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Characterizing the autism spectrum phenotype in *DYRK1A*-related syndrome

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Abstract

Likely gene-disrupting (LGD) variants in *DYRK1A* are causative of *DYRK1A* syndrome and associated with autism spectrum disorder (ASD) and intellectual disability (ID). While many individuals with *DYRK1A* syndrome are diagnosed with ASD, they may present with a unique profile of ASD traits. We present a comprehensive characterization of the ASD profile in children and young adults with LGDs in *DYRK1A*. Individuals with LGD variants in *DYRK1A* (n = 29) were compared to children who had ASD with no known genetic cause, either with low nonverbal IQ (n = 14) or average or above nonverbal IQ (n = 41). ASD was assessed using the ADOS-2, ADI-R, SRS-2, SCQ, and RBS-R. Quantitative score comparisons were conducted, as were qualitative analyses of clinicians' behavioral observations. Diagnosis of ASD was confirmed in 85% and ID was confirmed in 89% of participants with *DYRK1A* syndrome. Individuals

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Ethical Oversight: Ethical oversight was provided by the University of Washington (UW) Institutional Review Board (IRB; local IRB numbers STUDY00000813 and STUDY00000660). All procedures performed were in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all parents of children participating in the study; children provided written assent as developmentally appropriate

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with *DYRK1A* syndrome showed broadly similar social communication behaviors to children with idiopathic ASD and below average nonverbal IQ, with specific challenges noted in social reciprocity and nonverbal communication. Children with *DYRK1A* syndrome also showed high rates of sensory seeking behaviors. Phenotypic characterization of individuals with *DYRK1A* syndrome may provide additional information on mechanisms contributing to co-occurring ASD and ID and contribute to identification of genetic predictors of specific ASD traits.

Lay summary:

DYRK1A syndrome has been identified as a genetic cause of autism spectrum disorder (ASD). We found that individuals with *DYRK1A* syndrome had high rates of ASD and intellectual disability (ID). Individuals with *DYRK1A* syndrome showed many similarities in ASD traits when compared to individuals with ASD and ID without a known genetic cause, but individuals with *DYRK1A* syndrome showed particular differences in social reciprocity, nonverbal communication, and sensory-seeking behaviors.

Keywords

DYRK1A ; genetics; intellectual disability; autism phenotypes

INTRODUCTION

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder (NDD) characterized by social communication differences and restricted, repetitive behaviors and interests (RRBs); RRBs include repetitive speech, movements, or use of objects, insistence on sameness, intense interests, and hyper- or hypo-reactivity to sensory stimuli (American Psychological Association, 2013). Attempts are underway to identify biological mechanisms underlying ASD to explain phenotypic heterogeneity and inform interventions. Biological mechanisms of interest include single likely gene-disrupting (LGD) variants and copy number variations (CNV), which are rare individually but taken together account for up to 25% of ASD cases (Iossifov et al., 2012; Iossifov et al., 2014; Kaufman et al., 2010; McCarthy et al., 2014). Given the heterogeneity of ASD and broad range of characteristics encompassed within the ASD diagnosis, there is a current need to understand how specific biological mechanisms contribute to specific ASD features to expand both etiological models and invention efforts.

LGD variants in *DYRK1A*, a dual kinase located in the Down syndrome critical region on chromosome 21, have been consistently associated with ASD, intellectual disability (ID), and broader social deficits (Kim et al., 2017; van Bon et al., 2011; van Bon et al., 2016; Widowati et al., 2018). LGD variants in *DYRK1A* impact auto-phosphorylation, which in turn alters multiple pathways and processes related to cellular signaling and neurological functioning (Laham et al., 2021; Lee et al., 2020). The primary clinical characteristics of LGD variants in *DYRK1A* (described clinically as *DYRK1A* syndrome) are intellectual disability, speech problems, ASD, and microcephaly, with other common characteristics including seizures, feeding and gastrointestinal problems, hypertonia, and gait and foot abnormalities (Van Bon et al., 2021). *DYRK1A* syndrome is considered to be rare, with 68

individuals previously reported across published studies as of 2021 (Van Bon et al., 2021) and 97 unique cases reported in a recent manuscript (Fenster et al, 2022). Specific features of *DYRK1A* and its expression may contribute to characteristic ASD phenotypes; for example, *DYRK1A* is expressed prenatally across brain regions, including those associated with increased social communication impairment (Trinh et al., 2020). By examining the ASD phenotype in *DYRK1A* syndrome, we may inform clinical care through precision medicine and identify mechanisms that impact functioning in ASD without a known genetic cause (Arnett et al., 2021).

Associations between LGD variants in *DYRK1A* and ASD were initially established in a cohort of 8 patients with loss of function variants; 7 out of these 8 patients received an ASD diagnosis following a comprehensive evaluation (van Bon et al., 2016). The ASD phenotype was later expanded in a broader cohort of individuals with LGD variants in *DYRK1A*, in which 73% of individuals assessed with traditional autism diagnostic tools met DSM-5 criteria for ASD (Earl et al., 2017). However, estimates of ASD prevalence are likely affected by a number of factors. First, nearly all published *DYRK1A* syndrome cases report ID or global developmental delay, with cognitive and adaptive impairments frequently in the moderate, severe, or profound range (Earl et al., 2017). Diagnostic decision-making for ASD in the context of severe to profound ID is complex and not well standardized across clinicians, with few tools and guidelines available for valid and reliable assessment in the population (Thurm et al., 2019). Second, published *DYRK1A* syndrome cases drawn from broader neurodevelopmental disability cohorts may or may not have been ascertained for ASD. For example, participants in a more recently described *DYRK1A* syndrome cohort reported a lower rate of professional ASD diagnosis than identified by Earl and colleagues (29.8%; Fenster et al., 2022). It is unknown whether these participants were previously evaluated for ASD and did not meet criteria, whether they have not yet been able to access an ASD evaluation, or whether ASD is not currently of clinical concern for these participants. Durand and colleagues (2022) found that 57% of individuals with *DYRK1A* syndrome met criteria for ASD on the Autism Diagnostic Interview-Revised, which may or may not fully correspond with expert clinical diagnosis of ASD using a multi-method assessment approach (Thurm et al., 2019). Finally, both phenotyping batteries and ASD diagnostic thresholds may vary widely across studies, which limits the ability to draw conclusions about true ASD prevalence when individuals with *DYRK1A* syndrome are combined or compared (Myers et al., 2020).

Despite uncertainty as to the precise prevalence of ASD diagnosis in *DYRK1A* syndrome, quantitative work examining adaptive, language, and behavioral characteristics using survey and interview methodologies (Fenster et al., 2022; Morison et al., 2022) suggests potentially unique features of ASD in *DYRK1A* syndrome. Notably, parent report of ASD-related behaviors suggests that social motivation may be a relative strength in *DYRK1A* syndrome, while other social communication challenges as well as RRBs are comparatively elevated (Morison et al., 2022). However, additional quantitative comparisons of individuals with *DYRK1A* syndrome to others with ID and ASD are needed to determine whether features are specific to the ASD phenotype in this population or associated with ASD and ID more generally. Parent-report measures often lack reliability and specificity in individuals with moderate to profound ID and other complex challenges (e.g., medical and sensory

impairments) that are prevalent in *DYRK1A* syndrome (Beighley et al., 2020; Constantino et al., 2000; Gergoudis et al., 2020). As such, deep phenotyping approaches that include standardized assessments administered by expert clinicians have the potential to provide a more nuanced characterization of ASD features in *DYRK1A* syndrome. In addition, deep characterization of cognitive, adaptive, and behavioral functioning in LGD groups such as *DYRK1A* provides detailed and standardized phenotypic information across multiple key domains. This complements the results of recent large-scale exome sequencing studies (e.g., Satterstrom et al., 2020), in which the focus is on categorical diagnosis and studies with different ascertainment approaches may be pooled (Myers et al., 2020).

The current investigation aims to characterize ASD features in a relatively large group of children with LGDs in *DYRK1A* to better understand this gene variant as a possible etiology of ASD. Individuals with *DYRK1A* syndrome were compared to two groups of participants with idiopathic ASD (ASD without known genetic cause), one with average nonverbal cognition and one with nonverbal cognition in the ID range. In addition, qualitative clinical observations of individuals with *DYRK1A* syndrome were examined to further elucidate the ASD phenotype among individuals with LGDs in *DYRK1A*.

Method

Participants

Individuals were recruited as part of two genetics-first research projects at the University of Washington (UW). The study included two groups of participants: (1) individuals with a disruptive mutation that is associated with ASD and NDDs via the TIGER study (Beighley, Hudac, et al., 2020); and (2) a comparison group of individuals with idiopathic ASD via the ZEBRA study (Hudac et al., 2023). The TIGER and ZEBRA studies are both focused on comprehensive genotypic and phenotypic characterization of individuals with ASD and/or ASD-associated genetic disorders, with participants receiving genetic testing and an aligned battery of clinical measures as described further below. Of note, the ZEBRA study excluded participants with severe uncorrected vision, hearing, or motor impairment (e.g., deaf, blind, or non-ambulatory participants) as well as individuals with a history of significant prematurity (defined as gestational age less than 36 weeks and birth weight less than 2000 grams); these were not exclusionary criteria for the TIGER study. Children with other indicators of possible syndromic ASD (e.g., dysmorphic features or medical complexity) were not excluded from the ZEBRA study. In alignment with the genetics-first approach of these studies, *DYRK1A* syndrome participants were recruited and included based on the presence of an LGD variant in *DYRK1A* as opposed to previous clinical diagnosis of *DYRK1A* syndrome or the presence of specific phenotypic features.

Analyses included a total of 29 individuals with LGD variants in *DYRK1A* who were compared to (1) a group of children with ASD, no known ASD-associated LGD, and low Nonverbal intelligence quotient (IQ; ≤ 70; $n = 14$, iASD+ID) and (2) a group of children with ASD, no known ASD-associated LGD, and average Nonverbal IQ (85–115; $n = 41$, iASD). Nonverbal IQ was selected given that a large portion of the *DYRK1A* syndrome group is minimally verbal, and, thus, overall IQ scores that include verbal ability would not be representative of these individuals' abilities.

Comprehensive clinical and behavioral characterization was conducted by research clinicians. Children with ASD without known ASD-associated genetic variants completed testing locally at UW. *DYRK1A* syndrome participants participated either on-site at UW ($n = 23$), via home visit at the participant's home ($n = 4$), or remotely via telehealth evaluation ($n = 2$). Certain measures were only conducted during in-person visits, thus, the two telehealth *DYRK1A* participants did not complete a cognitive assessment or ASD observation measures (ADOS-2). One in-person participant was lost to follow-up and did not complete the ADI-R. All data collection and research procedures were approved by the University of Washington Institutional Review Board. Written and/or informed consent and assent were obtained, as appropriate.

Genetic characterization

For the *DYRK1A* syndrome group, the presence of an LGD variant was confirmed through a review of a clinical genetic testing lab report, targeted sequencing (e.g., MIP panel), or whole exome sequencing conducted as part of previous research participation. See supplementary Table 1 for full genetic characterization. All participants in the iASD and iASD + ID groups received genetic testing to confirm the absence of ASD-associated LGDs. The genetic testing performed in this group included whole exome sequencing, whole genomic sequencing, and molecular inversion probe (MIP) panels consisting of known ASD-associated genes, including *DYRK1A*. If whole exome or genome sequencing was available for a participant, genetic testing was not repeated; if not available, a MIP panel was performed.

Measures

Cognitive Ability—IQ was assessed using the Differential Ability Scales, 2nd Edition (DAS-II; Elliot et al., 1990) for children ages 5–17 years, the Wechsler Scale of Intelligence, 4th Edition (WISC-IV; Wechsler, 2003), or the Mullen Scales of Early Learning (Mullen, 1995) for participants who were unable to complete DAS-II or WISC-IV items and whose mental age was below 4 years per caregiver report measures and expert clinician judgment. Cognitive test selection and cognitive assessment procedures were derived from the Simon Simplex Collection cognitive assessment battery (Fischbach & Lord, 2010). We extracted verbal (VIQ) and nonverbal IQ (NVIQ), in addition to full-scale IQ (FSIQ), given disparities in VIQ and NVIQ in this population. On the DAS-II, VIQ was measured using the Verbal Composite score and NVIQ was measured using the Special Nonverbal Composite score. On the WISC-IV, the Verbal Comprehension Index was used for VIQ and the Perceptual Reasoning Index was used for NVIQ. On the Mullen Scales of Early Learning, VIQ was calculated by summing verbal subdomains (Receptive and Expressive Language), and NVIQ was calculated using nonverbal subdomains (Visual Reception and Fine Motor), consistent with the process standardized by the Simons Simplex Collection (Fischbach & Lord, 2010). IQ scores were generated using standardized deviation scores ($M = 100$, $SD = 15$) or ratio scores (mental age equivalent / chronological age × 100) if the participant's performance was below the floor and could not be calculated as a deviation score.

Adaptive Functioning—Adaptive functioning was measured using the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) caregiver interview (Sparrow et

al., 2005). On this measure, parents answer questions on the frequency of their child's behavior (0 = behavior never performed, 2 = behavior usually performed independently). The Vineland includes an adaptive behavior composite score, which is composed of communication, daily living, and social subscale scores. Composite scores are standard scores with an average of 100 and standard deviation of 15.

ASD Measures—Research reliable clinicians administered the Autism Diagnostic Observation Schedule-Second Edition (ADOS-2; Lord et al., 2012). The ADOS-2 is a semi-structured play-based assessment, during which clinicians observe and then rate a child's social affect (SA) and restricted and repetitive behaviors (RRB). Selected items contribute to algorithms related to SA and RRB subscale scores, and to a total score that has a cut-off for informing whether the child meets diagnostic criteria for ASD. The subscale and total algorithm scores can be converted to a Calibrated Severity Score (CSS), a measure of "overall symptom severity" that allows for comparisons across modules on a scale from 1 (minimal-to-no evidence of ASD) to 10 (high evidence; Hus & Lord, 2014; Hus et al., 2012). There are five modules, which are administered depending on the individual's age and expressive language level.

In addition to the ADOS-2, caregiver report measures of ASD features were included in order to provide additional information on participant behaviors outside of the clinical assessment setting. The Autism Diagnostic Interview –Revised (ADI-R; Lord et al., 1994) was used to assess developmental history and parent report of ASD symptoms. The ADI-R is a semi-structured interview that evaluates current and historical difficulties in social development, communication, and restricted or repetitive behaviors and interests. Based on parents' responses, clinicians rate the child's behaviors on 93-items in terms of current and historical behavior on a scale of 0 (no behaviors indicative of ASD) to 3 (behaviors strongly indicative of ASD). Selected items contribute to algorithm scores for social, communication, and restricted/repetitive behavior and interests, and scores across domains are summed for a total score. For the current study, specific ADI-R items were selected *a priori* by a team of clinicians with expertise in ASD assessment and rare genetic disorders. Items were selected that both characterize ASD symptomology based on DSM-V diagnostic criteria and are appropriate for individuals with intellectual disability and/or language impairment (i.e., speech items were not included). The specific items analyzed are presented in Table S2.

The Social Responsiveness Scale, Second Edition (SRS-2) is a 65-item parent report of ASD behaviors (Constantino & Gruber, 2012). On the SRS-2, parents report their child's behavior over the past six months on a 4-point Likert scale (1 = "not true", 4 = "almost always true). The SRS-2 includes five subscales related to social awareness, social cognition, social communication, social motivation, and RRBs. The first four subscales may also be summed into a composite score called the Social Communication Index. All subscales also yield a total composite score. T-scores are generated for total and subscale scores with a mean of 50 and standard deviation of 10, with higher scores indicating higher levels of behaviors associated with ASD.

The Social Communication Questionnaire is also a parent-report of ASD behaviors. Parents answer 40 yes/no items about their child's behavior (Rutter et al., 2003). A cutoff of 11

is recommended for distinguishing between children who likely do and do not have ASD behaviors (Corsello et al., 2007).

Parents also completed the Repetitive Behavior Scale-Revised (RBS-R; Bodfish et al., 2000). On the RBS-R, parents rate their child's behaviors on 43-items on a 4-point Likert scale (0 = "behavior does not occur", 3 = "behavior occurs and is a severe problem"). The RBS-R yields a total T-score and T-scores for subdomains of sensorimotor behaviors, restricted interests, self-injurious behaviors, compulsive behaviors, and a need for sameness.

Clinical diagnoses

ASD and ID diagnoses were provided or ruled out according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria as determined via expert clinician judgment and using all available sources of clinical information. Clinicians were licensed psychologists with expertise and training in the diagnosis of neurodevelopmental disorders and evaluation of individuals with rare genetic disorders.

Analytic plan

For quantitative analyses, a series of linear mixed-effects models were computed in R version 4.0.3 using the "lme4" package (Bates et al., 2014) to determine the main effects of group (i.e., *DYRK1A* compared to ASD comparison groups without known genetic events). Pairwise comparisons were addressed using Bonferroni correction. Analyses on ADI-R items were conducted using chi-square tests between qualitative level of impairment (None, Unclear, Clear) and group.

Qualitative analyses were also conducted for the *DYRK1A* syndrome participants who completed comprehensive in-person ASD evaluations. Analyses were conducted using a deductive approach (Creswell & Plano Clark, 2017). Licensed psychologists with expertise in ASD assessment and rare genetic disorders and a trained coder reviewed clinical case reports and clinician assessment notes for each participant. Clinician notes and case reports were drafted by the clinician following each participant's evaluation, with the purpose of describing behavior observations throughout the evaluation process. Coders reviewed these documents and recorded whether specific behaviors reflecting DSM-5 ASD criteria (e.g., unusual intonation of vocalizations, reduced social motivation, restricted interests) were described as present or absent, or if the behavior was not mentioned in the clinician note or case report. The coder also recorded whether motor deficits or delays were noted as present or absent. Of note, given the young age of some participants, limited information available about motor development in older individuals with *DYRK1A* syndrome, and the fact that direct assessments of motor skills were not included in this battery, it is unknown whether the motor challenges presented by some participants represent motor delays or distinct motor disorders.

Results

Demographic and clinical features

Participants ranged in age from four years to 24 years. See Table 1 for full participant characterization and group differences. Differences between groups were analyzed using chi-square for categorical variables and ANOVA for continuous variables There were no group differences in sex ratio or age, p's < .10. As anticipated, the *DYRK1A* group did not differ from the iASD+ID group in nonverbal IQ, $p = .86$, but was lower than the iASD group, $p < .0001$.

Participants in the DYRK1A group presented with several different LGD variant types, including frameshift, stop-gained, missense, and splice-donor variants. All three missense variants are categorized as pathogenic or likely pathogenic per American College of Medical Genetics (ACMG) guidelines. Two sibling participants presented with an inherited LGD variant and are described further below. This variant is classified as likely pathogenic per ACMG guidelines and is non-mosaic per allele balance and review of raw sequence data. These participants received whole exome sequencing, and secondary variants of interest were not identified. Eight participants presented with variants of unknown inheritance due to unavailable genetic testing for one or more biological parents, and the remaining 17 participants had confirmed de novo variants. Several of these participants have been previously described in publications, including publications presenting earlier results from the TIGER study (Earl et al., 2017) and publications resulting from the Simons Simplex Collection (e.g., O'Roak et al., 2012) and Simons Variation in Individuals Project/Simons Searchlight (e.g., Fenster et al., 2022). Participant IDs from these studies and full variant information are presented in Table S1.

Clinically assessed ASD severity and ASD traits

As reported in Table 1, ASD diagnosis was clinically confirmed in 85.2% (23 of 27) of participants with LGDs in *DYRK1A*. Of the 27 participants who were administered the ADOS-2, the majority of children were administered Module 1 (63.0%). Module 2 was administered to 11.1% of the sample and Module 3 was administered to 25.9% of the sample. ADOS-2 modules were selected based on the participant's expressive language level per research reliability standards. Standardized ADOS-2 CSS scores (see Table 2) indicated similar ASD severity for all groups, $F(2,79) = 1.27$, $p = .29$, including social affect and RRB subdomains, $p > .11$, suggesting that intensity or frequency of clinician-observed ASD traits was comparable across modules. Of the participants ($n = 2$) that completed telehealth testing only, one parent reported a previous community diagnosis of ASD, and the ADI-R was consistent with ASD for a second participant who had not previously been evaluated for ASD.

Next, we examined caregiver-reported ASD phenotypes using the ADI-R ($n = 28$), such that items with scores of 2 or 3 indicated current clear, problematic social behaviors and impairing RRBs (full proportions available in Supplemental Table 2). As illustrated in Figure 1, the *DYRK1A* group parents reported elevated autistic traits above and beyond iASD on nearly all social items, $p < .05$, including socioemotional reciprocity

(items 51, 52, 54, 59; e.g., social smiling, seeking to share enjoyment with others), nonverbal communication (items 42, 45, 57; e.g., pointing, gestures, facial expressions), and relationships (items 62, 63, 65; e.g., interest and appropriate response to approach by other children). There was one exception with no significant differences for social disinhibition (item 66, $p = .11$). In addition, two socioemotional items (item 51: social smiling; item 54: seeking to share enjoyment with others) indicated elevated parental endorsement above and beyond iASD+ID, $p < .05$.

Related to group differences on RRB items (Figure 2), there were Chi-square group differences, $p < .05$, but pairwise comparisons indicated no significant differences for the *DYRK1A* group relative to the iASD+ID group, $p > .51$. Overall differences indicated that the *DYRK1A* group parents reported elevated repetitive motor movements or use of objects (items 69, 77, 78) and elevated unusual preoccupations (item 67). Lastly and of note, individuals in the *DYRK1A* group had fewer abnormal, idiosyncratic negative responses to specific sensory stimuli than those in the iASD group.

Parent-reported ASD traits

Full descriptive statistics and group significance testing with Bonferroni correction are provided in Table 2, which compares caregiver reported ASD features and adaptive skills across the *DYRK1A*, iASD+ID, and iASD groups.

Broadly, social responsiveness and social skills as measured via the SCQ and SRS-2 were similar between *DYRK1A* and idiopathic ASD with one exception: iASD had greater strengths (i.e., lower T-scores) in the social awareness domain relative to both *DYRK1A* and ASD+ID.

The VABS-2 indicated lower adaptive abilities for *DYRK1A* in a graded pattern (*DYRK1A* < iASD+ID < iASD) for overall composite score, as well as communication and daily living subdomains. Both *DYRK1A* and iASD+ID had lower VABS-2 socialization scores relative to iASD.

Lastly, the *DYRK1A* group exhibited lower RBS-R scores relative to iASD+ID, including overall total score, as well as subdomains of compulsive behaviors and sameness. Individuals with *DYRK1A* syndrome exhibited lower sensory motor scores relative to iASD.

Intellectual disability.—Out of 27 participants, 24 met criteria for ID/global developmental delay, with severity ranging from mild to profound. Three participants with *DYRK1A* syndrome did not meet criteria for either ID or global developmental delay. The first participant (T188.03) was a 5-year-old male with a *de novo* pathogenic missense variant in *DYRK1A*. He obtained a full scale IQ score of 87, verbal IQ of 99, and nonverbal IQ of 84 based on cognitive testing with the DAS-II. He met criteria for speech sound disorder, developmental coordination disorder, attention-deficit hyperactivity disorder, combined type, and unspecified disruptive, impulse control and conduct disorder; he did not meet criteria for ASD. The participant presented with microcephaly, dysmorphic facial features, and toe and dental anomalies. Medical history was notable for feeding problems, obstructive hearing loss, chronic constipation, tremors, gastroesophageal reflux (GERD), abnormal

MRI, plagiocephaly, recurrent otitis media, cleft palate, kidney abnormalities, and sleep problems.

The second participant (T201.04) was a 14-year-old male with an inherited pathogenic frameshift variant in *DYRK1A*. He obtained a full scale IQ score of 133, verbal IQ of 119, and nonverbal IQ of 133 based on cognitive testing with the DAS-II. He met criteria for ASD, depressive disorder, and developmental coordination disorder. This participant presented with dysmorphic facial features, pectus excavatum, scoliosis, foot and toe anomalies, and hypermobility. Medical history is notable for seizures, chronic constipation, inguinal hernia, motor coordination difficulties, and sleep problems.

Of note, this participant has a 16-year-old brother (T201.03) with the same inherited variant in *DYRK1A;* this participant met criteria for ASD and severe intellectual disability. This participant presented with dysmorphic facial features and toe and finger anomalies. Medical history was notable for feeding problems, strabismus, gastrointestinal problems, seizures, motor coordination difficulties, and sleep problems. The parent from whom this event is inherited presented with a full scale IQ score of 102 and elevated ASD traits as per self-report, informant report, and observational measures completed as part of the TIGER study caregiver battery; as this parent's event was not identified until after study participation, more comprehensive medical and diagnostic information is not available.

The third participant (T261.03) was a 4-year-old male with a *de novo* pathogenic frameshift variant in *DYRK1A*. This participant obtained a full scale IQ of 68, verbal IQ of 84, and nonverbal IQ of 65 based on cognitive testing with the DAS-II. His adaptive skills were in the low average range with a VABS-2 Adaptive Behavior Composite of 86. Based on the patient's age-appropriate adaptive skills and strength in verbal cognition, a clinical diagnosis of ID or global developmental delay was not provided. He did meet criteria for ASD and developmental coordination disorder. This participant presented with microcephaly, micrognathia, sacral dimple, and dysmorphic facial features. Medical history was notable for feeding problems, strabismus, optic nerve anomaly, GERD, motor coordination problems, hypotonia, hypertonia, abnormal MRI and EEG, skin problems, febrile and non-febrile seizures, and sleep problems.

Clinical case reports.—Qualitative examiner notes and case reports were available for all but one of the *DYRK1A* syndrome participants who completed in-person evaluations (n = 26). The majority of participants were described as minimally verbal (no words or single words only; n = 19/26, 73%), with minimally verbal status present across the age range. RRB trends were noticed amongst the group of participants with *DYRK1A* and ASD (hereafter described as *DYRK1A*+ASD). Of the participants with notes regarding intonation of vocalizations or verbalizations, the vast majority were reported to have demonstrated unusual vocalizations during testing (e.g., repetitive non-word vocalizations or vocalizations with atypical pitch or tone, n = 8/9, 89%). Half of *DYRK1A*+ASD participants were noted to have restricted interests or behaviors by clinicians (n = 11/22, 50%). The majority of *DYRK1A*+ASD participants also noted inflexible adherence to routines or rituals and difficulties with minor changes (n = 12/22, 55%). Most *DYRK1A* syndrome participants (with or without ASD) did not appear to be motivated by social interaction with the

examiner (*n* = 16/26, 62%). Few participants were described as having appropriate social responses (*n* = 3/26, 12%). Of the participants who had examiner notes commenting on motor skills, the majority of participants were described to have a motor deficit or delay (*n* = 9/11, 82%). Overall, participants did not direct attention as a form of communication (*n* = 14/26, 54%). Participants most commonly used showing and directing attention as a form of communication (*n* = 12/26, 46%), followed by pointing to objects of interest (*n* = 10/26, 38%).

DYRK1A syndrome participants were then stratified by presence (22/26, *DYRK1A+*ASD) and absence (4/26, *DYRK1A+*no ASD) of an ASD diagnosis to determine qualitative ASD profile differences for children who did not receive an ASD diagnosis by the clinical research team. In the *DYRK1A+*no ASD group (*n* = 4), social-communication skills were rated as commensurate with their developmental level, although one child had inconsistent social overtures and responses. Similarly, most *DYRK1A+*no ASD participants scored below the “spectrum” cut-off on the ADOS-2, indicating low likelihood of a clinical ASD diagnosis based on the ADOS-2 algorithm (*n* = 3/4, 75%). Regarding individual behaviors and scores on items, all *DYRK1A+*no ASD children were described as socially motivated during testing, and most made frequent social overtures (*n* = 3/4, 75%). Most *DYRK1A+*no ASD participants also showed appropriate social responsiveness, including showing shared enjoyment with the examiner and/or caregiver (*n* = 4/4,75%), in addition to appropriate eye contact (3/4, 75%). One child in the *DYRK1A+*no ASD group was noted to exhibit inappropriate facial expressions and social disinhibition. In contrast, only a minority of *DYRK1A+*ASD children were described as socially motivated (*n* = 7/22, 31.8%). Several children in the *DYRK1A+*ASD group showed some social responsiveness (*n* = 9/22, 41%), although several of these children only showed responsiveness to caregivers. Five children with *DYRK1A+*ASD were noted to show inappropriate social disinhibition, such as inappropriately hugging examiners. All children in the *DYRK1A+*ASD group made minimal eye contact, and a small minority of *DYRK1A+*ASD participants engaged in shared enjoyment and obtained a score of 0 on that ADOS-2 item (*n* = 4/23, 17%). Regarding RRBs, both groups showed definite sensory interests in play materials as well as repetitive body movements (*DYRK1A+*no ASD *n* = 2/4, 50%, *DYRK1A+*ASD *n* = 10/22, 45%). Many children in the *DYRK1A+*ASD group were noted to have restricted or unusual interests (*n* = 10/22, 50%) and routines and repetitive behaviors (*n* = 13/22, 59%).

Discussion

In a comprehensively phenotyped sample of 29 individuals with LGD mutations in *DYRK1A*, 85% met DSM-5 criteria for a diagnosis of ASD, while 89% met criteria for ID. While *DYRK1A* has been previously described as an ID-predominant gene (e.g., Bronicki et al., 2015), not all individuals with LGD variants in *DYRK1A* met full criteria for ID. However, these patients presented with other developmental concerns such as ASD, ADHD, and/or developmental coordination disorder. This provides evidence that the *DYRK1A* syndrome phenotypic spectrum includes individuals whose cognition may be less severely impacted, which is consistent with a recent study identifying variable adaptive functioning in *DYRK1A* syndrome (Fenster et al. 2022). Future efforts should examine factors that may contribute to higher cognitive skills in *DYRK1A* syndrome and similar rare disorders

associated with ID and ASD; potential factors may include variant type and stochastic developmental variation (Constantino, 2021; Myers et al., 2020).

Most participants met criteria for both ASD and ID, indicating that social communication challenges in *DYRK1A* syndrome are frequently above and beyond those expected based on developmental level. Previous reports of lower rates of ASD diagnoses in this population may have been confounded by variable access to a multi-method ASD diagnostic assessment (e.g., delays due to long waitlists, distance from assessment providers) combined with features of ASD that may be overshadowed by cognitive deficits, medical complexity, and sensory impairments in individuals with syndromic ID (Durand et al., 2022; Thurm et al., 2019). These results highlight the importance of standardized deep phenotyping that utilizes multiple measurement types and informants in characterization of rare ASD-associated genetic disorders.

When compared to similarly characterized individuals with ASD and below average NVIQ, individuals with *DYRK1A* syndrome show broadly similar patterns of social communication deficits to children with idiopathic ASD. As such, *DYRK1A* syndrome may function as an effective model of ASD with co-occurring ID and a well-defined genetic cause, suggesting possible utility in model organism or natural history studies. These studies are necessary components of clinical trial readiness in rare genetic disorders associated with ASD and ID, and genetics-first phenotyping efforts are currently contributing to clinical trial readiness in developmental disorders including *SCN2A*-associated developmental and epileptic encephalopathies, *ADNP* syndrome, and Rett syndrome (Berg et al., 2020; Leonard et al., 2022; Levine et al., 2022). Phenotype, mechanism, and treatment studies in rare ASD-associated disorders also increase understanding of the genetic and biological pathways that may contribute to ASD without a currently identified genetic cause, with the potential to inform treatment efforts outside of specific single-gene disorders (Arnett et al., 2021; Trinh et al., 2020).

Examination of item-level data from the ADI-R identified specific areas of social communication impairment in *DYRK1A* syndrome compared to others with ASD and ID, such as increased deficits in social-emotional reciprocity and nonverbal communication. Standardized rating scales measuring ASD traits on a continuous scale may have reduced sensitivity in individuals with significant language and cognitive impairments, limiting their use in comparative analyses involving individuals with ASD-associated genetic disorders (Thurm et al., 2019). Item-level and expert clinician observation data may illuminate nuances in profiles for these populations. In addition, ID- or syndrome-specific measures (e.g., Berg et al., 2021) or standardized observation methods designed to be sensitive to change (e.g., BOSCC; Grzadzinski et al., 2016) may enhance future efforts to understand social communication in *DYRK1A* syndrome and similar disorders.

Across measures, individuals with *DYRK1A* syndrome showed few RRBs that would be classed as “insistence on sameness” behaviors (e.g., compulsions, rituals, restricted interests, difficulties with changes in routine; Bishop et al., 2013). In contrast, repetitive sensory motor behaviors often defined as “sensory seeking” such as hand and finger mannerisms and repetitive use of objects were commonly observed and reported, even in participants without

ASD. As “insistence on sameness” behaviors are unrelated to cognitive skills (Bishop et al., 2012), these findings provide preliminary evidence that specific genetic contributors to ASD may be associated with particular classes of RRBs. This may inform efforts to identify genetic mechanisms of specific RRBs (e.g., Cantor et al., 2018).

The results of this study contribute to other recent efforts to characterize the ASD phenotype in individuals with rare genetic disorders such as *ADNP* and *CHD8* (Arnett et al., 2018; Beighley et al., 2020; Siper et al., 2021). Taken together, these results demonstrate that ASD-associated genetic disorders may also be associated with specific symptom profiles within ASD. These findings may inform precision medicine efforts to identify predictors of variable outcome and response to ASD intervention (Arnett et al., 2021). Ultimately, the goal of this approach will be to use genetic and phenotypic information to identify tailored support and interventions for heterogenous individuals with ASD.

Limitations of this study include its sample recruited largely based on previous clinical diagnosis of *DYRK1A* syndrome. While genetics-first recruitment allows for a broad range of phenotypes to be included, individuals with characteristics suggestive of a potential genetic disorder (e.g., microcephaly, dysmorphic features, non-febrile seizures) are presumably more likely to have received genetic testing for LGDs in *DYRK1A* than individuals without these characteristics. As access to genetic testing, particularly whole exome and genome sequencing, for ASD and ID expands, our understanding of the *DYRK1A* syndrome phenotype will likely broaden to include participants with milder presentations and more variable phenotypes. In addition, the sample in this study consisted largely of young children and likely does not reflect ASD characteristics in *DYRK1A* across the lifespan. For example, some of the young children who presented with motor and speech challenges may develop additional skills in these domains as they progress through later childhood. Following participants with *DYRK1A* syndrome and other ASD-associated genetic disorders as they reach adulthood and offering new or updated genetic testing to adults with ASD and ID will also inform our understanding of phenotype in *DYRK1A* syndrome. Finally, while this study presents a large group of individuals with LGDs in *DYRK1A* given the rarity of this syndrome, issues related to sample size and uneven sample size across comparison groups may have impacted our ability to identified more nuanced phenotypic characteristics. As not all participants in the *DYRK1A* syndrome, iASD, and iASD + ID groups received whole genome or exome sequencing, it is likely that some individuals in this group present with yet unidentified variants that may impact phenotype (e.g., variants associated primarily with ID but not ASD). In addition, the inclusion of a comparison group of individuals with ID and without ASD may have been beneficial given that not all individuals with *DYRK1A* syndrome meet criteria for ASD.

A key next step is to conduct a more fine-grained examination of the relationship between specific *DYRK1A* variant characteristics (e.g., variant type or location) and phenotypic characteristics. Given the range of variant types reported in this study, the absence of identified recurrent LGDs in *DYRK1A*, the shared loss-of-function effect of these variants, and the available sample size, variant-level correlations are challenging to identify and outside of the scope of the current study. Instead, our goal was to expand the current characterization of ASD in *DYRK1A* syndrome using both quantitative (e.g., standard

statistical testing) and qualitative approaches at the syndrome level. We hope to expand our understanding of variant-level characteristics in *DYRK1A* syndrome as sample sizes increase due to genetic testing access and as N-of-1 clinical trials become more common (Smith & Kingsmore, 2014). Finally, it should be noted that most individuals with *DYRK1A* syndrome would meet criteria for profound autism as described by the Lancet Commission (minimally verbal status or IQ below 50; Lord et al., 2022). As the construct of profound autism is further defined and the clinical and research needs of this community are identified, individuals with *DYRK1A* syndrome and other ASD-associated genetic disorders should be included and prioritized in these efforts.

In conclusion, this study identified that while individuals with *DYRK1A* syndrome present with social communication challenges and RRBs that are broadly consistent with ASD and co-occurring ID, they also demonstrate a specific profile of ASD features best captured by item-level analysis and direct observation. Specifically, the ASD phenotype in *DYRK1A* syndrome is categorized by increased challenges with social reciprocity and nonverbal communication combined with elevated sensory-seeking behaviors. These findings have the potential to enhance clinical care of individuals with *DYRK1A* syndrome and contribute to precision medicine research in ASD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Availability of Data and Materials:

The underlying raw data used in the preparation of this article resides in the NIMH Data Archive Repository under Collection ID C2093 (https://nda.nih.gov/edit_collection.html?id=2093).

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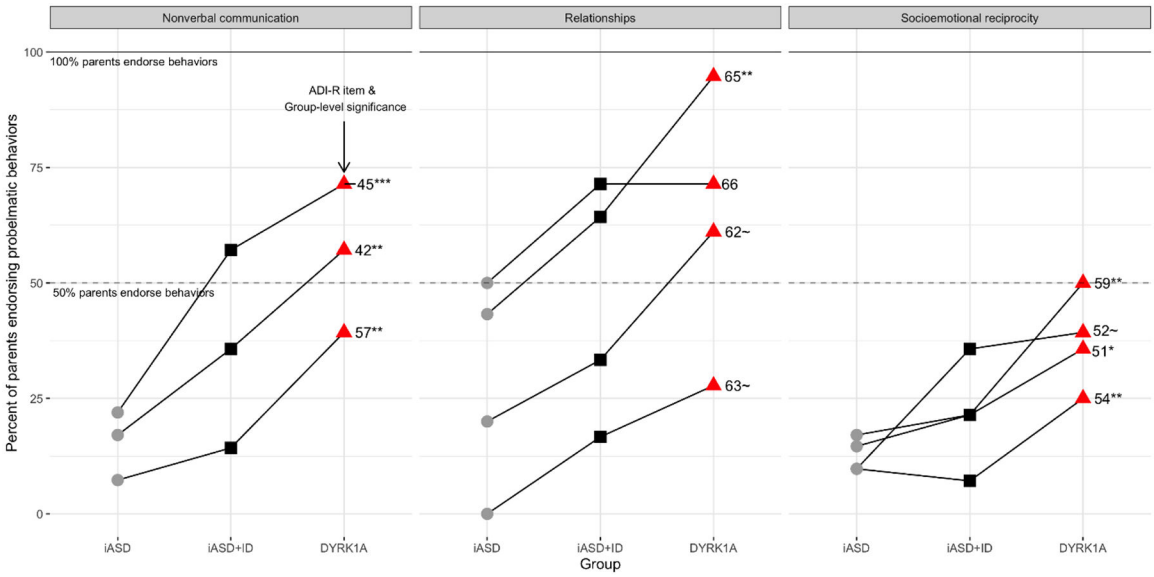

Figure 1. Percent of parents endorsing problems on social ADI-R items.

Social ADI-R items are clustered within larger categories, as represented by the category titles at the top of each column. Lines between groups are used to illustrate relative group differences. Horizontal dashed line indicates that 50% of the parents endorsed the problematic behaviors. Average percent of parents endorsing problems on each ADI-R item is reflected as a point / shape for each item per group: iASD (group with idiopathic autism spectrum disorder, ASD; grey circles), ASD+ID (group with ASD and intellectual disability; black squares), and *DYRK1A* (red triangles). The item number is listed to the right of the *DYRK1A* group shape (red triangle) with group-level chi-square test significance (*** = $p < .001$, ** = $p < .01$, * = $p < .05$, ~ = $p < .1$).

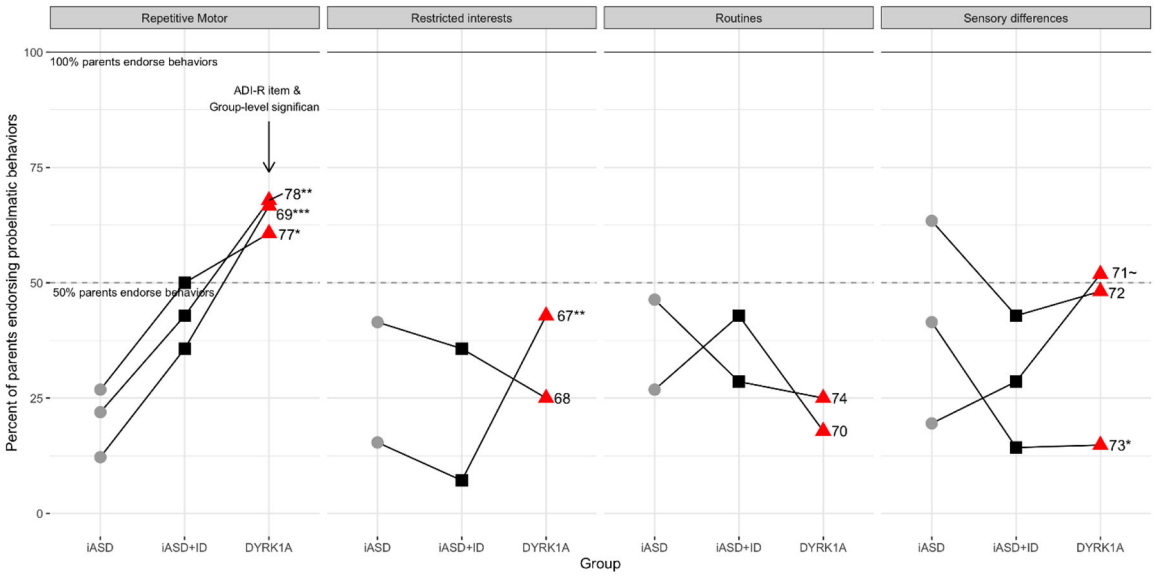

Figure 2. Percent of parents endorsing problems on RRB ADI-R items.

Restricted and Repetitive Behaviors (RRB) ADI-R items are clustered within larger categories, as represented by the category titles at the top of each column. Lines between groups are used to illustrate relative group differences. Horizontal dashed line indicates that 50% of the parents endorsed the problematic behaviors. Average percent of parents endorsing problems on each ADI-R item is reflected as a point / shape for each item per group: iASD (group with idiopathic autism spectrum disorder, ASD; grey circles), ASD+ID (group with ASD and intellectual disability; black squares), and *DYRK1A* (red triangles). The item number is listed to the right of the *DYRK1A* group shape (red triangle) with group-level chi-square test significance (*** = $p < .001$, ** = $p < .01$, * = $p < .05$, ~ = $p < .1$).

Table 1.

Age, sex, cognition, and diagnostic status across comparison groups.

			ASD No Known Event				Group differences	
	(1)DYRK1A	N	(2) iASD+ID	N	(3) iASD	N	p	Description
Female : Male	13:16	29	2:12	14	10:31	41	0.069	
Age in years *M*(SD)	10.35(6.29)	29	13.33 (2.62)	14	12.22 (2.66)	41	0.070	
Range	4–24		9–17		8–17			
NVIQ	46.11(23.69)	27	50.64(15.45)	14	100.83(8.9)	41	<.0001	1 & 2 < 3
Range	12–133		30–70		86–115			
VIQ	43.7 (27.69)	27	47.64(19.25)	14	97.83(19.95)	41	<.0001	1 & 2 < 3
Range	12–119		30–0		86–115			
ASD Diagnosis [A]	85.2%	27	100.0%	14	100.0%	41	0.007	1 < 2 & 3
ID Diagnosis [A]	88.9%	27	100.0%	14	0%	41	<.0001	1 & 2 < 3

Abbreviations: ASD=Autism Spectrum Disorder, ID=Intellectual Disability, M=Mean, N=Number of participants, NVIQ=Nonverbal Intelligence Quotient, SD=Standard Deviation, VIQ=Verbal Intelligence Quotient

Diagnoses confirmed by expert clinical judgment per DSM-5 criteria.

[A]Note: 23 out of 27 *DYRK1A* syndrome participants (77.8%) had both diagnoses of ASD and ID; 1 *DYRK1A* syndrome participant had neither diagnosis. N refers to the total number of participants with available data for a specific variable.

Table 2.

Descriptive statistics of ADOS-2 and parent-reported scores.

Measure	(1) DYRK1A Mean (SD)	N	ASD No Known Event (2) iASD+ID Mean (SD)	N	(3) iASD Mean (SD)	N	Group differences p	Description
ASD Severity (ADOS-2 CSS)	7.33 (2.29)	27	8.29 (2.16)	14	7.32 (1.85)	41	0.2858	
RRB	7.81 (2.11)	27	7.93 (2.59)	14	6.78 (2.28)	40	0.220	
Social affect	6.81 (2.53)	27	7.93 (2.37)	14	7.7 (2.15)	40	0.110	
Social skills (SRS-2) Total	76.96 (12.93)	28	80 (10.3)	14	73.07 (11.67)	41	0.134	
Awareness T	77.29 (11.01)	28	77 (8.95)	14	68.88 (10.73)	41	0.003	3 < 1 & 2
Cognition T	73.86 (10.2)	28	75.79 (12.08)	14	68.51 (11.27)	41	0.047	None with correction
Communication	78.64 (12.83)	28	78.71 (10.79)	14	72.68 (12.47)	41	0.094	
Motivation T	63.04 (14.23)	28	71.07 (10.09)	14	67.54 (11.34)	41	0.112	
Mannerisms T	74.68 (16.11)	28	79 (13.08)	14	73.05 (13.3)	41	0.408	
ASD Screener (SCQ)	21.08 (7.06)	12	23.85 (5.01)	13	18.85 (6.21)	33	0.050	3 < 2
Adaptive skills - Composite (VABS-2)	53.36 (14.32)	28	62.57 (6.88)	14	76 (10.16)	41	<.0001	1 < 2 < 3
Socialization	54.75 (18.44)	28	61.29 (8.98)	14	73.95 (13.41)	41	<.0001	1 & 2 < 3
Communication	53.57 (18.57)	28	63.64 (8.14)	14	78.2 (9.94)	41	<.0001	1 < 2 < 3
Daily living	52.32 (16.42)	28	66.14 (8.38)	14	81.32 (11.22)	41	<.0001	1 < 2 < 3
Repetitive behaviors (RBS-R) Total	19.96 (13.12)	28	30.57 (22.01)	14	19.15 (12.25)	41	0.038	1 & 3 < 2
Compulsive	3.29 (3.81)	28	9.36 (6.63)	14	4.78 (4.3)	41	<.0001	1 & 3 < 2
Self-injurious	3.36 (3.85)	28	3.57 (4.54)	14	2.15 (2.67)	41	0.241	
Sensory motor	6.61 (4.72)	28	6.36 (6.69)	14	3.68 (2.99)	41	0.016	1 < 3
Restricted	2.36 (1.81)	28	2.5 (2.1)	14	2.41 (1.86)	41	0.973	
Sameness	4.36 (5.77)	28	8.79 (8.17)	14	6.12 (5.58)	41	0.093	1 < 2

Abbreviations: ASD=Autism Spectrum Disorder, iASD = Idiopathic ASD; ADOS-2=Autism Diagnostic Observation Schedule-2nd Edition, CCS=Clinical Comparison Score (Range=1 to 10), ID = Intellectual disability; SRS-2 T-score <59 = Within Normal Limits, 60 to 65 = Mild traits, 66 to 75 = Moderate traits, >76 = Severe traits; SCQ = Social Communication Questionnaire Range = 0 to 39; VABS-2 Standard Score Mean=100, SD=15; RBS-R=Repetitive Behavior Scale-Revised Total (Range=0 to 129), Compulsive Subscale Range=0 to 30, Self-Injurious Subscale Range=0 to 24, Sensory Motor Subscale Range=0 to 21, Restricted Subscale Range=0 to 6, Sameness Subscale Range=0 to 33); RRB=Restricted and repetitive behaviors; SCQ = Social Communication Questionnaire; T=T-score; VABS=Vineland Adaptive Behavior Scale