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An Exploration of Common Dopaminergic Variants and Behavior Problems in Siblings at High Risk for Autism Spectrum Disorder

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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.

Keywords

high-risk siblings; dopamine; behavior problems

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

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(e.g., Comings et al., 1996; Schmidt, Fox, Rubin, Hu, & Hamer, 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, Warnell, Parr, Couteur, & McConachie, 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 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 (Mörcke, 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, Lee, Ko, & Lin, 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*, $\chi^2(1)=0.00$, $p=.82$, and *DRD2*, $\chi^2(1)=0.11$, $p=.85$ (Rodriguez, Gaunt, & Day, 2009). Genotype frequencies for *DRD4*, $p=.57$, *DRD2*, $p=.41$, and dopamine composite scores, $p=.81$, 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*, $p=.43$, or dopamine composite scores, $p=.052$, but did differ for *DRD2*, $p=.037$.

The association of the cumulative gene score and behavior problems was assessed in regression models, in which dopamine gene score, risk group status, and dopamine gene score*risk group status interaction were entered as predictors of CBCL Internalizing and Externalizing Problems. Ethnicity was included as a dichotomous covariate in these analyses, and did not affect results. For the Internalizing Problems regression model, adjusted $R^2=0.16$, $F(4, 56)=3.89$, $p=.007$, there was no main effect of group status, $b=-3.17$, $t=-0.99$, $p=.34$, or dopamine score, $b=-2.73$, $t=-0.98$, $p=.33$. There was a dopamine score*status interaction effect, $b=11.00$, $t=3.03$, $p=.004$. Regression analyses by risk group indicated a significant effect of dopamine score for high-risk siblings (adjusted $R^2=0.22$, $F(2, 33)=5.77$, $p=.007$), $b=8.54$, $t=3.36$, $p=.002$, such that higher dopamine scores were associated with higher Internalizing scores, but not for low-risk siblings (adjusted $R^2=0.03$, $F(2, 26)=0.65$, $p=.53$), $b=-2.79$, $t=-1.01$, $p=.32$ (see Figure 1). For the Externalizing Problems regression model, adjusted $R^2=0.03$, $F(4, 56)=1.41$, $p=.24$, there was no main effect of group status, $b=0.13$, $t=0.04$, $p=.97$, or dopamine score, $b=-2.57$, $t=-2.57$, $p=.40$. There was no dopamine score*status interaction effect, $b=6.19$, $t=1.58$, $p=.12$.

This study examined the relationship between dopaminergic genotypes and behavior problems in children at risk for ASD at 36 months of age. Among high-risk siblings, dopaminergic genotypes linked to less efficient dopaminergic functioning were associated with elevated levels of internalizing problems as predicted. A similar pattern was observed for externalizing problems, though the association did not reach statistical significance. While genotypes associated with less efficient dopaminergic functioning seemed to indicate potential risk for elevated behavior problems in high-risk siblings, genotypes associated with more efficient dopaminergic functioning may serve as a resilience factor among high-risk siblings.

Low-risk siblings did not exhibit the same predicted association between dopaminergic genotype and behavior problems; dopamine scores did not significantly predict behavior problems for low-risk siblings. This suggests that the relationship between genotypes and behavior problems may differ by familial risk for ASD. Gene-environment interactions, in which the *DRD4* or *DRD2* genotype is differentially associated with internalizing or externalizing problems depending on an environmental context, have been previously found in samples without familial ASD risk. For example, the 7-repeat allele of *DRD4* has been associated with children's elevated behavior problems in contexts of less favorable environments, such as when children have experienced peer victimization (DiLalla, Bersted, & John, 2015), when children have experienced maternal insensitivity (Bakermans-Kranenburg & van IJzendoorn, 2006), or when mothers have experienced prenatal stress (Zohsel et al., 2014). The A allele of *DRD2* has also been associated with elevated behavior problems in contexts of less favorable environments, such as negative parenting (Zhang et al., 2015) or low levels of family closeness (Boardman et al., 2014). In the current study, familial ASD risk is conceptualized as an endogenous "environment," likely including a number of unknown genetic and possibly environmental factors. These dopaminergic genotypes indexing less efficient dopaminergic functioning have also exhibited similar patterns of association with another behavioral phenotype in the context of familial risk for ASD. A recent study, in which participants from the current study were included, found that high-risk siblings with dopaminergic genotypes indexing less efficient dopaminergic

functioning exhibited lower levels of initiating joint attention, an important social-communicative skill, in the first year of life, while low-risk siblings exhibited the opposite pattern (Gangi, Messinger, Martin, & Cuccaro, 2016).

Results of this study should be interpreted with caution, particularly given the limited sample size, as there is a possibility that results reflect chance findings. However, this study does suggest that links between dopaminergic genotypes and behavior problems in high-risk siblings are worth investigating and may help to explain heterogeneity among high-risk siblings. Future work replicating these results with larger samples would strengthen the indication that dopaminergic variants are related to behavior problems in high-risk siblings. Additionally, interactions between dopaminergic genotype and risk status could possibly reflect effects of a genotype not measured, and future work with additional genotyping may be better able to rule out such effects. Although most children in this study had reported levels of behavior problems below the clinical cutoff on the CBCL, there was variability in internalizing and externalizing behavior problems. Associations suggest that meaningful links may still be present for individuals with subclinical as well as clinical levels of behavior problems.

This study suggests that common genetic variants may provide insight toward understanding heterogeneity in high-risk siblings in important behavioral domains. High-risk siblings with genotypes associated with more efficient dopaminergic functioning were at lower risk of developing behavior problems. This may constitute a resilience factor, helping to explain relatively propitious outcomes among individuals at familial risk for ASD. Among high-risk siblings, genotypes associated with less efficient dopaminergic functioning were linked to elevated behavior problems. Links between genotypes and behavioral phenotypes, such as internalizing and externalizing symptoms, in high-risk siblings may aid in early identification of risk for difficulties in these domains, paving the way for targeted prevention and intervention efforts.

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Highlights

- In high-risk siblings, dopamine genotypes predicted internalizing problems.
- Links between genotypes and behavior problems may depend on familial ASD risk.
- In this risk context, genotypes may confer risk for additional difficulties.

Figure 1.

Mean levels of CBCL Internalizing Problems by group.

Note. Error bars reflect ± 1 SE. Internalizing Problems reflects a mean of CBCL t-scores.

Table 1

Genotype frequencies by risk group.

	High-risk Siblings		Low-risk Siblings	
	Frequency	Percentage	Frequency	Percentage
<i>DRD4</i>				
7-repeat allele	8	23.5%	9	33.3%
No 7-repeat allele	26	76.5%	18	66.7%
<i>DRD2</i>				
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%

CBCL Internalizing Problems were correlated with Externalizing problems for both high-risk siblings, $r=.62$, $p<.001$, and low-risk siblings, $r=.54$, $p=.004$. Means of Internalizing and Externalizing Problems t-scores are presented by risk group and genotype in Table 2.

Table 2

CBCL Internalizing and Externalizing T-Scores by Genotype and Risk Group.

	Internalizing T-Scores Mean (SD)		Externalizing T-Scores Mean (SD)	
	High-risk Siblings	Low-Risk Siblings	High-risk Siblings	Low-Risk Siblings
<i>DRD4</i>				
7-repeat allele	46.75 (13.54)	35.89 (9.96)	48.00 (12.38)	36.11 (9.35)
No 7-repeat allele	41.42 (9.33)	40.78 (7.91)	42.92 (9.13)	42.28 (9.13)
<i>DRD2</i>				
A allele	49.46 (8.37)	39.00 (8.41)	46.46 (8.70)	41.71 (8.60)
No A allele	38.48 (9.55)	39.20 (9.11)	42.67 (10.70)	39.70 (9.95)
Dopamine Score				
0 risk genotypes	38.59 (9.44)	40.85 (7.94)	42.29 (10.49)	41.08 (9.94)
1 risk genotype	44.08 (8.97)	38.00 (9.93)	44.15 (8.27)	40.58 (9.48)
2 risk genotypes	55.50 (9.57)	35.00 (8.49)	51.75 (12.15)	32.50 (6.36)