia have been reported.[2–4]

We review here the evidence for and against a role for the regulator of G-protein signaling 4 gene (RGS4) in SZ genesis. We begin with a summary of the known function of RGS4 and of the post-mortem studies that first indicated a role for altered RGS4 mRNA expression in SZ pathogenesis. We follow with a description of published genetic linkage and association studies. The evidence that the associated *RGS4* polymorphisms have corresponding functional differences is next discussed. We then conclude by discussing the strengths and weaknesses of the evidence for *RGS4* in SZ genesis.

Functional Biology

Regulators of G-protein signaling (RGS) are so named because they control the duration and regulate the timing of intracellular signaling of many G-protein coupled receptors (GPCRs). In the absence of binding of a specific neurotransmitter, the cytoplasmic domain of a GPCR is tightly bound to a heterotrimeric G protein composed of subtypes of G_α, G_β, and G_γ subunits. When a neurotransmitter binds to a GPCR, the guanine diphosphate (GDP) attached to the G_α subunit is rapidly replaced with guanine triphosphate (GTP), and the G-protein subunits dissociate. The independent subunits are then able to interact with specific cellular effectors, resulting in the activation or inhibition of a variety of signaling cascades. RGS proteins function as GTPase-activators and thus accelerate the hydrolysis of the G_α-bound GTP back to GDP. As a consequence, the G-protein subunits reassociate, effectively ending signaling via the GPCR.[5] To date, 28 RGS proteins have been identified, and most appear to have selective patterns of expression in the brain, although the specificity of their GPCR targets remains under investigation.[5,6] Of these genes, few have

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been more widely studied than the regulator of G-protein signaling 4 (RGS4), particularly with regard to psychiatric genetics.

Post-Mortem Studies

RGS4 was first implicated in SZ pathogenesis following a microarray study of the prefrontal cortex in post-mortem SZ brain samples. A consistent reduction in the RGS4 transcript was detected among the samples from cases compared with control samples.[7] As the effects of a number of neurotransmitters (e.g., dopamine, serotonin, and glutamate) of potential importance in the pathophysiology or pharmacotherapy of SZ are mediated by GPCRs, which are in turn regulated by RGS proteins, these results were intriguing. The findings appeared to be specific to RGS4 mRNA and not to other RGS proteins. The results were confirmed by *in situ* hybridization histochemistry in the same samples, and were replicated in additional samples. Similar findings have been reported by other investigators.[8] Reduction in RGS4 mRNA levels was also found in motor and visual cortices of the same subjects with SZ, regions that differ substantially from the prefrontal cortex in structure, connectivity, and function. In contrast, no changes in RGS4 expression were observed in the prefrontal cortex of subjects with major depression or in monkeys exposed chronically to haloperidol in a manner that mimicked the clinical treatment of SZ. Thus, decreased RGS4 expression in SZ appears to be selective for this particular regulator of G-protein signaling, to present broadly across the neocortex, to be selective to the clinical syndrome of SZ, and not to be merely a consequence of potentially confounding factors such as treatment with antipsychotic medications.

Genetic Studies

Linkage Analysis

RGS4 maps to chromosome 1q23.3, a region that has been implicated in two independent linkage studies.[9,10] Another study also found suggestive evidence for linkage in this region.[11] Linkage to SZ at more telomeric positions on 1q has been reported.[12–15] A recent meta-analysis of published studies provided suggestive evidence for linkage to genetic polymorphisms on the long arm of chromosome 1, but the linked region does not overlap precisely with the *RGS4* locus.[16] In addition, there have been large studies that did not detect evidence for linkage.[17] Conflicting results between the published linkage studies are consistent with genetic heterogeneity. Alternately, it may not be feasible to detect linkage with loci that confer relatively modest risk or if the alleles conferring risk are relatively common.[18] In summary, some published reports suggest linkage with SZ at chromosome 1q23, but inconsistencies between studies have hindered identification of specific regions harboring SZ susceptibility loci. Therefore, these findings do not provide particularly compelling evidence for linkage between 1q23.3 and SZ.

Genetic Association Studies

Initial Findings. We investigated genetic association studies with *RGS4* based on the post-mortem studies described above, with the coincidental linkage findings serving as supportive evidence to initiate such studies. We intensively investigated common polymorphisms in the exonic, intronic, 5′ and 3′ untranslated regions (minor allele frequency, MAF $> 10\%$). We detected nominally significant associations between polymorphisms at *RGS4* using family-based analyses in two independent US Caucasian samples from Pittsburgh and the National Institutes of Mental Health Collaborative Genetics Initiative, but not in case-control analyses. Suggestive evidence was also present in a family-based sample recruited at New Delhi.[19] In all three samples, transmission distortion of individual alleles and/or haplotypes was observed at four SNPs, denoted SNPs 1, 4, 7, and 18 (rs10917670, rs951436, rs951439, and rs2661319, respectively). However, the associated alleles and haplotypes differed between samples. The over-transmitted haplotypes were G-G-G-G in the Pittsburgh sample and A-T-A-A in the NIMH and Indian samples at SNPs 1, 4, 7, and 18, respectively. Curiously, the associated haplotypes were the two most common haplotypes detected among unaffected Caucasian individuals, with estimated frequencies of 0.44 and 0.39, respectively. The associations with common polymorphisms are consistent with current theories about the genesis of genetically complex common disorders, but there was no satisfactory explanation for the different associations. We concluded that the results were suggestive of an association with SZ at this gene, but that they could not be considered conclusive without further replications.

Replicate Studies. In contrast with replicate studies of other putative genetic risk factors elsewhere in the genome, all but one of the published replicate studies investigating *RGS4* associations have investigated the same variants that we reported on (rs10917670, rs951436, rs951439, and rs2661319; denoted SNPs 1, 4, 7, and 18, respectively, in the literature; see Table 1).

The first three reported studies investigated Caucasian participants. Williams and colleagues conducted case-control analyses in a large sample and detected significant associations with the T and A alleles at SNPs 4 and 18, but not with the 4 SNP haplotype.[20] A case-control study by Morris and colleagues observed significant associations at SNPs 1 and 7, as well as multiple haplotypes, with the G alleles at each SNP. They also found a significant association with the 4 SNP haplotype (G-G-G-G)

Table 1. Published Results of RGS4 Association Studies

Study	Country/Ethnicity	SNPs	Families	Cases	Controls	SNPs/Haplotype Associated[b]	Associated Allele(s)
Chowdari et al. 2002[19]	US/Caucasian	1, 4, 7, 18	93	93	174	1-4-7-18	G-G-G-G
Chowdari et al. 2002[19]	US/Caucasian[a]	1, 4, 7, 18	39			1-4-7-18	A-T-A-A
Chowdari et al. 2002[19]	India/Indian	1, 4, 7, 18	269			1-4-7-18	A-T-A-A
Williams et al. 2004[20]	UK/Caucasian	1, 4, 7, 18		711	708	4-18	T-A
Morris et al. 2004[21]	Ireland/Caucasian	1, 4, 7, 18		249	231	1-4-7-18[c]	G-G-G-G
Chen et al. 2004[22]	Ireland/Caucasian	1, 4, 7, 18	267			1-4-18	G-G-G
Cordeiro et al. 2005[23]	Brazil/Mixed	1, 4, 7, 18	49	271	576	7-18	G-G
Sobell et al. 2005[24]	US/Caucasian	1, 4, 7, 18		612	704	Not significant	
Zhang et al. 2005[25]	Scotland/Caucasian	1, 4, 7, 18		580	620	1-4-7-18	A-T-A-A
Zhang et al. 2005[25]	China/Asian	1, 4, 7, 18	322			Not significant	
Fallin et al. 2005[26]	US/Ashkenazi Jewish	SNP 7, rs2842030, rs2344671	274			7, rs2842030	Not reported

Summary of all published RGS4 studies as of 01/10/06. [a]NIMH collaborative genetics initiative. [b]SNPs and/or haplotypes showing significant associations. [c]Four SNP haplotypes significant in schizophrenia cases only, not in cases with schizoaffective disorder. SNPs 1, 4, 7, and 18 correspond to rs10917670, rs951436, rs951439, and rs2661319, respectively.

when their sample was restricted to a narrow diagnosis of SZ, excluding schizoaffective disorder (SZA).[21] An independent family-based study utilized multiply affected pedigrees from Ireland and revealed similar associations with the G allele at SNP 18 and the G-G-G haplotype at SNPs 1, 4, and 18.[22] Thus, the first set of replicate studies continued to report associations. Surprisingly, though the samples were relatively homogenous with regard to ethnicity and were recruited from a well-defined region, differences in associated alleles/haplotypes were noted and were reminiscent of those reported in the ethnically less homogenous US samples analyzed by our group. A fourth study from Brazil involved individuals of mixed ethnicity. Trends for over-transmission of the G allele at SNP 18, as well as the G-G haplotype at SNPs 7 and 18, were reported, but significant case-control differences were not observed.[23] These replicate studies appeared to support an association with *RGS4*, but there was no consensus on the potential risk alleles or haplotypes across studies, and this suggested that more replicates were necessary.

Recently, analyses of several other samples have been published. Significant associations were not detected in a well-powered Caucasian cohort from the US.[24] Another study analyzed both a Chinese family-based sample and a larger Scottish cohort.[25] Associations were not detectable in the Asian sample. In contrast, significant associations were noted in the Scottish cohort with several SNPs and haplotypes, including the A-T-A-A haplotype at SNPs 1, 4, 7, and 18. After correction for multiple testing, only the association with SNP 7 remained significant. These findings were consistent with those of the NIMH and Cardiff samples, but not with the Pittsburgh, Brazilian, or Irish samples reported earlier. The most recent publication reports on 64 candidate genes (440 SNPs) in a sample of 274 Ashkenazi Jewish families and concluded that *RGS4* was one of only six genes meeting significant criteria for an association with SZ.[26] The analyzed polymorphisms included only one of the previously investigated SNPs: SNP7. This SNP and related haplotypes were significantly over-transmitted to SZ/SZA probands ($p < 0.01$). The alleles conferring risk were not reported.

Though all the published studies reported on patients diagnosed using DSM-IV criteria, and a uniform set of SNPs were analyzed, interpretation needs to take account of other differences; e.g., variations in recruitment criteria, sample size, and analytic design (case-control versus family-based). Despite these differences, nominally significant associations were reported in nine of the eleven samples that have been published to date. However, the patterns of associations are complex and variable. Thus, the replicate studies as a whole appear to reflect the differences in the associated alleles/haplotypes reported in our initial analyses.[19] The samples from Pittsburgh and Brazil and both Irish studies find associations with SNPs comprising the G-G-G-G haplotype, while the NIMH, Indian, UK, and Scottish studies identified associations with SNPs comprising the A-T-A-A haplotype. It is possible that these differences merely reflect stochastic variation. Therefore, we initiated meta-analysis from genotypes of 13,807 individuals across 13 samples.[27] This study includes the reports discussed above, as well as additional unpublished samples. We concluded that a

significant association is present, but that the statistical significance is derived from *both* of the common haplotypes in the populations at the expense of rare haplotypes. These data, in their entirety, are currently in review.

Functional Genetics. The aforementioned genetic analyses merely evaluate statistical associations. It would be helpful to know whether variation within this gene leads to functional changes that could explain the findings of Mirnics and colleagues.[7] Despite intensively sequencing DNA pools (200 cases, 200 controls), as well as 48 individual cases, we have not detected any coding-sequence polymorphisms (Chowdari et al., unpublished data). Functional variation may therefore be due to changes in the transcription and/or translation of *RGS4*, rather than to structural changes in the protein. While SNP 18 is localized to the first intron, SNPs 1, 4, and 7 are localized to the 5′ genomic sequence. We are presently evaluating promoter activity for these SNPs using in vitro expression assays (Chowdari et al., unpublished data).

We have also investigated the functional correlates of these SNPs "*in vivo*." We detected a significant correlation between all four SNPs and gray-matter volume in the dorsal lateral prefrontal cortex (DLPFC) of neuroleptic naïve first-episode SZ patients.[28] The alleles at SNPs 1, 4, 7, and 18 that were correlated with decreased DLPFC volume were those comprising the A-T-A-A haplotype, which was associated with SZ in a number of the studies described above. Intriguingly, these correlations were not observed among matched, unaffected controls. Thus, it is necessary to invoke unidentified, illness-related factors to explain the correlations.

Discussion

In a recent review, we discussed the level of evidence required to establish the credibility of a putative genetic risk factor.[4] We stressed the need for replicate studies to observe *identical* associations using multiple analytic designs. We also highlighted the need to demonstrate functional effects for the associated genetic variants that could explain pathogenesis, and suggested that a consensus be established with regard to the number of replicates required. In addition, we suggest here that adequate knowledge of all variation within a gene is necessary to conclusively identify susceptibility loci. As discussed below, all the relevant evidence relating to *RGS4* is not yet available, though progress has been made.

We continue to believe that replicate studies should demonstrate associations with *identical* alleles in order to be considered bona fide replications. Such proof has been difficult to garner for putative risk alleles for genetically complex disorders. With respect to *RGS4*, the majority of studies have detected significant associations. Thus, we cannot confidently accept the null hypothesis that no association exists. To the contrary, the bulk of evidence presented here suggests that associations do exist, but the replicate studies have lacked consistency with regard to the associated variants and cannot be considered strict replications (see Table 1). This problem is not unique to *RGS4* and has been found for virtually all genes implicated as risk factors for schizophrenia. Accounting for these varied associations is difficult. Chance variation could certainly account for these results, but our meta-analysis indicates otherwise. Notably, even the meta-analysis continues to suggest the presence of more than one risk haplotype. Genetic heterogeneity could also be invoked, but this may not be a satisfactory explanation. Three of the four largest samples included individuals of Caucasian ancestry from European countries, but all of these samples observed different patterns of associations.

Phenotypic heterogeneity could account for these differences. Though the patients in all the replicate samples were diagnosed using current diagnostic criteria, it remains possible that the researchers sampled different proportions of genetically relevant subgroups. This question has been difficult to resolve. Since various groups ascertained the relevant clinical data using different interview questionnaires, they are not strictly comparable. Our analyses of the first five samples described above suggest that subgroups based on gender or age at onset may not explain the discrepancies.[29]

It remains possible that primary associations exist with hitherto unidentified variants at *RGS4*. While the exonic regions are typically prioritized, the effects of promoter polymorphisms, enhancers, repressors, and splice variants cannot be ignored. Indeed, all the associations observed at *RGS4*, as for many other risk genes for schizophrenia, have involved non-coding sequences. Thus, we stress the need for identifying all variation within a gene before concluding evidence of association does or does not exist. It is noteworthy that *RGS4* is one of the few genes that appear to have been substantially evaluated in this regard. We recently sequenced the region from SNP 1 to the 3′ end of the last *RGS4* exon using a design intended to identify all common polymorphisms (Chowdari et al., unpublished data). Our linkage disequilibrium (LD) analyses suggest that the four measured SNPs (SNPs 1, 4, 7, and 18) are substantially correlated with 12 of the 18 common polymorphisms identified and account for approximately 75% of the common variation in this genomic region. Still, it is possible that the associated SNPs and haplotypes identified to date are surrogates for unidentified and relatively infrequent liability locus/loci. Simulations suggest that in the presence of an unidentified liability locus, patterns of associations can be complex among measured SNPs.[30] This appears the most plausible explanation for the disparate published associations. Investigating this possibility would require sequencing many individuals extensively across the gene. We speculate that this may be a

tractable means of resolving the inconsistencies in the reported studies to date.

The functional effects of the associated SNPs and their relation to pathogenesis are another key question. There is compelling evidence to suggest that RGS4 is an important protein in neurological development and function. The replicated post-mortem studies reveal consistent reduction in RGS4 mRNA levels in the brains of patients with SZ. The key evidence linking the associated genetic variants with the reduced transcription is presently unavailable, though recent MRI studies suggest genotype-specific changes in DLPFC volume of SZ patients, but not controls.[28]

One other unresolved question germane to the entire field of genetic association studies is the number of replicate studies that are required. Thus far, analyses have been reported using three US Caucasian samples, four European Caucasian samples, and one sample each from India, China, and Brazil. Most of these studies had adequate power to replicate the initial associations, and they included both case-control and family-based study designs. Despite the substantial number of replicate studies and the meta-analysis, consensus has not been reached. Such difficulties highlight the likely etiological complexity of SZ. We are aware of a number of other *RGS4* studies that were included in our meta-analysis and/or are being peer-reviewed. It may be helpful to review these studies at a meeting of interested experts in order to achieve consensus about the further course of action. Additional association studies, if conducted, would need to investigate a larger panel of variants than these four SNPs to convey additional and potentially more meaningful information than the published studies to date. The ultimate goal of these studies must be to provide conclusive evidence for risk, thus enabling development of novel therapeutics or diagnostic tests.

Conclusions

RGS4 has emerged as a promising schizophrenia susceptibility candidate gene based on the intersection of evidence from functional biology, gene expression, linkage, and association studies. RGS4 plays an important role in G-protein coupled receptor signaling, and post-mortem evidence supports SZ specific changes in RGS4 mRNA levels. Linkage and associations with genetic variations have been reported and replicated in several samples. The four variants investigated in association studies appear to represent a substantial proportion of all common polymorphisms within this gene. Yet, the complex pattern of association, inconsistencies across studies, and failure to replicate in some studies implies that other unidentified variants may confer risk. Alternately, the published results may point to associations with SZ subgroups or SZ-related quantifiable variables.

In summary, we view the evidence that *RGS4* variants increase risk for SZ genesis as enticing, but not conclusive. We find that this evidence could be viewed favorably with that of other putative SZ susceptibility genes. However, similar to these other candidates, we suggest that the inconsistencies in replication studies for *RGS4* to date do not meet a stringent threshold for replication in establishing a credible risk factor in a disorder with complex, non-Mendelian inheritance such as SZ. This conclusion may highlight the need for alternative research strategies to determine whether the signals detected represent bona fide vulnerability to the illness.

Acknowledgments

Our research is supported by NIMH grants to V. L. Nimgaonkar (MH56242 and MH53459) and the NIMH Conte Center for the Neuroscience of Mental Disorders to D. A. Lewis (MH051456).

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