



Blood gene expression profiles suggest altered immune function associated with symptoms of generalized anxiety disorder



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ABSTRACT

Prospective epidemiological studies found that generalized anxiety disorder (GAD) can impair immune function and increase risk for cardiovascular disease or events. Mechanisms underlying the physiological reverberations of anxiety, however, are still elusive. Hence, we aimed to investigate molecular processes mediating effects of anxiety on physical health using blood gene expression profiles of 336 community participants (157 anxious and 179 control). We examined genome-wide differential gene expression in anxiety, as well as associations between nine major modules of co-regulated transcripts in blood gene expression and anxiety. No significant differential expression was observed in women, but 631 genes were differentially expressed between anxious and control men at the false discovery rate of 0.1 after controlling for age, body mass index, race, and batch effect. Gene set enrichment analysis (GSEA) revealed that genes with altered expression levels in anxious men were involved in response of various immune cells to vaccination and to acute viral and bacterial infection, and in a metabolic network affecting traits of metabolic syndrome. Further, we found one set of 260 co-regulated genes to be significantly associated with anxiety in men after controlling for the relevant covariates, and demonstrate its equivalence to a component of the stress-related conserved transcriptional response to adversity profile. Taken together, our results suggest potential molecular pathways that can explain negative effects of GAD observed in epidemiological studies. Remarkably, even mild anxiety, which most of our participants had, was associated with observable changes in immune-related gene expression levels. Our findings generate hypotheses and provide incremental insights into molecular mechanisms mediating negative physiological effects of GAD.

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1. Introduction

Individuals with generalized anxiety disorder (GAD) experience daily excessive, uncontrollable, and often irrational worry (Torp et al., 2011). GAD is fairly common with a lifetime prevalence of 5.7% (Kessler et al., 2005). Prospective epidemiological studies have found that GAD is a risk factor for cardiovascular diseases and cardiac events over many ensuing years (Dimsdale, 2010; Martens et al., 2010; Janszky et al., 2010; Roest et al., 2010). For instance, a prospective cohort study following 1015 patients for a mean of 5.6 years found that GAD was associated with a 62% higher rate of cardiovascular events (defined as stroke, transient ischemic attack, heart failure, myocardial infarction, or death) after

comorbid conditions, including major depressive disorder, hypertension, history of myocardial infarction, diabetes, congestive heart failure, stroke, cardiac disease severity, medication use, and age have been accounted for (Martens et al., 2010). Another prospective study of 49,000 young Swedish men followed for 37 years found multi-adjusted hazard ratios for coronary heart disease and acute myocardial infarction to be 2.17 and 2.51 respectively for anxious men (Janszky et al., 2010). Interestingly, a variety of potential mediators for the association of GAD and cardiovascular diseases and events have been examined, including C-reactive protein level, heart rate variability, smoking, medication non-adherence, and physical inactivity, but they did not explain the association (Martens et al., 2010). Why anxiety increases risks of cardiovascular disease and events is still poorly understood.

Along the same lines, several studies have shown that that psychological stress, such as feeling stressed, anxious, or depressed, has a negative impact on immune functions, including reducing

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immune response to influenza (Miller et al., 2004; Vedhara et al., 1999) or pneumococcal pneumonia vaccines (Glaser et al., 2000), reactivating latent herpes virus (Cohen et al., 1999), and increasing severity and duration of infectious diseases (Godbout and Glaser, 2006; Arranz et al., 2007; Stone et al., 1992). For example, in a prospective study of 83 healthy young adults, those who felt more stressed had a slower rate of production of antibody titer and less maintenance of the produced antibody titer to the influenza vaccination over the 4-month follow-up period (Miller et al., 2004). Consistently, an epidemiological study found that having any anxiety disorder in the past year was associated with 1.7 times higher risk of having infectious conditions such as tuberculosis or bronchitis after comorbid depressive disorders, substance use disorders, and relevant sociodemographic factors have been adjusted for (Sareen et al., 2005). Understanding biological mechanisms by which psychological stress influences immune function has important clinical implications in treatment and prevention.

Hence, we aimed to investigate molecular mechanisms underlying these observed physiological consequences of anxiety symptoms using peripheral blood gene expression profiles of anxious and control individuals. Specifically, we performed a genome-wide differential gene expression analysis in anxiety versus control groups, followed by gene set enrichment analysis to gain insights into biological mechanisms of the differentially expressed genes. Additionally, we examined associations between anxiety and the nine highly conserved major axes of covariation in blood gene expression, also followed by gene set enrichment analysis.

The notion of major axes of covariance in blood gene expression arose from observations that gene expression profiles in human tissues typically have complex and pervasive co-regulation patterns (Chaussabel et al., 2008; Preininger et al., 2013). To capture the covariance structure of peripheral blood gene expression, Chaussabel and colleagues queried multiple blood gene expression datasets for conserved modules of transcripts that differ by disease state (Chaussabel et al., 2008). These modules were further refined by Preininger and colleagues into nine major axes of covariation which are consistently observed in whole blood from healthy adults (Preininger et al., 2013). Each of the nine major axes of covariation consists of 99–1028 strongly co-regulated genes (Preininger et al., 2013). The nine axes collectively capture 37% to 51% of the blood transcriptomic variance depending on the population. These nine axes were shown to be highly repeatable across six studies that were carried out in different geographical locations (Atlanta, Morocco, Finland, Australia, and England) (Preininger et al., 2013). These axes were also differentially expressed under a wide variety of disease conditions, and in response to environmental and genetic stimuli (Preininger et al., 2013; Nath et al., 2012).

2. Methods

2.1. Study participants

Participants were recruited by the Center for Health Discovery and Well-being (CHDWB), which was established by Emory University in 2008 as a research center to evaluate the effectiveness and utility of a health and prevention-focused rather than disease-focused care setting. Participants of the CHDWB were Emory University employees who were randomly selected and invited to participate. Inclusion criteria were 18 years of age or older and being able to give informed consent. Exclusion criteria consisted of (a) current malignant neoplasm, (b) history of malignancy during the previous five years, (c) having an acute illness in the two weeks prior to baseline assessment, (d) hospitalization in the preceding year due to acute or chronic disease or psychiatric disorder, (e) significant change in a chronic medical condition (such as

hypertension or diabetes) requiring new medication, and (f) history of substance abuse or alcoholism (Ferranti et al., 2013). A total of 546 of the approximately 700 participants were included in this study on the basis of availability of gene expression data.

2.2. Anxiety phenotype

Anxiety symptoms were assessed with the GAD-7 scale (Spitzer et al., 2006), a well-validated and efficient tool for screening and assessing symptoms of generalized anxiety disorder. The GAD-7 has been validated both in the general population (Lowe et al., 2008) and primary care setting (Spitzer et al., 2006) showing excellent internal consistency (Cronbach $\alpha = 0.92$), and very good test-retest reliability (intraclass correlation = 0.83). Its score ranges from 0 to 21, with higher scores reflecting more anxiety symptoms. Additionally, the GAD-7 is not only highly sensitive (up to 92%) and specific (up to 82%) in detecting generalized anxiety disorder, but also very good at detecting social anxiety disorder and post-traumatic stress disorder when compared with diagnoses made via interview by mental health professionals (Spitzer et al., 2006). Further, the GAD-7 scores were shown to be strongly correlated with WHO-DAS-II disability score ($r = 0.704$; $p < 0.001$), particularly for Participation in Society ($r = 0.741$), Understanding Communication ($r = 0.679$), and Life Activities ($r = 0.638$) dimensions (Ruiz et al., 2011). A score of 5–9 on the GAD-7 indicates mild anxiety, 10–14 moderate, and 15–21 severe anxiety symptoms (Spitzer et al., 2006). In our sample of 546 participants, we categorized participants with GAD-7 scores of ≥ 5 as having anxiety symptoms and those with GAD-7 scores ≤ 1 as controls. Thus, there were 157 anxious and 179 control participants, and anxiety was included in all the analyses as a dichotomous variable.

2.3. Gene expression profiles

RNA was extracted from whole blood collected in Tempus tubes during the participants' first visit to the CHDWB. All samples had RIN (Bioanalyzer RNA Integrity Number) > 8 indicating high quality. Complementary DNA was derived from RNA and then hybridized, and raw probe intensities were generated on Illumina HT12 v3 or v4 beadchip arrays. Probes with expression levels below background were filtered out, namely 33,120 and 33,220 probes respectively, leaving 14,111 probes for inclusion in the analysis. These 14,111 probes have been found to express consistently across multiple studies. We then performed \log_2 transformation and normalization, using the Supervised Normalization Method, (Mecham et al., 2010) modeling standardized average GAD-7 score as the biological variable and removing the effects of the adjustment variables batch, RIN, and self-reported ethnicity. The sample included 370 females and 176 males, 134 African American, 26 Asian American, 1 Native American, and 382 Caucasian American participants. The dataset has been submitted to GEO with the accession number GSE61672.

2.4. Nine major axes of covariance of blood gene expression

Each of the nine major axes of covariance is defined by 10 blood informative transcripts (BITs), and the derivation of these 10 BITs has been described in detail elsewhere (Preininger et al., 2013). Briefly, these axes capture conserved patterns of co-regulation of gene expression as observed across multiple peripheral blood gene expression studies performed by different groups. Each axis includes hundreds to thousands of genes that suggest roles in specific aspects of immune and hematological functions. Each axis is represented by an Axis score, which is the first principal component of the 10 highly co-regulated BITs, and captures, on average, 79% of the variance of these 10 BITs (Preininger et al., 2013).

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