

Research report

A translational approach to the genetics of anxiety disorders

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ARTICLE INFO

Keywords:

Anxiety
Genetics
Childhood trauma
Animal model
Epigenetics

ABSTRACT

There have been important advances in our understanding of the genetic architecture of anxiety disorders. At the same time, relatively few genes have reached genome wide significance in anxiety disorders, and there is relatively little work on how exposure to an adverse environment impacts on gene expression in either animal models or human clinical populations. Here we assessed differential expression of genes of the dorsal striatum involved in synaptic transmission in an animal models of early adversity (maternal separation followed by restraint stress), and investigated whether variants in these genes were associated with risk for anxiety disorders, particularly in the presence of environmental stressors. Fifty-two male Sprague Dawley rats underwent maternal separation, and gene expression was studied using array technology. The human homologues of the differentially expressed genes were screened and analysed in a DSM-IV anxiety disorders cohort, and healthy controls (patients, $n = 92$; controls, $n = 194$), using blood. Two candidate genes (*Mmp9* and *Bdnf*) were aberrantly expressed in the experimental rodent group relative to controls. Four single nucleotide polymorphisms (SNPs) in the human homologues of these genes were significantly associated with susceptibility for anxiety disorders (*MMP9*: rs3918242 and *BDNF*: rs6265, rs10835210 and rs11030107). Three of these (*BDNF*: rs6265, rs10835210, rs11030107) were found to interact significantly with childhood trauma severity resulting in increased likelihood of an anxiety disorder diagnosis. This study provides insights into the utility of rat models for identifying molecular candidates for anxiety disorders in humans.

1. Introduction

There have been important advances in our understanding of the genetic architecture of anxiety disorders. Attempts have also been made in both animal models and clinical populations to look at alterations in gene expression that may underpin the development of anxiety disorders [1,2]. The clinical heterogeneity of anxiety disorders, and the contribution of environmental factors [3–6] have made it complex to fully elucidate the pathogenesis of anxiety disorders. Understanding how gene variation and factors such as adverse environments impact on gene expression, may lead to more detailed understanding of the relevant biological pathways involved in these prevalent and disabling conditions.

At the same time, relatively few genes have reached genome wide significance in anxiety disorders, and there is relatively little work on how exposure to an adverse environment impacts on gene expression in either animal models or human clinical populations [7]. Animal models

continue to be useful tools for investigating the pathophysiology of human anxiety disorders, with rodents being especially appropriate as 1) the central nervous system is sufficiently developed to mimic aspects of human anxiety, and 2) there are multiple strains of rats available to choose from (inherently calm vs. inherently anxious) [8,9]. Despite this there has been relatively little work attempting to translate between animal findings on genes involved in processes such as synaptic transmission, a key process believed to be involved in the psychopathology of anxiety [10–13], and the clinical manifestation of anxiety in humans. Furthermore early adversity is a well-established risk factor for human anxiety [14–17]. Pre-existing genetic vulnerability (genetic risk) may interact with adverse life events to result in the development of anxiety disorders [18,19].

Here we assessed differential expression of genes involved in synaptic transmission in an animal model of early adversity (maternal separation followed by restraint stress), and investigated whether variants in these genes were associated with risk for anxiety disorders,

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particularly in the presence of environmental stressors. Our hope was to provide proof of principle for better translation between gene expression studies in animal studies of adversity and anxiety, and gene association studies in humans suffering from anxiety disorders.

2. Results

2.1. Animal work

2.1.1. Behavioural tests

The animal material, work and behavioural analyses formed part of a larger study and full methodology and further data analyses are described by Van Zyl et al. [20].

Briefly, a total of 52 Sprague Dawley rats were divided into four groups (Those exposed to restraint-stress (indicative of a mild adulthood stressor), those exposed to maternal separation (indicative of a major early-life trauma), those exposed to both (to provide insight in terms of early developmental stress and subsequent adulthood stress), and an unexposed control group). Depression- and anxiety-like behaviours we evaluated by subjecting each group to standardised behavioural tests, namely the forced swimming test, the elevated-plus maze test and the open-field test [20].

The core behavioural findings revealed significant depression and anxiety-like findings comparing maternal separation, restraint stress, and combination maternal separation-restraint stress to controls [20].

2.1.2. RT² Profiler gene expression data

The RT² Profiler array (Qiagen) and online data analysis software (www.sabiosciences.com/dataanalysis.php) identified several candidate genes (*Bdnf*, *Mmp9*, *Egr2*, *Egr4*, *Ntf4*, *Grm2* and *Arc*) to be either up- or down-regulated at greater than 1.7-fold in the dorsal striatum of animals subjected to maternal separation, restraint stress and a combination of maternal separation-restraint stress; relative to the control group using the 2^{-ΔΔCt} methodology (Fig. 1).

2.2. Human anxiety disorders cohort

2.2.1. TagSNP identification

A tagSNP approach was employed using the HapMap project online database (www.hapmap.org); HapMap genome browser release #27 (Phase II & III – merged genotypes and frequencies) on Feb09, on NCBI B36 assembly, dbSNP b126. SNPs were identified based on MAFs of ≥0.2 and R² ≥ 0.8 as cut-offs. The only human homologue genes for which sufficient HapMap data were available to perform a tagSNP

Table 1
tagSNPs selected for BDNF and MMP9 screening based on CEU.

GENE	TagSNPs	Other alleles Captured
<i>BDNF</i>	rs6265	None
	rs7103411	rs6484320
	rs11030104	rs16917237
	rs1401635	rs11030108
		rs1013402
		rs7124442
		rs7127507
	rs10835210	rs7103873
	rs11030107	rs11030101
		rs10835211
<i>MMP9</i>	rs11030109	None
	rs28383487	n/a
	rs2274755	None
	rs2236416	rs2274756
		rs3918261
	rs3918253	rs3918256
	rs3787268	None
	rs3918242	n/a
	rs17577	n/a
	rs13925	n/a

*n/a refers to SNPs already captured elsewhere; CEU: central European from Utah.

approach were *BDNF* and *MMP9*. The CEU (Utah residents with ancestry from Northern and Western Europe) population was used in tagSNP identification and all the identified tagSNPs were selected for inclusion in this study (Table 1).

2.2.2. Bi-allelic loci association testing

Table 2 depicts the significant results of case-control bi-allelic locus association analyses for unadjusted, adjusted and interaction with childhood trauma questionnaire (CTQ) [21], total score values for the polymorphisms considered. Statistically significant associations were observed for 4 (*MMP9*: rs3918242; *BDNF*: rs6265 (Val66Met), rs10835210, rs11030107) polymorphisms.

Significant associations with anxiety disorders diagnoses were observed for *MMP9* (rs3918242) and *BDNF* (rs6265 and rs10835210). Further statistical evaluation of rs3918242 indicated an OR value much higher than 1 (4.674; CI: 2.34–10.4) (Table 3) for the CT genotype, suggesting that this variant is associated with increased susceptibility risk to develop anxiety disorders. The rs6265 (*BDNF*) polymorphism presented with OR values less than 1 for the AG (OR = 0.001;

Synaptic Plasticity Fold-Regulation

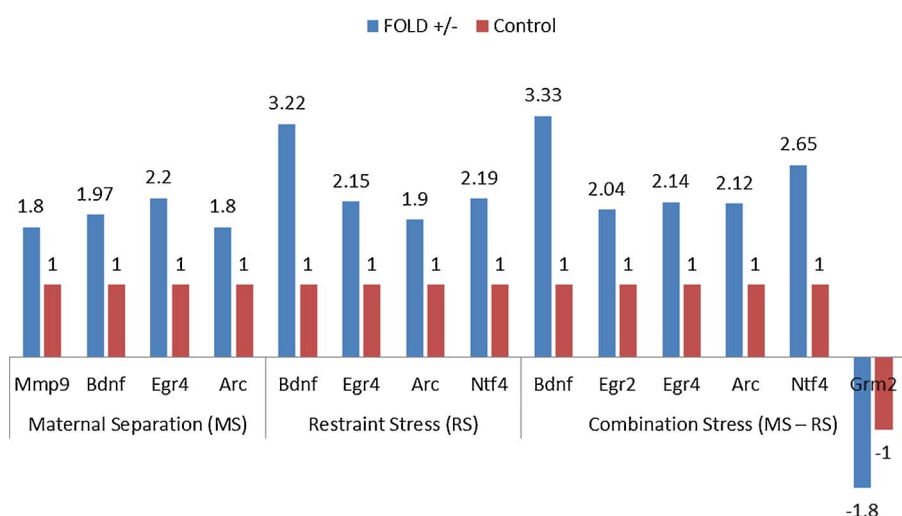


Fig. 1. Graphical representation of fold-regulation increases and decreases in dorsal striatal gene expression for genes in the synaptic plasticity RT² Profiler Array (PARN-126E, SABiosciences; housekeeping genes included), normalized to 1 (relative to control (nRS nMS) rats). Fold-regulation values > 1.7-fold were considered and are depicted. N = 13 for each group.

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