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Follow-up association study of novel neuroticism gene *MAMDC1*

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Neuroticism is a personality trait reflecting a tendency towards negative affective states. Extant research supports its role as a risk marker for, and its potential shared genetic basis with, mood and anxiety disorders (Hettema *et al*., 2006). Our group recently performed a genomewide association study (GWAS) of neuroticism in 1227 US Caucasion participants in which the most promising markers were subsequently tested for replication in a German sample (N = 1880) (van den Oord *et al*., 2008). The strongest associations derived from four correlated single-nucleotide polymorphisms (SNPs) in the gene *MAMDC1* (also known as *MDGA2*), with P values of 10^{-5} to 10^{-6} in the original sample and 0.006–0.025 in the replication sample and with the same direction of effects. Despite these encouraging results, conventional wisdom emphasizes the need for replication of such GWAS findings in multiple independent samples (McCarthy *et al*., 2008).

In this study, we attempted a second replication of the *MAMDC1* gene for association with neuroticism in 2722 US Caucasion participants from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders [see (Kendler and Prescott, 1999) for sample details]. Neuroticism was assessed with the Eysenck Personality Questionnaire, the same instrument used in the original GWAS analysis. The four SNPs in *MAMDC1* that showed association in the original study (rs7151262, rs1288334, rs1959813, and rs3007105) were in very high linkage disequilibrium, each tagging the same two haplotypes accounting for 94% of the haplotypic variation. Using the Tagger module of HAPLOVIEW 4.0 (Barrett *et al*., 2005) with HapMap Phase II data, we confirmed their high correlation (r^2 = 1) in a 12kb block within *MAMDC1*. We genotyped one marker (rs7151262) that captured 11 of 13 HapMap SNPs with minor allele frequency >0.05 at $r^2 > 0.8$ in this block. This SNP was tested for association through linear regression assuming an additive genetic effect, as in the original study.

The genotypes for rs7151262 were available for 2686 participants in our sample. They were in Hardy—Weinberg equilibrium and the minor allele frequency (0.40) was the same as that found in the prior US and German samples. No association of rs7151262 with neuroticism was found ($P > 0.6$), although there was a nonsignificant trend for mean neuroticism scores to increase with the number of copies of the minor allele, consistent with the direction of effects in the original study.

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In a large, independent sample, we attempted to replicate an association identified in a prior GWAS study between neuroticism and marker rs7151262 within the *MAMDC1* gene. We followed 'best practice' recommendations of testing the same marker with the same phenotype in a sample of similar ethnicity as in the original study (McCarthy *et al*., 2008). Our large sample possessed sufficient power (about 80%) to detect the predicted effect size attributable to this marker (explaining 0.3% of individual variation in neuroticism estimated from the original German replication sample). Allele frequencies obtained in the current sample were similar to those in the original samples, suggesting comparability of genetic make-up of the samples and genotyping accuracy. Despite satisfying all of these conditions, the current analysis failed to detect a significant association signal, underscoring the importance of multiple replication attempts in independent samples for GWAS findings.

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