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Genetic association study between *RGS2* and anxiety-related phenotypes

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As reviewed by Fullerton (2006), a behavioral quantitative trait locus for fear-related behaviors has been reliably localized to a 4.8 Mb region on mouse chromosome 1, and its syntenic region on human chromosome 1 coincides with linkage peaks reported for several human internalizing phenotypes, such as neuroticism, anxiety, and depression. Further genetic dissection of that region provided support for three separate murine quantitative trait loci, including effects attributable to the gene encoding regulator of G-protein signaling 2 (*RGS2*). The *RGS2* gene itself has since been reportedly associated with several human anxiety disorders, including panic disorder (Leygraf et al., 2006) and generalized anxiety disorder (Koenen et al., 2009). Another study found several markers in *RGS2* associated with more basic anxiety-related phenotypes: increased limbic activation during emotional processing, and inhibited temperament as indexed by behavioral inhibition or introversion (low extraversion) (Smoller et al., 2008). Given that genetic epidemiological studies suggest that many of these phenotypes share genetic risk factors in common (Hettema et al., 2006), we hypothesized that *RGS2* might express its effects differentially across these various human phenotypes.

In this study, we examined the pattern of potential association of *RGS2* to multiple anxiety-related phenotypes, attempting to replicate and extend previous findings. We genotyped the three most consistently associated *RGS2* single nucleotide polymorphisms (rs10801152, rs6428136, rs4606) in a sample of 2661 independent Caucasian individuals from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders. We obtained lifetime psychiatric diagnoses through face-to-face or telephone structured psychiatric interview for generalized anxiety disorder ($N = 395$), panic disorder ($N = 150$), social phobia ($N = 159$), agoraphobia ($N = 110$), and specific phobia ($N = 485$). Neuroticism ($N = 2274$) and extraversion ($N = 2310$) were assessed with the short form of the Eysenck Personality Questionnaire. We conducted association analyses assuming an additive genetic effect using trend tests for categorical diagnoses and linear regression for ordinal measures of

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Conflicts of interest

There are no conflicts of interest.

personality, respectively. None of the single nucleotide polymorphisms showed deviations from Hardy–Weinberg equilibrium. No significant associations were detected, with *P*-values greater than 0.2 between each *RGS2* marker, respectively, and each phenotype examined. Thus, we were unable to replicate or extend prior association findings between *RGS2* variants and various anxiety-related phenotypes using a large, independent sample.

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