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ORIGINAL PAPER

Social Impairments in Chromosome 22q11.2 Deletion Syndrome (22q11.2DS): Autism Spectrum Disorder or a Different Endophenotype?

Kathleen Angkustsiri · Beth Goodlin-Jones · Lesley Deprey · Khyati Brahmbhatt · Susan Harris · Tony J. Simon

Abstract High prevalence of autism spectrum disorders (ASD) has been reported in 22q11.2DS, although this has been based solely on parent report measures. This study describes the presence of ASD using a procedure more similar to that used in clinical practice by incorporating history (Social Communication Questionnaire) *AND* a standardized observation measure (Autism Diagnostic Observation Schedule) and suggests that ASD is not as common as previously reported in 22q11.2DS. Differences in methodology, along with comorbid conditions such as anxiety, likely contribute to false elevations in ASD prevalence and information from multiple sources should be included in the evaluation of ASD.

Keywords Autism · ASD · 22q11.2 deletion syndrome · Velocardiofacial syndrome

Introduction

Many children with chromosome 22q11.2 deletion syndrome (22q11.2DS), also known as Velocardiofacial or DiGeorge syndrome, have medical, psychiatric, and learning difficulties. Medical conditions associated with 22q11.2DS include congenital heart disease, immune difficulties, hypocalcemia, and velopharyngeal dysfunction, as well as many others. The neurocognitive impairments in individuals with 22q11.2DS include full scale IQ in the borderline to low average range (Moss et al. 1999). These averages are often misleading due to relative strengths in verbal abilities compared with nonverbal skills, although there is significant individual variability (Bearden et al. 2001; De Smedt et al. 2007; Simon 2007). There is a higher prevalence of childhood mental health disorders such as anxiety and attention deficit hyperactivity disorder (Jolin et al. 2012) in children with this syndrome.

Elevated (10–40 %) (Antshel et al. 2007; Fine et al. 2005; Niklasson et al. 2009; Vorstman et al. 2006) rates of autism spectrum disorders (ASD), including autism (autistic disorder) and Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS), have been reported. These figures are based on only a few studies relying on screening measures and parental report rather than the "gold-standard" diagnostic procedure that includes both the Autism Diagnostic Interview-Revised (ADI-R) based on parent report (Rutter et al. 2003b) and direct observation via the Autism Diagnostic Observation Schedule (ADOS) (Lord et al. 1999). According to the DSM-IV-TR (American Psychiatric Association 2000), autistic disorder is diagnosed by meeting a minimum number of impairments in the three domains of social interaction, communication, and restricted repetitive and stereotyped patterns of behavior, interests and activities. PDD-NOS is a less clearly defined condition where there are impairments in social interaction, communication, and/or restricted behaviors, but the criteria for autistic disorder are not fully met (American Psychiatric Association 2000).

Of the 3 studies reporting ASD based on the ADI-R parent report only, sample sizes range from 41 (Antshel

K. Angkustsiri
Department of Pediatrics, University of California at Davis Medical Center, Sacramento, CA, USA

K. Angkustsiri (✉) · B. Goodlin-Jones · L. Deprey · K. Brahmbhatt · S. Harris · T. J. Simon
MIND Institute, University of California at Davis, 2825 50th St., Sacramento, CA 95817, USA
e-mail: kathleen.angkustsiri@ucdmc.ucdavis.edu

B. Goodlin-Jones · K. Brahmbhatt · T. J. Simon
Department of Psychiatry and Behavioral Sciences, University of California at Davis, Sacramento, CA, USA

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et al. 2007) to 98 (Fine et al. 2005), with elevated ADI-R scores in at least 2 domains present in only 14 % of the largest sample (Fine et al. 2005). Elevated ADI-R scores in 2 or more domains were reported in 21 % (Antshel et al. 2007) and 45 % (Vorstman et al. 2006) of the other 2 studies. Other reports based on DSM-IV criteria and expert opinion also estimate ASD at 20–40 % (Niklasson et al. 2001, 2009), with autism present in only 3–5 % of participants. This is congruent with other studies noting a predominance of PDD-NOS over autistic disorder.

A clinical diagnosis of ASD requires both parent report/history as well as direct observation of the child's behavior (Charman and Baird 2002; Johnson and Myers 2007). In research studies, the true ascertainment of ASD diagnoses in 22q11.2DS is difficult due to sole reliance on parent report (ADI-R or screening measure) without inclusion of a standardized observation assessment such as the ADOS. To our knowledge, there are no known published reports of ASD in the 22q11.2DS literature using the ADOS and none reporting diagnoses based on *both* parental history and observation using standardized measures, such as the ADI-R and the ADOS. Since, in clinical practice, structured interviews such as the ADI-R are time-consuming, ASD-specific screening questionnaires such as the Social Communication Questionnaire (Rutter et al. 2003a) are often substituted for the ADI-R in the assessment of ASD (Charman and Baird 2002). In addition, general behavioral screeners, such as the Behavioral Assessment System for Children, 2nd edition Parent Rating Scales (BASC-2 PRS; Reynolds and Kamphaus 2006) have been used to identify behavioral profiles that are useful in differentiating high-functioning ASD from typically developing children, including elevated scores in atypicality, withdrawal, and developmental social disorders (Volker et al. 2010).

As stated above, the application of these screening instruments has led to reports of 20–40 % of children with 22q11.2DS being sufficiently impaired in terms of their social functioning that they meet superficial criteria for an ASD diagnosis. Many children who have 22q11.2DS exhibit considerable impairment in their social competence, especially during interactions with other children of their own age in naturalistic settings such as school or social gatherings. However, careful history and extended observation of these children provide clear evidence that the impairments tend to be context specific rather than pervasive in multiple environments which is the case in idiopathic ASD. We hypothesize that the social impairments displayed by many children with 22q11.2DS might better be explained by a combination of intellectual delays and affective dysregulation rather than autism spectrum disorders *per se*.

Clinical observations from our team suggest that children with 22q11.2DS often exhibit considerable social drive, empathy, and even a sense of humor. In fact, on measures of adaptive functioning such as the Adaptive Behavior Assessment System for Children-2nd edition (Harrison and Oakland 2003), children with 22q11.2DS often have relative strengths on the socialization subscale (unpublished data). They may thrive socially with children matched to their cognitive developmental stage rather than their chronological age. Because of this, a small study to administer standardized ASD diagnostic assessments was conducted on 29 participants consecutively recruited into a large, ongoing research study of neurocognitive function in children with 22q11.2DS. We hypothesized that few, if any, would meet strict criteria for autism or even milder forms of ASD when taking into account history and direct observation by research-reliable clinicians (Study 1). We also predicted that applying broad behavioral screening methods (here using the BASC-2) to our larger sample would result in similar estimates of ASD as the published reports summarized earlier (Study 2). Here we report the findings of these 2 studies and suggest some features of the cognitive and affective endophenotype of children with 22q11.2DS that might generate the set of behaviors that are superficially consistent with the appearance of ASD. This endophenotype is distinct from that of children with idiopathic ASD, which suggests differences in early intervention and treatment of the social impairments seen in 22q11.2DS compared with idiopathic ASD.

Methods

Participants

One hundred children with molecularly confirmed 22q11.2DS ages 7–14 (mean age 10.7 yrs, SD 2.1 yrs) participated in a larger study of neurocognitive function that included neuroimaging. Fifty-five percent were male. Mean WISC-IV (Wechsler 2003) Full-Scale IQ was 74.6 (SD 14.3). Subjects were recruited through the Cognitive Analysis and Brain Imaging Laboratory web page or the MIND Institute's Volunteer Research Registry. Participants were not selected from clinical or subspecialty visits related to 22q11.2DS. Instead, almost all families contacted our team asking to participate. Inclusion criteria included English speakers and availability of a parent or legal guardian who could provide consent and complete standardized measures of the child's behavior. Any children with contraindication to magnetic resonance imaging (pacemaker, etc.) were excluded due to the requirements for participation in the larger neurocognitive study. All procedures were approved by the Institutional Review Board at the University of California at Davis, and all participants (or their parents) provided informed consent prior to inclusion in the study.

Measures

Autism Diagnostic Observation Schedule (ADOS)

The ADOS (Lord et al. 1999) is a semi-structured standardized interactive assessment of social and communication behaviors that provides two cut-off scores, one for autism and another for the broader diagnosis of autism spectrum disorder/PDD-NOS. Module 1 is for children who are non-verbal or do not yet use phrase speech and Module 2 is for those who use phrase speech but are not verbally fluent. Module 3 is for verbally fluent children and Module 4 is for verbally fluent adolescents and adults. All three research personnel who administered the ADOS had attained research reliability. Individual items are scored from 0 to 3, with scores of "0" indicting typical responses (no abnormality related to autism) and higher scores representing increasingly abnormal behaviors. ADOS total scores fall under the classifications of "autism", "ASD", or "nonspectrum".

Social Communication Questionnaire (SCQ)

The SCQ (Rutter et al. 2003a) is a parent-completed 40-question ASD screening tool of communication and social functioning with similar content to the ADI-R. It can be used in children over the age of 4 years with a mental age greater than 2 years. A cut-off score of 15 or more differentiates ASD from other diagnoses (sensitivity 0.85, specificity 0.75) and the correlation between ADI-R total score and SCQ total score is 0.71 (Berument et al. 1999).

Behavioral Assessment System for Children, 2nd Edition Parent Rating Scales (BASC-2 PRS)

The BASC-2 (Reynolds and Kamphaus 2006) is a comprehensive rating scale that evaluates clinical and adaptive aspects of behavior. The Parent Rating Scale (PRS) is a 134 (child form) −160 (adolescent form) question assessment of a child's behaviors. Standardized T scores (mean 50; SD 10) are normed with higher scores on clinical scales representing more problematic behaviors, with T scores between 60 and 69 considered "at-risk" and T scores ≥70 considered "clinically significant". For the adaptive scales, lower scores are more problematic, with T scores between 31 and 40 considered "at-risk" and T scores ≤40 considered "clinically significant". We focus on the scales measuring atypicality, withdrawal, and Developmental Social Disorders, with sensitivities ranging from 0.87 to 0.98 and specificities of 0.9–0.95 in differentiating high-functioning ASD from typically developing children (Volker et al. 2010).

Study 1: ASD diagnosis based on clinical diagnostic criteria

ASD diagnosis based on both positive SCQ *and* ADOS scores was calculated similarly to the procedure often used in clinical practice.

1. The ADOS was administered to 29 participants (16 boys and 13 girls) consecutively enrolled in the larger research study for 28 months. One child was evaluated with Module 2, 22 with Module 3, and 5 received Module 4. The number of children scoring above the ASD and autism cut-off is reported.
2. A cut-off score of 15 on the SCQ was used to indicate concern for symptoms of an autism spectrum disorder.
3. Areas of relative strengths and weaknesses in ADOS performance are reported for children scoring above the ASD or autism cut-off (Group A) and those scoring in the unaffected (below ASD cut-off) range (Group B).

Study 2: ASD diagnosis based on parental report questionnaire

The BASC-2 PRS was routinely collected as part of the larger neurocognitive study and scores for the 29 participants analyzed in Study 1 were combined with scores from participants that continued to enroll in the larger study (but did not receive ADOS testing) for a total of 100 participants. Mean age was 10.7 ± 2.4 years and 55 % were male, just as it was for the smaller group of 29. WISC-IV FSIQ was 75.6 ± 13.1, also similar to the subgroup analyzed in Study 1 (Table 1). The percentage of children with scores ≥60 on the scales identified by Volker et al. (2010) (atypicality, withdrawal, and Developmental Social Disorders) are reported for all 100 participants.

Analysis

Frequencies/percentages of individuals with scores greater than the cut-off scores specified above are reported.

Results

Study 1

Of the 29 children with ADOS scores, five (18 %) scored in the elevated range on the ADOS. One (3 %) individual scored above the autism cut-off and 4 (15 %) were above the ASD cut-off but below the autism cut-off. Four (80 %) of these 5 individuals with elevated ADOS scores had elevated BASC-2 PRS anxiety and/or somatization scores

Table 1 Participant characteristics

	Study 1 (n = 29)	Study 2 (n = 100)
Mean age, yrs (SD)	10.7 (2.1)	10.7 (2.4)
Percentage male	55 %	55 %
WISC-IV FSIQ (SD)	74.6 (14.3)	75.6 (13.1)

Table 2 Children scoring above cut-offs on the SCQ, ADOS, and both SCQ + ADOS (Study 1)

	Positive		Total
SCQ	2 (7 %)		2 (7 %)
ADOS	4 (15 %) ASD	1 (3 %) Autism	5 (18 %)
SCQ + ADOS	0		0

as well. Only 2 (7 %) of the 29 had SCQ scores above the cut-off of 15 (Table 2). No child had *both* SCQ and ADOS scores in the elevated range.

Relative Strengths and Weaknesses

Children with 22q11.2DS and elevated ADOS scores (Group A) were compared to children with ADOS scores in the typical range (Group B) (Table 3). At least 75 % of Group B scored "0" or not impaired on all individual items comprising the ADOS domains of Social Interaction and Communication with the exception of "Insight" (12/24; 50 % not impaired) and "Facial Expressions" (16/24; 67 % not impaired). Both groups had typical scores in the "Amount of Reciprocal Social Communication", which is part of the Social Interaction Domain. It captures how frequently the child used verbal and non-verbal behaviors for social interchange, commenting, etc. Scores of "0" are considered unimpaired, and 60 % (3/5) of children in Group A and 88 % (21/24) of children in Group B scored "0". Both groups also had weaknesses in "Insight" (0 % Group A and 50 % Group B scored "0") and "Imagination" (20 % of Group A and 54 % Group B scored "0"). The Communication domain, specifically the items "Conversation" and "Gestures", was a relative weakness in Group A, with no child scoring "0" in Conversation (back and forth flow of conversation) and only 1 scoring "0" in "Gestures". On the other hand, simple communication was a relative strength in Group B, with 19 (95 %) scoring "0" for "Reporting of Events".

Study 2

1. *BASC-2 PRS*: Forty-four percent of 100 children with 22q11.2DS screened positive based on an atypicality T score ≥60, 51 % had elevated withdrawal T scores (≥60), and 68 % had elevated T scores (≥60) on the Developmental Social Disorders scale.

Table 3 Relative strengths and weaknesses on ADOS items of children with elevated ADOS scores compared with normal ADOS scores

	Strengths	Weaknesses
Group A (+ADOS)	Social:	Communication:
	Social interaction	Conversation
		Gestures
		Insight
		Imagination
Group B (−ADOS)	Social:	
	Social interaction	
	Communication:	Insight
	Reporting	Imagination

Discussion

As far as we know, this is the first study to report ASD diagnosis in 22q based on the use of a gold standard approach to diagnosis, i.e. using a combination of the ADOS and the SCQ. While it is important to note that research evaluations are not substitutes for clinical evaluations, it is useful to examine the yield of ASD diagnoses based on criteria that more closely resemble what is used in clinical practice (both directly administered assessment and parental history). In this study, not one child met strict diagnostic criteria for ASD using results of both the ADOS and SCQ.

Given the similar prevalence rates (44–68 %) we found based on BASC-PRS, it seems that the difference in diagnostic methodology is the primary reason for the discrepancy between the percentage of children meeting criteria for an ASD diagnosis in our study and the prevalence of ASD in the 22q11.2DS literature for children in this age range (Vorstman et al. 2006; Niklasson et al. 2001, 2009). All of the papers published to date use the ADI-R alone as a proxy for ASD diagnosis, which tends to over-estimate ASD compared with more comprehensive clinical evaluations that also include behavioral observation. In addition, our clinical experience (which matches the informal reports of many of our colleagues) is that there are qualitative differences in nature of social impairments in 22q11.2DS compared with idiopathic ASD (Eliez 2007; McCabe et al. 2013; Kates et al. 2007).

The results suggest that different methodologies produce different diagnostic outcomes. Two questions need to be addressed. (1) Are there are really widespread significant social impairments in children with 22q11.2DS and (2) If there are and our data can be replicated, indicating that these are really not ASD, then what is the set of behaviors (that can be explained in more dimensional rather than diagnostic terms, as set out in the goal of the NIMH

Research Domain Criteria initiative) that explain WHY these children generate behaviors that are so often mistaken for ASD? The importance of understanding this is clear because this kind of explanation, if it can be developed, will point to specific targets for intervention that are appropriate and effective for children with 22q11.2DS where interventions for ASD might well not be.

There is no doubt that a very large proportion of children with 22q11.2DS exhibit impairments in social behavior, especially with their age-matched peer group and in the absence of supportive others such as parents and siblings. Indeed, the impression of many professionals who work closely with children with 22q11.2DS is that these social impairments in 22q11.2DS differ and are not as pervasive as those in children with idiopathic autism (Eliez 2007). Such professionals, including our team, frequently observe a high motivation to engage socially. Parents report that their children with 22q11.2DS engage frequently and effectively with younger children (more suited to their intellectual rather than their chronological age) or with adults who are more flexible in their social interactions. During research assessments unrelated to ASD diagnosis our team frequently notes a strong sense of empathy, sense of humor and other complex social skills. This suggests that social impairments in young children with 22q11.2DS are penetrant but are highly context dependent and not indicative of general social avoidance. A socioemotional training program, Vis A Vis, improved ASD-like behaviors, including focusing attention particularly to the eyes, in children with Intellectual Disability (Glaser et al. 2012). It has been reported to be equally effective for children with 22q11.2DS (Glaser et al. 2010).

ASD-like behaviors exist in 22q11.2DS and are sufficiently similar at the symptom level to be considered by many to be ASD, yet many children with the deletion appear socially competent in some situations. We are interested in the set of functional domains that can be measured dimensionally (to account for variation) that might explain why so many young children with 22q11.2DS exhibit age-appropriate social competence in some situations and not others. While this will be the subject of future hypothesis-driven research, we speculate that the social impairments in children with 22q11.2DS can often be explained by robust characteristics of the phenotype reported in children with 22q11.2DS. We propose that the social impairments in children with 22q11.2DS and idiopathic ASD are manifestations of different functional profiles.

Reciprocal Social Interaction

Similar to children with idiopathic ASD, children with 22q11.2DS have difficulties with social competency, with weaknesses in perspective taking, theory of mind (ToM) (Ho et al. 2012; Jalbrzikowski et al. 2012), and non-verbal communication. Many of these difficulties may be explained by multiple factors, including developmental delay, with conceptual immaturity relative to peers. Anxiety, along with problems sustaining attention and processing emotions, are other contributing factors. While ToM and understanding false beliefs are impaired in children with 22q11.2DS (Jalbrzikowski et al. 2012), this seems to improve with age, as adults with 22q11.2DS are relatively unimpaired in ToM tests, although other weaknesses (such as attention) persist (Chow et al. 2006). Borderline cognitive abilities lead to ineffective social interactions because of limitations in the ability to attribute appropriate mental states (Ho et al. 2012). This also leads to problems understanding non-concrete, indirect, pragmatic speech such as idioms, metaphors and irony. Together these cognitive weaknesses may account for the ineffective communication with age-matched peers. This reduced social competence of children with 22q11.2DS is, in turn, likely to result in exclusion or rejection from social interactions, if not outright teasing or bullying, of children with 22q11.2DS by age-matched peers. The effect of continued exposure to such situations is likely to induce quite reasonable anxiety and withdrawal from social interaction opportunities. Indeed, emotional problems, which are quite prevalent in 22q11.2DS, have been related to social competence (Ho et al. 2012). These factors and the fear they engender, along with other visual processing impairments (Campbell et al. 2010; Glaser et al. 2007) may result in gaze avoidance, which is also superficially consistent with the ASD phenotype.

Difficulties in attention regulation may also lead to social impairments. Individuals with ASD and 22q11.2DS tend to have a shared underlying deficit in attention shifting (Barneveld et al. 2011). Problems with joint/sharing attention is present in individuals with 22q11.2DS, regardless of ASD diagnosis (Kates et al. 2007). Other explanations for problems with social interaction can be attributed to difficulties in emotion recognition and facial processing in 22q11.2DS (Campbell et al. 2011).

Communication

Verbal abilities are often stronger than non-verbal cognition in 22q11.2DS; however, children with 22q11.2DS have significant communication problems (Barneveld et al. 2011), particularly with more complex and abstract language. Concrete language and thinking is characteristic of 22q11.2DS, and this observation is supported by the weaknesses in Insight and Imagination on the ADOS for all individuals with 22q11.2DS, not just the ones with elevated overall ADOS scores. On the ADI-R, individuals with

22q11.2DS scored worse on the communication, but not social interaction or repetitive interest, domain (Esterberg et al. 2013). Our results also support that communication is an area of weakness in 22q11.2DS, especially for those with ADOS scores in the ASD and autism range (group A). Difficulties with communication have been noted in 22q11.2DS, including poverty of speech and content (Rumsey et al. 1986; Dykens et al. 1991), which in turn, affect conversation and reciprocity. These factors, along with anxiety, and the well-documented impairments in inhibitory and executive functioning as well as time perception (Simon 2008), are likely to lead to repetition, perseveration, and restricted conversation.

Repetitive and Restricted Behavior, Interests

Many children with 22q11.2DS frequently manifest perseverative and repetitive behaviors, which overlap with the 3rd domain in ASD of repetitive and restricted behaviors and interests. However, the causes for those behaviors in the two disorders may be quite different. Anxiety, along with limited verbal abilities, contributes to repetitive and restricted conversation, as children rely on a few familiar themes to compensate for poverty of speech. Poor cognitive control also contributes to the obsessive compulsive behaviors commonly seen in 22q11.2DS, as difficulty with attention shifting leads to repetitive behaviors. Anxiety and ADHD are common comorbid conditions with ASD but may also be confused with symptoms of ASD. For example, the most common non-ASD diagnoses in children classified as ASD by the ADOS were anxiety and ADHD (Murray et al. 2010).

Comparison of children with idiopathic ASD versus those with 22q11.2DS and a concomitant diagnosis of ASD suggests some differences (Kates et al. 2007). Children with 22q11.2DS and ASD have better communication and socioemotional reciprocity compared to children with ASD alone (Kates et al. 2007). The same study found that nonverbal social interaction and peer relationships were not impaired in children with 22q11.2DS (and no ASD) (Kates et al. 2007). Our ADOS results and clinical impression support this, as social interaction is a relative strength in 22q11.2DS. In addition, the developmental trajectory differs in idiopathic ASD, where nonverbal skills are often better than verbal skills. In 22q11.2DS, there are early language difficulties, but later on, verbal abilities are stronger than non-verbal abilities (Eliez 2007).

Our study has some limitations which should be addressed in future studies. One issue is the limited age range of the subjects (7–14 years). It is possible that younger children with 22q11.2DS, who generally have more significant language delays, are more difficult to differentiate from idiopathic ASD. The subset of children studied participated in a larger study of neurocognition that requires MRI imaging, so perhaps our sample included higher functioning children with 22q11.2DS, yet this seems unlikely given the participants' wide range of cognitive function, with mean FSIQ of 75, which is the same as that reported in the 22q11.2DS literature (Moss et al. 1999). ADOS testing was only performed on 29 participants, and a larger study is needed to replicate these findings. We did not perform detailed language assessment, and future studies should include more detailed investigation of language if communication difficulties are a central part of the diagnostic confusion between ASD and 22q11.2DS. Teacher reports of behavior were not available for analysis, and this is another limitation. It is important to mention that while this study is more similar to the diagnostic procedure implemented in clinical practice, these assessments were performed in the context of a research study and are not a substitute for a clinical evaluation.

The true prevalence of ASD in 22q11.2DS is important. This study suggests that it is truly lower than the generally accepted prevalence of 20–40 % and has implications for differences in treatment and intervention. The behavioral interventions for treatment of ASD, such as Applied Behavior Analysis (ABA) and others, are resource intense and may not be appropriate for children with 22q11.2DS if there is an underlying difference between ASD and 22q11.2DS. Some forms of ABA are highly structured and repetitive, and are effective for the treatment of ASD (National Research Council 2001) but may lead to rigid and/or oppositional behaviors if no ASD is present. Another relevant issue is characterization of the subgroup of children with 22q11.2DS who present with ASD symptoms. Further research is needed to identify if these children are prodromal or at higher risk for psychosis and schizophrenia, given the already increased risk due to the 22q11.2 deletion. Theory of Mind performance predicts positive symptoms on the Structured Interview for Prodromal Symptoms (SIPS) in adolescents and young adults with 22q11.2DS (Jalbrzikowski et al. 2012) and social cognition may be an intermediate marker of psychosis vulnerability (Penn et al. 2008).

In conclusion, based on best practice assessment, ASD is not as common as previously reported in 22q11.2DS and highlights the importance of integrating multiple sources of information when considering an ASD diagnosis. Elevated scores on single measures are not sufficient for a clinical diagnosis of ASD, and this study is the first to use the ADOS in addition to parent report, in the evaluation of ASD symptoms in 22q11.2DS. All children with 22q11.2DS had strengths in social interaction and weaknesses in imagination and insight on the ADOS. Children with elevated ADOS scores tended to have relative weaknesses in communication. Further investigation is

warranted to explain how the social impairments, difficulty with communication, and repetitive behaviors in children with 22q11.2DS are similar and different from ASD. Comorbid conditions such as anxiety and cognitive impairments likely contribute to false elevations on individual ASD measures, and future research should proceed with both components to ascertain accurate levels of ASD in 22q11.DS populations. This would directly impact treatment recommendations and patient care procedures.

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Conflict of interest The authors declare that they have no conflict of interest related to this research study. Dr. Angkustsiri is involved in clinical trials in autism and fragile X syndrome for Roche, Curemark, Forest Pharmaceuticals, Seaside Therapeutics, and Novartis. Dr. Brahmbhatt receives grant funding from Shire. These authors have not taken any personal salary from any pharmaceutical company.

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