The Autism Spectrum Phenotype in ADNP Syndrome

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Pathogenic disruptions to the activity-dependent neuroprotector homeobox (*ADNP*) gene are among the most common heterozygous genetic mutations associated with autism spectrum disorders (ASDs). Individuals with *ADNP* disruptions share a constellation of medical and psychiatric features, including ASD, intellectual disability (ID), dysmorphic features, and hypotonia. However, the profile of ASD symptoms associated with *ADNP* may differ from that of individuals with another ASD-associated single gene disruption or with ASD without a known genetic cause. The current study examined the ASD phenotype in a sample of representative youth with *ADNP* disruptions. Participants (N = 116, ages 4–22 years) included a cohort with *ADNP* mutations (n = 11) and three comparison groups with either a mutation to *CHD8* (n = 11), a mutation to another ASD-associated gene (other mutation; n = 53), or ASD with no known genetic etiology (idiopathic ASD; n = 41). As expected, individuals with *ADNP* disruptions had higher rates of ID but less severe social affect symptoms compared to the *CHD8* and Idiopathic ASD groups. In addition, verbal intelligence explained more variance in social impairment in the *ADNP* group compared to *CHD8*, other mutation, and idiopathic ASD comparison groups. Restricted and repetitive behaviors in the *ADNP* group were characterized by high levels of stereotyped motor behaviors, whereas the idiopathic ASD group showed high levels of restricted interests. Taken together, these results underscore the role of *ADNP* in cognitive functioning and suggest that social impairments in *ADNP* syndrome are consistent with severity of verbal deficits. ***Autism Research*** *2018, 11: 1300–1310.* © 2018 International Society for Autism Research, Wiley Periodicals, Inc.

Lay Summary: Disruptions to the *ADNP* gene (i.e., *ADNP* syndrome) have been associated with autism spectrum disorder (ASD). This article describes intellectual disability, mild social difficulties, and severe repetitive motor movements in a group of 11 youth with *ADNP* Syndrome. We found lower rates of ASD than previously reported. Verbal skills explained individual variability in social impairment. This pattern suggests that the *ADNP* gene is primarily associated with learning and memory, and level of social difficulties is consistent with level of verbal impairment.

Keywords: ADNP; autism spectrum disorder; intellectual disability; genetic syndrome; developmental disorder

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social communication as well as restricted and repetitive interests and behaviors. Within these broad symptom domains, the behavioral profiles of individuals with ASD are extremely heterogeneous. In recent years, disruptive gene mutations involving several hundred different genes have been identified as putative causes of ASD, yet they account for only 30% of ASD cases altogether [De Rubeis et al., 2014; Iossifov et al., 2014; O'Roak et al., 2014; Sanders et al., 2012]. One of the most commonly affected genes is activity-dependent neuroprotector protein (*ADNP*), a transcription factor-encoding gene located on the long arm of chromosome 20 (20q13.13). Heterozygous mutations involving *ADNP* have been identified in multiple individuals with ASD providing strong evidence that ADNP is an autism risk gene [Helsmoortel et al., 2014].

Individuals with *ADNP* mutations share common psychiatric and medical features, including ASD symptoms, intellectual disability (ID), dysmorphic craniofacial features and hypotonia [Gozes et al., 2017; Helsmoortel et al., 2014]. This constellation of features has led to a syndromic clinical classification associated with *ADNP* disruptions, sometimes called Helsmoortel-Van der Aa Syndrome (HVDAS) or *ADNP* Syndrome [National Institute of Health, 2017; Vandeweyer et al., 2014]. Despite these commonalities, there remains substantial variability among individuals with mutations to *ADNP*, particularly regarding severity of ASD symptoms. Among a sample of 11 *ADNP* mutation patients described previously [Helsmoortel et al., 2014; Vandeweyer et al., 2014] all were diagnosed with ASD; however, two were characterized as

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having "mild" symptoms. Critically, this sample was ascertained primarily for a diagnosis of ASD or ID; thus, rates of ASD symptoms are expected to be biased. In contrast, fewer than 70% of a large international cohort of *ADNP* cases (ascertained via previous publication in genetic literature or via a parents' social media network) carried an ASD diagnosis [Van Dijck et al., in press] and a recent case report has highlighted lack of ASD features in at least one affected child [Li, Wang, & Szybowska, 2017]. To address the ascertainment bias, our laboratory has employed a "genetics-first" approach, wherein participants are recruited primarily for a known disruptive mutation to *ADNP* and/or other ASD-linked genes. The process of referral for clinical genetic testing introduces bias to our sample as well, due to the increased likelihood of testing in individuals presenting with intellectual or psychiatric impairment. In addition, one of our *ADNP* participants was initially identified via participation in an ASD-focused study that included genomic sequencing [Fischbach & Lord, 2010]. Nonetheless, our approach has resulted in an *ADNP* sample with a broader neuropsychological phenotype than has previously been described.

Unlike the broader ASD population, among which ID is noted in approximately 30% of U.S. cases (D.D.M.N.S.Y., 2014), ID is a consistent (100%) finding in individuals reported to have a *de novo ADNP* mutation [Helsmoortel et al., 2014; Vandeweyer et al., 2014; Li et al., 2017], and some individuals are nonverbal. Functional gene classes associated with ASD- and ID-linked genes overlap substantially, suggesting that phenotypic expression depends on a number of factors including location and effect of the variant and genetic and environmental interactions [Iossifov et al., 2014]. Moreover, behavioral symptoms of ID and ASD can be difficult to disentangle, and the DSM-5 ASD criterion "symptoms are not better explained by ID," is reliant on clinical judgment. However, there are some notable exceptions. Disruptions to *CHD8*, for example, account for 20% of the most common *de novo* mutations in ASD [O'Roak et al., 2014]. Although most reported individuals with a *CHD8* mutation have an ASD diagnosis, only 60% have comorbid ID [Bernier et al., 2014]. Thus, while the cognitive behavioral phenotype associated with *CHD8* appears similar to idiopathic ASD populations, both are notably different from that of *ADNP*.

Restricted and repetitive behaviors (RRBs), which make up the second category of symptoms necessary for a DSM-5 ASD diagnosis [American Psychiatric Association, 2013], are likewise common among other neurodevelopmental disorders, including and especially ID. A subset of RRBs, stereotyped, or repetitive motor movements (e.g., hand flapping and whole-body rocking), are particularly frequent in ID and related genetic syndromes such as Fragile X and Prader-Willi [Leekam, Prior, & Uljarevic, 2011]. This subtype of RRBs were moderately correlated with nonverbal IQ in an ASD sample ($r = -.29$) and thus appear to be the least specific to an ASD diagnosis [Bishop et al., 2013]. Likewise, within ASD samples, stereotyped motor movements are more frequent among lower functioning and younger children. However, while no specific RRB is unique to ASD, individuals with ASD do consistently show a range of RRBs that are present across situations. In contrast, syndromic groups and those with other childhood psychopathology (e.g., obsessive compulsive disorder) show more limited RRB phenotypes [Leekam et al., 2011]. The profile of RRB subtypes in individuals with mutations to *ADNP* has not been previously described. Given the heterogeneity of the ASD phenotype and increasing recognition of monogenic syndromes associated with ASD and ID, we believe it could be useful to clinicians and other providers to better understand the pattern of RRBs that characterize a more representative sample of youth with *ADNP* Syndrome.

We report on a cohort of 11 participants (10 previously unreported) with a disruptive mutation to *ADNP*. Based on clinical observations of these individuals during research testing, we expect that the profile of ASD symptoms associated with *ADNP* disruption is distinct from idiopathic ASD and from individuals with other ASD-associated monogenic disruptions. Our goal in this study is to add to the extant literature by thoroughly describing ASD symptoms in a group of individuals ascertained primarily for known disruptions to *ADNP*. We chose comparison groups that offer behavioral and genetic contrasts. The idiopathic ASD group offers a clear behavioral contrast; the *CHD8* group provides contrast with a well characterized genetic subtype of ASD; the other mutation group provides a comparison to ASD-linked genetic events more broadly. We planned exploratory analyses to evaluate the following phenotypic characteristics among individuals with *ADNP* Syndrome relative to comparison groups: (a) severity of social communication deficits, (b) severity of RRB deficits, (c) association between intelligence and ASD symptom severity, and (d) profile of RRBs. We approached each of these analyses in two ways: first, we examined the phenotype within the full *ADNP* cohort and second, we examined the phenotype of individuals with both *ADNP* Syndrome and an ASD diagnosis.

Methods and Materials

Participants

Participants included 11 individuals with a likely gene disrupting (LGD) event to *ADNP* (ages 4–14 years), recruited to The Investigation of Genetic Exome Research (TIGER) study at the University of Washington. Comparison cohorts recruited through TIGER included

Table 1. Participant Characteristics

	ADNP	*CHD8*	Other mutation	Idiopathic ASD
N	11	11	53	41
Age in years	8.25 (3.25)	11.71 (5.48)	11.92 (4.80)	12.55 (2.55)
Female (%)	27	27	34	20
ASD (%)	64	100	85	100
ID (%)	100	55	62	24
Ascertained via clinical genetic testing (%)	91	67	74	0
SA severity	5.27 (2.45)	7.91 (1.64)	6.51 (2.49)	7.76 (1.83)
RRB severity	6.81 (2.44)	9.27 (1.10)	7.02 (2.35)	7.27 (2.52)
NVIQ	32.18 (10.33)	59.91 (25.51)	62.92 (30.57)	90.00 (25.66)
VIQ	31.64 (10.54)	61.36 (29.14)	61.21 (30.47)	86.95 (30.34)
Vineland adaptive behavior composite	51.00 (10.06)	64.73 (18.74)	60.57 (13.50)	72.22 (9.95)

SA Severity = ADOS-2 Social Affect comparison severity score. RRB Severity = ADOS-2 Restricted and Repetitive Behavior comparison severity score. NVIQ = nonverbal intelligence quotient. VIQ = verbal intelligence quotient.

11 participants with an LGD mutation in *CHD8* (age range: 4–21 years) and 53 participants with a disruptive mutation in another (i.e., not *ADNP* or *CHD8*) gene previously identified in connection to ASD (other mutation; age range: 4–22 years). Inclusion criterion for TIGER was a confirmed, likely pathogenic frameshift event affecting a gene previously associated with ASD (excluding events associated with Fragile X and Rett syndrome). An ASD diagnosis was not necessary for inclusion. Finally, a comparison cohort of 41 individuals with Idiopathic ASD (age range: 8–17 years) was recruited as part of another ongoing study at the University of Washington using the same phenotype test battery. Inclusion criteria for the Idiopathic ASD cohort were (a) a diagnosis of ASD confirmed by study clinicians and (b) no deleterious gene events identified by targeted resequencing of 232 genes putatively associated with autism [Stessman, Bernier, & Eichler, 2014]. All participants were fluent in English and had normal or corrected-to-normal vision. Approval was obtained from the University of Washington's Institutional Review Board, and all participants and caregivers completed informed consent and/or assent, as age and developmentally appropriate, prior to participation. Participant demographics are detailed in Table 1.

Genomic Sequencing

Participant DNA underwent whole-exome sequencing or targeted molecular inversion probe (MIP) resequencing of 232 candidate ASD/ID genes [Stessman et al., 2014]. The majority of participants with gene mutations were initially ascertained by clinical geneticists for the presence of a disruptive mutation in a candidate autism gene; however, a proportion were recruited based on results of genetic testing as part of a previous ASD research study [Fischbach & Lord, 2010]. Genetic events were considered disruptive if they resulted in a frameshift mutation or other LGD event, such as a stop-gain, or a missense event with a combined annotation-dependent deletion score greater than 30 [Kircher et al., 2014]. Individuals in the Idiopathic ASD group were ascertained for presence of ASD, and whole exome or targeted sequencing (Stessman et al., 2014 found no disruptive mutation or high-impact missense event in any autism candidate gene. Inheritance was determined by Sanger sequencing of the parent–child trio; Table 2 and Supporting Information.

Clinical Evaluation

Autism symptoms. Participants and their caregivers completed 6–8 hr of behavioral and cognitive batteries, either in the laboratory or in the participant's home. Caregivers completed questionnaires and clinical interviews regarding the child's behavioral, developmental, family, psychiatric, and medical history. ASD diagnoses were made in accordance with DSM-5 criteria by a licensed clinical psychologist naïve to the gene event. Behavior assessments included gold standard ASD evaluations involving the appropriate module of the Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2) [Lord et al., 2012], standardized parent interview using the Autism Diagnostic Interview-Revised (ADI-R) [Le Couteur, Lord, & Rutter, 2003], cognitive test results, and medical and developmental history.

ADOS-2 calibrated severity scores reflecting severity of social affect (SA) or RRB deficits were calculated by following published algorithms [Hus, Gotham, & Lord, 2014]. The ADOS-2 SA and RRB calibrated severity scores range from 1 (mild/minimal) to 10 (severe) symptom presentations. The scores were standardized in a large sample of children with (n = 551) and without (n = 60) ASD who represented a broad range of ages (2–16 years), verbal abilities and overall functioning. Thus, the scores were developed to be comparable across ages, intellectual functioning, and ADOS-2 modules. Intellectual ability explained a modest amount of variance in SA (10.9%), but very little of RRB (4.0%) in the normative sample

Table 2. *ADNP* and *CHD8* Individual Genetic Variants

ADNP								
ID	Chr.	Position	Ref.	Alt.	c.DNA	p.Variant	Effect	Inheritance
13545.p1	20	49509094	G	GT	c.2156_2157insA	p.Tyr719Ter	F	*de novo*
T146.03	20	49510911	AG	A	c.339del	p.Phe114SerfsTer47	F	unknown
T149.03	20	49510203	CCA	C	c.1046_1047del	p.Leu349ArgfsTer49	F	*de novo*
T164.03	20	49508964	AA	A	c.2287del	p.Ser763ProfsTer9	F	unknown
T171.03	20	49510963	GA	G	c.287del	p.Val96AlafsTer65	F	unknown
T176.03	20	49510149	G	A	c.1102C > T	p.Gln368Ter	ST-G	unknown
T186.03	20	49510431	TG	T	c.819del	p.Lys274AsnfsTer31	F	*de novo*
T195.03	20	49508751	CTTTA	C	c.2496_2499del	p.Asn832LysfsTer81	F	*de novo*
T204.03	20	49509094	G	T	c.2157C > A	p.Tyr719Ter	ST-G	*de novo*
T206.03	20	49518564	GT	GTT	c.190_191insA	p.Thr64AsnfsTer35	F	*de novo*
T219.03	20	49508976	GACCCTTGGGGT CTAAAGCTAAAACA	G	c.2250_2274del	p.Val751MetfsTer13	F	*de novo*

CHD8								
ID	Chr.	Position	Ref.	Alt.	c.DNA	p.Variant	Effect	Inheritance
14016.p1	14	21870169	G	A	c.4009C > T	p.Arg1337Ter	ST-G	*de novo*
11654.p1	14	21871373	T	C	c.3519-2A > G	N/A	SSA	*de novo*
12991.p1	14	21861643	TCTTC	T	c.6307_6310del	p.Glu2103ArgfsTer3	F	*de novo*
14233.p1	14	21859175	A	AT	c.7112_7113insA	p.Asn2371LysfsTer2	F	*de novo*
T126.03	14	21863460	C	A	c.5179G > T	p.Glu1727Ter	ST-G	*de novo*
T132.03	14	21869200	G	A	c.4204C > T	p.Arg1402Ter	ST-G	*de novo*
T162.03	14	21871807	A	AT	c.3322_3323insA	p.Ile1108AsnfsTer7	F	*de novo*
T178.03	14	21876929	TT	T	c.2420del	p.Asn807ThrfsTer78	F	*de novo*
T181.03	14	21875068	G	A	c.2854C > T	p.Arg952Ter	ST-G	*de novo*
T199.03	14	21878028	GT	G	c.2345del	p.His782ProfsTer7	F	*de novo*
T202.03	14	21870494	C	T	c.3882 + 1G > A	N/A	SS	*de novo*

Note: Reference genome = hg19. ADNP Accession number = NM_015339.2. CHD8 Accession number = NM_001170629.1. Effect abbreviations F = Frameshift, ST-G = stop-gained, SS = splice site, SSA = splice site acceptor.

[Hus et al., 2014]. SA and RRB scales were weakly correlated (r = .25) [Lord et al., 2012].

The Repetitive Behavior Scale-Revised (RBS-R) [Bodfish, Symons, & Lewis, 1999] is a 43-item, caregiver-report questionnaire reflecting severity and frequency of restrictive and repetitive symptoms across multiple domains. Unlike the ADOS-2, this questionnaire captures a variety of specific RRBs associated with ASD, including those that may be rare and thus unobserved by a clinician during diagnostic evaluation. Each item is rated to reflect degree of severity from 0 (does not occur) to 3 (severe). Several independent studies of the RBS-R have replicated nearly identical five-factor models of RRB subtypes in ASD samples [Bishop et al., 2013; Lam & Aman, 2007; Mirenda et al., 2010]. These factors reflect (a) stereotyped motor and sensory behaviors, (b) self-injurious behavior, (c) ritualistic and insistence-on-sameness behaviors, (d) compulsive behaviors, and (e) restricted interests and have been shown to have high internal consistency (0.72–0.90) [Bodfish, Symons, Parker, & Lewis, 2000]. The current study used the subscales published by Bishop et al. [2013], who analyzed a large, well characterized ASD sample from the Simons Simplex Collection [Fischbach & Lord, 2010]. The number of items in each subscale ranges from 2 to 11. To create scores that reflected both severity and number of symptoms endorsed in each domain, we calculated continuous scores for each individual as *mean severity of items endorsed x percentage of items endorsed* within each subscale. The resulting scores ranged from zero to three, with three indicating endorsement of all items in that subscale at the highest severity.

Cognitive and adaptive functioning. Cognitive functioning was measured using the Differential Ability Scales, 2nd Edition (DAS-II) (Elliott, 2007) School-Age and Early Years forms or, for individuals over 18 years, the Wechsler Abbreviated Scales of Intelligence, 2nd Edition (WASI-II) [Wechsler, 2011]. For participants unable to complete the age appropriate test, ratio IQ scores were derived by dividing the mean age equivalencies of performance on DAS-II subtests by chronological age and multiplying by 100. Four *ADNP* participants were unable to complete enough items on any DAS-II Core battery to estimate age-equivalencies; these missing data were imputed with floor age-derived ratio IQ scores (n = 2) or floor deviation IQ scores (n = 2 children under age 7, due to lower limits of the age equivalency estimates). Adaptive functioning was evaluated via clinical interview on the Vineland Adaptive Behavior Scales, 2nd Edition [Sparrow, Cicchetti, & Balla, 2005]. Diagnoses of ID were made by licensed clinicians following DSM-5 criteria [American Psychiatric Association, 2013].

Results

ASD in ADNP *Syndrome*

Cognition and language. Among individuals with a mutation to *ADNP*, seven (64%) met DSM-5 diagnostic criteria for ASD. Those with ASD had lower full scale IQs (M = 26.14, SD = 6.69) than those who did not meet criteria for ASD (M = 40.75, SD = 8.18; $t(9) = 3.23$, $P = .010$); however, all individuals had a diagnosis of ID with moderate to profound impairment. Individuals with *ADNP* and ASD were more likely to be male ($\chi[1] = 7.22$, $P = .007$) and had more severe ADOS-2 SA calibrated severity scores ($t[9] = -4.22$, $P = .002$).There were no significant differences between diagnostic groups on age ($P = .46$) or severity of ADOS-2 RRB calibrated severity score (ASD M = 7.71, SD = 1.80 vs. non-ASD M = 5.25, SD = 2.87; $t[9] = -1.78$, $P = .110$). Nine of the 11 individuals with *ADNP* Syndrome were minimally verbal and thus completed Module 1 of the ADOS-2. Two minimally verbal individuals did not use any meaningful words or approximations during the ADOS-2; of these, one was diagnosed with ASD. Two individuals spoke in phrase speech and thus completed Module 2; neither of the Module-2 individuals was ultimately diagnosed with ASD.

Social communication. Clinical observations via the ADOS-2 and parent-report on the ADI-R indicated an overall pattern in which individuals with *ADNP* Syndrome showed compensation for verbal weakness through use of nonverbal communication. Among those with *ADNP* who were diagnosed with ASD, relative strengths included some use of sign language, and direction of smiles to communicate affect. Most individuals followed the examiner's gaze and half responded to their names when called. In contrast, weaknesses included limited interest in peers and odd social approach, such as standing physically close to or touching others. Those with *ADNP* who did not meet criteria for ASD showed regular integration of eye contact, directed facial expressions, and instrumental or descriptive gestures to communicate. They expressed clear shared enjoyment during interactions and social routines with the examiners. They made regular attempts to gain others' attention by making eye contact, sharing items of interest, or verbalizing. Parents reported some interest in peers but limited success with friendships and occasional social disinhibition.

Repetitive and restricted behaviors. Whether or not they met full criteria for an ASD diagnosis, individuals with *ADNP* Syndrome demonstrated or had a reported history of sensory seeking behaviors, such as licking or visual inspection of toys. Repetitive motor movements, such as hand flapping, were often observed and reported.

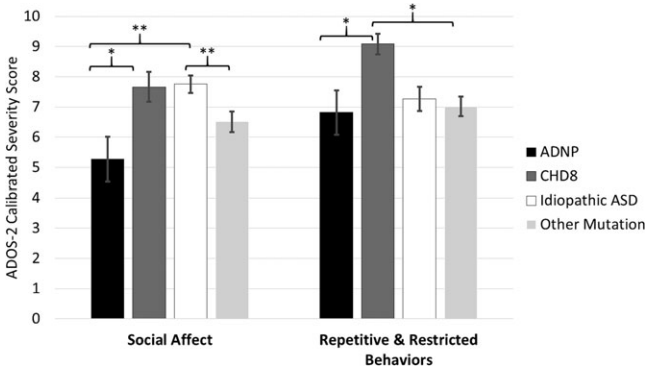

Figure 1. ADOS-2 SA and RRB comparison severity scores by group. Error bars represent ±1 SE. *P < .05; **P < .01. Significance values for the pairwise comparisons are based on estimated marginal means with IQ and age covaried.

Severity of SA and RRB ADOS-2 Symptoms

One-way analyses of covariance (ANCOVAs) with Bonferroni-corrected post hoc pairwise tests were conducted to compare severity of ADOS-2 SA and RRB calibrated severity scores across *ADNP* and comparison groups, with verbal IQ and age as continuous covariates. With the full *ADNP* cohort included, the overall model was significant for SA ($F[5,110] = 5.084$, $P < .001$) and RRB ($F[5,110] = 2.38$, $P = .043$) severity. Main effects of verbal IQ and age explained additional variance in SA severity ($P = .032$ and $P = .040$, respectively) but not RRB severity (P's = .263). Post hoc comparison estimates indicated that the *ADNP* group had less severe SA symptoms relative to *CHD8* ($P = .029$), and idiopathic ASD ($P = .005$) samples; however, there was no difference between *ADNP* and the other mutation group ($P = .519$). In comparison, estimated mean SA severity for the *CHD8* group was not different from that of idiopathic ASD ($P = 1.00$) or other mutation ($P = .283$). There were fewer differences between *ADNP* and comparison groups with respect to RRB severity. The *ADNP* group had less severe RRB symptoms than *CHD8* ($P = .034$) but not the idiopathic ASD ($P = 1.00$) or other mutation ($P = 1.00$) groups (Fig. 1). *CHD8* had more severe RRB symptoms than the Other mutation group ($P = .027$).

We then repeated these analyses including only individuals with ASD diagnoses (i.e., reducing the *ADNP* group to $n = 7$ and the other mutation group to $n = 45$). Although the pattern of results was similar to the full sample analyses, with the *ADNP* group showing less severe SA and RRB severity relative to comparison groups, the differences were no longer significant (P's > .19), likely due to low statistical power.

Association between verbal intelligence quotient and ASD Symptom Severity

Given higher rates of ID and very low verbal skills in the *ADNP* group, as well as the results of the ANCOVAs

Table 3. Association Between ASD Symptom Severity and Intelligence Across Groups

	Social affect with verbal intelligence		
	B	R^2	Wald test
ADNP	−.176, SE = .046, *P* < .001	.568, SE = .196, *P* = .004	-
CHD8	−.036, SE = .013, *P* = .006	.403, SE = .228, *P* = .077	**$\chi(1) = 8.499$, *P* = .004**
Other mutation	.001, SE = .011, *P* = .899	.000, SE = .005, *P* = .950	**$\chi(1) = 13.901$, *P* = .002**
Idiopathic ASD	−.024, SE = .009, *P* = .005	.164, SE = .106, *P* = .121	**$\chi(1) = 10.382$, *P* = .001**
	Social Affect with Nonverbal Intelligence		
	B	R^2	Wald test
ADNP	−.147, SE = .056, *P* = .009	.381, SE = .230, *P* = .098	-
CHD8	−.049, SE = .013, *P* < .001	.574, SE = .195, *P* = .003	$\chi(1) = 2.878$, *P* = .089
Other mutation	.003, SE = .011, *P* = .809	.001, SE = .009, *P* = .904	**$\chi(1) = 6.768$, *P* = .009**
Idiopathic ASD	−.018, SE = .011, *P* = .095	.064, SE = .074, *P* = .389	**$\chi(1) = 5.038$, *P* = .025**

Note. Coefficients are unstandardized. Significant Wald test values (bold) indicate a difference between the regression coefficient for the comparison group vs. that of *ADNP*.

above, we tested whether verbal IQ would explain greater variance in SA severity within the *ADNP* group relative to comparison groups, using the whole sample. We conducted comparison analyses with nonverbal IQ and RRB scores to test for specificity of the association. These hypotheses were addressed using path (linear regression) models that were permitted to vary freely across groups in Mplus 7.31 [Muthén, 2013]. As expected, the models indicated a significant association between verbal IQ and ADOS-2 SA severity in *ADNP*. This was also true for *CHD8* and idiopathic ASD comparison groups but not the other mutation group (Table 3). R^2 values indicated that greater than half (57%) the variance in SA severity in *ADNP* group was explained by verbal IQ, which was greater than the *CHD8* (40%), other mutation (0.0%), and idiopathic ASD (16%) groups. (Table 3). Results for the association between SA severity and nonverbal IQ were similar, except that SA variance explained by nonverbal IQ was greatest in the *CHD8* (57%) group. In contrast, RRB severity was not well explained by verbal or nonverbal intelligence in any group (RRB and verbal IQ R^2 range: 0.3–22%; RRB and nonverbal IQ R^2 range: 0.0–4.7%).

Next, we used Wald Chi-Square testing [Liao, 2004] to test equivalence of the fit of nested models when the regression coefficients were constrained to be equal across *ADNP* and each comparison group. A significant Wald test indicates that the *ADNP* regression coefficient is significantly different from that of the comparison group. As predicted, *ADNP* had a significantly stronger association between low verbal IQ and high SA severity relative to all other groups (Table 3, Fig. 2). Comparative analyses using nonverbal intelligence indicated that *ADNP* and *CHD8* groups showed comparable associations between SA severity and nonverbal intelligence, but the *ADNP* group had a stronger association between these two variables relative to idiopathic ASD and other Mutation groups. As expected, the association between RRB severity and verbal or nonverbal intelligence did not differ between *ADNP* and comparison groups.

We next repeated the path analyses with SA severity and verbal intelligence quotient (VIQ) among our subsample of individuals who met DSM-5 criteria for ASD. Surprisingly, among the *ADNP* group, the amount of behavioral variance explained was much lower (1%), perhaps due to lack of variance in VIQ (range: 16–30) in this restricted group.

RRB Profile in ADNP

To evaluate the phenotypic profile of RRBs associated with disruptive mutations to *ADNP*, we compared levels of the five RRB subtypes (stereotyped motor and sensory behaviors [sensory/motor], restricted interests, self-injurious behaviors, compulsive behaviors and ritualistic/sameness behaviors) both within and between groups. We conducted a repeated measures 5 × 4 ANCOVA (RRB subtype × group) with Greenhouse–Geisser correction. As a first pass, covariates were not included in this model due to low statistical power and this is further justified by the lack of main effects of verbal IQ and age on RRB severity in the first analyses. Results indicated a significant main effect of RRB subtype (F[2.6, 287.2] = 28.94, P < .001), a nonsignificant main effect of group (F[3,111] = 2.16, P = .097) and a marginally significant group by RRB subtype interaction (F[3, 111] = 1.80, P = .079).

Next, we examined the profile of RRB subtypes within *ADNP*, using post hoc comparisons with Bonferroni correction for multiple comparisons. The *ADNP* group had more severe ratings on the sensory/motor subscale relative to the self-injurious (P = .001), compulsive (P = .001), and ritualistic/sameness (P = .008) behavior scales but no difference between sensory/motor and restricted interests (P = .284) or any other subscales. The *CHD8* group showed comparable levels of sensory/motor behaviors to restricted interests (P = 1.00) and ritualistic/sameness behaviors (P = .084), and higher levels of sensory/motor behaviors than self-injurious (P = .054) and compulsive

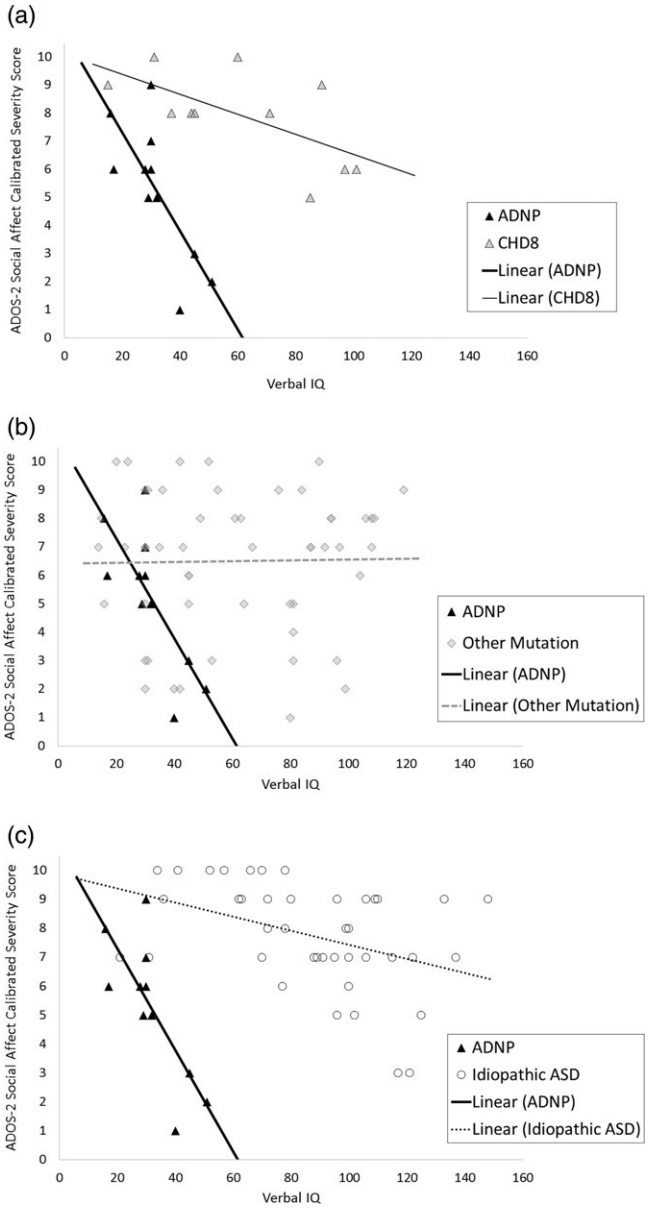

Figure 2. The *ADNP* group shows stronger linear correlations between high SA severity and low verbal IQ relative to (a) *CHD8*, (b) other mutation, and (c) idiopathic ASD groups.

(P = .041) behaviors relative to the other RRB subtypes. In contrast, the other mutation group had higher levels of restricted interests than all other subtypes (P's < .02) except sensory/motor (P = .216). The idiopathic ASD group had higher levels of restricted interests than all other RRB subtypes (P's < .001) and higher levels of ritualistic/sameness behaviors relative to self-injurious behaviors (P = .005).

Next, we examined differences in levels of specific RRB subtypes between *ADNP* and each comparison groups. *Post hoc* comparisons using LSD indicated that the *ADNP* group's sensory/motor behaviors were significantly more severe than the other mutation group (P = .013) and the idiopathic ASD group (P = .036) but comparable to the *CHD8* group (P = .284). *ADNP* did not differ from comparison groups on severity of any other RRB subtypes (P's ≥ .117). *CHD8* did not differ from comparison groups on any RRB subtype (P's ≥ .064). Altogether, the *ADNP* group showed a unique profile of RRBs characterized by high severity and number of behaviors that fell into the sensory/motor and restricted interest categories, but low severity and number of other RRB behaviors. The idiopathic ASD group showed a different, distinct profile of RRBs characterized by high levels of restricted interests, compulsive, and ritualistic behaviors. (Fig. 3).

Next, we repeated these analyses with our subsample of individuals with a DSM-5 ASD diagnosis. Within the *ADNP* group, results were comparable, with higher levels of sensory/motor behaviors relative to other RRBs (P's < .007) except restricted interests (P = 1.00). Similarly, the overall profile of RRBs appeared similar (Supporting Information, Fig. S1). As before, the *ADNP* group had more severe sensory motor behaviors than idiopathic ASD and other mutation groups (P's < .020).

Finally, we repeated analyses with the full sample with nonverbal IQ and age as covariates. Age did not show main or interaction effects (P's > .144) so was dropped from the ultimate model. Nonverbal IQ showed a main effect on RRB severity (F[1,110] = 11.84, P = .001) as did group (F[3,110] = 4.62, P = .004). Post hoc pairwise comparisons indicated no significant differences in RRB subtype severity within the *ADNP* group (P's > .120). With IQ covaried, the *CHD8* group showed more severe restricted interests relative to ritualistic/sameness behaviors (P = .036); RRB differences within the other mutation and idiopathic ASD groups remained consistent with the original analyses.

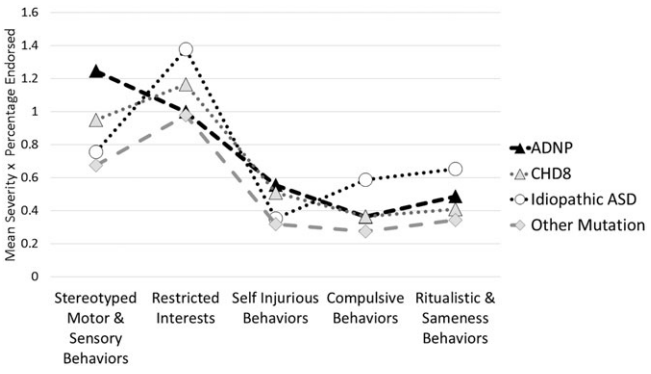

Figure 3. RBS-R subscale profile by group. Y-axis values reflect the mean severity of items endorsed multiplied by the percentage of items endorsed, within each subscale.

Discussion

Although *ADNP* syndrome has previously been strongly associated with ASD, the profile of social communication and RRB deficits is notably different from other ASD subtypes and may be more consistent with that of ID. Given that clinical genetic testing is typically performed only in cases of significant medical or psychiatric impairment, ascertainment bias for studies of psychiatric occurrence in rare mutations cannot be avoided. However, the current study attempted to minimize this bias by recruiting based on known genetic event rather than a specific phenotype. In our sample of 11 individuals recruited for a putative causal mutation to *ADNP*, only 64% met full diagnostic criteria for ASD. In contrast, ID was present in 100% percent of our *ADNP* participants, consistent with prior reports. This pattern is further substantiated by the fact that *ADNP* mutations are more frequently detected in ID or developmental disability research cohorts than in strict ASD research cohorts (http://denovo-db.gs.washington.edu).

We propose that *ADNP* dysfunction be conceptualized as consistently affecting learning and memory, with social communicative symptoms congruent with the level of verbal impairment. Consistent with this conceptualization, the profile of ASD symptoms in our *ADNP* group reflected less severe social communication impairments than other mutation and idiopathic ASD comparison groups, despite comparable severity of RRB symptoms. The linear path models indicated that severity of social communication impairment was strongly associated with verbal IQ in the full *ADNP* group. Although restricted variance in cognitive ability among those with both *ADNP* Syndrome and ASD limits our conclusions somewhat, this result generally suggests when verbal intelligence was accounted for, there was little remaining variance to be explained in individual social communication behaviors. This may indicate downstream effects of cognition on ASD symptoms in *ADNP* Syndrome or it may indicate shared neurogenetic etiology with equal effects on both traits. In contrast, our other mutation group, which demonstrated a broad range of SA and verbal IQ, showed no association between these variables.

Diagnostic differentiation between ASD and ID is challenging and underscores the degree of symptom overlap across these phenotypes [Sappok et al., 2013; Matson & Shoemaker, 2009]. Increasingly, individuals who would have previously been diagnosed with ID are receiving an ASD diagnosis instead; this is evidenced by epidemiological patterns wherein rates of ASD diagnoses have increased proportional to decreasing rates of ID [Polyak, Kubina, & Girirajan, 2015] from 2000 to 2010. This presents a theoretical and epidemiological problem, as there is a potential artificial inflation of the prevalence of ASD and how it is defined. In our study, our blinded clinicians gave comorbid ASD and ID diagnoses when the ASD symptoms were over and above what would be expected for the individual's developmental level, consistent with DSM-5 guidelines. The lack of association between IQ and ASD severity in the other mutation group provides evidence the correlation between SA and verbal IQ in the *ADNP* group was not artifact resulting from difficulty with the clinical evaluation of ASD symptoms in the context of ID. Furthermore, it seems that this association is specific to *ADNP*, suggesting enormous impact of this gene on a broad scope of cognitive and behavioral functioning. Our study highlights potential drawbacks to categorical, behavioral diagnoses for individuals with a known genetic etiology. With or without a DSM-5 diagnosis of ASD, our sample of individuals with *ADNP* syndrome showed a spectrum of social communication deficits and a predominant category of RRBs; thus, it may be more informative for treatment planning and developmental prognosis to characterize affected individuals by the genetic syndrome rather than multiple behavioral labels.

The *ADNP* group had a profile of RRBs that was characterized by stereotyped motor and sensory behaviors. This was notably distinct from the idiopathic ASD group and consistent with syndromic ID groups [Leekam et al., 2011] and the overall profile was consistent even when excluding individuals who did not meet diagnostic criteria for ASD. Possibly, low rates of restricted interests in the *ADNP* group could be due to impaired language that would be necessary to communicate these interests. However, this is likely only part of the explanation at most, because the restricted interests factor on the RBS-R comprised only 2 items, one of which was not language dependent (Item 40: *Strongly attached to one specific object*) and the other of which was not necessarily language dependent (Item 41: *Fascination, preoccupation with one subject or activity, e.g. trains, computers weather, dinosaurs*). Recently, researchers have put forth a concerted effort to identify homogenous etiological subtypes of ASD, resulting in characterization of many single gene events, including *ADNP* and *CHD8* [Bernier et al., 2014; Helsmoortel et al., 2014]. The results of our RRB profile analyses suggest idiopathic ASD (as it is currently defined) may in fact constitute its own etiological subtype with a relatively homogenous behavioral endophenotype, despite heterogeneous genetic influences.

Our results also highlight a particularly interesting comparison between *ADNP* and *CHD8* cohorts. Despite opposite penetrance of ASD versus ID diagnoses, the ontology of these genes overlaps, with both genes expressed in embryo, involved in chromatin remodeling and characterized as FMRP targets [Krumm, O'Roak, Shendure, & Eichler, 2014; Iossifov et al., 2014]. Prior research on these functional gene categories has focused on ASD cohorts and has not used a genetics-first ascertainment approach.

Our study suggests that, by recruiting a large sample of individuals identified primarily for a putative genetic event in a known functional pathway, we may see greater phenotypic variance across individuals. This model creates potential for stronger detection of small-effect ontological differences and interactions that may explain variance in cognitive-behavioral phenotypes.

The etiology of covariance between social communication and RRB symptoms is not well understood, and several studies suggest that genetic influences on RRBs and social traits may actually be separable [Alarcón, Cantor, Liu, Gilliam, & Geschwind, 2002; Ronald, Happé, & Plomin, 2005; Ronald, Happé, Price, Baron-Cohen, & Plomin, 2006]. Yet, the co-occurrence of SA and RRB deficits is the crux of the ASD diagnosis and thus we know these behaviors are highly comorbid, at least. Several explanations for psychiatric comorbidity exist, including genetic linkage, pleiotropy, and shared endophenotypes [Plomin, DeFries, Knopik, & Neiderheiser, 2013]. The current study suggests that genetic subtypes of ASD may each be associated with a unique etiology of ASD trait covariance. Within the idiopathic ASD group, for whom we currently assume the etiology of neurodevelopmental differences is polygenic, linkage is a plausible explanation. However, within single gene LGD groups, individual differences in the location and effect of the genetic variant could have vastly different effects on protein functioning. Yet, these disparate events frequently produce a similar behavioral, physical, and/or medical phenotype, implying convergence on a common neurobiological endophenotype. What the *ADNP* individuals do have in common is substantial impairment in cognitive functioning, underscoring *ADNP* as crucial to learning and memory. The associated deficits in social communication may be conceptualized as consistent with the level of cognitive impairment.

We acknowledge that our sample remains skewed by the fact that clinical and research genetic testing is most likely to occur in cases of early, profound impairment. Missense, mosaic, or even deleterious mutations to *ADNP* that do not result in either ASD or ID are plausible and would likely go undetected for lack of clinical indication for genetic testing. This possibility is evidenced by the identification of maternally inherited *ADNP* mutations in other, unpublished samples (ADNP Kids [ADNPkids.com] Parent Group, email communications). This underscores the challenge of describing a set of heterogeneous genetic events with a single clinical syndrome. Moreover, our sample size for genetic subgroups is small, and the analyses conducted with the subgroup of individuals who met DSM-5 criteria for ASD were underpowered, particularly within the *ADNP* group. This limits the extent to which we can generalize to future, larger samples.

Altogether, we report that ASD symptoms among youth ascertained for *ADNP* Syndrome are characterized by relatively mild social communication deficits (despite impaired verbal intelligence and low expressive language abilities) coupled with stereotyped motor RRBs. The social communication deficits are mild enough as to not warrant a diagnosis of DSM-5 ASD in about 30% of our cases. From a clinical standpoint, social communication skills may serve as a strength on which to capitalize during intervention with individuals with *ADNP* Syndrome. However, children with *ADNP* Syndrome will nonetheless benefit from interventions designed specifically for ASD, especially therapies that adopt a behavior analysis approach, which has proven effective among youth with ID and specifically for reducing severity and frequency of RRBs [Asmus et al., 2004; Matson, Neal, & Kozlowski, 2012].

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Disclosure Statement

Dr. Eichler is on the scientific advisory board (SAB) of DNAnexus, Inc. Dr. Arnett reports no biomedical financial interests or potential conflicts of interest. Ms. Rhoads reports no biomedical financial interests or potential conflicts of interest. Ms. Hoekzema reports no biomedical financial interests or potential conflicts of interest. Dr. Turner reports no biomedical financial interests or potential conflicts of interest. Dr. Gerdts reports no biomedical financial interests or potential conflicts of interest. Dr. Wallace reports no biomedical financial interests or potential conflicts of interest. Ms. Sermone reports no biomedical financial interests or potential conflicts of interest. Dr. Bernier reports no biomedical financial interests or potential conflicts of interest.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. RBS-R subscale profile by group, including only the subsample of individuals with an ASD diagnosis (n = 104). Y-axis values reflect the mean severity of items endorsed multiplied by the percentage of items endorsed, within each subscale.

Table S1. Gene Variants within the Other Mutation group