

ORIGINAL ARTICLE

Variation in the Williams syndrome *GTF2I* gene and anxiety proneness interactively affect prefrontal cortical response to aversive stimuliM Jabbi^{1,2}, Q Chen³, N Turner^{1,2}, P Kohn^{1,2}, M White³, JS Kippenhan^{1,2}, D Dickinson², B Kolachana², V Mattay^{3,4}, DR Weinberger^{3,5} and KF Berman^{1,2}

Characterizing the molecular mechanisms underlying the heritability of complex behavioral traits such as human anxiety remains a challenging endeavor for behavioral neuroscience. Copy-number variation (CNV) in the general transcription factor gene, *GTF2I*, located in the 7q11.23 chromosomal region that is hemideleted in Williams syndrome and duplicated in the 7q11.23 duplication syndrome (Dup7), is associated with gene-dose-dependent anxiety in mouse models and in both Williams syndrome and Dup7. Because of this recent preclinical and clinical identification of a genetic influence on anxiety, we examined whether sequence variation in *GTF2I*, specifically the single-nucleotide polymorphism rs2527367, interacts with trait and state anxiety to collectively impact neural response to anxiety-laden social stimuli. Two hundred and sixty healthy adults completed the Tridimensional Personality Questionnaire Harm Avoidance (HA) subscale, a trait measure of anxiety proneness, and underwent functional magnetic resonance imaging (fMRI) while matching aversive (fearful or angry) facial identity. We found an interaction between *GTF2I* allelic variations and HA that affects brain response: in individuals homozygous for the major allele, there was no correlation between HA and whole-brain response to aversive cues, whereas in heterozygotes and individuals homozygous for the minor allele, there was a positive correlation between HA sub-scores and a selective dorsolateral prefrontal cortex (DLPFC) responsivity during the processing of aversive stimuli. These results demonstrate that sequence variation in the *GTF2I* gene influences the relationship between trait anxiety and brain response to aversive social cues in healthy individuals, supporting a role for this neurogenetic mechanism in anxiety.

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INTRODUCTION

Although anxiety disorders are among the most frequent psychopathological presentations¹ and are highly heritable,² their clinical heterogeneity and underlying pathophysiological complexities pose a challenge for studying the neurogenetic origins of these conditions. A promising approach that could have therapeutic implications is to characterize neurogenetic mechanisms related to known copy-number variations (CNVs) associated with clinically relevant phenotypes. In the context of anxiety, one such strategic target is the general transcription factor gene, *GTF2I* (Gene ID: 2969). *GTF2I* (located approximately between base pair 74 657 664 and 74 760 691 on chromosome 7) is one of a set of genes that, in the rare disorder Williams syndrome (MIM 194050), is hemizygotously deleted from chromosomal location 7q11.23, thereby leaving only one remaining copy of affected genes.^{3,4} Interestingly, individuals with the more recently discovered and even rarer 7q11.23 duplication syndrome (Dup7q11.23; MIM 609757) have three copies of this same set of genes.⁵ With one copy of the genes, individuals with Williams syndrome show hypersociability together with very little social anxiety,^{6–9} whereas persons with the duplication syndrome are highly socially

anxious¹⁰ and even have autistic spectrum symptoms.¹¹ Particular importance of *GTF2I* is suggested by the fact that mouse models constructed to specifically have one, two or three copies of *GTF2I* show relationships between anxiety and *GTF2I* copy number that parallel observations in the human hemideletion and duplication syndromes: compared with mouse pups with one or two *GTF2I* copies, pups with additional *GTF2I* copies exhibited significantly increased maternal separation-induced anxiety as measured by ultrasonic vocalizations.¹⁰ In another study, mice with *GTF2I* haploinsufficiency showed increased social interaction with unfamiliar mice and did not show typical social habituation processes,¹² again consistent with the Williams syndrome personality.

A potential molecular mechanism that may contribute to this pattern of *GTF2I* copy-number-related anxiety phenotype in both model animals and humans is suggested by the role of *GTF2I* protein in the induction of c-fos,¹³ the latter being a behaviorally relevant marker for neural activity. *C-Fos* expression is functionally influenced by *GTF2I* expression in a *GTF2I* gene-dosage-dependent manner, in line with recent evidence of anxiolytic-induced changes in brain c-fos expression in mice with different *GTF2I*

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CNV.¹⁴ *GTF2I* can also bind to promotor elements of other genes,¹³ some of which are known to functionally impact major neurotransmitter systems with antianxiety and antidepressant effects, such as the glutamatergic and monoaminergic systems.

These data point to a gene-dosage-sensitive relationship between *GTF2I* CNVs and socially relevant anxiety in both mice^{10,12} and humans,^{10,11} and thereby suggest that *GTF2I* functionality may have implications for understanding neurobiological mechanisms that could contribute to the heritable component of anxiety. However, the neural mechanism by which *GTF2I* alterations might impact neurobehavioral correlates of anxiety phenotypes in clinical cohorts and in the general population remains to be elucidated.

Here, in a large cohort of healthy humans studied with functional magnetic resonance imaging (fMRI) and the Tridimensional Personality Questionnaire, we examined the effect of sequence variation in this gene, specifically choosing rs2527367, a common intronic *GTF2I* single-nucleotide polymorphism (SNP) that is in very high linkage disequilibrium with many other *GTF2I* SNPs between chromosomal location 73706683 and 73777987. Our choice of this high linkage disequilibrium tag SNP obviates the need to investigate a number of related *GTF2I* SNPs, thus minimizing the number of statistical procedures necessary to test our hypothesis. Because genes code for molecular processes that act on neurons and neural systems,¹⁵ which, in turn, are the intermediaries of genetic effects on complex behaviors,¹⁶ brain phenotypes may be more proximately related to genes than are behaviors.^{15,16} Indeed, the effect size of risk genes at the level of neural structure and function has been demonstrated to be considerably higher than what has been found for association of the same gene variants with neuropsychiatric diagnosis.¹⁵ Therefore, we reasoned that, particularly in light of the fact that sequence variation is generally less altering of a gene's function than is a CNV, the mechanism by which the effects of a *GTF2I* SNP interact with trait anxiety in the general population would be more robust and best experimentally observed in a neurofunctional circuit activated by processing aversive stimuli. We applied this reasoning to test the hypothesis that *GTF2I* sequence variation affects the relationship between trait anxiety proneness and behaviorally relevant regional brain responsiveness to anxiety-laden social stimuli.

MATERIALS AND METHODS

Participants

A sample of 260 healthy participants (mean age = 30.00 ± 9.12 years, range 18–54; and mean intelligence quotient (IQ) = 110.30 ± 8.59, range 86–132; 141 females) participated in the study after giving written informed consent in accordance with NIH institutional review board-approved procedures. To minimize population stratification artifacts, only Caucasians of self-identified European descent were included. Each participant completed history, physical and laboratory tests to assess for medical conditions that could affect the brain. Those with current or past medical or neuropsychiatric conditions (the latter as determined by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders Version IV carried out by qualified raters), including alcohol or drug abuse or head trauma, were excluded, as were those with abnormalities on structural MRI.

Genotyping

The standard Taqman allelic Discrimination 5' exonuclease assay was applied to DNA from peripheral blood. SNP probe and primer sets were obtained from Applied Biosystems (Foster City, CA, USA). *GTF2I* sequences were amplified using allele-specific Taqman fluorescent probes, and PCR was performed in an ABI (Applied Biosystems) 9700 thermal cycler. The amplified fluorescent amplicon was read in an ABI 7900 sequence detection system. Genotype accuracy was assessed by re-genotyping within a subsample, and reproducibility was routinely > 99%.

Of the 260 participants of self-identified European ancestry, 115 were homozygous for the major *GTF2I* rs2527367 allele (*t/t*), 118 were

heterozygotes (*t/c*) and 27 were homozygous for the minor allele (*c/c*). Given that our sample includes individuals of northern, eastern, western and southern European origin, the allelic frequency of *t* = 348 (66.92% of our sample) and *c* = 172 (33.07% of our sample) does not represent any specific HAPMAP population.

Trait anxiety scores

The Tridimensional Personality Questionnaire Harm Avoidance (HA) subscale, a trait measure of anxiety proneness that specifically taps into characterological disposition to excessive worrying, shyness and pessimism, as well as general fearfulness, doubtfulness and fatigability,¹⁷ was administered to all 260 participants. In the current study, HA scores were used (a) for the purpose of assessing the effects of *GTF2I* genotype on trait anxiety scores, and (b) as covariates of interest in the analysis of *GTF2I* genotypic effects on neural response to aversive affective stimuli during fMRI.

Aversive face-viewing task

This well-established fMRI paradigm consists of two experimental conditions: an emotional face identity-matching condition and a low-level sensorimotor control task.¹⁸ Each sensorimotor and emotion block consisted of six 5-s duration trials. Each trial involved the presentation of two images in the lower panel and one image in the upper panel. For sensorimotor trials, the two lower images were shapes, and the upper panel image was identical to one of the shapes in the lower panel. For emotional face trials, the lower panel consisted of two faces, one angry and one afraid, derived from a standard set of pictures of facial affect;¹⁹ the upper panel consisted of one of the two faces shown in the lower panel. Subjects responded using button presses (left or right) to indicate which lower panel item matched the item in the upper panel, a matching parameter that was chosen with the goal of keeping the processing of the aversive emotional content of the faces implicit.¹⁸ In addition to promoting implicit processing of aversive social stimuli, keeping in mind that implicit behavioral processes are likely more proximate to trait measures such as HA than explicit behavioral processes, this fMRI paradigm taps into the neural substrates of innate socially relevant threat perception,²⁰ and has been shown to be sensitive to genetic effects.^{7,21–23} Stimuli were displayed through a back-projection system and participants' responses were recorded through a fiber-optic connection.

Image acquisition

fMRI was performed on a 3-Tesla scanner (General Electric, Milwaukee, WI, USA) equipped with a real-time functional imaging upgrade and a standard head coil. We acquired two experimental runs containing blocks of emotional and sensorimotor trials using the following acquisition parameters: Echo planar imaging BOLD fMRI, 24 axial slices (4 mm thick, 1 mm gap) encompassing the whole cerebrum and the majority of the cerebellum (TR/TE = 2000/30 ms, 170 volumes for each subject, FOV = 24 cm, matrix = 64 × 64).

Image processing and analysis

Using Statistical Parametric Mapping software version 8 (SPM8; <http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>), we preprocessed (realignment, coregistration, normalization and 8-mm smoothing) and applied a first-level one-sample *t*-test, to compare BOLD reactivity during blocks of aversive face processing with that during shape processing (aversive faces > shapes). In a second-level analysis, the results of the main-effect-of-task analysis were thresholded at $P < 0.001$ to provide a mask within which to assess the relationship between the behavioral (HA) scores and BOLD response to aversive social cues using a voxel-wise regression. This approach was used to ensure that the results of our next step, identifying HA-related BOLD findings, were restricted to task-relevant areas. We then performed a multiple regression, this time including HA scores as the covariate of interest, and IQ, age and sex as control variables, and thresholded the results at $P < 0.05$. The results of this analysis were similarly used as a mask for the next step, which was aimed to assess the main hypothesis of this paper that is as follows: sequence variation in the *GTF2I* gene affects the relationship between HA and neural response to processing aversive stimuli. We then performed a full factorial analysis by including *GTF2I* genotype as a group factor, and HA scores as predictors, whereas age, sex and IQ were included as control variables.

RESULTS

GTF2I genotype is not associated with behavioral or demographic measures

To control for potential confounding effects, we first assessed the association between *GTF2I* genotype and the demographic measures (sex and age) and found no relationship between genotype and sex ($F = 0.497, P = 0.609$) or age ($F = 0.986, P = 0.381$). We then assessed the gene–behavior relationship and found no direct effect of *GTF2I* sequence variation on participants' IQs ($F = 0.089, P = 0.915$), HA scores ($F = 0.76, P = 0.469$) or face identity-matching performance ($F = 0.773, P = 0.463$), together suggesting a lack of potential behavioral confounds in our study.

Aversive face processing recruits frontolimbic and occipital BOLD response

As reported previously,^{18,24} we found a main effect of the task ($P < 0.001$, Figure 1a) in the bilateral amygdala, parahippocampal gyrus and primary visual cortices extending into the fusiform gyrus, as well as in a right dorsolateral prefrontal cortex (DLPFC).

Harm avoidance scores are associated with BOLD response to aversive face processing

To examine the effects of HA scores on whole-brain response, we conducted a simple regression analysis using SPM8 by including HA scores in the model as predictors and age, sex and IQ as control variables, and we limited our search area to the region defined by the brain response to aversive faces. We found that the right DLPFC locus responding to the main effect of task described above (centered on the Montreal Neurological Institute (MNI) coordinates $x, y, z = 51, 30, 12$) was modulated by individual differences in HA tendencies at $P < 0.05$ (Figure 1b), such that the higher an individual's trait measure of anxiety, the greater their DLPFC response to aversive social stimuli.

GTF2I genotype affects the relationship between HA and DLPFC BOLD response to aversive faces

Although a direct assessment of a relationship between *GTF2I* sequence variation and BOLD response to aversive cues yielded no significant findings as expected, a multiple regression analysis using a full factorial design with *GTF2I* sequence variation as a group factor and HA scores as predictors (along with age, sex and IQ as control variables) demonstrated that the relationship between HA scores and BOLD signal differed as a function of *GTF2I* genotype within the DLPFC region defined by the HA-by-task interaction analysis. Specifically, an F-test assessing the interaction between HA and *GTF2I* variation identified a genotype-dependent differential relationship between HA and the BOLD signal ($P = 0.001$; cluster-level statistics) at MNI $x, y, z = 51, 30, 12$ within the same DLPFC locus that has been previously implicated in regulating top-down guidance of attention and thought²⁵ and in choice-related decision making²⁶ and shown here to be correlated with HA scores (see Figure 1a) across the entire group (Figure 1c). Performing the same analysis by using a mask created from task-negative response data (regions showing negative BOLD response to face processing), we found no interaction between *GTF2I* variation and HA scores, suggesting relative regional specificity of our DLPFC findings.

Finally, we performed a *post hoc* graphical exploration to delineate the nature of this genotype-dependent differential relationship between HA and DLPFC responsivity. From the one-sample *t*-test (main effect of task), we extracted the raw BOLD signals from the DLPFC locus shown to be commonly active in (1) the one-sample *t*-test of the main effect of task, (2) the HA-associated brain response and (3) the F-test of *GTF2I* rs2527367-HA interactive response. To better understand the F-test results, we plotted and tested the relationship between HA scores and DLPFC BOLD responses (MNI $x, y, z = 51, 30, 12$) for each genotype group separately. This *post hoc* visualization revealed a genotype-related association such that individuals homozygous for the major allele (*t/t* variants) showed no association between percent BOLD signal changes in DLPFC and HA scores ($R = -0.122$,

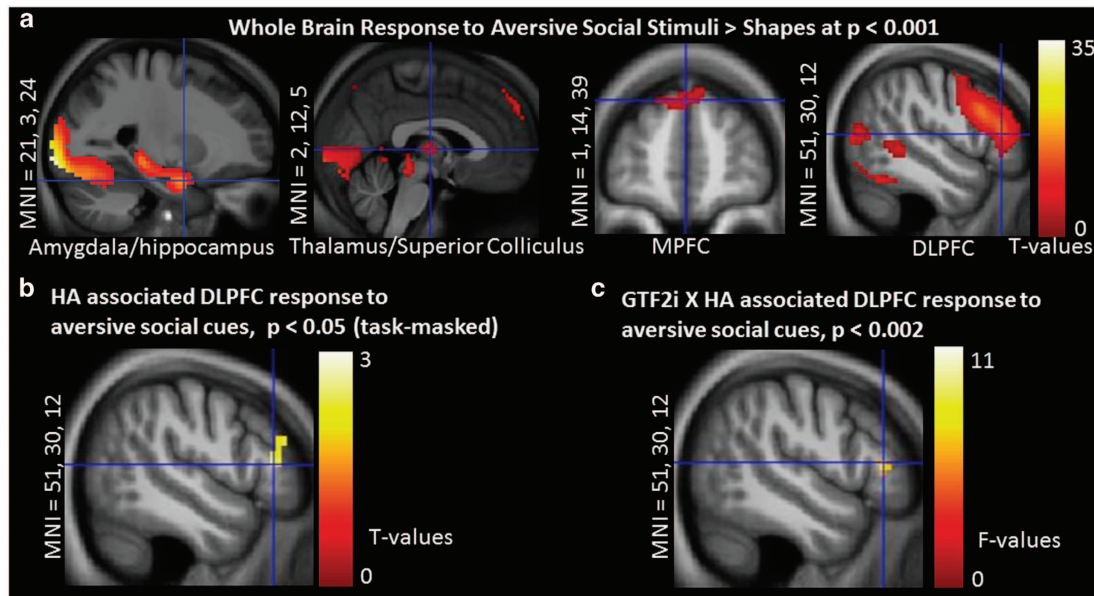


Figure 1. Voxel-wise brain response to aversive social cues > geometric shapes. (a) Whole-brain response to aversive cues independent of genotype as derived from a one-sample *t*-test thresholded at $P < 0.001$; the color bar represents *t*-statistics. (b) DLPFC response to aversive cues as related to individual variability in anxiety proneness scores of HA centered on MNI coordinates $x, y, z = 51, 30, 12$, thresholded at $P < 0.05$; the color bar represents *t*-statistics. (c) Contrast images of the effect of *GTF2I* allelic variation on HA-predicted prefrontal response to aversive social cues centered on MNI coordinates $x, y, z = 51, 30, 12$ at $P = 0.002$, with the results masked with HA-predicted BOLD response to aversive content; the color bar represents F-statistics. DLPFC, dorsolateral prefrontal cortex; HA, harm avoidance; MNI, Montreal Neurological Institute.

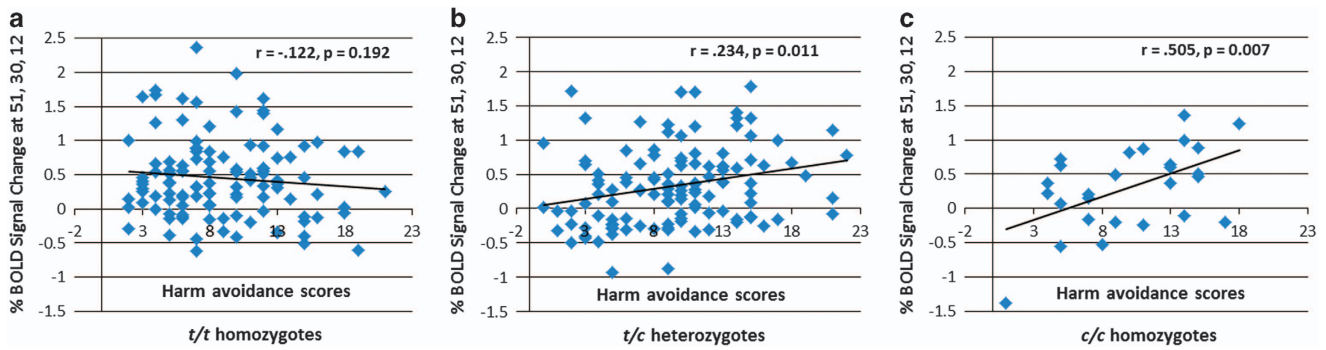


Figure 2. Post hoc visualization plots showing the association between HA scores and DLPFC BOLD response for each *GTF2I* allelic variant separately. (a) Correlation plot showing no association between HA scores and DLPFC BOLD response to aversive social stimuli in individuals homozygous for the *GTF2I* major *t/t* allele. (b, c) Correlation plots show a robust positive association between HA scores and DLPFC response in *GTF2I* heterozygous *t/c* carriers and those homozygous for the minor *c/c* alleles, respectively. Signal values were extracted from the DLPFC cluster centered on MNI coordinates $x, y, z = 51, 30, 12$ representing the maximal voxel in the DLPFC where BOLD response was also predicted by HA scores and their interaction with *GTF2I* allelic variation, as shown in Figure 1a (upper right image). DLPFC, dorsolateral prefrontal cortex; HA, harm avoidance; MNI, Montreal Neurological Institute.

$P = 0.192$, two tailed; Figure 2a), whereas heterozygotes (*t/c* variants) showed a positive association between DLPFC response and HA ($R = 0.234$, $P = 0.011$, two tailed; Figure 2b), and individuals homozygous for the minor allele (*c/c* variants) showed a more robust positive association between signal change in DLPFC response to aversive cues and HA scores ($R = 0.505$, $P = 0.007$, two tailed; Figure 2c).

DISCUSSION

CNVs of the ~25 genes contained at chromosomal location 7q11.23, specifically the hemizygous deletion of Williams syndrome and the duplication of Dup7, are associated with distinctly contrasting behavioral phenotypes involving social anxiety: individuals with Williams syndrome (one copy of affected genes) show hypersociability and very little social anxiety,⁶ whereas persons with the duplication syndrome (three gene copies) are highly socially anxious¹⁰ and even have autistic spectrum symptoms.¹¹ For example, children with Williams syndrome show less separation anxiety than control children, but those with Dup7 show more.¹⁰ Despite these intriguing clinical observations, the role of individual 7q11.23 genes in the etiology of anxiety remains to be defined. Guided by convergent findings of gene-dose dependent anxiety in mouse models constructed to have CNVs specifically in *GTF2I*¹⁰—findings that parallel observations in the human hemideletion and duplication syndromes¹⁰—we focused our study on this particular gene. With a neuroimaging experiment in a large adult cohort of 260 healthy participants, we demonstrated an interactive effect between *GTF2I* rs2527367 genotype and the degree of a trait measure of anxiety proneness on right-DLPFC responsivity to aversive social stimuli: homozygous carriers of the major allele (*t/t*) showed no association between HA scores and DLPFC response to aversive social cues, whereas heterozygotes and homozygote carriers of the minor allele (*t/c* and *c/c*, respectively) instead displayed a positive association between DLPFC response and HA scores, such that the greater an individual's propensity for anxiety proneness as measured with HA scores, the greater an individual *c* carrier's DLPFC response to aversive social stimuli.

Considerable neurobiological evidence supports the importance of the DLPFC's top-down inhibitory influence on related frontal and limbic circuitry in facilitating the regulation of cognition and emotion.²⁷ Of interest to our findings and to the regulatory role of the DLPFC and related circuitry in emotional behavior more generally, a recent study showed that HA was positively associated with white matter fiber connectivity from the DLPFC to the striatum via the posterior cingulate.²⁸ In addition,

the magnitude of amygdala resting-state functional connectivity with the dorsal region of the frontal cortex was shown to be predictive of HA tendency in healthy female individuals.²⁹

The importance of the DLPFC in emotional regulation has also been supported by several findings in clinical populations. First, our group previously demonstrated aberrant functional interaction between the amygdala and frontal regions including the DLPFC in adult Williams syndrome patients during aversive face processing.⁷ Second, within this same neuroanatomical circuitry, dysregulated amygdala connectivity with DLPFC was selectively observed in generalized social anxiety disorder patients during perception of threatening information, and, moreover, the strength of the amygdala–DLPFC connectivity was related to measures on the Liebowitz Social Anxiety Scale.³⁰ Another study using fMRI to measure resting functional connectivity in children with anxiety disorders as well as in anesthetized young monkeys identified a relationship between functional connectivity and early-life anxiety that appeared to be evolutionarily conserved: across primate species, reduced functional connectivity between the DLPFC and the central nucleus of the amygdala was found to be predictive of increased measures of anxiety.³¹ As childhood anxiety, including separation anxiety, predicts the eventual emergence of adult anxiety,^{32–34} these findings, as well as the separation anxiety findings in children with 7q11.23 CNVs including *GTF2I*,¹⁰ are directly relevant to our brain-imaging findings in adults.

Despite the strong evidence implicating DLPFC-associated circuitry in anxiety, a molecular framework for these system-level dynamics in the context of anxiety has not been delineated. Our current results regarding an effect of *GTF2I* genotype extend previous systems-level brain circuitry findings by identifying one potential molecular candidate that may contribute to biasing the response of relevant neural circuitry to aversive stimuli. The *GTF2I* gene has been identified as a transcriptional factor that binds to promoter elements of many relevant genes,¹³ making it a candidate effector gene that may influence other genes of relevance in the etiology of anxiety, as well as molecular pathways that may be therapeutic targets. For example, it has recently been shown that serotonergic-targeting drugs exhibited a *GTF2I* gene-dose-dependent effect, whereby the anxiolytic effects of these drugs were found to be reduced as a function of the *GTF2I* gene copy-number increase in a mouse model.¹⁴

In summary, our results support the hypothesis that *GTF2I* sequence variation impacts neural correlates of anxiety-related behavior in normal controls, demonstrating a genetic influence on the response repertoire of the DLPFC in processing aversive social cognition. In addition to the implications of our findings of DLPFC-

associated circuitry in anxiety proneness, our current results uncovered a putative neurogenetic mechanism that may, in part, account for the individual difference in behaviorally relevant anxiety traits across the normal population and thereby inform the search for genetic contributors to anxiety disorders. Nonetheless, the correlational nature of our findings in healthy individuals cannot infer causality in anxiety *per se*. Furthermore, additional research examining the influence of *GTF2I* sequence variation and CNV in cell and animal models of disease, as well as in patient populations with contrasting 7q11.23 CNVs is necessary to better understand the full impact of *GTF2I* and related genetic involvement in human anxiety. At a healthy population level, the present findings may suggest an intermediate brain phenotype that could contribute to a better mechanistic understanding of the role of *GTF2I* in anxiety and may provide information to guide the search for new pharmacotherapeutic targets.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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