Infant Behavior and Development 49 (2017) 267–271

Contents lists available at ScienceDirect

Infant Behavior and Development

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

An exploration of common dopaminergic variants and behavior problems in siblings at high risk for autism spectrum disorder

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ARTICLE INFO

Keywords:
High-risk siblings
Dopamine
Behavior problems

ABSTRACT

Younger siblings of children with ASD often exhibit elevated internalizing and externalizing problems. We investigated common dopaminergic variants (*DRD4* and *DRD2*) in relation to behavior problems at 36 months. Genotypes linked to less efficient dopaminergic functioning were associated with higher internalizing problems in high-risk siblings.

1. Introduction

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental condition characterized by social-communication deficits and restricted/repetitive interests and behaviors (American Psychiatric Association, 2013). Younger siblings of children with ASD (high-risk siblings) often display subclinical levels of ASD symptoms and are at elevated risk of receiving an ASD diagnosis (Georgiades et al., 2013; Messinger et al., 2013; Ozonoff et al., 2011). Children with ASD often have comorbid psychological diagnoses, which significantly impact ASD symptoms and other outcomes including quality of life of the individual (Kuhlthau et al., 2013) and parental and family stress (Davis & Carter, 2008). Both internalizing and externalizing behavior problems may also be elevated in high-risk siblings (Rodrigue, Geffken, & Morgan, 1993). However, limited work has examined behavior problems in high-risk siblings or potential predictors of these difficulties. The robust effect of common dopaminergic variants on behavior problems in typically developing children (e.g., Comings et al., 1996; Schmidt et al., 2002) is likely present in children with ASD and high-risk siblings as well. The purpose of this study was to examine the association of two of these dopaminergic variants, *DRD4* and *DRD2*, with internalizing and externalizing behavior problems in high-risk siblings.

Behavior problems encompass internalizing symptoms such as anxiety, depression, and withdrawal, and externalizing symptoms such as high activity level, impulsivity, and aggression. Behavior problems are elevated in children with ASD and are associated with the severity of ASD symptomatology, with children displaying higher levels of ASD symptoms also exhibiting more behavior problems (Pearson et al., 2006). Behavior problems in children with ASD are also associated with family-level functioning, such as increased parent stress and depression (Bauminger, Solomon, & Rogers, 2010; Davis & Carter, 2008; Ekas & Whitman, 2010).

Elevated levels of internalizing and externalizing problems are often reported in siblings of children with ASD (Fisman et al., 1996; Orsmond & Seltzer, 2007; Rodrigue et al., 1993; Verté, Roeyers, & Buysse, 2003). Parents of high-risk siblings eventually diagnosed with ASD report higher levels of internalizing and externalizing behavior problems than parents of high-risk siblings who do not receive an ASD diagnosis (Mahan & Matson, 2011; Maskey et al., 2013; van Steensel, Bögels, Magiati, & Perrin, 2014). Even high-risk siblings who do not receive an ASD diagnosis often exhibit more behavior problems by parent report than low-risk siblings, who

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http://dx.doi.org/10.1016/j.infbeh.2017.10.002
Received 2 June 2017; Received in revised form 13 October 2017; Accepted 13 October 2017

have older siblings without ASD (Schwichtenberg et al., 2013). In fact, behavior problems have been linked to ASD-like traits even in low-risk samples (Möricke, Swinkels, Beuker, & Buitelaar, 2010).

The dopaminergic system plays a role in reward sensitivity and motivation in typically developing children and adults. Outside the context of familial risk for ASD, common variants in two dopaminergic genes, *DRD4* and *DRD2*, associated with the efficiency of dopaminergic functioning, have been linked to attentional and behavioral difficulties (Cerdá, Sagdeo, Johnson, & Galea, 2010; Papageorgiou & Ronald, 2013). Typically developing children with the 7-repeat allele of the *DRD4* gene exhibit elevated levels of behavior problems (e.g., Schmidt, Fox, & Hamer, 2007; Schmidt et al., 2002). Among children with ASD, those with the 7-repeat allele tend to have greater behavior problems than those without the 7-repeat allele (Gadow, DeVincent, Olvet, Pisarevskaya, & Hatchwell, 2010). Children with the A allele of the Taq1A polymorphism on *ANKK1* associated with *DRD2* (hereafter *DRD2*) have exhibited elevated behavior problems (Comings et al., 1996; Hayden et al., 2010; Lu et al., 2001). The A allele has also been associated with risk for ASD, as well as related social interaction and communication difficulties (Hettinger et al., 2012; Salem et al., 2013). Gene-environment interactions with dopaminergic variants have also been linked to behavior problems (e.g., Weeland, Overbeek, de Castro, & Matthys, 2015). To our knowledge, these common dopaminergic variants have not been examined in relation to children's behavior problems among siblings at elevated risk for ASD. Links between genotypes and behavior problems in high-risk siblings could aid in early identification of individuals at greatest risk for internalizing or externalizing difficulties and targeted prevention and intervention efforts.

The current study investigated the relationship between common dopaminergic variants, *DRD4* and *DRD2*, and levels of internalizing and externalizing behavior problems in the context of familial risk for ASD. Given prior research exhibiting relationships between genotypes associated with less efficient dopaminergic functioning and behavior problems, we expected that these genotypes would be associated with greater behavior problems in high- and low-risk siblings.

Participants were part of a larger longitudinal study of social and emotional development in younger siblings of children with and without ASD. High-risk siblings (n = 34; male = 22) had at least one older sibling diagnosed with ASD, confirmed upon study enrollment. Low-risk siblings (n = 27; male = 10) had at least one older sibling and no family history of ASD in first degree relatives. Participants were included in the current study if they had complete data on behavior problems (collected at three years of age) and genotypes (collected via saliva samples during the longitudinal study). The final sample was 52.0% Hispanic/Latino, 36.8% non-Hispanic White/Caucasian, and 11.2% other ethnicities. All procedures were reviewed and approved by the University of Miami Institutional Review Board, and written informed consent was obtained from parents of all participants.

The Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001), a 99-item parent-report measure of behavioral and emotional problems in children ages 1.5-5 years, was completed by parents at 36 months. Two domain scale scores are derived: Internalizing, designed to capture symptoms of anxiety and depression, and Externalizing, designed to capture rule-breaking and aggressive behaviors. Domain scale t-scores were used for analyses.

Participants provided saliva samples using Oragene DNA collection kits. Genotyping was conducted at the John P. Hussman Institute for Human Genomics at the University of Miami Miller School of Medicine. Genotypes for *DRD4* (rs1805186) were grouped according to the presence or absence of the 7-repeat allele ("0" = no 7-repeat, "1" = at least one 7-repeat). Genotypes for *DRD2* (rs1800497) were grouped according the presence or absence of the A allele ("0" = no A allele, "1" = at least one A allele). Substantive analyses utilized a cumulative dopamine gene score (indexing dopaminergic functioning across both *DRD4* and *DRD2* genotypes). This score was created by summing the grouped *DRD4* and *DRD2* genotypes indicating less efficient functioning (*DRD4* 7-repeat allele present [1] or not [0] + *DRD2* A allele present [1] or not [0])—resulting in scores of 0, 1, or 2 "risk" genotype sets. Higher dopamine scores reflected more genotypes associated with less efficient dopaminergic functioning (e.g., a participant with a *DRD4* 7-repeat allele and no *DRD2* A allele would receive a dopamine score of 1).

Genotypes were consistent with Hardy-Weinberg equilibrium for *DRD4*, $\chi^2(1) = 0.00$, $p = 0.82$, and *DRD2*, $\chi^2(1) = 0.11$, $p = 0.85$ (Rodriguez, Gaunt, & Day, 2009). Genotype frequencies for *DRD4*, $p = 0.57$, *DRD2*, $p = 0.41$, and dopamine composite scores, $p = 0.81$, did not differ between high-risk and low-risk siblings (see Table 1 for genotype frequencies by risk group). Genotype frequencies also did not differ between ethnicities (coded Non-Hispanic or Hispanic/Latino) for *DRD4*, $p = 0.43$, or dopamine composite scores, $p = 0.052$, but did differ for *DRD2*, $p = 0.037$.

Table 1
Genotype frequencies by risk group.

	High-risk Siblings		*Low-risk Siblings*	
	Frequency	Percentage	Frequency	Percentage
DRD4				
7-repeat allele	8	23.5%	9	33.3%
No 7-repeat allele	26	76.5%	18	66.7%
DRD2				
A allele	13	38.2%	7	25.9%
No A allele	21	61.8%	20	74.1%
Dopamine Score				
0 risk genotypes	17	50.0%	13	48.1%
1 risk genotype	13	38.2%	12	44.4%
2 risk genotypes	4	11.8%	2	7.4%