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Symptoms of Attention-Deficit/Hyperactivity Disorder in Down Syndrome: Effects of the Dopamine Receptor D4 Gene

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Abstract

This study examined individual differences in ADHD symptoms and executive function (EF) in children with Down syndrome (DS) in relation to the dopamine receptor D4 (DRD4) gene, a gene often linked to ADHD in people without DS. Participants included 68 individuals with DS (7-21 years), assessed through laboratory tasks, caregiver reports, and experimenter ratings. Saliva samples were collected from the DS group and 66 children without DS to compare DRD4 allele distribution, showing no difference between the groups. When the sample with DS was stratified for ethnicity ($n = 32$), the DRD4 7-repeat allele significantly related to parent and experimenter ratings, but not to laboratory assessments. These results suggest that nontrisomy genetic factors may contribute to individual differences in ADHD symptoms in persons with DS.

Key Words: *attention-deficit/hyperactivity disorder; Down syndrome; intellectual disabilities; dopamine; executive function; Trisomy 21; cognitive assessment*

In the decades since Trisomy 21 was identified as the common genetic basis of Down syndrome (DS; Lejeune, Gautier, & Turpin, 1959), researchers have made significant advances in discerning the neuropsychological profile of DS (Edgin, 2013). Within this profile, many assert that children with DS display symptoms of attention-deficit/hyperactivity disorder (ADHD), including difficulties in executive function (EF). Laboratory tasks have identified impairments in *working memory*, operationalized as the ability to hold rules in mind and apply them to new information, and *set-shifting*, the ability to switch rules in response to new task demands (Lanfranchi, Jerman, Dal Pont, Alberti, & Vianello, 2010). Other studies (Borella, Carretti, & Lanfranchi, 2013) have noted difficulties in *inhibition*, the ability to override salient distractors and stop activity when instructed (Miyake & Friedman, 2012). Caregiver reports in naturalistic contexts have also suggested EF impairment, including attention deficits (Clark & Wilson, 2003; Raitano-Lee et al., 2011). The prevailing literature, therefore, suggests that children with DS show impairments in EF that are characteristic of ADHD (Barkley, 1997), including deficits in inhibitory control and attention.

Although there is now consistent evidence for EF difficulties in DS at group levels of analysis, impairments vary considerably across individuals. Whereas such difficulties were once considered inseparable from cognitive impairment in populations with neurodevelopmental disorders (Capone, Goyal, Ares, & Lannigan, 2006), studies have demonstrated enough variability in DS to necessitate a separable comorbid diagnosis of ADHD. For instance, a recent study using comprehensive ADHD screenings for children with DS found that 43.9% of the sample distinctly met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision* (*DSM-IV-TR*; 2000) criteria for ADHD (Ekstein, Glick, Weill, Kay, & Berger, 2011). These results suggest that ADHD diagnosis is elevated in DS, but not present in the majority.

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Considering the variation in attention difficulties and EF in DS, a key challenge is to identify mechanisms underlying this variability. Executive function relies on a network of brain regions, including the prefrontal cortex (PFC) and subcortical structures (Durston, de Zeeuw, & Staal, 2009; Munakata et al., 2011). Within this network, dopamine plays a key role in modulating synaptic transmission through activation of both excitatory (D1-like) and inhibitory (D2-like) receptors (Beaulieu & Gainetdinov, 2011). In accordance with EF difficulties, individuals with DS show reductions in both the volume of the PFC and myelination between frontal and posterior regions (Edgin, 2013). Prenatal dopamine levels are reduced (Whittle, Sartori, Dierssen, Lubec, & Singewald, 2007), and at later ages, dopaminergic cells arereduced in the ventral tegmental area, a region important for dopamine signaling (Mann, Yates, & Marcyniuk, 1987). Given these findings, it is important to consider the dopamine system when examining potential contributions to EF difficulties in people with DS.

Previous investigations have found a relation between individual EF differences and genetic variability in dopamine's receptors. Among these receptors, the *dopamine D4 receptor* (DRD4), a D2-like receptor on chromosome 11, has been the most frequently and reliably linked to EF and attention (Durston et al., 2009). DRD4 modulates signaling cascades dependent on cyclic adenosine monophosphate (cAMP) by inhibiting adenylyl cyclase (AC). In doing this, DRD4 helps modulate excitatory (glutamatergic) and inhibitory (GABAergic) receptor currents in brain areas important for EF (Rubinstein et al. 2001; Wang, Zhong, & Yan, 2002). This function makes DRD4 especially pertinent for people with DS because such receptors are affected in DS pathology (Rissman & Mobley, 2011). Furthermore, DRD4 is more selectively expressed in brain areas specifically affected in people with DS, including the PFC, medial temporal lobes, and cerebellum (Durston et al., 2009).

Regarding variability, the gene encoding DRD4 contains a 48-base pair variable-nucleotide tandem repeat (VNTR) polymorphism spanning from 2 to 11 repeats. The 7-repeat allele (7R) has suppressed expression and decreased affinity for dopamine-mediated activity relative to the 2- and 4-repeats (Asghari et al., 1995; Schoots & Van Tol, 2003). The 7R allele also relates to individual differences in EF, including effortful control (Smith et al., 2012) and impulsivity (Congdon & Canli, 2008) in samples of people without DS. In addition, previous meta-analyses have found a positive association between 7R overexpression and ADHD (for review, see Faraone & Mick, 2010).

Despite these findings, the relations between 7R and behavioral outcomes are not consistent across all contexts and populations. For instance, Martínez-Levy et al. (2009) showed that 7R was not overexpressed in Mexican individuals with ADHD, and that Mexican individuals homozygous for 7R and the 10/10 allele of DAT1 were less likely to have internalized comorbidities (e.g., anxiety disorders). In Han Chinese, Leung et al. (2004) found that the DRD4 2-repeat was overexpressed in ADHD. Other factors mediating 7R's effects include parenting; in a recent study, young children's turn-taking and reward delay was influenced by 7R, but only in the presence of highly negative parenting (Smith et al., 2012). Taken together, these findings imply not only that DRD4 variants relate to heterogeneity in EF, but that they interact with ecological variables to influence outcomes.

Though previous research has examined DRD4's effects in various populations, its effects on EF and attention in people with DS are unknown. Genetics studies in DS have historically evaluated the specific functions of Trisomy 21 genes in contributing to the DS phenotype (Dierssen & de la Torre, 2012); however, only a few studies have assessed whether Trisomy 21 is associated with preferential transmission of common nontrisomy gene alleles including 7R (Das Bhowmik, Dutta, Sinha, Chattopadhyay, & Mukhopadhyay, 2008), or how nontrisomy gene variants contribute to individual differences in the presence of Trisomy 21 (Alexander et al., 1997). Investigating these associations can illuminate whether Trisomy 21 overshadows nontrisomy gene variant effects, or whether such effects additively or interactively influence impairments.

Therefore, we investigated the contribution of the DRD4 7-repeat allele to differences in EF, attention, and behavior in children with Down syndrome. First, we assessed the frequency of 7R in DS. Only one study appears to have investigated this gene to date, suggesting that 7R is not preferentially expressed in Indian populations with DS (Das Bhowmik et al., 2008). We added to these findings by exploring the presence of 7R in a U.S. sample. Next, we examined whether 7R

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was associated with individual differences in ADHD symptoms and executive function using a multifaceted approach incorporating standard EF tasks, caregiver behavior ratings, and experimenter behavior ratings during the assessment. This work helps to establish whether allelic variation in DRD4 influences behavioral and cognitive outcomes in people with DS in the context of Trisomy 21.

Methods

Participants

Sixty-eight individuals with DS (34 female) 7–21 years were recruited across Arizona and California through advertisement or from parent support organizations. For inclusion, we required a medically verified Trisomy 21 diagnosis without comorbid autism or history of head injury/loss of consciousness. Among these participants, DRD4 genotyping failed in 6 cases, resulting in a final sample of 62. Thirty-two participants were White, non-Hispanic; 21 were Hispanic[a]; 2 were African American; 1 was Hawaiian/Pacific Islander; 5 were Bi/Multiracial (including children with parents falling into separate categories among those already defined); and 1 was unknown. Given past ethnic and environmental differences with DRD4, we conducted all analyses first in the full sample and then in the White (non-Hispanic) group separately. Within these groups, the percentages of individuals meeting ADHD criteria of any subtype (using parent *DSM-IV* reports; see *Conners' 3™* in a following section) were 30.4% and 44.4% in the full sample and White (non-Hispanic) group, respectively. With regard to other demographic variables (age, gender, socioeconomic status [SES]), there were no significant differences between those with or without the 7-repeat in either group (see Tables 1 and 2). Given the heterogeneity in racial background in the Hispanic sample, we focused our analyses on the White non-Hispanic group in the current report, but have included the relations in the Hispanic group to potentially guide future investigations that may include greater numbers of children of Hispanic origin.

Sixty-six typically developing (TD) children (ages 3 to 15 years, 35 female) also underwent genotyping to determine if the 7-repeat was present at the same frequency in children with DS as in a typical sample. This control sample was recruited as part of a larger project examining neuropsychological function, and did not complete an analogous set of measures that would allow for direct comparison to the DS group on ADHD symptoms or parent-reported EF. Thus, this group was not included in the EF comparisons, but was simply used to examine DRD4 allele frequencies. The sample included 30 White (non-Hispanic) participants with whom we conducted stratified allele comparisons, and exclusion criteria included presence of any neurodevelopmental disorder.

Measures

Laboratory-based executive assessment. We administered the Arizona Cognitive Test Battery (ACTB; Edgin et al., 2010), a specialized neuropsychological battery for people with DS. In this study we focused on the EF tests of the ACTB, which include the following:

"Frogs and Cats" Modified DOTS task. This paradigm is adapted from Diamond, Briand, Fossella and Gelbach's (2004) "Dots-Mixed" task assessing the ability to acquire a response (baseline phase), override an established response (inhibitory/shifting phase), and switch between response sets (combined phase). Experimenters instruct participants to press a button on a touch-screen on the same side or opposite side of a stimulus, and in the final phase rules alternate. We analyzed the mean percentage of correct responses in each phase after excluding participants who did not meet baseline criteria of 70% correct (there were no significant differences in the percentage of participants meeting baseline between genotype groups for any sample).

CANTAB Intra/Extra Dimensional Set Shift (IED). The Intra-Extra Dimensional Set Shift test (IED) is a measure of cognitive flexibility. In the initial stages, participants are first presented with two colored shapes, and must learn which shape is "correct" through trial and error. After several trials of recognizing the correct rule, the "correct" shape is reversed. In later stages, a second shape is transposed onto each shape, so that the partici-

[a](Note: The term "Hispanic" in our sample included children whose parents' ancestry originates from any of the countries encompassing Latin America or Spain, as well as children with one of such parent and one European American parent. Of these participants, 11 were of Mexican origin, 5 were Mexican and European American, 1 was from Panama, 1 was from Spain, 1 was Mexican, Spanish, and Pakistani, and 2 did not provide their country of origin.)

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Table 1
Background Characteristics of Children With Down Syndrome, All Ethnicities, Relative to DRD4 Genotype

	No 7R Alleles (N = 35)		At least 1 7R Allele (N = 27)		
Characteristic	Mean	*SD*	Mean	*SD*	T/MWW[a](p)
Age	11.89	3.35	11.04	3.76	388.50[a](0.23)
Mom's years of education	14.88	2.48	15.11	2.54	425.50[a](0.96)
Total annual income	5.15	2.49	5.96	3.09	−1.10(0.27)
Number of children in household	2.41	1.31	2.96	1.83	375.50[a](0.21)
Ethnicity	***N***	**% of Total**	***N***	**% of Total**	**χ^2/Fisher's(p)**
Non-Hispanic White	17	48.6%	15	55.6%	0.30(0.59)
Hispanic or Latino	11	31.4%	10	37.0%	0.21(0.64)
Black or African American	2	5.7%	0	0%	n/a(0.50)
Hawaiian or Pacific Islander	1	2.9%	0	0%	n/a(1.00)
Biracial/Multiracial	3	8.6%	2	7.4%	n/a(1.00)
Asked but unknown	1	2.9%	0	0%	n/a(1.00)
Sex	***N***	**% of Total**	***N***	**% of Total**	**χ^2(p)**
Female	16	45.7%	15	55.6%	0.59(0.44)

Note. DRD4 Genotype is a descriptor of the dopamine receptor *D4* (DRD4) gene, a gene often linked to ADHD in people without Down syndrome. 7R Allele = an indicator of repeated pairs of nucleotides associated with the DRD4 gene; ADHD = attention-deficit/hyperactivity disorder.
[a]Analyzed with Mann-Whitney U to adjust for deviations from normality within groups.

pant must take another dimension into consideration when determining which shape is "correct" (i.e., the extra-dimensional shift). The task progresses from rule shifts within a dimension (i.e., to a different stimulus of the same type) to responses outside of the trained dimension (i.e., between shapes in which one has never been rewarded) across nine stages of increasing difficulty. The outcome measure was the number of errors prior to the extra-dimensional shift.

Caregiver rating scales. In addition to the cognitive tasks, we evaluated caregiver reports of participants' everyday attention and executive skills. These reports offer insight into how children's executive difficulties and ADHD symptoms manifest in more naturalistic contexts.

Table 2
Background Characteristics of White (Non-Hispanic) Children With Down Syndrome Relative to DRD4 Genotype

	No 7R Alleles (N = 17)		At least 1 7R Allele (N = 15)		
Characteristic	Mean	*SD*	Mean	*SD*	T/MWW[a](p)
Age	12.94	3.47	12.33	4.17	0.45(0.66)
Mom's years of education	15.00	1.73	15.00	2.51	0.00(1.00)
Total annual income	5.41	2.50	6.21	3.14	−0.79(0.47)
Number of children in household	2.23	1.20	3.27	2.31	91.00[a](0.18)
Sex	***N***	**% of Total**	***N***	**% of Total**	**χ^2(p)**
Female	9	52.9%	9	60%	0.16(0.69)

Note. DRD4 Genotype is a descriptor of the dopamine receptor *D4* (DRD4) gene, a gene often linked to ADHD in people without Down syndrome. 7R Allele = an indicator of repeated pairs of nucleotides associated with the DRD4 gene; ADHD = attention-deficit/hyperactivity disorder.
[a]Analyzed with Mann-Whitney U to adjust for deviations from normality within groups.

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BRIEF® Behavioral Rating Inventory of Executive Function (Parent Report Form). This 86-item questionnaire measures 8 clinical scales within 2 broader EF indices. The *Behavioral Regulation Index* (BRI) includes *Inhibit*, *Shift*, and *Emotional Control*. The *Metacognitive Index* (MI) includes *Initiate*, *Working Memory*, *Plan/Organize*, *Monitor*, and *Organization of Materials*. The questionnaire has shown strong test-retest reliability ($r = 0.81$) and convergent validity with other rating scales (Gioia, Isquith, Guy, & Kenworthy, 2000). Our outcome measures included the BRI, MI, and Global Executive Index (a composite of the BRI and MI) standardized *T*-scores.

Nisonger Child Behavior Rating of Executive Function (CBRF). This form assesses behavioral difficulties commonly observed in children with intellectual impairment. We assessed the *Hyperactive*, *Conduct Problem*, *Insecure/Anxious*, and *Overly Sensitive* scales, because these scales capture behavioral excesses specifically associated with ADHD (Jensen, Martin, & Cantwell, 1997).

Conners' 3™ Parent Rating Scales, Revised for ADHD Symptoms. The Conners' 3™ Parent Form contains ADHD subscales (both Inattentive and Hyperactive-Impulsive) and other behavioral indices. In a normative sample, test-retest reliability coefficients ranged from 0.71 to 0.98, with strong discriminant validity between children with ADHD and other groups (Gallant et al., 2007). Our outcome measures were ADHD raw symptom counts for the Inattentive and Hyperactive-Impulsive subscales only.

Benchmark IQ and experimenter ratings. The Kaufman Brief Intelligence Test, 2nd Edition (K-BIT 2; Kaufman & Kaufman, 2004) assesses verbal (receptive and expressive) and nonverbal IQ across a wide age range (4-90 years old). Our outcome was standardized scores (mean IQ = 100 and standard deviation = 15).

During the laboratory assessment, experimenters blind to genotype also rated participants' cooperation after each task on a 5-point Likert scale with 1 signifying minimal cooperation and 5 signifying complete cooperation and engagement. This measure serves as an intermediary between EF laboratory tasks and caregiver ratings by assessing children's behavior during task performance.

Genetics collection. We collected saliva using Oragene®•DISCOVER OGR-250 collection kits in disk format, augmented by the Oragene® CS-1 "for Assisted Collection" accessory (5 saliva-collection sponges for people who have difficulty expelling saliva independently).

Procedure

All procedures were approved by the University of Arizona Institutional Review Board. The EF tasks (IED, Modified DOTS) were displayed on a touch-screen computer in counterbalanced order. Halfway through the assessment, we paused for a break and collected DNA. Parents filled out the behavioral questionnaires during the assessment.

After collection, DNA was analyzed by the Emory University Biomarker Service Center. DRD4 VNTR copy number was identified using fluorescent labeling and polymerase chain reaction (PCR) amplification. 20ng DNA were amplified in a 50 µl volume with fluorescently-labeled primer pairs flanking the VNTR, which were synthesized and purified using high-performance liquid chromatography by Integrated DNA technologies. Following PCR, the Applied Biosystems™ ABI 3100 Genetic Analyzer separated the VNTR-containing products via fluorescence-based capillary electrophoresis, and researchers identified VNTR length with GeneMapper software (Applied Biosystems). By comparing with a size standard series labelled with ROX dye (Applied Biosystems), the precise fragment length (in bp) can be determined, and correlated to the number of repetitive elements.

Statistical Analyses

Hardy-Weinberg equilibrium (HWE) was calculated using the Online Encyclopedia for Genetic Epidemiology studies toolkit (Rodriguez, Gaunt, & Day, 2009; http://www.oege.org/software/hwe-mr-calc.shtml), and Cohen's *d* effect sizes were verified using Becker's (2000) effect size toolkit. All other analyses were conducted in IBM SPSS 20.0. First, we examined 7R prevalence in children with DS in terms of Hardy-Weinberg equilibrium, and used Chi-square and Fisher's Exact Test to compare 7R prevalence in children with DS to that in the TD sample. We also examined presence of all allele types in the DS and TD samples. These analyses were completed for the full sample, then the White (non-Hispanic) group separately. Additionally, we assessed 7R presence between ethnicities (in DS and TD samples separately).

Next, we used independent-samples *t*-tests to examine neuropsychological and behavioral

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outcomes and group differences in background factors (e.g., age, maternal education, total family income, and number of children in household) for participants carrying at least one 7R allele vs. participants not carrying 7R. These analyses were conducted in the full sample, then in White (non-Hispanic) participants separately. Prior to analyses, we examined distributional properties within allele groups and used Mann-Whitney U to verify results of outcome variables violating assumptions of normality. Given the wide age range of our sample, we also conducted preliminary correlational analyses between age and executive function measures, and for EF outcomes correlated with age, we incorporated age as a covariate in general linear models analyzing the relation between DRD4 genotype and those outcomes. We used Spearman's Rho to analyze the relation between genotype and the Likert experimenter ratings.

Results

DRD4 7R Prevalence

In the full DS sample, 35 individuals did not carry 7R; 20 carried one 7R; and 7 were homozygous for 7R. Among White (non-Hispanic) participants, 17 did not carry 7R; 12 carried one 7R; and 3 were homozygous for 7R. These distributions did not depart from Hardy-Weinberg equilibrium (Full: $\chi^2(1, N = 62) = 2.23$, $p = 0.13$; White (non-Hispanic): $\chi^2(1, N = 32) = 0.17$, $p = 0.68$).

Fisher's exact test showed no difference in the percentage of individuals carrying no 7R, one 7R, and two 7R alleles between the DS and TD samples, either in the full group ($FET(N = 128) = 3.63$, $p = 0.15$), or White (non-Hispanic) participants alone ($FET(N = 62) = 0.97$, $p = 0.78$). Regarding individual alleles, we did not observe the 5R, 6R, and 8R–11R alleles in our sample with DS, though previous work has observed the 6-repeat (Das Bhowmik et al., 2008). In our TD sample, all allele types were observed except for the 9–11 repeats. Overall, there was no significant difference in allele presence between groups (Full sample: $FET(N = 256) = 6.87$, $p = 0.30$; White (non-Hispanic): $FET(N = 124) = 3.33$, $p = 0.54$).

Cognitive Assessment, IQ, and Caregiver Ratings

Tables 3 and 4 show the differences between individuals with DS relative to 7R genotype. In the full group containing both White (non-Hispanic) and Hispanic individuals (Table 3), there were no significant differences for any outcome ($p > 0.05$ for all). While age correlated with the K-BIT 2 verbal ($r = 0.41$, $p = 0.00$) and nonverbal sums ($r = 0.37$, $p = 0.00$), IED ($r = -0.43$, $p = 0.00$), and Modified DOTS inhibitory ($r = 0.413$, $p = 0.01$) and combined ($r = 0.34$, $p = 0.03$) measures, adding age as a covariate did not affect the non-significance of the association between DRD4 and these measures (for all GLMs, $p > 0.10$ for DRD4).

In the White (non-Hispanic) participants only (Table 4), children with at least one 7-repeat had caregiver reports suggesting greater difficulties, including elevated scores on the BRIEF BRI ($t(26) = -2.79$, $p = 0.01$, effect size = 0.47), BRIEF Global Executive composite ($t(23) = -2.68$, $p = 0.01$, effect size = 0.47), Conners Hyperactive-Impulsive Scale ($t(25) = -2.35$, $p = 0.03$, effect size = 0.41), Nisonger Hyperactive Subscale ($t(27) = -2.31$, $p = 0.03$, effect size = 0.39), Nisonger Conduct Problem Subscale ($t(27) = -2.06$, $p = 0.05$, effect size = 0.36), and Nisonger Insecure/Anxious Subscale (both with t-tests ($t(27) = -2.50$, $p = 0.02$, effect size = 0.42) and Mann-Whitney U (MWW = 49.00 $p = 0.01$, z-score effect size = 0.46)). Age did not correlate significantly with any of these measures, although there was a trend toward a significant correlation between age and the Nisonger Conduct Problem subscale ($r = -0.33$, $p = 0.08$). However, the effect of DRD4 on this measure remained significant after controlling for age ($F = 4.762$, $p = 0.04$) There were no significant relations between DRD4 and laboratory IQ/EF tasks. Age was significantly correlated with IQ ($r = -0.38$, $p=0.03$) and the inhibitory phase of the Modified DOTS task ($r = 0.46$, $p = 0.03$) for this group, and when controlling for age on these measures, the effects of DRD4 remained nonsignificant (IQ: $F = 0.60$, $p = 0.44$; Modified DOTS (inhibitory): $F = 0.00$, $p = 0.99$).

Experimenter Ratings

For the whole sample and White (non-Hispanic) group, there was a significant negative association between 7R and experimenter cooperation ratings in the Modified DOTS (Full Sample: $r_s(55) = -0.35$, $p = 0.01$; White (non-Hispanic): $r_s(27) = -0.42$, $p = 0.02$); individuals with 7R tended to receive less favorable ratings. However, 7R did not relate to cooperation on the IED ($p > 0.10$ for

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Table 3
Cognitive Performance and Caregiver Rating Scores as a Function of DRD4 Allele Type for Children With Down Syndrome, All Ethnicities

	No 7R alleles (N = 35)[a] Mean(*SD*)	At least one 7R allele (N = 27)[a] Mean(*SD*)	*T*	*P*
Background IQ Measures				
K-BIT-2 standardized IQ score	44.20(6.59)	45.07(7.17)	−0.50	0.62
K-BIT-2 verbal raw score sum	19.60(9.36)	16.74(11.69)	1.07	0.29
K-BIT-2 non-verbal raw score sum	10.83(5.70)	9.70(5.48)	0.78	0.44
Cognitive Executive Function Measures				
CANTAB IED pre-ED errors	18.66(14.81)	23.54(16.45)	−1.19	0.24
Modified Dots mean baseline % correct	0.96(0.06)	0.94(0.09)	0.91	0.37
Modified Dots mean inhibitory % correct	0.64(0.35)	0.68(0.37)	−0.34	0.73
Modified Dots mean combined % correct	0.58(0.20)	0.53(0.16)	0.83	0.41
Caregiver Ratings				
BRIEF Behavioral Regulation Index *T*-score	61.03(9.85)	62.96(12.56)	−0.64	0.53
BRIEF Metacognitive Index *T*-score	63.31(6.57)	64.64(12.26)	−0.46	0.65
BRIEF Global Executive difficulties *T*-score	63.41(7.56)	64.68(12.57)	−0.42	0.68
Conners Rating Scale ADHD Inattentive	3.39(2.62)	4.20(2.70)	−1.14	0.26
Conners Rating Scale ADHD Hyperactive-Impulsive	2.45(2.05)	3.08(2.77)	−0.98	0.33
Nisonger Hyperactive Subscale	8.24(4.12)	10.73(7.04)	−1.58	0.12
Nisonger Insecure/Anxious Subscale	4.31(4.05)	6.62(6.91)	−1.53	0.13
Nisonger Overly Sensitive Subscale	4.45(3.089)	5.04(3.05)	−0.71	0.48
Nisonger Conduct Problem Subscale	9.72(5.85)	13.04(9.91)	−1.49	0.14

Note. DRD4 Genotype is a descriptor of the dopamine receptor *D4* (DRD4) gene, a gene often linked to ADHD in people without Down syndrome. 7R Allele = an indicator of repeated pairs of nucleotides associated with the DRD4 gene; ADHD = attention-deficit/hyperactivity disorder; K-BIT 2 = Kaufman Brief Intelligence Test, 2nd Edition; CANTAB = Intra/Extra Dimensional Set Shift (IED); ED = the extra-dimensional shift; Modified dots = "Frogs and Cats" Modified DOTS cognitive task; BRIEF = Behavioral Rating Inventory of Executive Function (Parent Report Form).
[a]Group *N*s varied by individual test.
[b]Verified with Mann-Whitney U (MWW) to account for deviation from normality.

both). We presume that the full sample effects in the Modified DOTS were driven by the White (non-Hispanic) group, because 7R did not relate to cooperation on the Modified DOTS in the Hispanic sample (p = 0.38).

Hispanic Sample With DS: Preliminary Results

While the sample of Hispanic children is small (n = 21), we report preliminary results here to guide future investigations. With regard to DRD4 7R prevalence, 11 individuals within this sample did not carry 7R; 7 carried one 7R; and 3 were homozygous for 7R. This distribution did not depart from Hardy-Weinberg equilibrium ($\chi^2(1, N = 21) = 1.02$, p = 0.31). There were also no differences in 7R prevalence between ethnic groups (White, non-Hispanic, and Hispanic) (*FET* (N = 53) = 0.46, p = 0.85). Similar to the results found in the White, non-Hispanic, and full group samples, IQ and laboratory tasks did not differ as a function of 7R in the Hispanic sample. However, the group *without* 7R showed heightened difficulties in caregiver behavioral reports, with higher scores on BRIEF BRI ($t(18) = 2.23$, p = 0.04, effect size = 0.45), BRIEF MI ($t(17) = 2.82$, p = 0.01, effect size = 0.54), and BRIEF Global Executive difficulties composite *T*-scores ($t(17) = 2.95$, p = 0.01, effect size = 0.56). There was also a significant *positive* association between 7R and experimenter ratings of cooperation on the IED ($r_s(15) = 0.57$, p = 0.02); individuals with

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Table 4
Cognitive Performance and Caregiver Rating Scores as a Function of DRD4 Allele Type for Children With Down Syndrome, White (Non-Hispanic) Only

	No 7R alleles (N = 17)[a] Mean(*SD*)	At least one 7R allele (N = 15)[a] Mean(*SD*)	*T*	*P*
Background IQ Measures				
K-BIT 2 standardized IQ score	46.12(8.48)	44.60(6.77)	0.55	0.58
K-BIT 2 verbal raw score sum	22.00(9.99)	17.93(11.98)	1.05	0.30
K-BIT 2 nonverbal raw score sum	12.47(6.01)	10.13(5.89)	1.11	0.28
Cognitive Executive Function Measures				
CANTAB IED pre-ED errors	15.38(15.30)	19.73(10.38)	−0.92	0.36
Modified Dots mean baseline % correct	0.96(0.05)	0.97(0.04)	−0.35	0.73
Modified Dots mean inhibitory % correct	0.68(0.36)	0.64(0.42)	0.29	0.78
Modified Dots mean combined % correct	0.59(0.19)	0.52(0.19)	0.87	0.39
Caregiver Ratings				
BRIEF Behavioral Regulation Index T-score	60.00(8.75)	70.00(10.14)	−2.79	**0.01***
BRIEF Metacognitive Index *T*-score	63.92(7.02)	71.83(9.70)	−2.35	0.03(0.11)[b]
BRIEF Global Executive difficulties *T*-score	63.38(7.37)	72.50(9.56)	−2.68	**0.01***
Conners Rating Scale ADHD Inattentive	3.71(2.79)	5.08(2.75)	−1.28	0.21
Conners Rating Scale ADHD Hyperactive-Impulsive	2.21(1.72)	4.31(2.81)	−2.35	**0.03**
Nisonger Hyperactive Subscale	7.71(3.34)	12.53(7.32)	−2.31	**0.03**
Nisonger Insecure/Anxious Subscale	3.07(3.30)	8.60(7.87)	−2.50	**0.02(0.01)[b]**
Nisonger Overly Sensitive Subscale	4.07(2.50)	5.67(3.20)	−1.49	0.15
Nisonger Conduct Problem Subscale	9.50(6.50)	16.40(10.83)	−2.06	**0.05**

Note. DRD4 Genotype is a descriptor of the dopamine receptor *D4* (DRD4) gene, a gene often linked to ADHD in people without Down syndrome. 7R Allele = an indicator of repeated pairs of nucleotides associated with the DRD4 gene; ADHD = attention-deficit/hyperactivity disorder; K-BIT 2 = Kaufman Brief Intelligence Test, 2nd Edition; CANTAB = Intra/Extra Dimensional Set Shift (IED); ED = the extra-dimensional shift; Modified dots = "Frogs and Cats" Modified DOTS cognitive task; BRIEF = Behavioral Rating Inventory of Executive Function (Parent Report Form).
[a]Group *N*s varied by individual test.
[b]When assessed with Mann-Whitney U (MWW), BRIEF Metacognitive Index *T*-score became nonsignificant (p = 0.11). All other results assessed with MWW were verified.

7R tended to receive higher cooperation ratings. As noted in the previous section, no other experimenter ratings were significant.

Discussion

In this study, we explored the relation between variation in the dopamine D4 receptor gene and individual differences in EF, attention, and behavior in Down syndrome. First, we examined whether polymorphic variants of DRD4 are overexpressed in children with DS. Replicating previous findings in an Indian sample (Das Bhowmik et al., 2008), we found that the presence of 7R in DS was in line with Hardy-Weinberg equilibrium. Additionally, we found no significant difference in the presence of 7R or other allele types between the DS and TD groups. These findings suggest that 7R presence in children with DS is comparable to that in typically-developing individuals.

Next, we assessed whether 7R was associated with EF and ADHD symptoms in DS. Although 7R did not predict scores on laboratory-based EF tasks, it did relate to differences in experimenter and caregiver behavior ratings when stratifying for ethnicity. White (non-Hispanic) children with 7R had increased hyperactivity, anxiety, and caregiver-reported behavioral and EF difficulties and showed less cooperation on the Modified DOTS task.

There are various factors to consider when interpreting these results. First, the disparity between DRD4's effects on performance-based

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vs. observer measures complements findings that observational behavioral ratings and laboratory tasks assess separate constructs (Toplak, West, & Stanovich, 2012). While laboratory tasks assess abilities under highly standardized conditions in which the task goal is constantly reinforced, ratings measures give insight into children's behaviors in naturalistic settings, in which there are more degrees of freedom and goals are subject to feedback from familiar social agents (caregivers, teachers). Furthermore, laboratory tasks may record the end result of a response without capturing the behaviors a participant exhibits. In this study, our experimenter ratings provide a bridge between these measures because children showed genotype-dependent behavioral differences during the laboratory tasks while the neuropsychological test scores were not significantly different.

Another important note is that the effects of DRD4 were only observed after stratifying for ethnicity. This finding complements previous work suggesting that DRD4's alleles have disparate effects in different ethnic groups (Leung et al. 2004; Martínez-Levy et al. 2009). Although the White, non-Hispanic sample was the only ethnic group of sufficient sample size to merit inclusion in the main analyses of this study, a pilot analysis of our Hispanic group (see Appendix) also suggested that those *without* 7R tended to have less parent-reported EF and attentional difficulties, a finding consistent with previous work in Mexican populations with ADHD showing better outcomes for those carrying 7R (Martínez-Levy et al. 2009). Considering how ethnicity might mediate DRD4's effects, it is important to note that ethnicity is a societal construct encompassing not only biological race, but also cultural attitudes and practices. Previous work has shown that single-gene effects for complex behavioral traits can be mediated through polygenic and epigenetic interactions (Charney, 2012), and that epigenetic changes arise from environment (Kappeler & Meaney, 2010). Thus, ethnicity could mediate DRD4's effects through mechanisms such as preferential transmission of specific variants within racial groups of genes that interact with DRD4, or cultural differences in developmental environment that could influence DRD4 expression. Regarding the first possibility, one gene that interacts with DRD4 is the gene encoding *DRD2,* which has "long" and "short" variants that form heteromers with DRD4 7R differently than with 4R or 2R (Mota et al. 2013), and which has a polymorphism (rs2283265) that has been shown to affect the expression of the long and short variants and to differ in risk allele frequency among different populations (Sullivan et al. 2013). Future work should be devoted to teasing apart and exploring these associations in larger samples and determining whether they relate to cross-cultural differences in clinical outcomes.

A few limitations of this study should be noted. First, while this study is larger than other single-gene association studies in people with DS (Alexander et al., 1997), a larger sample size would have been ideal. Our study, however, is unusual in its size, compared to most studies conducted in special populations. Second, we did not have a comparison group, although our effects were in the moderate range and are strong compared to DRD4 studies in typically developing samples. Future studies should explore whether DRD4 effects on EF and behavior in children with DS are additive or enhanced relative to effects in TD individuals. Although the goal of this study was to elucidate how individual differences in dopamine-regulated processes may relate to attention and EF in people with DS through investigation of allelic variation in DRD4, future studies should also consider the influence of other catecholaminergic systems on EF processes in this population, as well as whether the effects observed for DRD4 result from differences in dopamine affinity per se. Another catecholamine system of interest may include the noradrenergic system, because prior work in DS mouse models has also indicated neurodegeneration of locus coeruleus neurons (Salehi et al., 2009).

Regarding how Trisomy 21 might influence background genes, recent studies suggest that Trisomy 21 may have epigenetic effects on certain nontrisomy genes (Sanchez-Mut, Huertas, & Esteller, 2012). Such studies support the notion that the DS phenotype is due not only to overexpression of the triplicated genes on chromosome 21, but also results from functional alteration of certain genes off of the chromosome. Our study evaluated whether allelic variants of a specific nontrisomy gene could help explain cognitive outcomes in children with DS, and our results indicate that Trisomy 21 does not mask DRD4's effects. More work is needed, however, to determine whether these effects are unaffected or significantly enhanced by Trisomy 21 on molecular (epigenetic) and behavioral levels.

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Finally, how do these findings inform us about the extent to which ADHD symptoms are a core facet of the DS phenotype? First, there is substantial variability in outcome, suggesting that ADHD is not universal across all children. Second, these symptoms relate to DRD4, which is also linked to ADHD in the typical population. Thus, it is likely that background genes or other factors contribute to this variable profile and that ADHD cannot then be a universal facet of DS. More work should examine other factors potentially associated with variation in executive skills in this population, such as Obstructive Sleep Apnea (OSA), which can be present in up to 70% of individuals with DS. Obstructive Sleep Apnea recently has been linked to EF difficulties in this syndrome (Breslin, 2011; Chen, Spanò, & Edgin, 2013). In total, ADHD symptoms are present in children with DS with variable expression, and nontrisomy genes seem to drive at least some aspects of this phenotype.

Although much remains to be explored, our findings indicate that variation in background genes should be addressed when considering cognitive outcomes in children with DS. Doing so may help contribute to clinical interventions and may increase our knowledge of how Trisomy 21 interacts with nontrisomy gene effects.

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Appendix

Pilot Analysis of Hispanic Group

Appendix Table 1
Background Characteristics of Children With Down Syndrome, Hispanic Only, Relative to DRD4 Genotype

	No 7R Alleles ($N = 11$)		At least one 7R Allele ($N = 10$)		
Characteristic	Mean	*SD*	Mean	*SD*	T/MWW[a](*p*)
Age	10.18	2.68	9.80	2.53	0.34(0.74)
Mom's years of education	14.18	3.31	15.00	2.36	54.50[a](0.97)
Total annual income	4.30	1.95	5.11	3.10	−0.69(0.50)
Number of children in household	2.91	1.30	2.50	0.97	0.81(0.43)
Sex	***N***	**% of Total**	***N***	**% of Total**	**Fisher's(*p*)**
Female	4	36.4%	4	40.0%	n/a(1.00)

Note. DRD4 Genotype is a descriptor of the dopamine receptor *D4* (DRD4) gene, a gene often linked to ADHD in people without Down syndrome. 7R Allele = an indicator of repeated pairs of nucleotides associated with the DRD4 gene; ADHD = attention-deficit/hyperactivity disorder.
[a]Analyzed with Mann-Whitney U to adjust for deviations from normality within groups.

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Appendix Table 2
Cognitive Performance and Caregiver Rating Scores as a Function of DRD4 Allele Type for Children With Down Syndrome, Hispanic Only

	No 7R alleles ($N = 11$)[a]	At least one 7R allele ($N = 10$)[a]	T	P
Background IQ Measures				
K-BIT 2 standardized IQ score	41.91(3.81)	46.50(8.45)	−1.63	0.12
K-BIT 2 verbal raw score sum	15.09(7.89)	16.10(12.62)	−0.22	0.83
K-BIT 2 nonverbal raw score sum	8.09(4.11)	10.10(4.84)	−1.03	0.32
Cognitive Executive Function Measures				
CANTAB IED pre-ED errors	21.00(11.10)	23.44(16.05)	−0.39	0.70
Modified Dots mean baseline % correct	0.94(0.07)	0.89(0.13)	0.85	0.42
Modified Dots mean inhibitory % correct	0.49(0.29)	0.74(0.36)	−1.41	0.18
Modified Dots mean combined % correct	0.53(0.20)	0.56(0.15)	−0.26	0.80
Caregiver Ratings				
BRIEF Behavioral Regulation Index T-score	63.60(12.78)	52.70(8.73)	2.23	**0.04**
BRIEF Metacognitive Index T-score	64.20(6.89)	54.44(8.17)	2.82	**0.01*(0.02)**[b]
BRIEF Global Executive difficulties T-score	65.00(9.01)	53.67(7.58)	2.95	**0.01***
Conners Rating Scale ADHD Inattentive	4.10(2.60)	2.60(1.90)	1.47	0.16
Conners Rating Scale ADHD Hyperactive-Impulsive	3.30(2.21)	1.70(2.26)	1.59	0.13
Nisonger Hyperactive Subscale	10.40(5.02)	7.11(5.53)	1.36	0.19
Nisonger Insecure/Anxious Subscale	6.10(5.28)	4.44(4.61)	0.72	0.48
Nisonger Overly Sensitive Subscale	5.90(3.78)	4.11(2.52)	1.20	0.25
Nisonger Conduct Problem Subscale	10.90(5.53)	8.56(7.11)	0.81	0.43

Note. DRD4 Genotype is a descriptor of the dopamine receptor *D4* (DRD4) gene, a gene often linked to ADHD in people without Down syndrome. 7R Allele = an indicator of repeated pairs of nucleotides associated with the DRD4 gene; ADHD = attention-deficit/hyperactivity disorder; K-BIT 2 = Kaufman Brief Intelligence Test, 2nd Edition; CANTAB = Intra/Extra Dimensional Set Shift (IED); ED = the extra-dimensional shift; Modified dots = "Frogs and Cats" Modified DOTS cognitive task; BRIEF = Behavioral Rating Inventory of Executive Function (Parent Report Form).
[a]Group *N*s varied by individual test.
[b]Verified with Mann-Whitney U to account for deviation from normality.