Journal of Psychiatric Research 83 (2016) 195–202

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

A genome-wide association study of emotion dysregulation: Evidence for interleukin 2 receptor alpha

Abigail Powers [a, *], Lynn Almli [a], Alicia Smith [a], Adriana Lori [a], Jen Leveille [a], Kerry J. Ressler [a, b], Tanja Jovanovic [a], Bekh Bradley [c, a]

[a] Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, United States
[b] McLean Hospital, Harvard Medical School, United States
[c] Atlanta VA Medical Center, United States

ARTICLE INFO

Article history:
Received 1 February 2016
Received in revised form
1 July 2016
Accepted 8 September 2016

Keywords:
Emotion dysregulation
Genome-wide association study
Genetics
Traumatized population
Transdiagnostic risk

ABSTRACT

Emotion dysregulation has been implicated as a risk factor for many psychiatric conditions. Therefore, examining genetic risk associated with emotion dysregulation could help inform cross-disorder risk more generally. A genome-wide association study (GWAS) of emotion dysregulation using single nucleotide polymorphism (SNP) array technology was conducted in a highly traumatized, minority, urban sample (N = 2600, males = 774). Post-hoc analyses examined associations between SNPs identified in the GWAS and current depression, posttraumatic stress disorder (PTSD), and history of suicide attempt. Methylation quantitative trait loci were identified and gene set enrichment analyses were used to broadly determine biological processes involved with these SNPs. Among males, SNP rs6602398, located within the interleukin receptor 2A gene, *IL2RA*, was significantly associated with emotion dysregulation ($p = 1.1 \times 10^{-8}$). Logistic regression analyses revealed this SNP was significantly associated with depression ($Exp(B) = 2.67$, $p < 0.001$) and PTSD ($Exp(B) = 2.07$, $p < 0.01$). This SNP was associated with differential DNA methylation ($p < 0.05$) suggesting it may be functionally active. Finally, through gene set enrichment analyses, ten psychiatric disease pathways (adjusted $p < 0.01$) and the calcium signaling pathway (adjusted $p = 0.008$) were significantly associated with emotion dysregulation. We found initial evidence for an association between emotion dysregulation and genetic risk loci that have already been implicated in medical disorders that have high comorbidity with psychiatric disorders. Our results provide further evidence that emotion dysregulation can be understood as a potential psychiatric cross-disorder risk factor, and that sex differences across these phenotypes may be critical. Continued research into genetic and biological risk associated with emotion dysregulation is needed.

Understanding both genetic and environmental factors contributing to risk and resilience for psychiatric disorders is critical for developing better approaches to prevention and intervention. Recent research indicates many genetic and environmental factors contribute to risk and resilience across diagnostic boundaries (Belsky et al., 2007; Caspi et al., 2003, 2014; Kim-Cohen and Gold, 2009). These findings shift the focus of research towards intermediate phenotypes associated with cross-disorder psychological functioning. One promising phenotype to consider in understanding psychopathology is emotion dysregulation (Bradley et al., 2011a; Cicchetti et al., 1995; Gross, 2002; Gross and Munoz, 1995; John and Gross, 2004).

Emotion dysregulation reflects deficits in the ability to regulate intense, negative, and shifting emotional states and is seen as a transdiagnostic process that is linked to increased risk for the development and maintenance of a range of psychopathology, including depression and posttraumatic stress disorder (PTSD) (Aldao et al., 2010; Berenbaum et al., 2003; Bradley et al., 2011b; Kring, 2008). While it is strongly related to the presence of negative affect, it is in fact a distinct construct representative of problems with the regulation of those negative emotions (Bradley et al., 2011a). Traumatic experiences, especially in early life, appear to put individuals at greater risk for the development of emotion regulation difficulties and subsequent psychopathology (Alink et al., 2009; Horwitz et al., 2001; Kim and Cicchetti, 2010; Southam-

* Corresponding author. Attn: Grady Trauma Project, 49 Jesse Hill Jr Dr., Atlanta, GA 30303, United States.
E-mail address: adpower@emory.edu (A. Powers).

http://dx.doi.org/10.1016/j.jpsychires.2016.09.006
0022-3956/

Gerow and Kendall, 2002). Despite growing evidence of the importance of emotion dysregulation across psychiatric conditions, there remains a great deal to understand about how this cross-disorder risk factor may contribute to psychiatric symptoms.

Only a limited number of studies have investigated genetic associations with emotion dysregulation and similar constructs. These have primarily focused on candidate genes already associated with a range of psychiatric and stress-related conditions, such as the oxytocin receptor gene (OXTR) (Bradley et al., 2011b; Kim et al., 2011), the serotonin transporter gene (5-HTT) (Canli and Lesch, 2007; Hariri and Holmes, 2006), catechol-o-methyltransferase (COMT) (Drabant et al., 2006), and monoamine oxidase A (MAOA) (Buckholtz and Meyer-Lindenberg, 2008; Williams et al., 2009). There are limitations to candidate gene studies, including the need for a priori hypotheses and subjective decisions in what genes to examine. Another method used to study genetic associations are genome wide association studies (GWAS), which use an unbiased approach to provide an evaluation of common genetic variation across the genome and can identify genetic risk loci. To date, there have been no GWAS with emotion dysregulation. However, a number of recent studies performed with major psychiatric disorders have shown evidence of cross-disorder risk genes (Green et al., 2010; Hodgkinson et al., 2004). As part of the Psychiatric Genomics Consortium (PGC), the largest genome-wide analysis of psychiatric illness thus far, investigators found initial evidence that specific SNPs are significantly associated with cross-disorder risk of both childhood-onset and adult-onset psychiatric conditions (Smoller et al., 2013). The investigators also examined shared genetic etiology and found evidence for shared genetic variation across schizophrenia, bipolar disorder, major depressive disorder, autism spectrum disorders, and attention-deficit/hyperactivity disorder (Kendler et al., 2013). In addition, a meta-analysis of GWAS studies for neuroticism, a personality trait characterized by strong negative emotions and associated with emotion dysregulation, found evidence for a genetic locus that has been associated with major depressive disorder, bipolar disorder, and schizophrenia (De Moor et al., 2015). Because emotion dysregulation has been implicated as a risk factor and component of a range of psychiatric conditions, gaining a better understanding of genetic risk loci associated with emotion dysregulation could help to inform cross-disorder risk more generally.

In this study, we present the results of an initial GWAS of emotion dysregulation, demonstrating sex-specific differences in the genetic architecture of this phenotype. Because of the data suggesting that emotion dysregulation is a phenotype that cuts across psychiatric disorders, we then conducted post-hoc analysis examining whether the SNPs identified in the GWAS were associated with current symptom levels of major depressive disorder and PTSD, as well as lifetime history of suicide attempt. Next, we performed additional genomic analyses demonstrating that these SNPs are likely functional in that they are associated with differential regulation of methylation (via meQTL analyses). Finally, using gene set enrichment analyses, we examined pathways related to the top genes within the entire GWAS of emotion dysregulation, to more broadly determine biological processes involved.

1. Methods and materials

1.1. Participants

A total of 2600 African American adults (aged 18–65 years; mean age = 39, 70% female) were enrolled as part of a larger study investigating genetic risk for stress-related disorders. The sample was predominantly low income with approximately 70% of participants unemployed and 85% reporting a household monthly income less than $2000. Participants were recruited from the general medical clinics of a publicly funded hospital, as detailed previously (Gillespie et al., 2009). Individuals were deemed eligible for participation if they could give informed consent and understand English, as determined by a study researcher. Study procedures were approved by the institutional review board of Emory University School of Medicine. After signing the informed consent approved by the Emory Institutional Review Board, an initial interview was administered by trained research assistants.

1.2. Phenotype measures

1.2.1. Emotion dysregulation scale (EDS)

The EDS is a 12-item self-report scale to measure the severity of current emotion dysregulation symptoms (Bradley et al., 2011a; Powers et al., 2015). Items are scored on a 7-point Likert scale ranging from 1 ("Not true") to 7 ("Very true"). Items assess domains of emotional experiencing (e.g., "Emotions overwhelm me"), cognition (e.g., "When I'm upset, everything feels like a disaster or crisis"), and behavior (e.g., "When my emotions are strong, I often make bad decisions"). The internal consistency of the EDS was high ($\alpha = 0.94$). Average total score for the overall sample was 37.19 (SD = 21.08, range = 12–84) with similar scores across sex; for males, mean = 35.04, SD = 20.20; for females, mean = 38.10, SD = 21.38.

1.2.2. Modified PTSD symptom scale (mPSS)

The mPSS (Falsetti et al., 1993) is a psychometrically valid 17-item self-report measure assessing frequency of PTSD symptoms over the prior two weeks. It distinguishes among re-experiencing, avoidance, and hyperarousal symptom clusters of PTSD. Current PTSD diagnosis was determined based on DSM-IV-TR (APA, 2000) criteria. In the overall sample, 769 (30.7%) met for current PTSD (males only, n = 220, 29%).

1.2.3. Beck depression inventory-II (BDI-II)

The BDI-II (Beck et al., 1996) is a widely used, 21-item self-report measurement of depressive symptoms. In the present study, current depression diagnosis was determined based on DSM-IV-TR (APA, 2000) criteria. In the overall sample, 753 (29.1%) met for current depression (males only, n = 201, 26.1%). In addition to the BDI, participants were also asked to self-report any history of suicide attempts (overall sample, n = 335, 13.1%; males only, n = 66, 8.7%).

1.2.4. Traumatic events inventory (TEI)

The TEI is a lifetime assessment of different categories of traumas based on a yes/no answer for natural disasters, accidents, life-threatening illnesses, military combat, witnessing a murder or assault of a family member or close friend, sexual/physical assaults, and childhood abuse for a total of 21 items (Gillespie et al., 2009; Schwartz et al., 2005). Overall level of trauma exposure variable reflects the sum of the different types of traumatic events experienced or witnessed by the participant (overall sample: mean = 4.50, SD = 3.28, range = 0–19; in males: mean = 5.24, SD = 3.29; in females: mean = 4.19, SD = 3.23). Within the overall sample, 40% of individuals reported exposure to child abuse (in males, n = 250; in females, n = 772).

1.3. Genotyping and quality control

Participants provided a saliva sample and/or blood sample. DNA was extracted from saliva in Oragene collection vials (DNA Genotek Inc, Ontario, Canada) using the DNAdvance kit (Beckman Coulter Genomics, Danvers, MA), while DNA from blood was extracted