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Behavioral characterization of dup15q syndrome: Toward meaningful endpoints for clinical trials

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Abstract

Duplication of 15q11.2-q13.1 (dup15q syndrome) is one of the most common copy number variations associated with autism spectrum disorders (ASD) and intellectual disability (ID). As with many neurogenetic conditions, accurate behavioral assessment is challenging due to the level of impairment and heterogeneity across individuals. Large-scale phenotyping studies are necessary to inform future clinical trials in this and similar ID syndromes. This study assessed developmental and behavioral characteristics in a large cohort of children with dup15q syndrome, and examined differences based on genetic subtype and epilepsy status. Participants included 62 children (2.5–18 years). Across individuals, there was a wide range of abilities. Although adaptive behavior was strongly associated with cognitive ability, adaptive abilities were higher than cognitive scores. Measures of ASD symptoms were associated with cognitive ability, while parent report of challenging behavior was not. Both genetic subtype and epilepsy were related to degree of impairment across cognitive, language, motor, and adaptive domains. Children with isodicentric duplications and epilepsy showed the greatest impairment, while children with interstitial duplications showed the least. On average, participants with epilepsy experienced seizures over 53% of their lives, and half of children with epilepsy had infantile spasms. Parents of children with isodicentric duplications reported more concerns regarding challenging behaviors. Future trials in ID syndromes should employ a flexible set of assessments, allowing each participant to receive assessments that capture their skills. Multiple sources of information should be considered, and the

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CONFLICT OF INTEREST

Vanessa Vogel-Farley is an employee of the Dup15q Alliance. Joerg F. Hipp is an employee of F. Hoffmann-La Roche Ltd. Shafali Jeste serves as a consultant for and has received funding from F. Hoffmann-La Roche Ltd. and Yamo Pharmaceuticals. C. DiStefano, R. Wilson, C. Hyde, E. H. Cook, R. L. Thibert, and L. T. Reiter have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

impact of language and cognitive ability should be taken into consideration when interpreting results.

Keywords

behavioral assessment; dupl5q syndrome; epilepsy; intellectual disability

1 | INTRODUCTION

Rapid advances in molecular diagnostic methods, including chromosomal microarray (CMA) and whole exome sequencing, have facilitated the identification of many genetic syndromes associated with neurodevelopmental disorders. These syndromes present opportunities for improved clinical care and more targeted therapeutics, informed by the molecular mechanisms as well as more homogeneous clinical symptomatology within a given syndrome. However, the identification of malleable clinical endpoints that reflect symptomatology amenable to therapeutic modification has been stymied by the paucity of large scale, clinical phenotyping studies. Clinical characterizations can generate meaningful subgroups and elucidate the role of medical comorbidities, particularly epilepsy, in domains such as cognition, social communication, and adaptive skills. Deep clinical phenotyping can also help to construct meaningful measures of cognition in individuals with severe intellectual disability (ID). Studies that can expand sample sizes and the clinical representation of the cohort through collaborations with patient advocacy groups (PAGs) and that implement a comprehensive set of assessments appropriate to participant abilities can address these gaps, thus improving the likelihood of success of clinical trials in these disorders.

To this end, we recently completed the largest clinical phenotyping study of dupl5qll-q13 syndrome (dupl5q syndrome), a copy number variant that is highly penetrant for autism spectrum disorder (ASD) and ID. The chromosome region 15qll.2-q13.1 is particularly prone to rearrangements, due to the presence of large low copy number DNA repeats (Makoff & Flomen, 2007; Pujana et al., 2002). Deletions in this region can result in either Angelman or Prader-Willi syndrome (depending on the parent of origin), while maternally derived duplications cause a constellation of symptoms referred to as dupl5q syndrome (Finucane et al., 2016). Dupl5q syndrome includes two primary types of multiplication: (a) an pseudoisodicentric chromosome 15 [idic(15)] that results in two or more additional maternally-derived copies of the 15qll.2-q13.1 region on a supernumerary chromosome that includes 15p and the proximal region of 15qll, most commonly leading to four copies of the region, or (b) an interstitial 15q multiplication [int(15)] in which one or more extra copy(ies) of the 15qll.2-q13.1 region occurs on the same chromosome, typically resulting in three copies of the region (Finucane et al., 2016; Kalsner & Chamberlain, 2015). The prevalence of dupl5q syndrome in the general population is unknown, but it may be as high as 1:5,000 (Kirov et al., 2014).

Like many genetic conditions associated with neurodevelopmental disorders, the developmental and behavioral characteristics of idic (15) include moderate to profound ID,

central hypotonia resulting in motor delays, moderate to profound language impairment, high rates of ASD, and an early onset epilepsy that is often treatment-resistant (Ageeli et al., 2014; Battaglia, Parrini, & Tancredi, 2010; DiStefano et al., 2016; Finucane et al., 2016; Kalsner & Chamberlain, 2015). Although exhibiting a typically milder clinical phenotype, *int(15)* is also associated with ASD, hypotonia, and mild to moderate ID (Finucane et al., 2016; Kalsner & Chamberlain, 2015; Urraca et al., 2013). Epilepsy in *dupl5q* syndrome often develops early in infancy, with rates of approximately 60–80% in *idic(15)* and 16% in *int(15)* (Battaglia, Bernardini, Torrente, Novelli, & Scarselli, 2016; Conant et al., 2014). Individuals with *idic(15)* that develop epilepsy typically have focal or multifocal seizures, with many progressing to a secondarily generalized epilepsy syndrome with multiple seizure types (e.g., myoclonic, tonic, atonic, and absence). In addition, infantile spasms occur frequently with a rate of 30–40% (Battaglia et al., 2016; Conant et al., 2014; Verrotti et al., 2017). Electroencephalogram studies in *idic(15)* have described a generalized background slowing, multi-focal epileptiform discharges, and disrupted sleep physiology, with frequency spike and wave discharges, abnormal delta and alpha oscillations, and persistence of beta oscillations (Battaglia et al., 2016; Conant et al., 2014; Frohlich et al., 2016; Verrotti et al., 2017). Although the rate of epilepsy is much lower, the pronounced EEG signature of increased beta oscillations in interstitial *dupl5q* individuals persists, and this EEG pattern may serve as a strong biomarker of the genetic condition (Frohlich et al., 2016; Urraca et al., 2013).

Considerable heterogeneity exists in neurodevelopmental outcomes in *dupl5q* syndrome, which may reflect gene dosage, additional rare or common genetic variation, variations in genetic background, timing and severity of epilepsy, or other unidentified factors (Battaglia et al., 2010; Finucane et al., 2016; Kalsner & Chamberlain, 2015). In a previous study, we examined behavioral and developmental characteristics in 13 children with *dupl5q* syndrome [10 *idic(15)*, 3 *int(15)*], and compared them to children with idiopathic ASD and ID, in order to ascertain syndrome-specific characteristics. Children with *dupl5q* syndrome demonstrated ASD characteristics, mild to severe cognitive and language deficits, impairments in adaptive functioning, and markedly decreased motor skills that were associated with the degree of symptoms across other domains (DiStefano et al., 2016). While children with *idic(15)* showed a more severe phenotype than children with *int(15)*, this difference was driven by the four participants with epilepsy [all *idic(15)*]. Those participants had striking delays across domains, while the *idic(15)* participants without epilepsy were functionally similar to those observed in the interstitial group across all testing domains. While a promising first step, this small sample size precluded analysis of meaningful clinical subgroups or characterizing the phenotypic heterogeneity within this genetic syndrome. No other studies to date have directly compared individuals with *dupl5q* by genetic subtype.

Here we follow-up the previous study by expanding our analysis to a large cohort of children with *Dupl5q* syndrome through direct assessment and parent report, in order to evaluate the cognitive, adaptive, and social communication features of these children and to examine the utility of traditional clinical tests that may be used as endpoints in future clinical trials. Our goals were to characterize the behavioral and cognitive features of children with *dupl5q* syndrome, examine differences based on genetic subtype and epilepsy severity, and evaluate the value of various standardized assessment tools for characterizing and stratifying

individuals with the syndrome, recognizing the large range of cognitive function and language ability in this cohort.

2 | METHODS

2.1 | Editorial policies and ethical considerations

All research was approved by the UCLA Institutional Review Board (IRB#15–001565) and parents/caregivers of all participants provided consent for their data to be used for related research.

2.2 | Participants

Participants included children with dupl5q syndrome ages 30 months–18 years. The 13 participants described in our previous pilot study (DiStefano et al., 2016) are also included in these analyses. Children were recruited from the national Dupl5q Alliance and the UCLA Dupl5q clinic. All participants had a confirmed genetic diagnosis of dupl5q syndrome (interstitial or isodicentric) based on clinical genetics reports. Parents provided clinical genetics reports to the research team, who reviewed them to ensure that all participants had a reported 15q11–q13 region duplication. For participants with int(15), reports were additionally reviewed for parent of origin testing. Four participants had confirmed maternally derived duplications, while the remaining participants did not report parent of origin testing. Sixty-two participants completed at least one of the primary measures (cognitive or adaptive behavior), and were therefore included in this analysis (Table 1).

2.3 | Procedures and measures

Participants were assessed over a 1- or 2-day period, either at the UCLA Dupl5q Clinic, or at one of two Dupl5q Alliance Family Conference (Orlando, FL, 2015 and Redondo Beach, CA, 2017). The assessment battery included a variety of measures to assess cognition, language, adaptive behavior, motor skills, challenging behaviors, and social communication characteristics. Due to time constraints at the Dupl5q Alliance Family Conferences, some participants were not able to complete all direct assessments. Parents reported on their child's development through interviews and survey forms which were available for parents to complete online following the child's in-person assessments. One parent questionnaire (Aberrant Behavior Checklist) was added to the assessment battery later in the study and was thus completed by fewer participants. Refer Table 2 for a complete list of measures and number of participants for each.

2.3.1 | Cognitive and language abilities—Cognitive development was assessed with either the Differential Abilities Scale-Second Edition (DAS-II; Elliot, 2007) or the Mullen Scales of Early Learning (MSEL; Mullen, 1995). The MSEL was used to assess participants who were under 68 months of age, and participants who were older but unable to achieve a basal score on the DAS-II. There is high convergent validity between the MSEL and the DAS-II, supporting the combination of assessments (Bishop, Guthrie, Coffing, & Lord, 2011; Farmer, Golden, & Thurm, 2016). Ratio scores for full-scale developmental quotient (FSDQ), nonverbal developmental quotient (NVDQ) and verbal developmental quotient (VDQ) were calculated for each child and based on division of the age-equivalent score by

chronological age. Ratio scores were used to account for the scores of children who performed outside of the standardized norms for their chronological age. For children who were tested with the DAS-II, NVDQ, and VDQ were calculated from the protocol-specific sub-scores. For children who were administered the MSEL, VDQ was calculated using the average of the Receptive Language and Expressive Language subscale scores, and NVDQ was calculated using the average of the Visual Reception and Fine Motor subscale scores (Akshoomoff, 2006).

2.3.2 | Adaptive behavior—Adaptive behavior was assessed via parent report, using the *Vineland Adaptive Behavior Scale-II* (VABS-II; Sparrow, Balia & Cicchetti, 2005). The VABS-II is a semi-structured interview conducted with the parent and assesses four domains of adaptive behavior: (a) communication, (b) daily living skills, (c) socialization, and (d) motor skills. The VABS-II yields standard scores and age-equivalent scores.

2.3.3 | ASD symptoms—The *Autism Diagnostic Observation Schedule-Second version* (ADOS-2; Lord et al., 2012), a semi-structured behavioral observation, is the gold standard instrument for confirming a clinical diagnosis of ASD. Four standard modules (1–4) plus an additional Toddler module (ADOS-T) are available and are chosen based on the child's age and language level. The ADOS yields numerical scores in the domains of social communication and repetitive behaviors, and score cutoffs are used to yield categories of “autism” (many ASD symptoms), “autism spectrum” (moderate ASD symptoms), or “no diagnosis” (few ASD symptoms). A calibrated severity score (CSS) can also be calculated, which can be used to compare scores across modules 1–4 (Gotham, Pickles, & Lord, 2009). The *Social Responsiveness Scale-Second Edition* (SRS-2; Constantino & Gruber, 2013) is a brief parent-report measure that quantitatively measures the child's ASD symptoms. It yields a total numerical score, indicating the degree of impairment. Unlike other measures, which are primarily intended to contribute to decisions about a clinical diagnosis in a categorical fashion, the SRS score can be used as a continuous variable. It is noteworthy that its manual states that this measure has not been validated in individuals with ID, although it has been used in numerous studies examining the ASD phenotype in children with syndromic forms of ID (e.g., Adviento et al., 2013; Channell et al., 2015; Dimitropoulos, Ho, & Feldman, 2012; Laje et al., 2010; Lane, 2016) and epilepsy (Ko, Kim, Kim, Song, & Cheon, 2016).

2.3.4 | Challenging behavior—Parents completed the *Aberrant Behavior Checklist-Second Edition* (ABC-2; Aman & Singh, 2017), which assesses a variety of challenging behaviors and has been used widely for children with neurodevelopmental disorders. The ABC-2 yields subscale scores in the areas of irritability, social withdrawal, stereotypic behavior, hyperactivity/noncompliance, and inappropriate speech.

2.3.5 | Epilepsy questionnaire—An epilepsy questionnaire was sent to families of participants with epilepsy to gather additional information. The questionnaire was modeled after the Early Childhood Epilepsy Severity Scale (E-Chess; Humphrey, Ploubidis, Yates, Steinberg, & Bolton, 2008), with modifications made based on the fact that we were collecting parent reports of epilepsy history. This questionnaire gathered information about age of first seizure, periods of seizure freedom, previous and current anti-epileptic

medications, and seizure semiology. The goal of this questionnaire was to approximate lifetime seizure burden as a measure of epilepsy severity, in order to examine a relationship between epilepsy severity, cognition, and behavior. However, given that this was a parent-report measure, we did not capture details about seizure semiology, EEG patterns, or clinician interpretation of the epilepsy subtype. Families completed the questionnaire online, and it was submitted directly to the research team.

2.4 | Data analytic plan

We first described the behavioral and developmental phenotype of the full cohort, focusing on overall patterns of strengths and weaknesses and relationships among abilities across domains. Mean scores are not presented in this section, as they are explored in more detail in the subgroup comparisons. Relationships between variables were examined using Pearson correlations, and scores across sub-domains were compared using repeated-measures ANOVA.

We then compared groups based on genetic subtype and epilepsy status. Group comparisons [idic(15) vs. int(15); epilepsy vs. no epilepsy] were performed using independent samples *t* tests (Student's or Welch's test as appropriate based on the variances) or ANCOVAs. Although the sample sizes are different between genetic subtypes, the scores within each group were normally distributed. Due to the relationship between cognitive ability and measures of ASD characteristics (ADOS, SRS), those comparisons were performed controlling for FSDQ. Due to the significant difference in ages between epilepsy and no epilepsy groups, epilepsy comparisons were carried out controlling for chronological age.

3 | RESULTS

3.1 | Full cohort description

3.1.1 | Cognitive and adaptive behavior—Cognitive assessments were completed for 56 participants. Twenty-nine participants [21 idic(15)] were older than 68 months, and therefore outside the standard age range for the MSEL. Of the eight older participants with int(15), half were able to achieve valid scores on the DAS-II, while the remaining four were assessed with the MSEL. Of the 21 older participants with idic(15), only four were able to achieve a valid score on the DAS-II, and the remaining 16 were assessed with the MSEL. Across all participants, verbal and nonverbal DQ scores were highly correlated ($r = .91$, $p < .001$; Figure 1), and did not significantly differ from each other ($t = .11$, $p = .91$). Verbal and nonverbal scores differed by fewer than 10 points in 68% of participants; 20% had scores that differed by 10–15 points; and 13% of participants had a score discrepancy of more than 15 points. The direction of the score discrepancy was equally split. Of the 18 participants who had a score discrepancy of at least 10 points, nine participants showed higher nonverbal abilities, while the other nine participants showed higher verbal abilities. Two participants (both interstitial duplications) had FSDQ scores in the average or borderline ranges (>70), while the remaining participants had cognitive scores in the ranges associated with ID— from the mild to severely impaired range (Table 3). As can be seen in Table 3, the majority of idic(15) participants (73%) were in the “severe impairment”

category, while the int(15) participants were more evenly distributed across impairment categories. FSDQ did not correlate with chronological age ($r = -.23$, $p = .08$).

Parent report of adaptive behavior (VABS-II) was collected from 52 participants. The distribution of impairment categories can be seen in Table 3. Most participants with int(15) were in the normal or mildly impaired range, with no participants in the severely impaired range. In contrast, only 2 (5%) idic(15) participants were in the normal range, with the remaining participants spread across mild, moderate, and severe impairment categories. Repeated measures ANOVA indicated that VABS-II scores were significantly different across domains ($F = 11.25$, $p < .001$). Post hoc tests showed that communication domain scores were significantly lower than all other domains (p values $< .001-.04$), daily livings skills domain scores were lower than socialization and motor skills ($t = -2.9$, $p = .005$; $t = -3.1$, $p = .004$, respectively), while socialization and motor skills did not differ from each other ($t = -.82$, $p = .42$). Adaptive behavior scores were highly correlated across domains, as well as with verbal and nonverbal DQ scores (r values ranging from $.65-.88$, all p values $< .001$). Although adaptive behavior was strongly associated with cognitive ability, overall VABS-II scores (Adaptive Behavior Composite) were higher on average than FSDQ scores ($t = 13.48$, $p < .001$). Adaptive behavior was not associated with chronological age ($r = -.21$, $p = .13$).

3.1.2 | ASD symptoms—Direct assessment of ASD symptoms (ADOS-2) was completed in 39 participants [27 idic(15)]. The remaining participants did not receive an ADOS due to time constraints at the family conferences ($N = 17$), nonambulatory status ($N = 2$), or the combination of adolescent age and limited language abilities rendering the ADOS assessment inappropriate ($N = 4$). Of the 27 idic(15) participants who received an ADOS, 25 exceeded cutoffs for “autism” and the remaining participants met cutoffs for “autism spectrum”. Six idic(15) participants received a Module 2 ADOS (indicating flexible phrase speech), while the remaining participants received Module 1 (indicating no speech or single words). Of the 12 int(15) participants who received an ADOS, 10 exceeded cutoffs for “autism,” one for “autism spectrum” and one participant (with FSDQ in the average range) fell in the “no diagnosis” category. Seven int(15) participants received a Module 1 ADOS, three received Module 2, and two received Module 3 (indicating fluent speech).

Parent ratings of ASD symptoms were collected using the SRS ($N = 47$). Six SRS assessments were invalid due to the number of questions skipped by parents. 97% of idic(15) and 83% of int(15) participants had elevated scores (indicating symptoms consistent with ASD). SRS scores were moderately associated with verbal and nonverbal DQ scores ($r = -.55$, $p < .001$; $r = -.64$, $p < .001$, respectively), while ADOS scores were moderately associated with verbal DQ only ($r = -.37$, $p = .03$). Additionally, SRS scores were moderately associated with irritability, social withdrawal, stereotyped behavior, and hyperactivity/noncompliance as reported on the ABC (r values $.55-.63$, p values $.001-.03$).

Although we conducted the ADOS with all available ambulatory participants, it is important to note that 14 of the 39 participants had a nonverbal mental age (based on MSEL scores) of less than 18 months, indicating that the results should be interpreted with caution.

3.2 | Comparison based on duplication type

Groups based on genetic subtype did not differ on chronological age ($t = -.63$, $p = .53$), or sex ($\chi^2 = .20$, $p = .65$). Participants with int(15) had significantly higher scores than children with idic(15) across all cognitive and adaptive behavior domains (p values .008 to $<.001$). As can be seen in Figure 2, there was a wide range of scores in both groups.

Given the significant difference in cognitive scores between genetic subtypes and the association between cognition and ASD symptom measures, ASD symptoms were compared using ANCOVA models, controlling for FSDQ. Int(15) and idic(15) groups did not differ on direct assessment of autism symptoms (ADOS-2: $F = 2.28$, $p = .12$), but parents reported significantly more ASD symptoms in the idic(15) group (SRS: $F = 9.09$, $p = .001$).

Regarding challenging behavior (ABC), parents of children with idic(15) endorsed more concerns related to social withdrawal ($t = -2.77$, $p = .01$) and hyperactivity/noncompliance ($t = -2.30$, $p = .03$). Groups did not differ in terms of irritability ($t = -.75$, $p = .46$), stereotypic behavior ($t = -.28$, $p = .14$) or inappropriate speech ($t = 1.30$, $p = .20$). See Table 4 for group means and comparisons.

3.3 | Comparisons based on epilepsy status

Consistent with previous research, there was a higher incidence of epilepsy in the idic(15) group (57%) compared with int(15) (6%; $N = 1$). In order to disentangle epilepsy from duplication type in understanding developmental and behavioral characteristics, we carried out two sets of comparisons. We first compared participants with and without epilepsy in the idic(15) group, as most participants with epilepsy have isodicentric duplications. Second, we compared participants without epilepsy based on genetic subtype, to examine differences in genetic subtypes without the added effect of epilepsy.

3.3.1 | Epilepsy status within the idic(15) group—Participants with epilepsy were significantly older than those without ($t = 3.06$, $p = .004$). Comparisons based on epilepsy status were carried out using ANCOVA models, controlling for chronological age. Within the idic(15) group, participants with epilepsy had lower scores across cognitive and adaptive behavior measures (Figure 3), with the exception of VABS socialization ($F = 3.06$, $p = .09$).

Groups did not differ on direct assessment or parent report of autism symptoms (ADOS $F = .085$, $p = .77$; SRS $F = .06$, $p = .81$). Challenging behaviors (ABC) did not differ by epilepsy status (p values .12–.90). See Table 5 for group means and comparisons.

3.3.2 | Comparisons by duplication type, no epilepsy—In participants without epilepsy, the idic(15) group had lower scores compared with the interstitial group across most cognitive and adaptive domains, although the group differences were attenuated following the removal of participants with epilepsy. Notably, VDQ did not differ between duplication types among participants without epilepsy ($t = 1.29$, $p = .21$). NVDQ and all VABS domains were significantly lower in the idic(15) group (p values .003–.04; Figure 4).

With regard to ASD symptoms and other challenging behaviors, removing participants with epilepsy had little effect on group comparisons by duplication type. Groups did not differ in

direct assessment or parent report of autism symptoms (ADOS $t = -1.40$, $p = .18$; SRS $t = -1.2$, $p = .23$). On the ABC, parents of children with idic (15) endorsed more concerns related to social withdrawal ($t = -2.93$, $p = .01$), stereotypic behavior ($t = -3.22$, $p = .006$) and hyperactivity/ noncompliance ($t = 2.55$, $p = .02$). Groups did not differ in terms of irritability or inappropriate speech. Table 6 summarizes group means and comparisons.

As can be seen in Figure 5, comparisons by duplication type and epilepsy status reveal a tiered pattern, with the greatest degree of impairment in children with idic(15) and epilepsy, the least degree of impairment in children with int(15) and no epilepsy, and children with idic(15) and no epilepsy in between.

3.3.3 | Epilepsy characteristics—Of the 27 participants with epilepsy, full detailed information was available for 22, partial information was available for an additional four participants, and one participant did not return any information (Table 7). This additional information was gathered to clarify seizure severity and to determine whether seizure severity relates to developmental or behavioral deficits. The average age of seizure onset was 33 months, ranging from 0 to 161 months. “Percent of life seizing” was calculated based on the age of seizure onset, age of last seizure, and periods of seizure control. On average, participants experienced active seizures over 53% of their lives, ranging from 0% to 96% (0% indicated that seizures were controlled the same month in which they emerged). Number of lifetime anti-epileptic medications used ranged from 1 to 15, and parents reported a range of seizure types. 48% of participants had a history of infantile spasms, and 56% of participants were still experiencing seizures at the time of assessment.

Percent of life seizing, seizure onset age, number of lifetime medications, and number of seizure types were not associated with cognitive ability (VDQ, NVDQ), adaptive behavior (VABS adaptive behavior composite), ASD symptoms (ADOS, SRS), or challenging behavior (ABC). Participants who had infantile spasms had significantly lower verbal ($t = 2.12$, $p = .04$) and nonverbal cognitive function ($t = 2.48$, $p = .02$), as well as more impaired motor skills ($t = 2.78$, $p = .02$) than those without, but did not differ on measures of adaptive behavior, or ASD symptoms (Figure 6).

4 | DISCUSSION

Here, we examined the developmental and behavioral characteristics of a clinically representative group of children with dupl5q syndrome. This is the largest cohort study of this syndrome to date, with the sample size achieved through a partnership with a patient advocacy group (Dupl5q Alliance) and testing performed through remote questionnaires and direct testing at family conferences. Our overarching goals were to identify clinical features that may serve as meaningful endpoints in trials, to identify meaningful subgroups within this syndrome, to elucidate the role of medical comorbidities, particularly epilepsy, in domains such as cognition, social communication, and adaptive skills, and to construct meaningful measures of cognition in this condition that has comorbid ID. Through both direct assessment and parent report, we evaluated multiple domains of development, including cognition, language, adaptive functioning, ASD characteristics, and other challenging behaviors. We examined the overall behavioral profile of the full cohort and

compared groups based on duplication type and epilepsy status. For children with epilepsy, we also collected detailed information about seizure types, seizure severity, and anti-epileptic medications, and then examined the relationship of these variables to behavioral characteristics. One important limitation is that parent of origin data was not available for many participants. This is especially relevant for participants with interstitial duplications, where maternally derived duplications have been more strongly linked with an ASD phenotype (Urraca et al., 2013).

4.1 | Summary of clinical characteristics of dup15q syndrome

Across all participants, there was a wide range of abilities. Verbal and nonverbal cognitive abilities were highly correlated, with most participants demonstrating roughly equal scores in each domain. Among participants who did display a score discrepancy, half showed better verbal skills, while the other half showed better nonverbal skills. Thus, the cognitive profile in dup15q syndrome appears to be one of the relatively consistent skills across domains. As expected, adaptive behavior was highly correlated with both verbal and nonverbal cognitive abilities. Although most participants evidenced impairments in adaptive behavior across domains, socialization, and motor domain scores were higher on average than communication and daily living skills. Additionally, adaptive behavior scores were higher than cognitive scores. This may reflect a parent bias toward reporting more independent abilities in their children, a difference in skills that are demonstrated in the assessment context versus everyday life, or a true strength in adaptive functioning over cognitive ability. Research in other syndromes has suggested that children with Fragile X syndrome and Down syndrome also show a strength in adaptive functioning relative to cognitive ability (e.g., Hatton et al., 2003; Hodapp, 2006), while children with ASD have greater impairment in adaptive skills compared to cognition (Mouga, Almeida, Cafe, Duque, & Oliveira, 2014). Our results suggest that the profile of abilities in children with dup15q syndrome is more similar to other neurogenetic syndromes than to children with idiopathic ASD.

Most participants showed elevated scores on measures of ASD symptoms (ADOS, SRS). However, similar to many other studies (e.g., Havdahl et al., 2016; Hus, Bishop, Gotham, Huerta, & Lord, 2012; Sturm et al., 2017), these measures were highly associated with cognitive ability, and the degree of ID in some participants calls into question the appropriateness of these measures (see Measurement section below.) In addition to core deficits in social communication and the presence of repetitive and restricted patterns of behavior, a DSM-5 diagnosis of ASD requires that the observed deficits not be better explained by ID. While many children with dup15q syndrome do show social communication deficits in excess of their cognitive abilities, care should be taken when interpreting these measures in isolation and elevated scores should not be viewed as meeting DSM-5 criteria for ASD (Soorya, Leon, Trelles, & Thurm, 2017).

Both genetic subtype (interstitial or isodicentric) and epilepsy were related to degree of impairment across cognitive, language, motor, and adaptive domains. Children with isodicentric duplications and epilepsy showed the greatest level of impairment, while children with interstitial duplications without epilepsy showed the least.

4.2 | Cognitive ability, adaptive skills, and challenging behavior affected by duplication type

Consistent with prior research, children with idic(15) showed a greater degree of impairment compared with int(15) across cognitive and adaptive domains. When participants with epilepsy were removed from the comparisons, the magnitude of the differences was attenuated, with only nonverbal cognitive skills remaining significantly different between groups.

Parents of children with idic(15) endorsed a higher degree of concern compared with int(15) in the areas of social withdrawal, stereotypic behavior, and hyperactivity/noncompliance. These concerns did not appear to be impacted by epilepsy, as the magnitude of the difference was not affected by removing participants with epilepsy from the comparison, and there were no significant differences by epilepsy status within the idic(15) group. Additionally, ABC subscales were largely unrelated to cognitive ability, suggesting that children with idic(15) may experience a higher rate of challenging behavior overall, not accounted for by their higher rate of epilepsy or more severe cognitive impairment and that challenging behaviors represent a meaningful treatment target. Higher rates of anxiety, mood, and stereotypic behavior problems have also been found in children with ASD and severe disability, compared to children with ID only (Bradley, Summers, Wood, & Bryson, 2004). Further research is needed to determine if the pattern of challenging behavior observed in children with idic(15) is similar to children with other neurodevelopmental disorders, and thus may be amenable to the same interventions.

4.3 | Epilepsy impairs cognitive and adaptive domains in Dup15q

Epilepsy characteristics were consistent with what has been previously reported in dup15q syndrome (Conant et al., 2014), as 55% of children with idic(15) and 6% of children with int(15) had epilepsy, with more than half still experiencing seizures at the time of assessment. Children with epilepsy had greater levels of impairment in cognitive and adaptive domains, but seizures appeared to have less impact on ASD-related and other challenging behaviors. There was substantial variability in the epilepsy phenotype reported, with some participants suffering from intractable epilepsy (multiple seizure types, poorly controlled seizures, and high number of failed medications), while other participants had seizures that were quickly controlled following onset. Approximately half of the participants with epilepsy experienced infantile spasms, which was associated with significantly lower verbal and nonverbal cognitive abilities. Although other epilepsy variables (percent life seizing, number of lifetime medications, number of current medications, and number of seizure types) were not associated with developmental or behavioral characteristics, the sample size, and high variability may obscure these relationships.

These findings document the importance of considering epilepsy when examining the developmental phenotype of children with dup15q syndrome, as the presence of epilepsy contributes to the observed differences between duplication types. The complex relationship between epilepsy and neurodevelopment is one that cannot be fully disentangled in this analysis but certainly warrants consideration and can guide future studies. Here, we show that children with epilepsy manifest greater impairment across all behavioral and cognitive

domains, particularly those with the epileptic encephalopathy of infantile spasms, or subsequent development of a Lennox-Gastaut syndrome. As considered in other pediatric epilepsy syndromes, several factors may contribute to epilepsy and behavior association, such as the seizures themselves, the altered neural physiology as might be reflected in interictal EEG abnormalities, the medications required for seizure treatment, or an underlying genetic effect that predisposes to overall greater disease burden. In the case of infantile spasms, the observed increased impairment could be due to the effects of spasms of the developing brain or due to more severe underlying neuropathology causing both the spasms and cognitive impairment (Karrasch et al., 2017; Widjaja, Go, McCoy, & Snead, 2015). It is likely that epilepsy is both causative and an epiphenomenon of greater disease burden (Jeste & Geschwind, 2014). The phenomenon of greater neurodevelopmental impairment in epilepsy occurs in other syndromic forms of neurodevelopmental disorders, such as Tuberous Sclerosis Complex (TSC) (Humphrey et al., 2014). In fact, the strong association between early-onset epilepsy, spasms, and neurodevelopmental impairment has motivated a trial of epilepsy prevention in TSC (PReVENT), with the goal of mitigating autism symptoms and cognitive impairment in early childhood. As clinical genetic testing becomes more routine in infancy (for instance, in the case of hypotonia), prior to the onset of seizures, such prevention strategies could yield tremendous benefit for children with Dup15q syndrome as well.

Additionally, we must consider the impact of including children with epilepsy in clinical trials, as the more severely impaired cognitive and adaptive abilities in these children may restrict the availability of appropriate developmental and behavioral measures. These children may also show a slower rate of change over time or a more variable rate of change based on epilepsy treatment and response. In future studies, it will also be important to distinguish those with focal seizures from those more significant epileptic encephalopathies, such as infantile spasms and Lennox-Gastaut syndrome. Those with multiple seizure types, including spasms, atonic, and tonic seizures, are more likely to have an abnormal EEG background (with greater spike burden), to take more medications over their lifetime, and to have a higher underlying disease burden, than those with only focal seizures.

4.4 | Measurement considerations in Dup15q syndrome

Given the severity and diversity of deficits in individuals with dup15q syndrome [particularly idic(15) and epilepsy], there are challenges to obtaining accurate assessment results, which warrant special consideration, particularly as we consider which measures may serve as the most robust clinical endpoints in clinical trials.

First, many children with dup15q syndrome are likely to perform at or near the floor of most standardized assessments, and older children are often unable to reach any score on assessments validated for their chronological age. This concern is especially relevant for children with idic(15) and epilepsy, although 40% of our int(15) participants also had developmental quotients in the “severely impaired” range, which is below the floor of most standardized assessments. In order to generate meaningful scores for the participants in this study, we addressed this challenge in two ways. First, we used a flexible set of cognitive assessments, which enabled us to “drop down” to an easier assessment for children who

were unable to obtain a score on their age-appropriate assessment. Second, we computed ratio scores using age equivalent scores and chronological age. This allowed us to generate scores for those participants outside of the standard chronological age range, as well as to avoid the “floor effect”, where variability across participants is obscured by the lower limit of the standard score range. Similar cognitive assessment batteries, including the use of assessments outside of their normed age range, have been used to characterize abilities in children with a variety of other neurogenetic disorders, including TSC (van Eeghen, Black, Pulsifer, Kwiatkowski, & Thiele, 2011), Angelman syndrome (Peters et al., 2004), Niemann-Pick disease (Thurm et al., 2015), and Phelan-McDermid syndrome (Zwanenburg, Ruiter, van den Heuvel, Flapper, & Van RavenswaaijArts, 2016; Soorya et al., 2017).

Second, significant deficits in cognitive and language ability influence scores on assessments meant to measure other domains, raising questions about the validity of such assessments in populations that include significant ID. For example, the SRS is a quantitative measure of symptoms related to ASD (Constantino & Gruber, 2013). Although the SRS has not been validated for individuals with ID, it has been widely used in research studies examining the ASD phenotype in children with genetic syndromes associated with ID (e.g., Adviento et al., 2013; Channell et al., 2015; Dimitropoulos et al., 2012; Laje et al., 2010; Lane, 2016) and epilepsy (Ko et al., 2016). Many items on the SRS assume that the child has a sufficient amount of spoken language to engage in social interaction, making it difficult for parents to answer the questions if their child is nonverbal. In this study, we instructed parents to skip questions if they felt that they did not apply to their child and were impossible to answer. Of the 46 parents who completed the SRS, 6 (15%) were invalid due to the number of questions that parents skipped. All of the skipped questions required spoken language. Previous research has demonstrated that SRS scores are associated with cognitive ability (van Eeghen, Black, Pulsifer, Kwiatkowski, & Thiele, 2011; Hus et al., 2012; Sturm et al., 2017), and a recent review of potential clinical endpoints in ASD research rated the SRS as only “potentially appropriate,” due to its vulnerability to language and cognitive level (Anagnostou et al., 2015). Despite these characteristics, many studies of genetic syndromes associated with ID rely on the SRS as a primary clinical measure. A recent study used item-response theory to develop a short-form version of the SRS, selecting items that were the least vulnerable to the effects of language, cognitive, other behavior problems, age, and gender (Sturm et al., 2017). Although the short-form SRS does not include a diagnostic threshold, the total score may be used as a continuous variable relevant to participant stratification and to measurement of treatment response. Continued research should further validate the short-form SRS in populations with ID, and additional work is needed to identify and adapt other measures for use in populations with significant cognitive and language impairment. When assessing skills in children with ID, like dup15q syndrome cohorts, inclusion of multiple measures and careful consideration of the language demands implicit in each measure will increase the accuracy of the conclusions drawn. These become even more crucial if researchers intend to include a broad range of participants, including those with significant intellectual and language impairment.

4.5 | Recommendations for clinical endpoints

With advances in molecular diagnostic methods, an increasing number of rare disorders are being identified, facilitating syndrome specific phenotyping studies that can provide guidance on outcome measure selection and study design for clinical trials. As demonstrated in the current study, genetic syndromes with comorbid ASD and ID should employ a flexible set of cognitive assessments that allow each participant to receive the assessment that represents the best fit for his/her skills. Although this approach introduces some inconsistency into the exact methods used across participants, it generates scores for each participant that reflect his/her developmental abilities and provides a range of scores that facilitate stratification. In conditions such as dupl5q syndrome, which include a wide range of impairment levels, researchers should decide ahead of time whether the full range of participants will be included, or whether enrollment will be restricted to a particular portion of the population. While there are many advantages to including the full range of participants (e.g., easier recruitment, more generalizable results), this will likely necessitate using a multiple assessments within the same construct.

When assessing other domains of behavior, multiple sources of information should be considered (both direct observation and parent report), and the impact of language and cognitive ability should be taken into consideration when interpreting results. With regard to adaptive behavior, the VABS showed a large range of scores and limited floor effect, even in participants with significant cognitive and language impairment. Given the applicability of the VABS to the heterogeneous group of participants in this study, it may serve as a robust candidate as a primary endpoint in future clinical trials, especially given that improvements in a variety of developmental domains can converge on an improvement in adaptive (real-world) skills. Although measures of ASD symptoms (such as the ADOS and SRS) are likely relevant to clinical trials, they are strongly correlated with cognitive ability in children with severe ID and may, therefore, show little or no change in a short trial. If such measures are used as clinical endpoints, they should be paired with additional measures (such as cognition and adaptive behavior) that can help disentangle the multiple factors contributing to a child's impairment. If trials are restricted to participants with mild to moderate ID, such measures may be more appropriate. Regarding challenging behavior, the ABC, which was designed specifically for children with ID, was a meaningful and appropriate measure in this study. Scores were largely unrelated to cognitive ability, and they appeared to show meaningful differences between-group differences. Given that primary purpose of the ABC is to measure change with intervention, it is an excellent candidate for inclusion as an outcome measure in trials for this syndrome and others with comparable levels and range of cognitive impairment.

Many treatment trials make use of clinical severity scales, such as the Clinical Global Impressions Scale (CGI), which is based on the clinician's rating of the severity and improvement in the patient's symptoms (Berk et al., 2008). Although not used in this study, results reported here can be used to inform the development of clinical severity scales for future research. Conditions such as dupl5q syndrome include individuals with a wide range of abilities, some of whom may make small but nonetheless meaningful progress. Clinical severity scales should be constructed to ensure that they are relevant for the full range of

participants to be included, and can capture the magnitude of change deemed meaningful for each individual. If scales apply to only a subset of participants or fail to capture small but meaningful change, trials that effect important individual change may nonetheless be deemed failures. Information from natural history and descriptive studies, such as presented here, can be used to anchor clinical scales that reflect realistic expectations for the target population.

We have entered an era of emerging targeted therapeutics for the neurodevelopmental and neurological sequelae of genetic syndromes. To inform the selection of our clinical endpoints for these treatments, we will need large-scale behavioral characterization of these populations that can inform the designation of meaningful subgroups, elucidate the interaction of genetic mechanisms and the complex role of epilepsy and its sequelae on neurodevelopment, and understand the properties and limitations of standardized behavioral assessments in these children. As demonstrated, in the current study, we can accelerate this area of investigation through productive partnerships with patient advocacy groups and the application of flexible and comprehensive assessment batteries that inform the key features of the target syndrome and can serve as models for newly identified syndromes that share similar clinical features of epilepsy, global developmental delay, and severe ID.

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FIGURE 1.

Correlation between verbal and nonverbal developmental quotient. Scatterplot showing the strong correlation between verbal and nonverbal developmental quotient scores [$r = .91$, $p < .001$] in children with both int(15) and idic(15)

FIGURE 2.

Scatter plots of cognitive and adaptive behavior scores by duplication type. Scatter plot showing cognitive and adaptive behavior scores, by genetic subtype. Children with idic(15) has significantly lower scores across all domains (p -values .008 to $<.001$)

FIGURE 3.

Scatter plots of cognitive and adaptive behavior scores by epilepsy status. Scatter plot showing cognitive and adaptive behavior scores by epilepsy status, within the idic(15) group. Participants with epilepsy had significantly lower scores across cognitive and domains (p values .001–.049), with the exception of VABS socialization ($F = 3.06$, $p = .09$)

FIGURE 4.

Scatter plots of cognitive and adaptive behavior scores by duplication type, no epilepsy. Scatter plot showing cognitive and adaptive behavior scores, by genetic subtype, among participants without epilepsy. Verbal developmental quotient did not differ between groups ($t = 1.29$, $p = .21$). NVDQ and all VABS domains were significantly lower in the idic(15) group (p values .003–.04), but differences were attenuated from the full group comparison including participants with epilepsy

FIGURE 5.

Assessment scores by duplication type and epilepsy status. Bar graph showing the mean scores across cognitive and adaptive domains, split by genetic subtype and epilepsy status. Comparisons reveal a tiered pattern, with the greatest degree of impairment in children with idic(15) and epilepsy, the least degree of impairment in children with int(15) and no epilepsy, and children with idic(15) and no epilepsy in between. All contrasts are significant at $p < .05$, with the exception of verbal developmental quotient which did not differ between the int(15) and idic(15)—no epilepsy groups

FIGURE 6.

Spasms versus no spasms. Scatter plot showing cognitive and adaptive behavior scores in participants with epilepsy, compared between participants who experienced infantile spasms and those who did not. Participants who had infantile spasms had significantly lower verbal ($t = 2.12$, $p = .04$) and nonverbal cognitive scores ($t = 2.48$, $p = .02$), as well as more impaired motor skills ($t = 2.78$, $p = .02$) than those without, but did not differ on other domains of adaptive behavior

TABLE 1

Participant characteristics

Group	N	Epilepsy	Gender (percent male)	Age in months <i>M</i> (<i>SD</i>)
Interstitial	16	6% (<i>N</i> = 1)	50%	85.88 (40.48)
Isodiscentric	46	57%	57%	94.50 (48.84)
Total	62	44%	55%	92.27 (46.66)

TABLE 2

Assessments

Domain	Assessment	Type	N (int)	N (tdic)
Cognitive	Mullen scales of early learning	Direct assessment	11	36
	Differential ability scales-II	Direct assessment	4	5
ASD symptoms	Autism Diagnostic Observation Scale-2	Direct assessment	12	27
	Social responsiveness scale	Parent report	14	33
Adaptive behavior	Vineland adaptive behavior scales-II	Parent report	14	38
Challenging behavior	Aberrant behavior Checklist-2	Parent report	9	19
Epilepsy	Epilepsy questionnaire	Parent report	1	25

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TABLE 3

Number of participants by level of impairment

Level of impairment (score range)	Normal (>70)	Mild impairment (50–70)	Moderate impairment (35–49)	Severe impairment (<35)
<i>Cognitive</i>				
Interstitial (<i>n</i> = 15)	2 (13%)	4 (27%)	3 (20%)	6 (40%)
Isodicentric (<i>n</i> = 41)	0 (0%)	3 (7%)	8 (20%)	30 (73%)
<i>Adaptive behavior</i>				
Interstitial (<i>n</i> = 14)	6 (43%)	6 (43%)	2 (14%)	0 (0%)
Isodicentric (<i>n</i> = 38)	2 (5%)	17 (45%)	15 (39%)	4 (11%)

TABLE 4

Assessment scores by duplication type

	<u>Interstitial</u>		<u>Isodicentric</u>		<i>F/t, p</i>
	M	SD	M	SD	
Verbal DQ	45.60	26.55	23.58	19.02	2.95, .008
Nonverbal DQ	45.46	21.32	23.43	15.39	4.26, <.001
<i>Adaptive behavior (VABS)</i>					
Communication	65.71	14.14	44.79	16.62	4.19, <.001
Daily living skills	64.14	13.65	49.13	15.01	3.28, .002
Socialization	69.50	13.76	51.67	14.67	3.96, <.001
Motor skills	69.42	12.46	54.77	10.95	3.77, .001
<i>ASD symptoms</i>					
ADOS severity score	6.50	2.15	7.07	1.24	<i>n.s.</i>
SRS T score	71.83	12.72	79.45	11.16	9.09, .001
<i>Challenging behavior (ABC)</i>					
Irritability	8.67	9.59	11.88	9.95	<i>n.s.</i>
Social withdrawal	5.00	5.17	14.59	10.94	-2.88, .008
Stereotypic behavior	3.44	4.16	6.76	4.79	<i>n.s.</i>
Hyperactivity/noncompliance	12.33	7.57	21.71	13.24	-2.30, .03
Inappropriate speech	2.78	3.23	1.59	1.91	<i>n.s.</i>

TABLE 5

Assessment scores by epilepsy status (Idic(15) only)

	No epilepsy		Epilepsy		<i>F</i> , <i>p</i>
	M	SD	M	SD	
Verbal DQ	36.15	18.05	15.53	15.06	12.69, .001
Nonverbal DQ	31.44	14.60	18.30	13.83	4.93, .032
<i>Adaptive behavior (VABS)</i>					
Communication	53.56	14.49	37.29	14.77	9.82, .003
Daily living skills	56.00	11.48	43.24	15.38	4.14, .049
Socialization	57.50	10.80	46.67	15.90	<i>n.s.</i>
Motor skills	59.73	9.24	49.80	10.50	7.01, .013
<i>ASD symptoms</i>					
ADOS severity score	7.00	1.30	7.15	1.21	<i>n.s.</i>
SRS T score	77.25	12.81	81.00	9.94	<i>n.s.</i>
<i>Challenging behavior (ABC)</i>					
Irritability	13.25	7.94	10.67	11.80	<i>n.s.</i>
Social withdrawal	13.75	8.00	15.33	13.49	<i>n.s.</i>
Stereotypic behavior	7.75	4.27	5.89	5.30	<i>n.s.</i>
Hyperactivity/noncompliance	22.25	11.77	21.22	15.13	<i>n.s.</i>
Inappropriate speech	2.00	2.33	1.22	1.48	<i>n.s.</i>

TABLE 6

Assessment scores by duplication type—no epilepsy

	<u>Interstitital</u>		<u>Isodicentric</u>		<i>t, p</i>
	M	SD	M	SD	
Verbal DQ	46.87	27.07	36.15	18.05	<i>n.s.</i>
Nonverbal DQ	46.07	21.99	31.44	14.60	2.17, .04
<i>Adaptive behavior (VABS)</i>					
Communication	66.23	14.58	53.56	14.49	2.40, .02
Daily living skills	65.54	13.13	56.00	11.48	2.15, .04
Socialization	71.08	12.93	57.50	10.80	3.18, .003
Motor skills	70.64	12.30	59.73	9.24	2.59, .02
<i>ASD/sodal communication</i>					
ADOS severity score	6.36	2.20	7.00	1.30	<i>n.s.</i>
SRS T score	72.09	13.31	77.25	12.81	<i>n.s.</i>
<i>Challenging behavior (ABC)</i>					
Irritability	6.13	6.22	13.25	7.94	<i>n.s.</i>
Social withdrawal	4.13	4.76	13.75	8.00	-2.93, .01
Stereotypic behavior	2.25	2.25	7.75	4.27	-3.22, .006
Hyperactivity/noncompliance	10.50	5.55	22.25	11.77	-2.55, .02
Inappropriate speech	1.88	1.88	2.00	2.33	<i>n.s.</i>

TABLE 7

Epilepsy characteristics

	N (total = 26)	M (SD)	Range
Age of onset (months)	24	33.0 (41.5)	0–161
% life seizing	22	53% (31)	0–96%
Lifetime medications	26	3.7 (3.4)	1–15
Current medications	26	2.2 (1.0)	1–5
Seizure types	22	2.6 (1.4)	1–6
Infantile spasms	27	48%	
Current seizures	27	56%	