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CORRESPONDENCE

Higher anxiety and larger amygdala volumes in carriers of a *TMEM132D* risk variant for panic disorder

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Recent case–control genome-wide association studies have linked common variants of *TMEM132D (KIAA1944, MOLT)* with panic disorder (PD), anxiety comorbidity in depression, and anxiety symptom severity in healthy and diseased subjects.[1] One risk genotype (rs11060369 AA) is associated with enhanced *TMEM132D* mRNA expression in the brain; brain mRNA expression is also higher in mice bred for extreme anxiety-like behavior.[1] The current study demonstrates enhanced amygdala gray matter volumetric estimates and an anxiety-related (but not panic-specific) personality profile in healthy normal carriers of the rs11060369 AA genotype. Our data suggest a role for *TMEM132D* in shaping threat processing.

TMEM132D is a transmembrane protein expressed in neurons and colocalized with actin filaments[2] that putatively functions as a cell-surface marker for oligodendrocyte differentiation.[3] The *TMEM132D* single-nucleotide polymorphisms related so far to PD in patients of European ancestry or to anxiety in general are intronic and presumably tag yet unknown intronic functional regulatory variants.[1,4] Next to common variants, rare *TMEM132D* variants have also been linked with pathological anxiety.[5]

We interrogated an independent sample of 315 healthy normal subjects (99 female) of Caucasian descent, of which 132 (22 female) underwent structural magnetic resonance imaging, for *TMEM132D* genotype effects on personality and brain morphology (see Supplementary Methods and Supplementary Table 1 for details). The variant rs11060369 was the only one that showed a significant omnibus effect on a battery of anxiety-related personality questionnaires ($F(8,32) = 3.34$, $P = 0.0008$, $\eta^2 = 0.07$). A homozygotes had higher scores than C carriers on general measures of trait anxiety ($F(1,302) = 12.72$, $P < 0.001$, $\eta^2 = 0.04$), behavioral inhibition ($F(1,302) = 8.53$, $P = 0.004$, $\eta^2 = 0.03$) and negative affect ($F(1,302) = 4.98$, $P = 0.026$, $\eta^2 = 0.02$; Figure 1a), but not on more disease-specific measures like anxiety sensitivity, agoraphobic cognitive style, worrying, social anxiety or depression (all *P*-values>0.17; see Supplementary Table 2).

rs11060369 A homozygotes also had higher gray matter volumetric estimates in the left amygdala ($Z = 3.39$, $P = 0.014$, small volume corrected for multiple comparisons (SVC); right side: $Z = 2.87$, $P(SVC) = 0.089$, trend; Figure 1b). Including trait anxiety, behavioral inhibition and negative affect scores into the volumetric analysis as covariates of no interest did not change the results (data not shown). An exploratory whole-brain analysis at an uncorrected threshold of $P < 0.001$ additionally yielded higher estimates in A homozygotes in the left hippocampus extending into the amygdala and the cerebellum (Supplementary Table 3; reported descriptively only). There were no supra-threshold voxels in the inverse contrast.

In a further exploratory analysis of the other common *TMEM132D* risk variants, carriers of the T/A rs11060369/7309727 combination showed a strong trend for higher estimates in the left amygdala ($Z = 3.17$, $P(SVC) = 0.026$ and $Z = 3.15$, $P(SVC) = 0.027$) than carriers of the C/A and C/C combinations (Supplementary Table 3, Supplementary Figure 1). At an uncorrected threshold, differences were also observed in the hippocampus, the insula and the other regions (Supplementary Table 3). At the same exploratory threshold ($P < 0.001$), we observed higher volumetric estimates in the right hippocampus and right caudate in T Carrier compared to C homozygotes in an additional common *TMEM132D* risk variant, rs7309727 (Supplementary Table 3). There were minor effects of variant rs7309727 and no effects of variants rs900256 and rs879560 (Supplementary Table 3).

rs11060369, rs7309727 and their combination have so far been more closely linked to a diagnosis of PD than to anxiety disorders in general or to non-disease-specific dimensional anxiety phenotypes.[1,4] A correlation with dimensional anxiety measures for rs900256 and rs879560 and the cited mouse *TMEM132D* expression data, however, have been taken to support a more generic role for the protein in threat processing.[1] Our observation in a sample of healthy normal volunteers of extended, genotype-dependent volumetric differences in a key neural structure associated with fear and anxiety[6–8] can be interpreted as pointing toward a generic role in threat processing. This conclusion is further supported by our personality data. Our results therefore highlight *TMEM132D* as having an important molecular role in fear and anxiety.

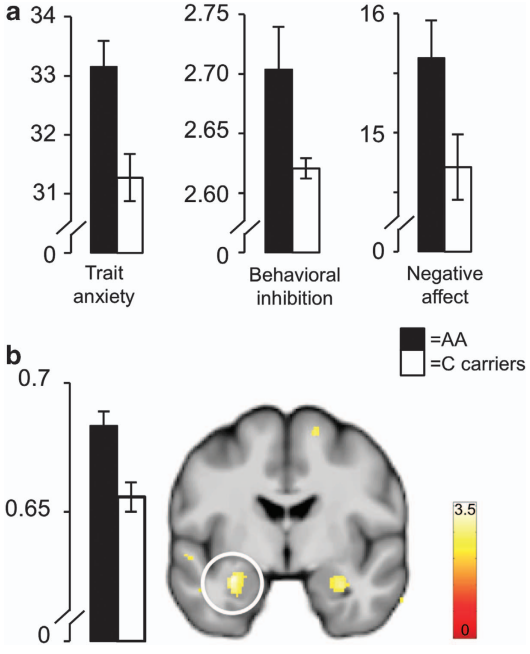

Figure 1. Higher anxiety-related personality scores in rs11060369 A homozygotes ($N = 164$) as compared to C carriers ($N = 151$). (**a**) Higher gray matter volumetric estimates in rs11060369 A homozygotes ($N = 68$) as compared to C carriers ($N = 65$) in the left amygdala (bars show maximum at Montreal Neurological Institute coordinates x, y, z = − 30, −6, −20) and, at trend level, right amygdala (30, −6, −20). (**b**) Color-coded effects are superimposed on average structural image. Color bar: *t*-scores. Display threshold: *P*(uncorrected) < 0.01. Error bars: s.e.m.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Translational Psychiatry website (http://www.nature.com/tp)