



## Examining gene–environment interactions in comorbid depressive and disruptive behavior disorders using a Bayesian approach



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### ABSTRACT

**Objective:** The objective of this study was to apply a Bayesian statistical analytic approach that minimizes multiple testing problems to explore the combined effects of chronic low familial support and variants in 12 candidate genes on risk for a common and debilitating childhood mental health condition.

**Method:** Bayesian mixture modeling was used to examine gene by environment interactions among genetic variants and environmental factors (family support) associated in previous studies with the occurrence of comorbid depression and disruptive behavior disorders youth, using a sample of 255 children.

**Results:** One main effect, variants in the oxytocin receptor (*OXTR*, *rs53576*) was associated with increased risk for comorbid disorders. Two significant gene  $\times$  environment and one significant gene  $\times$  gene interactions emerged. Variants in the nicotinic acetylcholine receptor  $\alpha 5$  subunit (*CHRNA5*, *rs16969968*) and in the glucocorticoid receptor chaperone protein FK506 binding protein 5 (*FKBP5*, *rs4713902*) interacted with chronic low family support in association with child mental health status. One gene  $\times$  gene interaction, 5-HTTLPR variant of the serotonin transporter (*SERT/SLC6A4*) in combination with  $\mu$  opioid receptor (*OPRM1*, *rs1799971*) was associated with comorbid depression and conduct problems.

**Conclusions:** Results indicate that Bayesian modeling is a feasible strategy for conducting behavioral genetics research. This approach, combined with an optimized genetic selection strategy (Vrieze et al., 2012), revealed genetic variants involved in stress regulation (*FKBP5*, *SERT*  $\times$  *OPMR*), social bonding (*OXTR*), and nicotine responsivity (*CHRNA5*) in predicting comorbid status.

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### 1. Introduction

There is overwhelming evidence that depression and disruptive behavior disorders co-occur more frequently than by chance alone (Angold et al., 1999). Despite the differences in presentation, a high proportion (22.7–83.3%) of children and adolescents with a diagnosis of depression have comorbid disruptive behavior disorders (conduct disorder, and/or oppositional-defiant disorder), and a

high proportion (8.5–45.4%) of those with disruptive behavior disorders meet criteria for co-morbid depression (Angold et al., 1999) (Wolff and Ollendick, 2006). Comorbid depression and disruptive behavior disorders are associated with increased impairment, school failure and suicidal behaviors (Wolff and Ollendick, 2006). The high prevalence and associated impairment have garnered research attention for this heterotypic comorbid condition. Researchers have suggested that the common occurrence of comorbidity across externalizing and internalizing dimensions is evidence for a broad construct of emotional distress that underlies different forms of psychopathology. Examination of the structure of comorbid depression and disruptive behavior disorders indicates that classes of conditions are differentiated by number of symptoms as opposed to symptom type (Mezulis et al.,

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2011). Krueger (2002) suggests that the co-occurrence of depression, anxiety, disordered conduct and substance dependence stems from the common vulnerability factors associated with both conditions (Krueger, 2002). In this context, co-morbid depression and disruptive behavior disorders could represent a particularly severe phenotype of emotional distress in youth.

### 1.1. Diathesis-stress framework

The diathesis-stress framework is the predominate model driving gene by environment interaction ( $G \times E$ ) research. Core to diathesis stress model is the view that some individuals are vulnerable due to biological underpinnings and disproportionately likely to be affected adversely by environmental stress. Despite focused attention in the identification of  $G \times E$  in association studies, identification of critical variants has been difficult to replicate. In a seminal  $G \times E$  study by Caspi and colleagues 5-HTTLPR was found to interact with a measure of stressful life events to predict adult depression (Caspi et al., 2003). A decade after the 2003 study, experts disagree about the nature of these interactions, and meta-analyses efforts to summarize findings support very different conclusions (Caspi et al., 2010; Caspi et al., 2003; Karg et al., 2011; Risch et al., 2009). The state of the literature has prompted researchers to evaluate the limitations of existing  $G \times E$  research findings and methods and to recommend new strategies for selecting genetic variants (Vrieze et al., 2012). A recommended strategy that may optimize analysis for  $G \times E$  interactions capitalizes on both genome wide association studies (GWAS) and candidate gene approaches by filtering the set of single nucleotide polymorphisms (SNPs) that have indicated promise in past empirical work (Vrieze et al., 2012). Using genetic variants that have been identified in the literature, rather than those based on hypothesized biological mechanisms, may open additional avenues of exploration unconstrained by knowledge of the putative mechanism of action.

### 1.2. Etiology of comorbid depression and disruptive behavior disorders

The underlying premises that drove phenotype select for this study are 1) adolescent depression and conduct disorders tap a common biological substrate, and 2) children who meet diagnostic criteria for both depression and conduct disorders are particularly vulnerable to damage due to this underlying substrate and constitute an uncontroversially affected group. Research probing possible mechanisms responsible for the phenotype of comorbid depression and disruptive behavior disorders has highlighted a common vulnerability model (Fergusson et al., 1996). Previous examination of etiological factors contributing to comorbid depressive and disruptive behavior disorders included in this study are identified in the following three sections: environmental factors, genetic factors, and  $G \times E$  factors.

The role of environmental influences in developmental trajectories of depressive and disruptive behavior disorders has been widely supported in research examining human and animal development, with studies indicating as much as two thirds of the variance accounted for by shared environmental risk factors (Fergusson et al., 1996). In particular, weak parent–child attachments and low family support lead to deficits in coping and self-regulatory behaviors (Repetti et al., 2002). Further, there is evidence that chronic exposure to unsupportive family environments increases risk for adolescent and later psychiatric illness in part through biobehavioral pathways, including detrimental impacts to developing neuroendocrine systems (Repetti et al., 2002). The association between chronic lack of family support and child

psychopathology has been highlighted both concurrently and prospectively for comorbid depressive and disruptive behavior disorders (Repetti et al., 2002). Previous studies indicate that families characterized by lack of support are more likely to have children with internalizing and externalizing problems, whereas higher quality parent–child relationships also predict lower symptoms in both domains (Galambos et al., 2003). Although family environmental influences have a robust literature connecting to depression and disruptive behavior disorders, most study designs focused solely on environmental factors and thus were not sensitive to genetic or  $G \times E$  as mechanisms of risk.

### 1.3. Genetic vulnerability for depressive and conduct disorder phenotypes

Variants important for the downregulation of emotional arousal and stress responses have driven a large portion of the  $G \times E$  studies, including the 43 bp insertion/deletion polymorphism (5-HTTLPR) in the promoter region of the serotonin transporter (SERT) gene, which influences the available amount of SERT protein with resultant effects on brain development (Jedema et al., 2010). This variant has been widely associated with emotional reactivity, stress response and depression occurring as a result of childhood abuse or neglect (Karg et al., 2011). The coding val66met (rs6265) variant of the brain derived neurotrophic factor (BDNF) affects stress resilience, either alone (Taliaz et al., 2011) or in combination with the 5-HTTLPR variant of SERT (Martinowich K, 2008). The coding val159met polymorphism of the catechol-O-methyltransferase (COMT, rs4680) gene has been associated with stress reactivity (Papaleo et al., 2008) and psychopathology both alone (DeYoung et al., 2010; Waugh et al., 2009) and in combination with 5-HTTLPR (Conway et al., 2010). Oxytocin is a neuropeptide with a strong role in human attachment and social function (Macdonald and Macdonald, 2010). A variant in its receptor (OXTR, rs53576) has been associated with stress reactivity and depression (Saphire-Bernstein S, 2011). Similar to the SERT, BDNF, and COMT genes described above, there is also evidence for interaction of OXTR variants with the 5-HTTLPR polymorphism of SERT (Montag et al., 2011). We included the coding asn40asp variant of the  $\mu$  opioid receptor (OPRM1, rs1799971) on the basis of a prior study showing its influence on parent–child relations (Copeland et al., 2011). The coding variant asp398asn of the nicotinic acetylcholine receptor  $\alpha 5$  subunit (CHRNA5, rs16969968) is associated with externalizing and reward-driven behaviors (Stephens et al., 2012). Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has been tied to an abnormal stress response and broad deficits in emotional reactivity and regulation (Ehlert et al., 2001). Consequently a number of common variants in genes which form part of the HPA axis are associated with depression and stress sensitivity in adolescents. The glucocorticoid receptor (GCCR) rs6198 variant has been linked to glucocorticoid sensitivity, depression in the presence of childhood adversity, and externalizing behaviors in children ((Bet et al., 2009). The chaperone protein FK506 binding protein 5 (FKBP5) alters glucocorticoid receptor function. Variants in this gene, among them SNP rs4713902, have been associated with cortisol reactivity, stress vulnerability, and depression in children and adults (Luijk MP, 2010; Menke A, 2013). Likewise, variants in the corticotropin-releasing hormone receptor 1 (CRHR1, rs1876831) and corticotropin releasing hormone binding protein (CRHBP, rs10055255) have been associated with cortisol reactivity in children (Sheikh HI, 2013). Finally, the variants rs2251219 in polybromo-1 (PBRM1) and rs1170169 in diacylglycerol kinase eta were included because they were among the few SNPs which have previously shown robust associations with affective disorders in genome-wide association studies (Weber et al., 2011).

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