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Anxious Temperament Related Gene Expression in the Primate Amygdala

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Abstract

Anxious temperament (AT) is a trait-like behavioral phenotype in children that represents a risk factor for the development of later anxiety, depression, and substance abuse disorders. Our group has validated a developmental rhesus monkey model of AT and, in a large (n=238) single family pedigree, demonstrated that AT is associated with increased amygdala metabolic activity measured using FDG-PET. By directly sampling tissue from the amygdala region identified to be predictive of AT in a subset of these animals (n=24), we sought to identify individual differences in mRNA levels that were predictive of individual differences in amygdala metabolism and AT. Data from rhesus macaque microarray GeneChips (Affymetrix) revealed a number of candidate genes with expression patterns that significantly correlated with both AT and amygdala metabolism. Establishing the involvement of these candidate genes is a critical step in understanding the extent to which genetic polymorphisms and/or epigenetic modifications account for the differential expression of genes that influence amygdala metabolism and AT. This approach provides a unique opportunity to understand molecular interactions among genetic and epigenetic influences relevant to the brain circuit that underlies the childhood risk to develop stress-related psychopathology.

Study Design

Selected Extreme Animals at Time 1

High Amygdala Reactive (n=12)

Low Amygdala Reactive (n=12)

About 1 year
(ranges 5 to 1.5 years)

Time 1: Correlation between AT and Amygdala Metabolism

There was no main effect of stress on AT or any of the components of AT (i.e., Freezing, Cooling, or Cortisol).

Time 1 Anxious Temperament

Stress (Standardized and Residualized for Age and Sex)

Time 1: Microarray Experiment

All analyses were performed using the open-source statistical package R, and the bioconductor libraries for Microarray analysis (http://www.bioconductor.org/). We used RMA background correction, normalized across chips with a constant, ignored mismatch probes, and summarized across probes with using the median-polish technique. Resulting expression estimates for each probe set were filtered based on mean expression levels (>log2(100)). Across subject analyses were performed using a robust regression and significance was assessed using an empirical bayes method (Smyth, 2004), and corrected for multiple comparisons using FDR. Genes were annotated using publicly available annotations that were verified by BLASTing against the transcript database (http://www.unmc.edu/rhesusgenechip/).

We examined genes in the “Neuroactive ligand-receptor interaction” pathway using the KEGG database (ko04080). Results demonstrated a number of significant correlations corrected for multiple comparisons within this pathway for correlations with both AT and Amygdala FDG.

KO04080: Significant correlations with mean AT

KO04080: Significant correlations with mean amygdala metabolism

Time 3: MicroArray Experiment

“Neuroactive ligand-receptor interaction” (KO04080)

KO04080: Significant correlations with mean AT

KO04080: Significant correlations with mean amygdala metabolism

All annotated transcripts

KO04080: Significant correlations with both mean AT and mean amygdala metabolism