Archival Report

Biological Psychiatry

A Common Polymorphism in a Williams Syndrome Gene Predicts Amygdala Reactivity and Extraversion in Healthy Adults

Johnna R. Swartz, Rebecca Waller, Ryan Bogdan, Annchen R. Knodt, Aditi Sabhlok, Luke W. Hyde, and Ahmad R. Hariri

ABSTRACT

BACKGROUND: Williams syndrome (WS), a genetic disorder resulting from hemizygous microdeletion of chromosome 7q11.23, has emerged as a model for identifying the genetic architecture of socioemotional behavior. Common polymorphisms in *GTF2I*, which is found within the WS microdeletion, have been associated with reduced social anxiety in the general population. Identifying neural phenotypes affected by these polymorphisms would help advance our understanding not only of this specific genetic association but also of the broader neurogenetic mechanisms of variability in socioemotional behavior.

METHODS: Through an ongoing parent protocol, the Duke Neurogenetics Study, we measured threat-related amygdala reactivity to fearful and angry facial expressions using functional magnetic resonance imaging, assessed trait personality using the Revised NEO Personality Inventory, and imputed *GTF2I* rs13227433 from saliva-derived DNA using custom Illumina arrays. Participants included 808 non-Hispanic Caucasian, African American, and Asian university students.

RESULTS: The *GTF2I* rs13227433 AA genotype, previously associated with lower social anxiety, predicted decreased threat-related amygdala reactivity. An indirect effect of *GTF2I* genotype on the warmth facet of extraversion was mediated by decreased threat-related amygdala reactivity in women but not men.

CONCLUSIONS: A common polymorphism in the WS gene *GTF2I* associated with reduced social anxiety predicts decreased threat-related amygdala reactivity, which mediates an association between genotype and increased warmth in women. These results are consistent with reduced threat-related amygdala reactivity in WS and suggest that common variation in *GTF2I* contributes to broader variability in socioemotional brain function and behavior, with implications for understanding the neurogenetic bases of WS as well as social anxiety.

Keywords: Amygdala, Emotion, Extraversion, fMRI, *GTF2I*, Williams syndrome

http://dx.doi.org/10.1016/j.biopsych.2015.12.007

Hemizygous microdeletion of ~25 genes on chromosome 7q11.23 causes Williams syndrome (WS), a developmental disorder characterized by a unique profile of social and cognitive phenotypes, including hypersociability and increased approach to strangers (1). Systematic investigation of the genes within the WS microdeletion is underway in an effort to better understand the genetic architecture of the disorder specifically and of socioemotional behavior broadly (2,3). Clinical and preclinical studies have highlighted the importance of the WS gene *GTF2I*, which encodes for general transcription factor IIi (GTF2I) implicated in transcriptional regulation of a wide range of genes. For instance, in one case study, the microdeletion of this region was partial and spared *GTF2I*. In contrast to the social profile typically seen in WS, the individual in this case did not exhibit hypersociability and instead was rated by her parents as much less likely to approach strangers compared with individuals with the full WS microdeletion (4,5). A case study for a different individual in which partial deletion spared *GTF2I* and the gene encoding general transcription factor IIi repeat domain-containing protein 1 (*GTF2IRD1*) revealed that this individual was categorized as a typically developing control subject based on multivariate pattern classification analysis with gray matter structure, implicating these genes more broadly in gray matter neuroanatomic abnormalities in WS (6).

More recent research has extended the characterization of *GTF2I* to the general population by examining the association between common single nucleotide polymorphisms (SNPs) in this region and variation in social and cognitive phenotypes. Specifically, two *GTF2I* SNPs in high linkage disequilibrium, rs13227433 and rs4717907, have been associated with individual differences on a composite WS profile score, including reduced communication abilities as rated on the Autism Spectrum Quotient scale, as well as reduced social anxiety (7). Moreover, *Gtf2i*-deficient mice evidenced increased social interaction but not alterations in learning and memory

SEE COMMENTARY ON PAGE 175

ISSN: 0006-3223

or general anxiety, suggesting that deletion of *GTF2I* may play a specific role in the social phenotype of WS (8).

In the present study, we employ an imaging genetics strategy to examine the effect of common variation in imputed *GTF2I* genotypes on a systems-level neural phenotype, threat-related amygdala reactivity, associated with socioemotional behavior broadly and the hypersociability observed in WS specifically (9–11). We further test if this neural phenotype mediates associations between *GTF2I* genotype and extraversion, a personality trait that encompasses increased sociability (12). One previous study reported a positive correlation between extraversion and amygdala reactivity to happy but not threat-related (i.e., angry and fearful) facial expressions (13). However, this study was limited by a small sample size that likely reduced power to detect significant effects and prevented the examination of potential moderators such as sex. We expect that lower threat-related amygdala reactivity to fearful and angry facial expressions will predict higher extraversion for several reasons. First, WS is consistently associated with reduced amygdala reactivity to threat-related facial expressions (9,10). Second, consistent with its role in hypersociability, decreased amygdala reactivity to fearful facial expressions predicts individual differences in social approach toward strangers in individuals with WS (11). Third, mirroring the findings in WS, social anxiety, which is negatively correlated with extraversion (12,14), is consistently associated with relatively increased threat-related amygdala reactivity (15). Based on this evidence, we hypothesized that the *GTF2I* rs13227433 A allele, which has been linked to reduced social anxiety, would be associated with relatively decreased threat-related amygdala reactivity. Moreover, we hypothesized that such genotype-related differences in threat-related amygdala reactivity would indirectly link rs13227433 genotype to variability in extraversion.

METHODS AND MATERIALS

Participants

Participants included 808 young adult university students 18–22 years old who completed the ongoing Duke Neurogenetics Study (DNS) as of March 2, 2015 (Table 1). All procedures were approved by the Duke University Medical Center, and participants provided informed consent before participating in the study. Recruitment and exclusion criteria have been described in detail elsewhere (16–18). Diagnosis of any past or current DSM-IV Axis I disorder or select Axis II disorders (antisocial personality disorder and borderline personality disorder), assessed with the electronic Mini International Neuropsychiatric Interview (19) and Structured Clinical Interview for the DSM-IV subtests (20), was not an exclusion criterion, as the DNS seeks to establish broad variability in multiple behavioral phenotypes related to psychopathology. Consistent with epidemiologic data and the dimensional nature of psychopathology, 157 participants (19%) in the final sample reported here met criteria for at least one current or past Axis I disorder, including 101 with substance use disorders, 39 with major depressive disorder, 7 with bipolar disorder, 13 with bipolar disorder not otherwise specified, and 36 with anxiety disorders (see Supplemental Table S1 for full breakdown of diagnoses). Analyses were restricted to non-Hispanic Caucasian (n = 427), African American (n = 110), and Asian (n = 271) participants, as these were the largest racial/ethnic subgroups available within the DNS (see Supplement for analyses by subgroup).

Table 1. Participant Characteristics as a Function of *GTF2I* rs13227433 Genotype and Race

	C Carrier	AA	Group Difference
Caucasian	n = 162	n = 265	
Age, years, mean (SD)	19.8 (1.3)	19.7 (1.2)	t_{425} = .15, p = .88
Sex (% female)	54%	52%	χ^2_1 = .20, p = .65
Diagnosis[a]	23%	22%	χ^2_1 = .22, p = .64
African American	n = 28	n = 82	
Age, years, mean (SD)	19.6 (1.1)	19.7 (1.2)	t_{108} = −.48, p = .63
Sex (% female)	61%	74%	χ^2_1 = 1.89, p = .17
Diagnosis[a]	21%	21%	χ^2_1 = .01, p = .94
Asian	n = 57	n = 214	
Age, years, mean (SD)	19.3 (1.2)	19.7 (1.3)	t_{269} = −1.96, p = .05
Sex (% female)	42%	59%	χ^2_1 = .5.12, p = .02
Diagnosis[a]	16%	14%	χ^2_1 = .12, p = .74
Total	n = 247	n = 561	
Age, years, mean (SD)	19.6 (1.3)	19.7 (1.3)	t_{806} = −.86, p = .39
Sex (% female)	52%	58%	χ^2_1 =2.27, p = .13
Diagnosis[a]	21%	19%	χ^2_1 = .93, p = .33

[a]Diagnosis is the percentage of participants in each group meeting criteria for at least one current or past psychiatric diagnosis.

Amygdala Reactivity Paradigm

Amygdala reactivity to threat was assessed using an emotional face-matching challenge paradigm shown to consistently elicit robust amygdala reactivity in this and in previous samples (17,18). The paradigm version used in the DNS consists of four blocks of a face-processing task interleaved with five blocks of a sensorimotor control task. During task blocks, participants view a trio of faces and match one of two faces (bottom) identical to a target face (top). Each trial in the face-matching blocks lasts for 4 seconds with a variable interstimulus interval of 2–6 seconds (mean = 4 seconds), for a total block length of 48 seconds. In the control blocks, each of the six shape trios is presented for 4 seconds with a fixed interstimulus interval of 2 seconds for a total block length of 36 seconds. Total task time is 390 seconds.

Blood Oxygen Level–Dependent Functional Magnetic Resonance Imaging Data Acquisition, Preprocessing, and Quality Assurance

Functional magnetic resonance imaging (fMRI) of participants was performed using a research-dedicated GE MR750 3-tesla scanner (GE Healthcare, Marlborough, Massachusetts) at the Duke-UNC Brain Imaging and Analysis Center. A series of 34 interleaved axial functional slices aligned with the anterior commissure–posterior commissure plane were acquired for full-brain coverage using an inverse-spiral pulse sequence to reduce susceptibility artifact (repetition time = 2,000 ms; echo