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Publication Date

2017-11-01

DOI

10.1016/j.infbeh.2017.10.002

Peer reviewed

HHS Public Access

Author manuscript

Infant Behav Dev. Author manuscript; available in PMC 2018 November 01.

Published in final edited form as:

Infant Behav Dev. 2017 November ; 49: 267–271. doi:10.1016/j.infbeh.2017.10.002.

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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Conflicts of interest: none.

(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 (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, 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.

Acknowledgments

This research was supported by the National Institute of Mental Health (T32 MH073124), National Institute of Child Health and Human Development (T32 HD07489), National Institutes of Health (R01 HD047417 and R01 HD057284), National Institute of General Medical Sciences (R01 GM105004), and Autism Speaks.

References

Achenbach, TM., Rescorla, LA. Manual for the ASEBA school-age forms & profiles. Burlington, VT: University of Vermont Research Center for Children, Youth, & Families; 2001.

Association, A.P. Diagnostic and Statistical Manual of Mental Disorders: DSM-V. Washington, DC: American Psychiatric Association; 2013.

Bakermans-Kranenburg MJ, van IJzendoorn MH. Gene-environment interaction of the dopamine D4 receptor (DRD4) and observed maternal insensitivity predicting externalizing behavior in preschoolers. Developmental Psychobiology. 2006; 48(5):406–409. DOI: 10.1002/dev.20152 [PubMed: 16770765]

Bauminger N, Solomon M, Rogers SJ. Externalizing and internalizing behaviors in ASD. Autism Research. 2010; 3(3):101–112. DOI: 10.1002/aur.131 [PubMed: 20575109]

Boardman JD, Menard S, Roettger ME, Knight KE, Boutwell BB, Smolen A. Genes in the dopaminergic system and delinquent behaviors across the life course: The role of social controls and risks. Criminal Justice and Behavior. 2014; doi: 10.1177/0093854813514227

Cerdá M, Sagdeo A, Johnson J, Galea S. Genetic and environmental influences on psychiatric comorbidity: A systematic review. Journal of Affective Disorders. 2010; 126(1):14–38. doi: https://doi.org/10.1016/j.jad.2009.11.006. [PubMed: 20004978]

Comings DE, Wu S, Chiu C, Ring RH, Gade R, Ahn C, … Muhleman D. Polygenic inheritance of Tourette syndrome, stuttering, attention deficit hyperactivity, conduct, and oppositional defiant disorder: The additive and subtractive effect of the three dopaminergic genes—DRD2, DβH, and DAT1. American Journal of Medical Genetics. 1996; 67(3):264–288. [PubMed: 8725745]

Davis NO, Carter A. Parenting stress in mothers and fathers of toddlers with Autism Spectrum Disorders: Associations with child characteristics. Journal of Autism and Developmental Disorders. 2008; 38(7):1278–1291. DOI: 10.1007/s10803-007-0512-z [PubMed: 18240012]

DiLalla LF, Bersted K, John SG. Peer victimization and DRD4 genotype influence problem behaviors in young children. Journal of Youth and Adolescence. 2015; 44(8):1478–1493. DOI: 10.1007/s10964-015-0282-4 [PubMed: 25869327]

Ekas N, Whitman TL. Autism symptom topography and maternal socioemotional functioning. American Journal on Intellectual and Developmental Disabilities. 2010; 115(3):234–249. DOI: 10.1352/1944-7558-115.3.234 [PubMed: 20441393]

Fisman S, Wolf L, Ellison D, Gillis B, Freeman TOM, Szatmari P. Risk and protective factors affecting the adjustment of siblings of children with chronic disabilities. Journal of the American Academy of Child & Adolescent Psychiatry. 1996; 35(11):1532–1541. doi: http://dx.doi.org/10.1097/00004583-199611000-00023. [PubMed: 8936921]

Gadow KD, DeVincent CJ, Olvet DM, Pisarevskaya V, Hatchwell E. Association of DRD4 polymorphism with severity of oppositional defiant disorder, separation anxiety disorder and repetitive behaviors in children with autism spectrum disorder. European Journal of Neuroscience. 2010; 32(6):1058–1065. DOI: 10.1111/j.1460-9568.2010.07382.x [PubMed: 20731709]

Gangi DN, Messinger DS, Martin ER, Cuccaro ML. Dopaminergic variants in siblings at high risk for autism: Associations with initiating joint attention. Autism Research. 2016; 9(11):1142–1150. DOI: 10.1002/aur.1623 [PubMed: 26990357]

Georgiades S, Szatmari P, Zwaigenbaum L, Bryson S, Brian J, Roberts W, Garon N. A prospective study of autistic-like traits in unaffected siblings of probands with autism spectrum disorder. JAMA Psychiatry. 2013; 70(1):42–48. DOI: 10.1001/2013.jamapsychiatry.1 [PubMed: 22945359]

Hayden EP, Klein DN, Dougherty LR, Olino TM, Laptook RS, Dyson MW, Singh SM. The dopamine D2 receptor gene and depressive and anxious symptoms in childhood: associations and evidence for gene–environment correlation and gene–environment interaction. Psychiatric Genetics. 2010; 20(6):304–310. DOI: 10.1097/YPG.0b013e32833adccb [PubMed: 20526230]

Hettinger JA, Liu X, Hudson ML, Lee A, Cohen IL, Michaelis RC, Holden JJ. DRD2 and PPP1R1B (DARPP-32) polymorphisms independently confer increased risk for autism spectrum disorders and additively predict affected status in male-only affected sib-pair families. Behavioral and Brain Functions. 2012; 8(1):19. [PubMed: 22559203]

Kuhlthau K, Kovacs E, Hall T, Clemmons T, Orlich F, Delahaye J, Sikora D. Health-related quality of life for children with ASD: Associations with behavioral characteristics. Research in Autism Spectrum Disorders. 2013; 7(9):1035–1042. doi: http://dx.doi.org/10.1016/j.rasd.2013.04.006.

Lu RB, Lee JF, Ko HC, Lin WW. Dopamine D2 receptor gene (DRD2) is associated with alcoholism with conduct disorder. Alcoholism: Clinical and Experimental Research. 2001; 25(2):177–184. DOI: 10.1111/j.1530-0277.2001.tb02196.x

Mahan S, Matson JL. Children and adolescents with autism spectrum disorders compared to typically developing controls on the Behavioral Assessment System for Children, Second Edition (BASC-2). Research in Autism Spectrum Disorders. 2011; 5(1):119–125. doi: http://dx.doi.org/10.1016/j.rasd.2010.02.007.

Maskey M, Warnell F, Parr JR, Couteur A, McConachie H. Emotional and behavioural problems in children with Autism Spectrum Disorder. Journal of Autism and Developmental Disorders. 2013; 43(4):851–859. DOI: 10.1007/s10803-012-1622-9 [PubMed: 22895777]

Messinger D, Young GS, Ozonoff S, Dobkins K, Carter A, Zwaigenbaum L, Sigman M. Beyond autism: A Baby Siblings Research Consortium study of high-risk children at three years of age. Journal of the American Academy of Child and Adolescent Psychiatry. 2013; 52(3):300–308.e301. [PubMed: 23452686]

Möricke E, Swinkels SHN, Beuker KT, Buitelaar JK. Predictive value of subclinical autistic traits at age 14–15 months for behavioural and cognitive problems at age 3–5 years. European Child & Adolescent Psychiatry. 2010; 19(8):659–668. DOI: 10.1007/s00787-010-0103-y [PubMed: 20390313]

Orsmond GI, Seltzer MM. Siblings of individuals with autism spectrum disorders across the life course. Mental Retardation and Developmental Disabilities Research Reviews. 2007; 13(4):313–320. DOI: 10.1002/mrdd.20171 [PubMed: 17979200]

Ozonoff S, Young GS, Carter A, Messinger D, Yirmiya N, Zwaigenbaum L, Stone WL. Recurrence risk for autism spectrum disorders: A Baby Siblings Research Consortium study. Pediatrics. 2011; 128(3):e488–e495. [PubMed: 21844053]

Papageorgiou KA, Ronald A. "He who sees things grow from the beginning will have the finest view of them" A systematic review of genetic studies on psychological traits in infancy. Neuroscience & Biobehavioral Reviews. 2013; 37(8):1500–1517. doi: http://dx.doi.org/10.1016/j.neubiorev.2013.04.013. [PubMed: 23644044]

Pearson DA, Loveland KA, Lachar D, Lane DM, Reddoch SL, Mansour R, Cleveland LA. A comparison of behavioral and emotional functioning in children and adolescents with Autistic Disorder and PDD-NOS. Child Neuropsychology. 2006; 12(4–5):321–333. DOI: 10.1080/09297040600646847 [PubMed: 16911976]

Rodrigue JR, Geffken GR, Morgan SB. Perceived competence and behavioral adjustment of siblings of children with autism. Journal of Autism and Developmental Disorders. 1993; 23(4):665–674. DOI: 10.1007/bf01046108 [PubMed: 8106306]

Rodriguez S, Gaunt TR, Day INM. Hardy-Weinberg Equilibrium Testing of Biological Ascertainment for Mendelian Randomization Studies. American Journal of Epidemiology. 2009; 169(4):505–514. DOI: 10.1093/aje/kwn359 [PubMed: 19126586]

Salem AM, Ismail S, Zarouk WA, Abdul Baky O, Sayed AA, Abd El-Hamid S, Salem S. Genetic variants of neurotransmitter-related genes and miRNAs in Egyptian autistic patients. The Scientific World Journal. 2013; 2013:7.doi: 10.1155/2013/670621

Schmidt LA, Fox NA, Hamer DH. Evidence for a gene–gene interaction in predicting children's behavior problems: Association of serotonin transporter short and dopamine receptor D4 long genotypes with internalizing and externalizing behaviors in typically developing 7-year-olds. Development and Psychopathology. 2007; 19(04):1105–1116. DOI: 10.1017/S0954579407000569 [PubMed: 17931437]

Schmidt LA, Fox NA, Rubin KH, Hu S, Hamer DH. Molecular genetics of shyness and aggression in preschoolers. Personality and Individual Differences. 2002; 33(2):227–238. doi: http://dx.doi.org/10.1016/S0191-8869(01)00147-7.

Schwichtenberg AJ, Young GS, Hutman T, Iosif AM, Sigman M, Rogers SJ, Ozonoff S. Behavior and sleep problems in children with a family history of autism. Autism Research. 2013; 6(3):169–176. DOI: 10.1002/aur.1278 [PubMed: 23436793]

van Steensel, FJA., Bögels, SM., Magiati, I., Perrin, S. Anxiety in individuals with ASD: Prevalence, phenomenology, etiology, assessment, and interventions. In: Patel, BV.Preedy, RV., Martin, RC., editors. Comprehensive Guide to Autism. New York, NY: Springer New York; 2014. p. 601-623.

Verté S, Roeyers H, Buysse A. Behavioural problems, social competence and self-concept in siblings of children with autism. Child: Care, Health and Development. 2003; 29(3):193–205. DOI: 10.1046/j.1365-2214.2003.00331.x

Weeland J, Overbeek G, de Castro BO, Matthys W. Underlying mechanisms of gene–environment interactions in externalizing behavior: A systematic review and search for theoretical mechanisms. Clinical Child and Family Psychology Review. 2015; 18(4):413–442. DOI: 10.1007/s10567-015-0196-4 [PubMed: 26537239]

Zhang W, Cao Y, Wang M, Ji L, Chen L, Deater-Deckard K. The dopamine D2 receptor polymorphism (DRD2 TaqIA) interacts with maternal parenting in predicting early adolescent depressive

symptoms: Evidence of differential susceptibility and age differences. Journal of Youth and Adolescence. 2015; 44(7):1428–1440. DOI: 10.1007/s10964-015-0297-x [PubMed: 25941120]

Zohsel K, Buchmann AF, Blomeyer D, Hohm E, Schmidt MH, Esser G, Laucht M. Mothers' prenatal stress and their children's antisocial outcomes – a moderating role for the Dopamine D4 Receptor (DRD4) gene. Journal of Child Psychology and Psychiatry. 2014; 55(1):69–76. DOI: 10.1111/jcpp.12138 [PubMed: 24102377]

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.

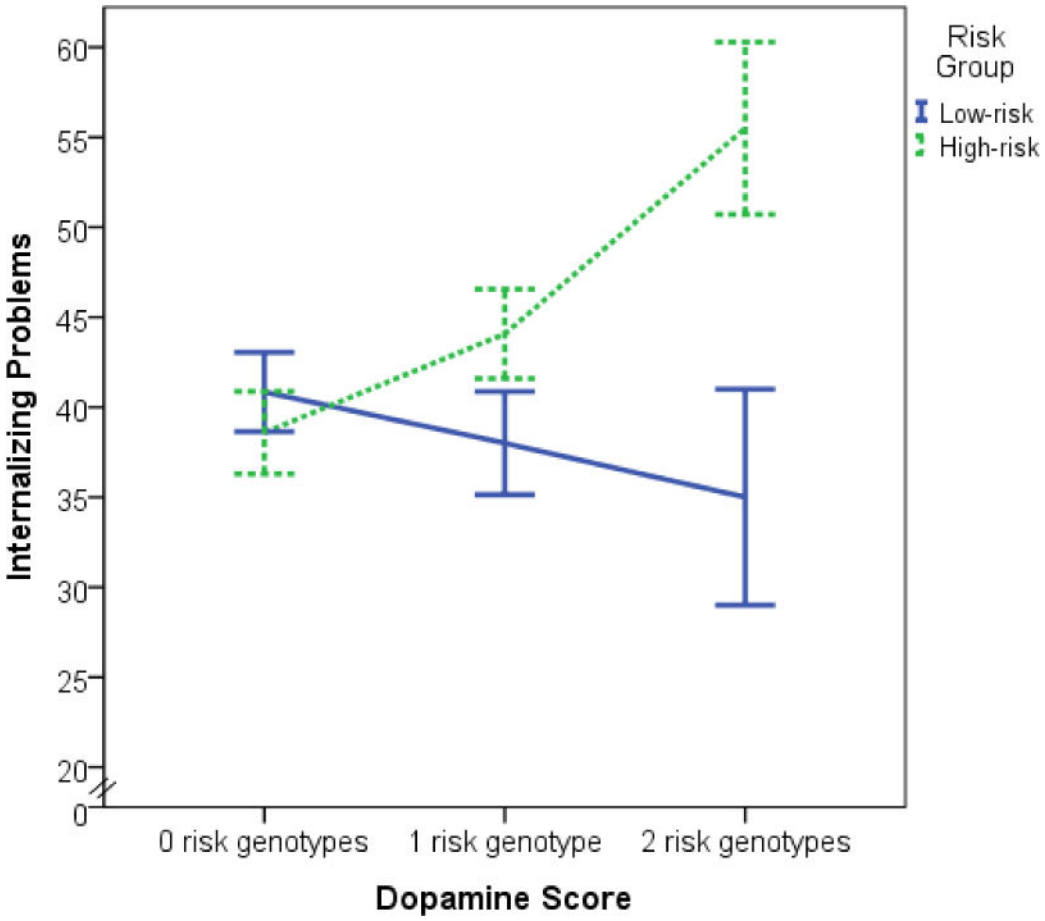

Figure 1.
Mean levels of CBCL Internalizing Problems by group.
Note. Error bars reflect +/− 1 SE. Internalizing Problems reflects a mean of CBCL t-scores.

Table 1

Genotype frequencies by risk group.

	High-risk Siblings		Low-risk Siblings	
	Frequency	**Percentage**	**Frequency**	**Percentage**
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%

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**
DRD4				
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)
DRD2				
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)