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Language characterization in 16p11.2 deletion and duplication syndromes

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[†]Approved researchers can obtain the Simons Searchlight dataset described in this study by applying at https://base.sfari.org.

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CONFLICT OF INTEREST

Drs Lord and Bishop have received royalties from Western Psychological Services for publication of the Autism Diagnostic Observation Schedule (ADOS). All other authors declare no conflict of interest.

SUPPORTING INFORMATION

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

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Abstract

Expressive language impairment is one of the most frequently associated clinical features of 16p11.2 copy number variations (CNV). However, our understanding of the language profiles of individuals with 16p11.2 CNVs is still limited. This study builds upon previous work in the Simons Variation in Individuals Project (VIP, now known as Simons Searchlight), to characterize language abilities in 16p11.2 deletion and duplication carriers using comprehensive assessments. Participants included 110 clinically ascertained children and family members (i.e., siblings and cousins) with 16p11.2 BP4-BP5 deletion and 58 with 16p11.2 BP4-BP5 duplication between the ages of 2–23 years, most of whom were verbal. Regression analyses were performed to quantify variation in language abilities in the presence of the 16p11.2 deletion and duplication, both with and without autism spectrum disorder (ASD) and cognitive deficit. Difficulties in pragmatic skills were equally prevalent in verbal individuals in both deletion and duplication groups. NVIQ had moderate quantifiable effects on language scores in syntax and semantics/pragmatics (a decrease of less than 1 *SD*) for both groups. Overall, language impairments persisted even after controlling for ASD diagnosis and cognitive deficit. Language impairment is one of the core clinical features of individuals with 16p11.2 CNVs even in the absence of ASD and cognitive deficit. Results highlight the need for more comprehensive and rigorous assessment of language impairments to maximize outcomes in carriers of 16p11.2 CNVs.

Keywords

16p11.2 deletion; 16p11.2 duplication; autism; genetics; language profiles

1 | INTRODUCTION

Expressive language impairment is one of the most frequently described clinical features associated with copy number variation (CNV) of the recurrent ~600 kb BP4-BP5 region on 16p11.2 (BP4–BP5). Past studies have identified marked expressive language impairments (Bijlsma et al., 2009; Fedorenko et al., 2016; Ghebranious, Giampietro, Wesbrook, & Rezkalla, 2007; Hanson et al., 2015; Weiss et al., 2008), which can occur in the absence of autism spectrum disorder (ASD) or intellectual disability (ID) (Sebat et al., 2007; Weiss et al., 2008; Zufferey et al., 2012). In fact, language impairment is a commonly documented feature in many genetic syndromes, copy number variants and monogenetic conditions, such as Down syndrome, Fragile X, and Williams syndrome (Rice, Warren, & Betz, 2005), *FOXP2* and *CNTNAP2* variants (Feuk et al., 2006; Shriberg et al., 2006; Vernes et al., 2008) and CNVs of chromosome 7q (Alarcón, Cantor, Liu, Gilliam, & Geschwind, 2002; Folstein & Mankoski, 2000). Impairments are observed in these conditions relative to cognitive

and receptive levels, and across the domains of syntax, lexicon, semantics and social use of language (pragmatics), and persist well beyond early development (Feuk et al., 2006; Finestack & Abbeduto, 2010; Laws & Bishop, 2003; Miller, 1999; Philofsky, Hepburn, Hayes, Hagerman, & Rogers, 2004).

There are few descriptions of language profiles across domains in 16p11.2 deletion and duplication, and few detailed comparisons between the two syndromes. An earlier study demonstrated that language delays were equally pervasive in both groups (Shinawi et al., 2010). Our previous work suggested that delays in duplication carriers were largely associated with global ID, while diagnoses of language disorders were more prevalent in pediatric deletion carriers (Green-Snyder et al., 2016; Hanson et al., 2010, 2015; Hippolyte et al., 2016), yet these findings warranted more careful examination.

First, ID and ASD have been linked to 16p11.2 deletion and duplication with relatively high prevalence (up to 25% for ASD; up to 80% for ID; Fernandez et al., 2010; Girirajan et al., 2013; Green-Snyder et al., 2016; Hanson et al., 2010, 2015; Kim, Paul, et al., 2014; Kumar et al., 2009; Kumar & Christian, 2009; Marshall et al., 2008; McCarthy et al., 2009; Sanders et al., 2011; Sebat et al., 2007; Walsh & Bracken, 2011; Weiss et al., 2008; Pinborough-Zimmerman et al., 2007; Zufferey et al., 2012), and these factors can affect language development in children.

Second, the limited scope of currently available standardized language measures is a significant barrier to the timely and accurate detection of language impairments in clinical populations, including 16p11.2 carriers. Many existing standardized measures are designed to determine the presence and severity of language impairments by gauging answers that are dependent upon pre-determined responses in a highly structured setting. Therefore, impairments in certain areas of language, such as spontaneous use of language in a natural environment or functional language in everyday contexts, may not readily be recognized by those instruments (Condouris, Meyer, & Tager-Flusberg, 2003). This highlights the need for a more comprehensive approach including assessment of language samples and pragmatics when studying language phenotypes in 16p11.2 (Tager-Flusberg et al., 2009).

To address these gaps in current knowledge, we attempted to thoroughly characterize the pattern of quantitative expressive language impairments in 16p11.2 deletion versus duplication carriers, specifically in syntax, semantics, pragmatics and functional communication (American Psychiatric Association [APA], 2013; Bishop et al., 2017; Bishop, Snowling, Thompson, & Greenhalgh, 2016). We examined the prevalence and severity of language impairments in the context of ASD and cognitive ability, using multiple, complementary language measures. These included clinician observations of syntax, pragmatics, and semantics in structured (Comprehensive Assessment of Spoken Language [CASL]; Carrow-Woolfolk, 1999) and natural contexts (Observation of Spontaneous Expressive Language [OSEL]; Kim, Paul, et al., 2014), as well as parent reports of communication (Children’s Communication Checklist-2 [CCC-2]; Bishop, 2003), including everyday functional language use (Vineland Adaptive Behavior Scale-II [VABS]; Sparrow, Balla, & Cicchetti, 2005).

2 | METHODS

2.1 | Participants

Participants with the recurrent ~600 kb 16p11.2 BP4-BP5 deletion or duplication identified through clinical diagnostic evaluations were invited to participate in Simons Searchlight. All deletion and duplication carriers had the same recurrent CNV and no additional pathogenic CNV or known monogenic disorders. See Simons VIP Consortium (2012), Hanson et al. (2015) and Green Snyder et al. (2016) for more details.

Following screening, families participated in data collection at one of three Simons Searchlight phenotyping sites at Boston Children's Hospital, Baylor College of Medicine or University of Washington for a comprehensive and standardized multiday evaluation. Data from participants were obtained from three core sites trained in the language battery. The study was approved by the institutional review board at each participating institution. Standardization of measurements across sites included mandatory formalized and standardized training on all measures through in-person training sessions and webinars for all clinicians, and maintenance of cross-site reliability with independent consultants.

One hundred ten (110) participants with the 16p11.2 deletion (53 females, 57 males) and 58 participants with 16p11.2 duplication (34 males, 24 females) aged 2–23 years were included. Fourteen (14) percent of the carrier sample were full-biological siblings (n = 16; 8 deletion and 8 duplication carriers), half-siblings (n = 2 duplication carriers) or cousins (n = 2 duplication carriers) of initially identified probands, identified through cascade genetic testing. Due to the small proportion of these cases, we decided to include them in the analyses because their presence yielded no differences in results (data available upon request). Out of the total 168 individuals, 26 deletion and 13 duplication carriers received a diagnosis of ASD based on DSM-IV-TR criteria (see Section 2.3 *below* for more details).

The number of individuals able to be included in analyses varied for each language measure according to their language level, and most analyses were conducted upon verbal individuals with at least phrase speech (see below).

2.2 | Measures

2.2.1 | Vineland-II—The Vineland Adaptive Behavior Scale-2nd Edition (Vineland-II; Sparrow et al., 2005) is a measure of adaptive behavior for individuals from birth to adulthood. Even though the Vineland-II is not typically used as a core measure of language, we were interested in examining impairments in the use of language skills in an everyday context. For the present study, we used the V-scale score from the expressive communication domain, which is standardized by age, with a mean of 15 and a standard deviation of 3. The Vineland-II was available for all but one case across a wide range of language level including minimally verbal and verbal individuals.

2.2.2 | Comprehensive Assessment of Spoken Language—The CASL (Carrow-Woolfolk, 1999) is a measure designed to assess oral language abilities in the Syntactic domain for children age 3–10 years and the Pragmatic domain for individuals age 3–21 years. For the present study, standard scores and age equivalents were examined. The

standard score has a mean of 100 and a standard deviation of 15. Seventeen deletion carriers and 7 duplication carriers could not complete the Syntactic subtests, and 15 deletion carriers and 8 duplication carriers could not complete the Pragmatic subtests, due to language limitations (lack of phrase or sentence speech), despite being within age range for the test (See Table S1).

2.2.3 | Children's Communication Checklist-2—The CCC-2 (Bishop, 2003) is a parent-report measure designed to assess communication skills in the areas of pragmatics, syntax, and semantics for individuals from 4 to 16 years. For this study, we used scaled scores (with an average of 10 and *SD* of 3) for 9 domains targeting *Syntax* (grammar), *Semantics* (vocabulary), *Coherence* (discourse), and various pragmatic skills (*Initiation, Scripted Language, Context, Nonverbal Communication, Social Relations, Interests*). Eleven (11) deletion carriers and 1 duplication carrier had language levels that were too low to receive the instrument (below the 4-year-old level; See Table S1).

2.2.4 | Observation of Spontaneous Expressive Language—The OSEL (Kim, Junker, & Lord, 2014) is a 30–45 min observational assessment which focuses on children's spontaneous expressive language use in standardized but natural contexts. The OSEL is intended to be used with children with ASD and other communication disorders from 2 to 12 years old whose expressive language levels are equivalent to typically developing children between 2 and 5 years. Thirty-seven (37) deletion carriers and 19 duplication carriers were unable to complete the measure due to limited language (below the 5-year-old level; See Table S1). OSEL syntax totals are computed by combining grammatical usages of 24 items, including different types of *pronouns* [e.-g., *subjective/objective/possessive*], *verb tenses* [e.g., *regular/irregular past, be + progressive* "*-ing*"], and *sentence forms* [e.g., *coordination/subordination*]. The OSEL pragmatic and semantic profile (PSP) totals include three domains: (a) *Initiation of Reciprocal Communication* (e.g., *Verbal request* and *Asks for information about others' experiences*); (b) *Narrative Skills* (e.g., *Reporting main ideas* and *Reporting sequence of events*); (c) *Unusual Features* (e.g., *Dominates conversations* and *Stereo-typed/idiosyncratic language*). The OSEL provides age equivalents based on established norms. A language quotient (LQ = [age equivalent/chronological age] × 100) was derived from the age equivalents following the convention for ratio quotients (Kim, Junker, et al., 2014). Because the age equivalent scores for the OSEL only go up to 60 months, LQ scores were not derived for individuals above 59 months who achieved ceiling scores, in order to minimize the risk of underestimating skills for this particular group of children (n = 12 deletion and n = 10 duplication carriers for Syntax; n = 10 deletion and 3 duplication carriers for the *Initiation of Reciprocal Communication* domain, and n = 17 deletion and n = 9 duplication carriers for the Narrative Skills domain).

2.2.5 | Cognitive measures—All participants were administered a developmentally appropriate cognitive measure: Mullen Scales of Early Learning (MSEL; Mullen, 1995) or Differential Abilities Scale, Second Edition (DAS; Elliott, 2007). When available, standard scores were used for Full-Scale IQ (FSIQ), Verbal IQ (VIQ), and Nonverbal IQ (NVIQ). For MSEL, deviation IQ scores were extrapolated using Visual Reception and Fine Motor T scores for NVIQ, and Receptive and Expressive Language T scores for VIQ. MSEL ratio

IQ scores were computed based on the age equivalent scores from the Visual Reception and Fine Motor domains for the NVIQ and from the Receptive and Expressive Language Scores for the VIQ (average of the age equivalents divided by chronological age; Bishop, Farmer, & Thurm, 2015).

2.2.6 | ADOS-2—The Autism Diagnostic Observation Schedule-2 (ADOS-2; Lord et al., 2012) is a play-based diagnostic instrument for core symptoms of ASD in the social communication (SC) and restricted and repetitive behaviors (RRBs) domains. Out of 168 individuals, 5 individuals did not have ADOS data available (e.g., individuals with mental ages below 15 months for whom the ADOS could not be validly administered). The Social Affect calibrated severity score (CSS; or Comparison scores; Hus, Gotham, & Lord, 2014) derived from the algorithm score was used to measure social communication impairment.

2.3 | Diagnostic procedure

Experienced, licensed clinicians gave best-estimate, clinical DSM-IV-TR (APA, 2013) diagnoses using all information obtained during the research evaluation. Diagnoses were based on information obtained from the standardized interview, questionnaires, and observations, as well as results from standardized administration of the Diagnostic Interview Schedule for Children (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) and review of available medical records and prior testing. For ASD diagnosis, information from the Autism Diagnostic Observation Scale (Lord et al., 2012) and the Autism Diagnostic Interview–Revised (Le Couteur, Lord, & Rutter, 2003) was used to reach the clinical best-estimate diagnosis.

2.4 | Data analysis

Because of inherent differences in the nature of deletion versus duplication of the 16p11.2 chromosomal region, deletion and duplication carriers were examined separately in analyses.

To examine potential sampling bias caused by the uneven numbers of deletion versus duplication carriers excluded on each instrument, we compared characteristics of included and excluded participants using *t* tests and chi-square analyses. For individuals with at least phrase speech, we examined the presence and severity of language impairments. Functional communication was examined for all individuals, including minimally verbal cases (e.g., no words or using single words).

First, we determined the proportion of participants with a delay in each language domain, defined as a score more than 1 *SD* below the mean. We compared the proportion of deletion versus duplication carriers with a delay in each measure, using chi-square tests. Mean language scores were also compared between the two groups using *t* tests. Effect sizes were calculated for the comparisons (using odds ratios for chi-square tests and Cohen's *d* for *t* tests).

Second, we conducted regression analyses on standardized language scores with ASD diagnosis and NVIQ as covariates. In these analyses, NVIQ was centered at 100 and divided by 10, such that estimates were interpreted as the change in a given language score with every 10-point unit change in NVIQ. Given that the 16p11.2 deletion and duplication are

distinct in mechanism and phenotype, we conducted regression analyses separately for the two groups. Beta weights were examined separately to examine the magnitude of specific ASD and NVIQ effects on language outcomes. We also examined the significant effects of the intercepts in the regression models to determine whether a participant's predicted language score *without* ASD and *with average* NVIQ is significantly lower than the average scores based on the test norms (e.g., a standard score of 100 on CASL, or ratio quotient of 100 in the OSEL). This was possible by using the centered normed scores as outcome variables (all centered at the mean: 100 for standard scores, 10 for V-scaled scores).

All results were corrected for multiple comparisons using Bonferroni correction.

3 | RESULTS

3.1 | Sample characteristics and language profiles for deletion and duplication carriers

Sample characteristics can be found in Table 1. Age ranged from 2 to 23 years with a mean age of 8 years ($SD = 4.5$), depending upon each language instrument (see below). VIQ and NVIQ ranged 13–122 ($M = 80$, $SD = 21$) and 26–130 ($M = 82$, $SD = 18$), respectively. Consis tent with findings reported previously, duplication carriers showed significantly lower NVIQ compared to deletion carriers ($p < .05$).

As expected, for each given measure, individuals who were unable to complete testing had significantly lower verbal or nonverbal IQ scores and were more likely to be diagnosed with ASD compared to those who completed testing (See Table S1). This was true for both deletion and duplication carriers and for nearly all measures. For those individuals who were within valid age range for each instrument (besides Vineland-II), 12–46% of deletion and 2–41% of duplication carriers did not receive the language testing due to limited language levels. There was no statistically significant difference in the proportions of individuals who were unable to complete the testing between deletion and duplication carriers across all measures.

As seen in Table 2, in verbal individuals, deletion carriers showed significantly lower scores than duplication carriers in the two language instruments targeting syntax (CASL and CCC-2; $p < .05$). No significant difference emerged between the two groups in the pragmatics domain. The proportion of individuals with delays on quantitative measures was also significantly higher in deletion than duplication carriers for all domains except for pragmatics ($p < .05$).

3.2 | The effects of ASD diagnosis and NVIQ on the severity of language impairments

Tables 3 and 4 display results of regression models in which the intercept, or constant, predict each language domain and the effects of ASD and cognitive deficit.

3.2.1 | Deletion carriers—As shown in Table 3, in verbal deletion carriers, a small but statistically significant association of ASD diagnosis emerged for pragmatic skills (CCC-2 Context) in deletion carriers, in which the presence of ASD was associated with lower language scores. A significant association of NVIQ also emerged for most language measures, including syntax (CASL, CCC-2), and pragmatic skills (CASL, CCC-2 Scripted

Language, Nonverbal Communication, OSEL Narrative Skills), in which NVIQ scores were positively associated with language scores. The presence of ASD and lower NVIQ also predicted more impairments in functional communication (Vineland-II Expressive Communication), including in minimally verbal deletion carriers. All p values were <.05. Other subtests showed effects of ASD and NVIQ which were not statistically significant following Bonferroni correction (CCC-2 Initiation and Interests domains, and OSEL Initiation, respectively). The largest estimated effects in verbal deletion carriers were those of NVIQ, upon CASL pragmatic and OSEL Narrative pragmatic scores, with an additive 7-point and 10-point increase respectively per 10 point-NVIQ increase, and upon CASL syntax, with an additive 6-point increase per 10-point NVIQ increase.

3.2.2 | Duplication carriers—As shown in Table 4, similar to the results from verbal deletion carriers, in verbal duplication carriers, a significant association of NVIQ emerged for syntax (CASL, CCC-2 and OSEL) and pragmatics (CASL; CCC-2 Semantics; OSEL Narrative Skills), in which NVIQ scores were positively associated with language scores. However, unlike in deletion carriers, no significant effect of ASD diagnosis emerged in verbal duplication carriers. This pattern was true of functional communication on the Vineland-II as well, including in minimally verbal duplication carriers. All p values were <.05. Other subtests showed effects of NVIQ which were not significant with Bonferroni correction (CCC-2 Scripted Language and Context; OSEL Initiation). The largest estimated effects in verbal duplication carriers were seen for NVIQ in the OSEL syntax language quotient, with an additive 9-point increase per 10-point NVIQ increase, and in the CASL Pragmatic and OSEL Narrative Skills scores, with an additive 5–7-point increase per 10-point NVIQ increase.

3.3 | Presence of language impairment after controlling for the effects of ASD diagnosis and cognitive deficit

3.3.1 | Deletion Carriers—As shown in Table 3, in verbal individuals with deletion, the coefficients for the intercepts (beta) indicated that each estimated mean language score for a deletion carrier without ASD and with an NVIQ of 100 would be significantly lower than the average score based upon test norms (Standard Score of 100). Across nearly all language domains, the model estimates indicated that a deletion carrier without an ASD diagnosis or cognitive deficit would still show a language score that is at least 1 *SD* below what would be expected. This was true also of minimally verbal individuals on the Vineland-II. Syntax and pragmatics showed the greatest predicted decrements controlling for ASD and cognitive deficit, with an approximate 20- to 45-point decrease in CASL and OSEL syntax scores, and 28- to 49-point decrease in the OSEL pragmatic language quotients, relative to those expected.

3.3.2 | Duplication Carriers—As shown in Table 4, in verbal duplication carriers, intercepts in the regression models were significant for some pragmatic and semantic domains when adjusting for ASD and NVIQ (CCC-2 Initiation, Context, Nonverbal Communication; OSEL Initiation of Reciprocal Social Communication and Narrative Skills). Other pragmatic measures showed differences that were not significant with Bonferroni correction (CCC-2 Interests). Intercepts for syntax and Vineland-II functional

communication were not significant. Using this method, the magnitude of the predicted differences in verbal duplication carriers with average IQ and no ASD were smaller and more varied than in verbal deletion carriers, with many language test scores falling within 1 *SD* of the mean. Pragmatic skills, especially for the Initiation of Social Communication domain of the OSEL, showed the greatest predicted decrements controlling for ASD and cognitive deficit, with a 31-point decrease in OSEL language quotients relative to those expected.

4 | DISCUSSION

The current study aimed to characterize the pattern of quantitative impairments in language measures in a sample of mostly verbal 16p11.2 deletion and duplication carriers with and without ASD diagnosis and cognitive deficits. Not surprisingly, cognitive deficit was a significant predictor of lower functional communication in everyday settings in both deletion and duplication carriers, including minimally verbal individuals. Among verbal individuals, cognitive skills also showed a significant effect on syntactic and pragmatic skills in both groups, with beta estimates suggesting 5- to 10-point increases on language indices for every 10-point increase in NVIQ. There was little to no effect of ASD diagnosis upon language in the current sample, but it is important to note that nonverbal ASD cases were excluded from most analyses, and so conclusions about the effects of ASD are limited.

Expressive language profiles in 16p11.2 duplication and deletion carriers continue to show impairments across different domains even after the effects of ASD diagnosis and NVIQ are controlled. Taken with the findings above, this lends support to the idea that at least in verbal individuals, language impairment is associated with the effects of 16p11.2 rearrangements themselves, and is neither entirely explained nor significantly exacerbated by other developmental diagnoses, especially ASD. This is consistent with previous research (Sebat et al., 2007; Weiss et al., 2008). These results may suggest that researchers characterizing genetic changes should keep in mind that not all language features traditionally considered “core” to ASD, such as pragmatic difficulties, are attributable to ASD but will be found in the absence of ASD as well.

4.1 | Clinical implications

It is important to note that results from the current study are likely most clinically relevant to individuals capable of a minimum level of expressive language, namely, phrase speech, and do not represent all 16p11.2 CNV carriers or those with the most severe impairments. In fact, 12–46% of deletion carriers and 2–41% of duplication carriers did not receive the language testing due to limited language levels. There was no significant difference between the deletion and duplication carriers in the proportion of individuals who did not receive the language testing. Further, the current measures of language ability required not only expressive language but also receptive demands (e.g., CASL Pragmatic domain, and CCC-2). Nonetheless, we found that the severity and type of language impairment varied between verbal deletion and duplication carriers. More specifically, impairments were quite prominent for deletion carriers, with scores for most language domains falling more than 1 *SD* below the mean even after controlling for ASD diagnosis and NVIQ. Duplication

carriers showed *less* severe difficulties in pragmatic and semantic domains than deletion carriers. This was especially striking given that cognitive impairment can be relatively severe for the duplication carriers, and could be an artifact of having to exclude the most severely cognitively and linguistically impaired individuals who could not complete testing.

Clinically it is important to note that *both* deletion *and* duplication carriers showed a wide range of language impairments in domains that varied by group. The presence of delays in pragmatic skills in verbal individuals were especially high (48–100%) for both deletion and duplication carriers, but have traditionally not been recognized in formal language diagnosis (e.g., with only 27% of duplication carriers having a clinical language disorder diagnosis in our previous reports). Therefore, it will be important for clinicians to consider if impairments warrant a separate diagnosis of language disorder to inform treatment planning with a more focused treatment goal on pragmatic skills.

In addition, clinicians working with individuals with 16p11.2 CNVs may readily notice more obvious abnormalities, such as deficits in grammatical structures. However, pragmatic impairments, including initiation of reciprocal social interaction (OSEL, CCC-2; e.g., requesting, commenting on one's own experiences), and narrative skills (OSEL, CCC-2; e.g., reporting main ideas from a story, sequencing ideas in conversation) in a more natural setting, as well as other pragmatic and semantic skills in a more structured context (CASL), may not be identified by clinicians, especially for deletion and duplication carriers who do not meet criteria for ASD.

Finally, it is important to note that some patterns in our findings varied by the type of instrument used. Although some of these instruments target similar domains of language (e.g., pragmatics), they vary in the source of information (e.g., parent-report vs. clinician observation) and the context in which the target skill is measured (e.g., home vs. lab-settings). For instance, instruments such as the CASL gauge the level of language skills based on pre-determined answers elicited in a highly structured setting. In contrast, language instruments such as the OSEL are intended to capture spontaneous use of language in a semi-structured setting, without many direct prompts, while parent report measures such as Vineland-II and CCC-2 are designed to target language skills that are functional and generalized in day-to-day settings. Further, profiles will vary within and between individuals. This highlights the need to take a comprehensive approach to language assessment across domains, and to combine different sources of information for individuals with 16p11.2 CNVs.

4.2 | Limitations and future directions

This study included a subset of individuals from a larger study focused on characterization of 16p11.2 deletion and duplication carriers (Green-Snyder et al., 2016; Hanson et al., 2015). We focused our observations on initially identified probands and their siblings and cousins but did not include other older family members, including parents and grandparents. Very young children under the age of 2 were not included in most analyses. In addition, while our sample included a wide age range, one of the instruments, the OSEL, was given to mostly younger children, or older children whose language skills were equivalent to 2-

to 5-year-old typically developing children. Therefore, generalization of the results may warrant caution.

One of the strengths of our study was the multi-measurement approach to profiling language in 16p11.2 CNVs. However, as these instruments were each validated for specific age groups and language levels, varying numbers of individuals falling below the basal or above the ceiling on each measure were excluded from analyses. In fact, those who were excluded were often minimally verbal, had significantly lower IQ and were more likely to be diagnosed with ASD compared to those who were included. Therefore, conclusions regarding effects of ASD and NVIQ on language are limited, and results should be considered specific to verbal carriers and to the instruments under study. Future studies also should examine interaction effects of NVIQ and ASD, in a larger and more inclusive sample. Studies could consider instruments appropriate for minimally verbal, younger children (e.g., Communication and Symbolic Behavior Scales; CSBS[34]) that focus on impairments in pre-verbal communication, to expand the scope of research in this area.

Finally, our results are based on a clinically ascertained sample that was brought to attention by their developmental and language delays, and are not necessarily reflective of the full spectrum of the 16p11.2 population. This problem is somewhat mitigated by the fact that we included family members (e.g., siblings) of clinically ascertained probands and have observations of language for individuals with varying levels of cognitive abilities. However, these limitations underscore the need for replication with other independent samples.

5 | CONCLUSION

Our findings demonstrate that specific types of language impairments in 16p11.2 deletion and duplication carriers can persist even in the absence of an ASD diagnosis and cognitive delay. These findings suggest that language impairments may be one of the core clinical features of 16p11.2 CNVs, even for those without ASD or cognitive deficits. Therefore, it is critical not to overlook pragmatic and other language impairments, even in the presence of more intact social and cognitive skills. Our results also confirm, not surprisingly, that the presence of cognitive deficit further exacerbates language impairments in both 16p11.2 deletion and duplication carriers in predictable and quantifiable ways. Careful, comprehensive examination of language is critical while considering other clinical features, such as ASD and cognitive deficits in these populations, in order to provide specific support for optimal development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Sample characteristics

	Deletion	Duplication
N	110	58
ASD, *n*	26	13
Age in months *M* (*SD*)	101.6 (49.7)	99.6 (62.8)
Range	24–250	24–281
Nonverbal IQ[a] *M* (*SD*)	86.2 (15.3)	74.8 (20.3)
Range	48–130	26–116
Verbal IQ *M* (*SD*)	79.1 (18.8)	79.1 (25.3)
Range	23–116	13–122
ADOS calibrated severity score *M* (*SD*)	3.3 (2.3)	3.4 (2.8)
Range	1–10	1–10
Vineland-II socialization standard score *M* (*SD*)	82.6 (15.4)	79.9 (15.8)
Range	34–131	42–118
Vineland-II daily living skills standard score *M* (*SD*)	83.3 (14.6)	78.7 (16.3)
Range	34–120	33–111
Vineland-II communication standard score *M* (*SD*)	78.6 (12.7)	80.8 (16.9)
Range	45–122	43.118

Abbreviations: ADOS, Autism Diagnostic Observation Schedule; Vineland-II, Vineland Adaptive Behavioral Scale.

[a]Significant differences emerged between the two groups ($p < .05$).

TABLE 2

The presence and severity of language impairments for 16p11.2 deletion and duplication carriers

		Deletion	Duplication	*t* (chi-square)	*p*	Effect size (Cohen's *d*/odds ratios)
Reported functional expressive communication						
Vineland-II	*N*	109	58			
	Expressive communication v-scale scores, *M* (*SD*)	10.6 (2.7)	11.7 (3.5)	−1.947	.055	*d* = 0.35
	% with delays	67%	48%	(5.536)	**.019**	OR = 0.45
Syntax						
CASL	*N*	58	35			
	Syntax standard scores, *M* (*SD*)	72.8 (16.6)	84.1 (15.5)	−3.311	**.001**	*d* = 0.70
	% with delays	78%	46%	(9.825)	**.002**	OR = 0.24
CCC-2	*N*	81	41			
	Syntax scaled scores, *M* (*SD*)	5.5 (3.8)	8.0 (3.8)	−3.325	**.001**	*d* = 0.66
	% with delays	84%	56%	(11.141)	**.001**	OR = 0.24
OSEL	*N*	43	27			
	OSEL syntax totals, *M* (*SD*)	62.4 (15.1)	67.6 (17.7)	−1.307	.196	*d* = 0.32
	% with delays	78%	41%	(6.793)	**.009**	OR = 0.27
Pragmatics and semantics						
CASL	*N*	91	48			
	Pragmatic standard scores, *M* (*SD*)	77.2 (16.7)	82.6 (17.0)	−1.776	.079	*d* = 0.32
	% with delays	63%	48%	(2.787)	.095	OR = 0.55
CCC-2	*N*	81	41			
	Initiation scaled scores, *M* (*SD*)	7.4 (2.8)	6.3 (3.4)	1.820	.071	*d* = 0.35
	Scripted language scaled scores, *M* (*SD*)	6.5 (3.3)	7.7 (3.0)	−1.848	.067	*d* = 0.38
	Context scaled scores, *M* (*SD*)	5.8 (2.9)	6.6 (3.3)	−1.391	.167	*d* = 0.27
	Nonverbal communication scaled scores, *M* (*SD*)	5.8 (3.1)	6.7 (3.6)	−1.538	.127	*d* = 0.27
	Interests scaled scores, *M* (*SD*)	8.0 (2.9)	7.7 (3.2)	0.510	.611	*d* = 0.10
	Semantics scaled scores, *M* (*SD*)	5.8 (3.2)	7.4 (2.9)	−2.635	.010[a]	*d* = 0.52
	% with delays	79%	76%	(0.183)	.952	OR = 0.82
OSEL	*N*	43	27			
	Initiation of reciprocal totals, *M* (*SD*)	3.5 (2.8)	3.7 (2.8)	−0.124	.902	*d* = 0.07

	Deletion	Duplication	*t* (chi-square)	*p*	Effect size (Cohen's *d*/odds ratios)
% with delays	98%	96%	(0.113)	.738	OR = 0.62
Narrative skills totals, *M* (*SD*)	5.7 (3.4)	6.4 (4.7)	−0.667	.507	*d* = 0.17
% with delays	95%	93%	0.023	.629	OR = 0.61

Note: t test with equal variance not assumed.

Bold values represents p-values <0.05.

Abbreviations: CASL, Comprehensive Assessment of Spoken Language; CCC-2, Children's Communication Checklist-2; OSEL, Observation of Spontaneous Expressive Language; Vineland-II, Vineland Adaptive Behavior Scales.

[a]No longer significant with Bonferroni correction.

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TABLE 3

Regression analyses predicting language scores while controlling for ASD diagnosis and NVIQ in deletion carriers

		B	*SE*	*t*	Sig.
Reported functional expressive communication					
Vineland-II	**Constant**	−3.303	.344	−9.606	**<.001**
	ASD diagnosis	−1.654	.551	−3.000	**.003**
	NVIQ (centered at 100)	.517	.153	3.372	**.001**
Syntax					
CASL	**Constant**	−18.884	2.662	−7.093	**<.001**
	ASD diagnosis	3.787	5.611	.675	.503
	NVIQ (centered at 100)	6.680	1.437	4.648	**<.001**
CCC-2	**Constant**	−3.815	.600	−6.363	**<.001**
	ASD diagnosis	−.980	.982	−.998	.220
	NVIQ (centered at 100)	.365	.295	1.236	.321
OSEL	**Constant**	−44.752	4.731	−9.459	**<.001**
	ASD diagnosis	−7.054	6.490	−1.087	.286
	NVIQ (centered at 100)	4.097	2.243	1.826	.078
Pragmatics and semantics					
CASL	**Constant**	−14.267	2.108	−6.768	<.001
	ASD diagnosis	−5.842	3.617	−1.615	.110
	NVIQ (centered at 100)	6.105	1.073	5.687	**<.001**
CCC-2 initiation	**Constant**	−1.799	.430	−4.183	**<.001**
	ASD diagnosis	−1.858	.704	−2.638	.010[a]
	NVIQ (centered at 100)	.309	.212	1.461	.148
CCC-2 scripted language	**Constant**	−2.755	.507	−5.439	<.001
	ASD diagnosis	.166	.249	.665	.508
	NVIQ (centered at 100)	−2.161	.830	−2.605	.011[a]
CCC-2 context	**Constant**	−3.272	.438	−7.477	**<.001**
	ASD diagnosis	−2.105	.717	−2.937	**.004**
	NVIQ (centered at 100)	.380	.216	1.764	.082
CCC-2 nonverbal communication	**Constant**	−3.743	.476	−7.866	**<.001**

		B	*SE*	*t*	Sig.
	ASD diagnosis	.010	.234	.042	.967
	NVIQ (centered at 100)	−2.147	.779	−2.755	**.007**
CCC-2 interests	**Constant**	−1.563	.440	−3.550	**.001**
	ASD diagnosis	−1.736	.720	−2.412	.018[a]
	NVIQ (centered at 100)	.046	.216	.212	.833
CCC-2 semantics	Constant	−1.181	.599	−1.971	.056
	ASD diagnosis	.761	1.069	.712	.481
	NVIQ (centered at 100)	.790	.208	.3.803	**<.001**
OSEL initiation of reciprocal social interaction	**Constant**	−48.656	3.813	−12.760	**<.001**
	ASD diagnosis	−1.738	5.696	−.305	.762
	NVIQ (centered at 100)	4.118	1.930	2.133	.041[a]
OSEL narrative skills	**Constant**	−28.416	6.176	−4.601	**.000**
	ASD diagnosis	−10.760	8.328	−1.292	.209
	NVIQ (centered at 100)	10.046	3.006	3.342	**.003**

Note: Significant results are bolded. NVIQ is centered at 100 and divided by 10 such that the beta estimates can be interpreted as increases/decreases in scores for every 10-point unit increase in NVIQ scores.

Abbreviations: CASL, Comprehensive Assessment of Spoken Language; CCC-2, Children's Communication Checklist-2; OSEL, Observation of Spontaneous Expressive Language; Vineland-II, Vineland Adaptive Behavior Scales.

[a]No longer significant with Bonferroni correction.

TABLE 4

Regression analyses predicting language scores while controlling for ASD diagnosis and NVIQ in duplication carriers

		B	*SE*	*t*	Sig.
Reported functional expressive communication					
Vineland-II	Constant	−.644	.570	−1.129	.264
	ASD diagnosis	−1.58	.898	−1.759	.084
	NVIQ (centered at 100)	.952	.186	5.13	**<.001**
Syntax					
CASL	Constant	−3.086	2.857	−1.080	.288
	ASD diagnosis	1.141	5.506	.226	.823
	NVIQ (centered at 100)	6.261	1.064	5.884	**<.001**
CCC-2	Constant	−.051	.743	−.0.68	.946
	ASD diagnosis	1.300	1.326	.981	.333
	NVIQ (centered at 100)	1.146	.258	4.448	**<.001**
OSEL	Constant	−3.288	6.736	−.488	.634
	ASD diagnosis	−37.161	18.239	−2.037	.064
	NVIQ (centered at 100)	8.683	2.173	3.996	**.002**
Pragmatics and semantics					
CASL	Constant	−4.701	3.018	−1.558	.126
	ASD diagnosis	−8.115	5.112	−1.587	.119
	NVIQ (centered at 100)	5.186	1.086	4.776	**<.001**
CCC-2 initiation	**Constant**	−2.954	.815	−3.625	**.001**
	ASD diagnosis	−1.609	1.455	−1.106	.276
	NVIQ (centered at 100)	.280	.283	.992	.328
CCC-2 scripted language	Constant	−1.306	.659	−1.981	.055
	ASD diagnosis	−1.105	1.177	−.938	.354
	NVIQ (centered at 100)	.469	.229	2.049	.048[a]
CCC-2 context	**Constant**	−2.346	.743	−3.159	**.003**
	ASD diagnosis	−.496	1.327	−.374	.711
	NVIQ (centered at 100)	.560	.258	2.173	.036[a]
CCC-2 nonverbal communication	**Constant**	−2.290	.775	−2.956	**.005**

		B	*SE*	*t*	Sig.
	ASD diagnosis	−2.101	1.383	−1.519	.138
	NVIQ (centered at 100)	.429	.269	1.596	.138
CCC-2 interests	Constant	−1.528	.746	−2.049	.048[a]
	ASD diagnosis	−2.053	1.332	−1.542	.132
	NVIQ (centered at 100)	.274	.259	1.061	.296
CCC-2 semantics	Constant	−1.015	.556	−1.825	.076
	ASD diagnosis	.733	1.056	.694	.492
	NVIQ (centered at 100)	.834	.199	4.200	**<.001**
OSEL initiation of reciprocal social interaction	**Constant**	−31.209	5.037	−6.196	**<.001**
	ASD diagnosis	−16.973	9.228	−1.839	.082
	NVIQ (centered at 100)	4.682	1.686	2.776	.012[a]
OSEL narrative skills	**Constant**	−22.944	7.518	−2.976	**.004**
	ASD diagnosis	−15.627	14.029	−1.114	.284
	NVIQ (centered at 100)	7.170	2.121	3.380	**.004**

Note: Significant results are bolded. NVIQ is centered at 100 and divided by 10 such that the beta estimates can be interpreted as increases/decreases in scores for every 10-point unit increase in NVIQ scores.

Abbreviations: CASL, Comprehensive Assessment of Spoken Language; CCC-2, Children's Communication Checklist-2; CTOPP, Comprehensive Test of Phonological Processing; OSEL, Observation of Spontaneous Expressive Language; Vineland-II, Vineland Adaptive Behavioral Scale.

[a]No longer significant with Bonferroni correction.

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