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SYMPTOMS OF AUTISM SPECTRUM DISORDER IN CHILDREN WITH DOWN SYNDROME OR WILLIAMS SNYDROME

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Symptoms of Autism Spectrum Disorder in Children with Down Syndrome or Williams Syndrome

Abstract

Research suggests that individuals with a Williams syndrome (WS) or Down syndrome (DS) diagnosis display an increased prevalence of autism spectrum disorder (ASD) when compared to the general population. This study aimed to examine characteristics of ASD in a group of children with DS or WS. Results suggest that children with DS and WS exhibit higher levels of autism symptoms than the general population, particularly in the area of unusual behaviors, and that these elevations are not solely due to deficits in adaptive behavior. There are many possible explanations for these elevations, such as issues with measurement, etiological overlap, or similar behavioral phenotypes. More research is needed to further our understanding of the overlap of ASD symptoms in these populations.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social communication and restricted, repetitive patterns of behavior (American Psychiatric Association, 2013). Population based studies suggest that prevalence of ASD is 1 in 59 (1.69%) in the general population (Baio et al., 2018). Although the exact cause of autism remains unknown, research examining the etiology of ASD has led to the conclusion that there is a significant genetic component (Geschwind, 2013). Indeed, results of twin studies find a higher presence of autism in monozygotic when compared to dizygotic twins, which supports a genetic etiology (Geschwind, 2013). Due to this, a large focus of research lies in investigating the specific genetic mechanisms of the disorder. One method of investigating genetic underpinnings of ASD lies in examining disorders that are associated with increased risk of ASD, including those with distinct genetic causes. For example, research investigating Fragile X syndrome, an X-linked disorder associated with an increase in symptoms of autism, (Reddy, 2005) has increased knowledge of the genetic underpinnings of both disorders (Miles, 2011). As the characteristics of autism related to Fragile X syndrome are markedly similar to the characteristics of autism stemming from an unknown etiology, it is the hope of researchers that further investigation into the genetic bases of autism and Fragile X will lead to increased understanding of the molecular pathways leading to all forms of autism (García□Nonell et al., 2008). Indeed, due to its etiological heterogeneity, efforts to discover distinct genetic causes of ASD proves challenging, but research looking at genetic disorders with a high comorbidity of ASD demonstrates potential for discovering biological targets for intervention, as well as insight into the pathophysiology of the disorder. In the current study, we focused on children with Down

syndrome and Williams syndrome, two disorders with distinct genetic causes that display increased prevalence of ASD, despite seeming dissimilar phenotypically.

Down Syndrome and Williams Syndrome

Down syndrome (DS) and Williams syndrome (WS) are disorders with distinct genetic etiologies. Down syndrome is caused by partial or full duplication of Chromosome 21 material, and Williams syndrome is caused by a deletion of 26-28 genes on the seventh chromosome. Recent investigations of individuals with DS and WS show increased prevalence of ASD (Klein-Tasman, Mervis, Lord, & Phillips, 2007; Lincoln, Searcy, Jones, & Lord, 2007; Reilly, 2010). In regard to DS, research demonstrates a high rate of ASD, with prevalence estimates ranging from 5% to 39% (Reilly, 2010). The wide variety of prevalence rates can likely be attributed to the variety of methods employed to ascertain prevalence. Indeed, results of these studies have likely been influenced by the sample size, age range of the sample, and the instruments, informants, and diagnostic criteria employed (Kent, Perry, & Evans, 1998) For example, not all studies used gold-standard diagnostic tools to determine ASD comorbidity. However, studies aiming to use gold-standard diagnostic tools do find a higher prevalence than reported in the general population. A study by DiGuiseppi and colleagues (2010) examining a geographically based sample of children with Down syndrome with comprehensive diagnostic protocols and rigorous testing procedures found that the prevalence of ASD in children with Down syndrome is 17 to 20 times higher than the estimated ASD prevalence in the general population at the time (DiGuiseppi et al., 2010). Additionally, children with DS show elevated scores on a measure of ASD symptoms (Channell et al., 2015), often exhibit obsessive-compulsive behaviors that are salient enough to raise questions about an ASD diagnosis (Kent et al., 1999), and demonstrate a high frequency of restricted/repetitive behaviors (Evans & Gray, 2000). Children with DS may

also meet partial criteria for ASD due to repetitive behaviors and limited play but may not meet full criteria due to a lack of deficits in social relatedness (Hepburn et al., 2007). Although no population-based studies of ASD prevalence among individuals with WS exist, studies completing gold standard autism diagnostic evaluations with children with WS find that the rate of ASD among individuals with WS is higher than the population prevalence (Klein-Tasman et al., 2007; Klein-Tasman, van der Fluit, & Mervis, 2018; Lincoln et al., 2007). Additionally, individuals with WS also display elevated scores on the Social Responsiveness Scale (SRS; Constantino & Gruber, 2005), a questionnaire that is used to assess abilities and deficits in social reciprocity (Constantino et al., 2003).

Not only is it important to further investigate the overlap of ASD symptoms in DS and WS, but research is also warranted regarding the role of developmental level in ASD symptom severity. Indeed, a low developmental level can lead to false positives on early modules of the ADOS (Bishop et al., 2008), and research suggests that severity of intellectual disability is positively correlated with rate of ASD (La Malfa, Lassi, Bertelli, Salvini, & Placidi, 2004), such that individuals with lower cognitive functioning have higher rates of ASD diagnosis. Intellectual disability is diagnosed when a person displays deficits in both cognitive functioning and adaptive behavior; this study will use adaptive behavior as a proxy for developmental level. The American Association on Intellectual and Developmental Disabilities (AAIDD) defines adaptive behavior as the collection of conceptual, social, and practical skills that all people learn in order to function in their daily lives, and research suggests that that there is a negative correlation between adaptive behavior scores and symptoms of autism (Eaves et al., 2006, Witwer & Lecavalier, 2007). Although ASD, DS, and WS exhibit their own unique adaptive behavior profiles, research demonstrates that children with a genetic condition and a comorbid

ASD diagnosis (in this case DS) have significantly lower adaptive behavior scores than children with DS alone (Molloy et al., 2008). Indeed, research suggests that the adaptive behavior profile for people with ASD typically includes a relative strength in daily living skills, lesser delays in communication, and the greatest delays in socialization (Bölte & Poustka, 2002). On the contrary, people with WS typically demonstrate the largest relative strength in socialization, with communication being a strength as well, and typically have lower daily living domain scores (Greer et al., 1997). Although most studies of people with DS have found socialization to be a relative strength in comparison to communication, research on the daily living skills abilities of people with DS has been mixed (Dolva, Coster, & Lilja, 2004; Dykens, Hodapp, & Evans, 2006; Leonard, Msall, Bower, Tremont, & Leonard, 2002). Therefore, additional research that considers the relationship between adaptive behavior and ASD symptoms in people with DS and WS is warranted.

In the current study, we aimed to investigate overlap of ASD symptoms in school-aged children with two genetic conditions known to have increased prevalence of ASD, Down syndrome and Williams syndrome. We used an online survey platform to compare groups of individuals with ASD, DS, and WS. An ASD group was chosen as comparison in order to better understand areas of symptom overlap. In addition, all groups could be compared to the population norming data from the study measures as a proxy for a typically developing group. Parents completed a dimensional measure of ASD symptoms (Autism Spectrum Rating Scales; ASRS) to examine symptom profiles in more detail, and a screening measure (Social Communication Questionnaire; SCQ) to examine how many children in these groups screen positive for ASD. These measures were chosen as although the SCQ provides valuable information regarding the presence of autism symptoms, as it is only a yes/no questionnaire it

does not provide information about symptom frequency or intensity. We also investigated adaptive behavior profiles using the Adaptive Behavior Assessment System, Third Edition (ABAS-3; Harrison & Oakland, 2015a). This research may shed light on phenotypic overlap between ASD and these known genetic conditions, and the profile of ASD symptoms displayed on the ASRS within each group. This, in turn, could lead to new insights on how ASD manifests in both Down syndrome and Williams syndrome, and will develop future directions for new research in how to best screen, diagnose, and create interventions for these groups of individuals.

Methods

Participants

Recruitment. Participants in this study were contacted via email. Specifically, primary caregivers of individuals with Down syndrome were contacted via the National Institute of Health resource DS-Connect®. Primary caregivers of individuals with WS were contacted via the Williams Syndrome Association research registry (www.williams-syndrome.org/registry); owned by the WSA, as well as at the Williams Syndrome National Conference in Columbus, Ohio, July 4-8, 2016. Finally, primary caregivers of individuals with ASD were contacted via a clinic-based research registry, and through a Qualtrics recruitment pool. As an incentive to participate, survey respondents could elect to be placed in a drawing to receive a $25 gift card. The exception to this was the group recruited through Qualtrics, as they had a prearranged compensation agreement.

Inclusion criteria. To be eligible for the study, primary caregivers had to have a child, ages 6-18 years, with a diagnosis of ASD, Down syndrome, or Williams syndrome. Primary caregivers also had to be able to complete the survey in English, as the survey was only offered

in English. As this study is solely survey based, confirmation of diagnosis relied on parental report.

Exclusion criteria. For participants with a child with ASD, the individuals with ASD were required to screen positive for ASD on the Social Communication Questionnaire (SCQ) to be eligible for the study. Additionally, parents or primary caregivers of individuals with DS or WS had to report that their child had a genetic confirmation of their diagnosis. Additional subjects were also excluded from specific analyses due to incomplete data.

A total of 168 participants (ASD= 44, DS= 78, WS=46) participated in the survey. We excluded a total of 8 cases from the analyses, due to being in the ASD group and not screening positive on the SCQ (n=5) or being in the DS or WS group and not having genetic confirmation (DS=2, WS=1). Additionally, participant data was lost due to incomplete data or participant dropout. Of the 168 participants who began the study, 144 eligible participants completed all study measures (attrition rate of 14.3%)**.** A majority of the survey respondents in all groups identified their race as White (ASD=89.7%, DS=93.4% WS=93.3%) and their ethnicity as not Hispanic or Latino (ASD=82.1%, DS=96.1% WS=91.1%). English was the primary language spoken in the home for all groups (ASD=100.0%, DS=97.4% WS=91.1%). A Fisher's exact test revealed no significant differences between groups in relation to race (p=.34), ethnicity (p=.05), and primary language spoken in the home (p=.36). Although the majority of respondent in all groups were mothers (ASD=64.1%, DS=92.1%, WS=80.0%), a Fisher's exact test revealed this difference to be statistically significant (p<.05).

The average age of participants varied across groups, with the respondents in the DS group (M=47.91 years, SD=5.31) being significantly older than the individuals in both the ASD (M=42.97 years, SD=10.04 years) and WS groups (M=42.82 years, SD=7.12 years),

$F(2,156)=9.49$, $p< .001$, $\eta_p^2=.11$). A total of five of the 76 included respondents in the DS group (6.6%), and four of the 45 included respondents in the WS group (8.9%) indicated that their child had a comorbid ASD diagnosis. A summary of respondent demographics is displayed in Table 1.

In regard to the target children, there was a significant difference in sex, with a higher percentage of males in the ASD group (74.4%) than in the DS (38.2%) and WS groups (60.0%), $\chi^2(1, N = 160) = 14.96$ p <.05, $V=.31$) This difference was expected due to the known increased prevalence of ASD in boys compared to girls. Similar to respondent characteristics, a majority of participants noted their child's race as white (ASD=84.6%, DS=93.4%, WS=93.3%), and their ethnicity as not Hispanic or Latino (ASD=87.2%, DS=96.1%, WS=88.9%). A Fisher's exact test revealed differences to be non-significant both in regard to race ($p=.24$) and ethnicity ($p=.15$). Child age was not significantly different across groups. A summary of child demographics can be found in Table 2.

Procedures

The Institutional Review Board at [BLINDED FOR REVIEW] approved this study. Potential study participants were contacted via email. The survey consisted of demographic questions, and three assessments: the Autism Spectrum Rating Scales, the Social Communication Questionnaire, and the Adaptive Behavior Assessment System, Third Edition. Informed consent was obtained from all individual participants included in the study, with participants providing written consent.

Measures

Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003). The SCQ is a 40-item yes/no ASD screening questionnaire that is filled out by the child's parent or primary caregiver. This test can be used in children over the age of four, with a mental age over

2 years, and assesses the symptoms corresponding with autism spectrum disorder. The SCQ was developed from a current diagnostic interview, the Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 2005). When assessed for validity, 85% of the SCQ items significantly differentiated ASD from other diagnoses (Berument et al., 1999).

Autism Spectrum Rating Scales (ASRS; Goldstein & Naglieri, 2009). The ASRS are designed to assess behaviors associated with ASD in children aged 2-18. The full-length scale for ages 6-18 yields a total score, which is comprised of the three ASRS scales (Social/Communication, Unusual Behaviors, and Self-Regulation), as well as a DSM-IV-TR scale, and eight treatment scales. This specific form has exhibited strong reliability, with Total Score weighted average internal consistency being .97, and ASRS scales reliability ranging from .92-.95. Strong construct validity for this assessment is also evidenced by the three-factor structure found, corresponding to the three ASRS scales. Reliability of our current sample was α =.96.

Adaptive Behavior Assessment System, third edition (ABAS-3; Harrison & Oakland, 2015a). We used the ABAS-3 parent/primary caregiver form (ages 5-21) in this study. The ABAS-3 gives a General Adaptive Composite score, comprised of conceptual, social, and practical domain scores. These domains are further broken down into a total of 9 skill sets, which are as follows: communication, community use, functional academics, home-living, health and safety, leisure, self-care, self-direction, and social. Reliability of the ABAS-3 is strong, with coefficient alphas for the GAC ranging from .96-.99 (Harrison & Oakland, 2015b). The ABAS-3 also demonstrates good construct validity, evidenced by its moderate to strong correlations (average of .66) with the Vineland Adaptive Behavior Rating Scales, Second Edition.

Analyses

First, the distribution of ASD symptoms across the three groups (DS, WS, ASD) was examined using ANOVAS to probe for group differences in total scores on the ASRS and SCQ. The relationship between the two ASD symptom measures was further probed in both children with DS and WS by running two separate two-way ANOVAs to examine whether individuals who screened positive for ASD on the SCQ demonstrated elevated ASRS scores compared to individuals who screened negative for ASD on the SCQ. The role of adaptive behavior was examined by using regression to test the predictive value of group membership (DS, WS, ASD) on ASRS scores after controlling for demographic factors and adaptive behavior. Finally, a series of repeated measures ANOVAS were used to probe for differences on the individual subscales and treatment scales of the ASRS among individuals with DS or WS who screened negative on the SCQ, those who screened positive on the SCQ, and the ASD group to suggest which particular ASD-related behavioral characteristics might best characterize individuals with DS/WS and elevated ASD symptoms.

Results

ASD Symptoms in DS and WS

Seventeen out of the seventy-six individuals (22.4%) in the DS group who completed the SCQ scored above the cut off score of 15 on the *Social Communication Questionnaire* (SCQ), thus screening positive, and twenty out of the thirty-seven individuals with WS who completed the SCQ (54.1%) screened positive. Importantly, all children with DS or WS who had a parent reported comorbid ASD diagnosis screened positive on the SCQ. A Fisher's exact test revealed both of these proportions to be significantly different from the 4.4% general population screen positive rate reported in previous research (Chandler et al., 2007; *ps*<.001). Additionally, one-sample *t*-tests indicated that the average total score on the ASRS was significantly different from

the population normed mean ASRS score of 50 in the DS group (M= 58.96, SD=7.79), t= 10.03, p< .001, the WS group (M=65.24, SD=6.03), t=15.57, p<.001, and the ASD group (M= 71.74, SD=5.04), t= 26.97, p< .001. A one-way ANOVA revealed group differences as well, as the ASD, DS, and WS groups differed, on average, in their ASRS total scores, $F(2,150)=47.21$, p< .001, $\eta_p^2=.39$. Pairwise comparisons using the Games-Howell method to correct for multiple tests revealed that the ASD group had a higher mean ASRS total score than both the DS group (p<.001) and the WS group (p<.001). Additionally, the WS group had a higher mean ASRS total score than the DS group (p<.001). Descriptive statistics of ASRS scales are displayed in Table 3.

Relationship between ASRS and SCQ scores

Results of a two-way ANOVA revealed a significant main effect of screening positive on the SCQ on mean ASRS total scores, $F(1,108)=41.01$, p<.001, $\eta_p^2=.28$). Those who screened positive on the SCQ had a higher mean ASRS total score (M=67.86, SD=6.17) than those who screened negative (M=57.88, SD=6.44). In the DS group, results indicated that individuals who screened negative on the SCQ (M = 56.71, SD = 6.33) and those who screened positive (M = 66.76, SD = 7.43) differed, on average, on their ASRS total scores, $F(1,74)=30.68$, p<.001, $\eta_p^2=.29$). Similarly, those with WS who screened negative on the SCQ (M = 61.94, SD = 5.07) and those who screened positive (M = 68.84, SD = 4.77) also differed, on average, on their ASRS total scores [$F(1,34)=17.73$, p<.001, $\eta_p^2=.34$]. Importantly, elevations in ASRS scores were also seen in children who did not screen positive on the SCQ, as t-tests indicated that the average total score on the ASRS was significantly different from the population normed mean ASRS score of 50 in the DS screen negative group (M= 56.71, SD=6.34), t= 8.13, p< .001 and the WS screen negative group (M=61.94, SD=5.07), t=9.72, p<.001).

Role of Adaptive Behavior

Descriptive statistics of ABAS-3 scales are displayed in Table 3. Results of a Pearson correlation revealed a significant weak negative correlation between General Adaptive Composite Scores (GAC) and ASRS total scores, $r(144) = -.30$, $p<.001$. At the group level, there was a significant moderate negative correlation between GAC and ASRS total scores in the DS group, $r(73) = -.49$, $p<.001$, but there were no significant correlations in the WS or ASD group. A one-way ANOVA revealed significant differences between the DS-screen positive and DS screen negative groups, $F(1,71)=23.38$, $p< .001$, $\eta_p^2=.25$, as well as between the WS-screen positive and WS-screen negative groups $F(1,30)=6.14$, $p< .05$, $\eta_p^2=.17$, on GAC scores, such that the screen positive groups had lower GAC scores than the screen negative groups. To test the hypothesis that group membership would predict ASRS total scores, when controlling for age, sex, and adaptive behavior (as measured by the General Adaptive Composite on the ABAS-3), we performed a multiple regression analysis. Results of the analysis revealed that when controlling for sex, age, and GAC total scores, individuals with ASD had significantly higher ASRS total scores, on average, than individuals with DS, $R = 0.70$, β=-.75, $p < .001$, or WS, $R = .70$, β=-.34, $p < .001$[1]. These results are displayed in Table 4.

ASRS Analyses

As one of the secondary aims of this study was to use results of the ASRS to examine the ASD "profiles" both the WS and DS group, we used a repeated measures ANOVA to investigate differences within groups on the three ASRS subscales (Self-Regulation, Social/Communication, and Unusual Behaviors). After applying a Greenhouse-Geisser correction for a violation for the assumption of sphericity, results indicated a significant main effect among the subscales on the ASRS both within the DS, $F(1.73, 130.88)=25.64$; $p<.001$; $\eta_p^2=.26$, and WS, $F(1.47,$

[1] This remained significant even after removing individuals that had comorbid diagnoses of ASD and DS/WS

54.50)=5.28; $p<.05$; $\eta_p^2=.13$) groups. Following a Bonferroni correction, pairwise comparisons for the DS group revealed a significant difference between the Unusual Behaviors subscale (M = 61.79, SD = 8.23), and the Social Communication (M = 55.93, SD = 9.26) and Self-Regulation (M = 54.88, SD = 7.57) subscales (corrected p's<.001). Within the WS group, pairwise comparisons indicated a significant difference between the Unusual Behaviors (M = 65.53, SD = 6.42) and Social Communication (M = 60.84, SD = 8.69) subscales (corrected p's<.05). As a comparison, we also examined the ASRS profiles of the ASD group. After applying a Greenhouse-Geisser correction for a violation for the assumption of sphericity, results indicated a significant main effect among the subscales on the ASRS $F(1.83, 69.37)=5.31$; $p<.05$; $\eta_p^2=.12$ group. Following a Bonferroni correction, pairwise comparisons for revealed a significant difference between the Social Communication (M = 68.74, SD = 6.94) and Self-Regulation (M = 63.85, SD = 5.45) subscales (corrected p's<.05).

To further examine symptom clusters that may best distinguish those with DS or WS and significant ASD symptoms from those with fewer ASD symptoms, we compared the screen positive, screen negative, and ASD groups across the eight treatment subscales of the ASRS (peer socialization, adult socialization, social emotional reciprocity, atypical language, stereotypy, behavioral rigidity, sensory sensitivity, and attention) using a one-way ANOVA analysis.

For children with DS, when comparing the DS screen positive, DS screen negative, and ASD groups, results indicated a significant main effect among the three groups on all ASRS treatment scales (p's<.05*)*. Pairwise comparisons using a Bonferroni correction revealed a significant difference among all three groups only in the social emotional reciprocity scale and the sensory sensitivity scale. Specifically, on each scale, the ASD group had the highest score

and the DS-screen negative group has the lowest score, with the DS-screen positive group falling in the middle (corrected *p's*<.05). On the peer socialization, stereotypy, and behavioral rigidity scales, however, a different pattern emerged. On these scales, although the DS-screen negative group was significantly different from both the DS-screen positive and ASD groups (corrected *p's*<.05), there were no significant differences between the DS-screen positive and ASD groups on the peer socialization (*p*=.229), stereotypy (*p*=.220), or behavioral rigidity (*p*=.23) scales.

For children with WS, when comparing the WS-screen positive, WS-screen negative, and ASD groups across the treatment scales, a one-way ANOVA revealed a significant main effect across six of the eight treatment scales (*p's*<.05), with there being no significant difference between groups on the atypical language (*p*=.267) or attention (*p*=.351) scales. Following a Bonferroni correction, pairwise comparisons on the scales with significant main effects revealed that on the adult socialization and peer socialization treatment scales, there was a significant difference between the WS-screen negative and ASD groups (corrected *p's*<.05). However, on the adult socialization and peer socialization scales there was no significant difference between the WS-screen negative and WS-screen positive groups (p_{adult}=.12; p_{peer}=.08) or between the WS-screen positive and ASD groups (p_{adult}=.31; p_{peer}=.81). However, on the on the social emotional reciprocity, stereotypy, behavioral rigidity, and sensory sensitivity scales, although the WS-screen negative group was significantly different from both the WS-screen positive and ASD groups (*p's*<.05), there was no significant difference between the WS-screen positive and ASD groups on the social emotional reciprocity (*p*=.355), stereotypy (*p*=.142), behavioral rigidity (*p*=.474), or sensory sensitivity (*p*=.224) scales. A summary of these results is displayed in Table 5.

Discussion

The primary goal of this study was to examine the presence of ASD symptoms in individuals with Down syndrome and Williams syndrome. Overall, we found that children in both the DS and WS groups exhibited elevated ASD symptoms across two different measures of ASD symptoms. Lower developmental level, as measured by adaptive behavior scores, was associated with increased ASRS scores. However, differences in developmental level did not fully explain group differences in ASD symptoms.

Firstly, the percentage of individuals who entered the study with a comorbid diagnosis of ASD was higher than one would expect (DS=6.6%, WS=8.9%), based on the 1 in 59 (1.69%) prevalence reported by the CDC (CDC, 2014). This is in line with previous research, suggesting that the prevalence of ASD is higher in the DS and WS populations (Klein-Tasman et al., 2007; Lincoln et al., 2007; Reilly, 2010). Additionally, of the respondents who did not note that their child had a comorbid ASD diagnosis, three (3.9%) in the DS group and five (11.1%) in the WS group stated that a professional had suggested their child be referred for an autism spectrum disorder diagnostic evaluation in the past. This suggests that not only are children with DS or WS receiving ASD diagnoses at a higher rate than the general population, but they are also being flagged by professionals for ASD referrals. However, it is not known why professionals flagged these children as at-risk, and if these children had follow-up assessment. Results of this study do support previous findings suggesting an elevation in ASD diagnoses and referrals in the DS and WS population.

Along with this, more individuals with DS (22.4%) and WS (54.1%) screened positive on the SCQ than the 4.4% reported in previous research (Chandler et al., 2007), including all nine of the individuals noted to have a comorbid ASD diagnosis. Significantly more individuals in the WS group screened positive on the SCQ in comparison to the DS group, which suggests more

pronounced symptoms of ASD in those with WS. Although we had a relatively large number of individuals screen positive, results of this study cannot determine how many individuals in our sample have a comorbid diagnosis of ASD. Previous research demonstrates that for individuals with DS, the SCQ has excellent sensitivity (100.0%), but a specificity of 57.1%, suggesting the potential for false positives in the DS population (DiGuiseppi et al., 2010). However, as the creators of the SCQ adapted this screener from the Autism Diagnostic Interview-Revised, a gold standard ASD diagnostic assessment (Berument et al., 1999; Lord et al., 1994), it is likely that the children who have SCQ scores above the cutoff are exhibiting at least some symptoms associated with ASD. Additionally, children who screened positive on the SCQ had significantly higher total scores on a dimensional measure of ASD symptoms, in comparison to those who screened negative.

The significantly higher scores in both the DS and WS groups in comparison to the normative sample mean on ASRS total scores also suggest elevated levels of ASD symptoms in these populations. Again, this is similar to previous research, which found elevated ASD symptoms in the DS and WS populations (Channell et al., 2015; Evans & Gray, 2003; Järvinen et al., 2015; Kent et al., 1999; Klein-Tasman et al., 2009; Lough et al., 2015). Additionally, the WS group had significantly higher scores than the DS group, which suggests more pronounced ASD symptoms in the WS group in comparison to the DS group. Both groups' mean ASRS total scores were significantly lower than the ASD group, and this remained true after controlling for sex, age, and overall adaptive behavior levels. This suggests the most pronounced elevations of ASD symptoms in the ASD group, followed by the WS group, the DS group, and then the normative sample. Taken together, these findings regarding parent-reported rate of ASD diagnosis, elevated screen-positive rates on the SCQ, and elevated ASD symptom scores on the

ASRS suggest an increase in ASD diagnoses in both the DS and WS group, as well as an increase in ASD symptoms in both groups, particularly in the WS group.

ASRS Comparisons

As mentioned previously, we chose to use the ASRS as its three-factor structure allowed us to make meaningful comparisons using the ASRS subscales as well. Looking across subscales on the ASRS, we saw that all three subscales (Social Communications, Self-Regulation, and Unusual Behaviors) were significantly higher than the mean score of 50 in both the DS and WS groups. This suggests that there is not only one type of symptom associated with ASD elevated for individuals with DS and WS, rather, there are elevations across all areas of ASD symptoms. Additionally, these elevations are not only present for those who screen positive for ASD.

Looking at each group individually, different subscale patterns emerged. In the DS group, the Unusual Behaviors subscale was significantly more elevated than both the Social Communication and Self-Regulation subscales. For all three subscales, children with DS scored significantly lower than children with ASD (although still significantly higher than the normative sample mean). In the WS group, substantially different patterns emerged. ASRS scores in the areas of Unusual Behaviors and Self-Regulation were not significantly different between the WS group and the ASD group, suggesting that children with WS, on average, show substantially elevated ASD-related symptoms in these areas. In contrast, the scores of children with WS in the Social Communication area were significantly lower than their scores for Unusual Behaviors and Self-Regulation. Additionally, although still elevated when compared to the population norms, scores in the areas of Social Communication were significantly lower than the scores of children with ASD. This suggests that Social Communication behaviors may most clearly differentiate children with WS from children with ASD.

A more detailed examination of the ASRS subscales revealed that in the DS group, children who screened positive on the SCQ exhibited symptoms of autism that more clearly resembled the ASD group than the DS-screen negative group in the areas of peer socialization, stereotypy, and behavioral rigidity. However, there were no significant differences between the DS-screen positive and DS-screen negative groups in the areas of adult socialization, atypical language, or attention. This suggests that questions related to how children with DS interact with other children, how flexible they are with changes in their routine, and questions related to stereotyped play/movements might best differentiate those with DS who have substantial ASD symptoms from those with fewer ASD-related concerns. In the WS group, children who screened positive on the SCQ exhibited symptoms of autism that more clearly resembled the ASD groups than the WS-screen negative group in the areas of social emotional reciprocity, stereotypy, behavioral rigidity, and sensory sensitivity. There were no significant differences between any groups in the areas of atypical language or attention, and no significant differences between the WS-screen positive and WS-screen negative groups in the areas of peer socialization and adult socialization. This suggests that questions asking about flexibility and stereotyped play/movements might also best differentiate those with WS who have substantial ASD symptoms from those with fewer ASD-related concerns, in addition to questions about the ability to engage in back and forth social interactions and having sensory sensitivities. Indeed, items asking about understanding social cues and overreacting to loud noises seemed to best differentiate the groups, as on these items, the WS-screen positive group displayed the highest level of symptoms. Research also suggests that individuals with WS display a heightened sensitivity to sounds (Marler, Elfenbein, Ryals, Urban, & Netzloff, 2005), and may struggle with some complex social skills (Asada & Itakura, 2012; Stojanovik, 2006). Therefore, it is possible

that in relation to these specific questions, those with both WS and substantial ASD symptoms displayed symptoms levels above and beyond those seen in individuals with WS or ASD alone.

Potential Explanations

There are several potential explanations for the elevated ASD symptom scores observed in children with WS and DS in this study. One potential explanation for these findings could be false positives and ASRS elevations simply due to low developmental level, as seen in previous research (Bishop et al., 2008). Individuals with substantial developmental delays (especially in younger age groups) may show false positives on ASD measures due to not yet having attained important developmental milestones in the social area (e.g., using pointing gestures, engaging in reciprocal conversation). One way we attempted to alleviate this was by using an older sample, to hopefully reduce the effect of the confound of developmental delay. Additionally, results of this study suggest that developmental delay does not fully account for the elevations on measures of ASD symptoms, as group membership predicted ASRS total scores, even when controlling for adaptive behavior. If impairments in adaptive behavior fully explained the elevated ASRS scores, then group membership would not have been a significant predictor after adaptive behavior was added to the model. Therefore, we can assume that delayed development is not the primary reason for the elevated ASRS total scores.

A second potential explanation is that elevated scores on ASD measures are simply an artifact of measurement issues. Although the SCQ demonstrates good sensitivity/specificity, research does demonstrate a higher false positive rate for those with DS (DiGuiseppi et al., 2010), and although no known studies have investigated the sensitivity/specificity of the SCQ in the WS population, research demonstrates a higher false positive rate for those with ID (Witwer & Lecavalier, 2007). There is a possibility that certain questions on the SCQ may be

misunderstood by parents or apply differently to the DS or WS population. It is possible that certain questions on the SCQ may not differentiate those with DS and WS who have a comorbid diagnosis from those who do not. Screening for ASD in the DS or WS populations could be improved upon by examining individual items on screeners such as the SCQ, to determine which items are most successful in differentiating individuals with DS or WS who have a comorbid ASD diagnosis from those who do not. Interestingly, although parents of children with WS endorsed some questions asking about social-communicative behaviors at high rates, such as asking socially inappropriate questions or not engaging in imaginative play with others, results of the ASRS subscale analyses demonstrated that on the ASRS, questions about social communication were the only questions that differentiated the WS group from the ASD group. However, many questions on the social-communication subscale of the ASRS are related to empathy (e.g., "understand how someone else felt") and social interest (e.g., "share his/her enjoyment with others" or "show an interest in the ideas of others)." Therefore, it is possible that questions asking about social interest and empathy may better differentiate children with WS only from those with WS and a comorbid ASD diagnosis. Although children with DS were significantly different from those with ASD across all subscales of the ASRS, the significantly higher elevation on the Unusual Behaviors subscale combined with the fact that research demonstrates obsessive-compulsive behaviors in individuals with DS suggests that questions asking about social communication skills may be better at differentiating children with a comorbid ASD diagnosis in comparison to questions asking about unusual behaviors.

Although the measurement concerns discussed above may partially explain the high SCQ and ASRS scores, it is likely that this does not account for all of screen positives and elevated ASRS scores in this sample. Previous research using gold standard diagnostic assessments for

ASD, such as the ADOS, has found an increased number of individuals in the DS and WS population receiving a comorbid diagnosis of ASD (Hepburn et al., 2007; Klein-Tasman et al., 2007; Lincoln et al., 2007). Based on this, it is likely that true elevations in ASD symptoms account for all or part of these findings. Therefore, one explanation may be a potential etiological overlap between DS/WS and ASD. The genetic etiology of DS and WS may be known; however, much still needs to be learned regarding the roles of the genetic material that is duplicated or deleted in these conditions. It is possible that there is a similar genetic etiology in these genetic conditions and idiopathic ASD. Of course, research demonstrates that it is likely a combination of genes implicated in ASD, so it is highly unlikely that just one of these genes is driving the genetic etiology of ASD. Additionally, there is a possibility that although genetic etiology may differ, the neurological processes underlying each disorder may be similar.

Clinical Implications

As this study only used an ASD screener and a dimensional measure of ASD symptoms, we cannot make claims as to how many individuals in our sample would receive an ASD diagnosis. However, our results do show elevations in ASD symptoms in the DS and WS population, and we did have more individuals entering the study with an ASD diagnosis than we would expect based on the reported population prevalence. Therefore, we can conclude that our sample does have an increase in ASD diagnoses and symptoms in comparison to the population prevalence. This finding suggests that clinicians should be aware of the potential for comorbid ASD in children with DS and WS in order to clinically assess these characteristics and provide appropriately tailored interventions. Additionally, the overall elevations of autism symptoms seen in both populations (particularly in the WS group), suggest that a higher cutoff score on

measures such as the ASRS may better assist clinicians in determining which children should undergo further diagnostic evaluation.

However, ASD presentation within individuals with DS and WS has not been well characterized, and the extent to which features of ASD in individuals with DS or WS differ from those with idiopathic ASD in unknown. It is also unclear whether different presentations or etiologies of ASD symptoms would lead to different treatment recommendations. For example, if children with ASD and WS both have inappropriate social behavior, yet the mechanisms behind this behavior are different, how might that alter the effectiveness of intervention? Research demonstrates a decrease in fusiform face area (FFA) activation in individuals with ASD during facial recognition tasks (Corbett et al., 2009), with the potential of increasing FFA activation as a goal for social skills intervention. Yet, individuals with WS have enhanced FFA activation in response to faces, and a larger FFA volume (Golarai et al., 2010). It is not known whether this potential underlying etiological difference would diminish the effectiveness of ASD interventions for those with a comorbid diagnosis of ASD and WS. More research aimed at characterizing ASD prevalence and presentation in children with WS and DS is warranted, as well as research examining the efficacy of ASD interventions for children with comorbid diagnoses. A better understanding of these questions will help clinicians to better assess the functional utility of giving an additional ASD diagnosis in individuals who already have a genetic diagnosis.

Limitations and Future Direction

This study has several limitations. Firstly, the sample size was small. However, the sample was large enough to provide sufficient power for analyses. Additionally, the sex differences across groups was a limitation, as there were significantly more females in the DS

and WS group when compared to the ASD group. Diagnoses of the children in the study also solely relied on parent report. We tried to minimize the effects of this by screening out children with ASD who did not screen positive on the SCQ, and those with DS or WS whose parents did not report a genetic confirmation of their diagnosis. Perhaps the largest limitation of this study was the reliance on parent report of ASD symptoms and adaptive behavior. Previous research found that although teacher ratings of social deficits in children with ASD were associated with clinicians' observations of ASD symptom severity, parent ratings were not (Azad, Reisinger, Xie, & Mandell, 2016). Additionally, research demonstrates only fair inter-rater reliability between parents reporting about the same child on the SCQ (Möricke, Buitelaar, & Rommelse, 2016). Without a direct assessment of these children's behavior, we cannot determine whether or not these parent's reports are an accurate depiction of their child's behaviors. We were also unable to assess how many children who screened positive on the SCQ would actually receive a diagnosis of ASD based on a full clinical assessment; therefore, we are unable to comment on issues of sensitivity/specificity of the SCQ or ASRS based on this study.

Future research that follows up screening instruments with a full clinical evaluation is needed in order to assess sensitivity and specificity of these screening instruments in children with DS and WS. Additionally, further research is also needed examining the relationship between developmental level and symptoms of autism in individuals with DS or WS. Future studies should also examine individual items on screeners such as the SCQ to determine which items best discriminate ASD in individuals with DS or WS, as well as whether disorder-specific cutoffs are warranted in this population given the overall symptom elevation seen (especially in the WS group). This work also may inform diagnostic practices by providing information as to which behaviors clinicians should put more weight into when determining if a child with DS or

WS should receive a comorbid ASD diagnosis. Research is also needed in the area of intervention, to determine if empirically supported interventions for ASD, such as applied behavior analysis, would be effective for children with DS or WS and a comorbid ASD diagnosis, or if significant adaptations are needed.

Conclusion

In a sample of children and adolescents with DS and WS, more children entered the study with an ASD diagnosis in comparison to the reported population prevalence, and we saw elevated ASD symptoms in both groups across multiple measures. These elevations are not solely due to low developmental level, as group membership predicted ASRS total scores even when controlling for adaptive behavior. More research is needed to determine the types of questions needed to effectively screen for ASD in the DS/WS populations, to determine the accuracy of ASD diagnoses in these populations, and to investigate the utility of empirically supported interventions for those with DS/WS and a comorbid ASD diagnosis.

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Table 1. Respondent demographics by group

Variables	Mean (SD)/Percentage		
	ASD N=39	DS N=76	WS N=45
Respondent Age	42.97 (10.04)	47.91 (5.31)	42.82 (7.12)
Relationship to Child			
Mother	64.1%	92.1%	80.0%
Father	30.8%	7.9%	13.3%
Other	5.1%	0.0%	6.7%
Respondent Race			
American Indian or Alaska Native	2.6%	1.3%	0.0%
Asian	7.7%	3.9%	2.2%
Black or African American	0.0%	0.0%	2.2%
Native Hawaiian or Other Pacific Islander	0.0%	0.0%	0.0%
White	87.9%	93.4%	93.3%
Other	0.0%	1.3%	2.2%
Respondent Ethnicity			
Hispanic or Latino	17.9%	3.9%	8.9%
Not Hispanic or Latino	82.1%	96.1%	91.1%
Respondent Education Level			
Prefer Not to Answer	0.0%	1.3%	0.0%
Less than 7th Grade	0.0%	0.0%	0.0%
Junior High School, Including 9th Grade	0.0%	0.0%	0.0%
High School Graduate	25.6%	0.0%	11.1%
Partial College, at least one year of specialized training	17.9%	7.9%	15.6%
Standard College or University Graduation	38.5%	42.1%	31.1%
Graduate/Professional Training	17.9%	48.6%	48.6%
Household Income			
Less than $20,000	20.5%	0.0%	2.2%
$20,0001-$40,000	12.8%	5.3%	11.1%
$40,0001-$60,000	17.9%	6.6%	15.6%
$60,0001-$90,000	20.5%	14.5%	20.0%
More than $90,000	23.1%	64.5%	40.0%
Prefer Not to Answer	5.1%	9.2%	8.9%
Primary Language Spoken in Home			
English	100.0%	97.4%	91.1%
Spanish	0.0%	1.3%	4.4%
Other	0.0%	1.3%	4.4%

ASD = Autism spectrum disorder; DS = Down syndrome; WS = Williams syndrome

Table 2. Child demographics by group

Variables	Mean (SD)/Percentage		
	ASD N=39	DS N=76	WS N=45
Child Age (Years)	11.96 (3.61)	11.88 (3.28)	10.60 (3.62)
Child Sex			
Male	74.4%	38.2%	40.0%
Female	25.6%	61.8%	60.0%
Comorbid ASD Diagnosis			
Yes	N/A	6.6%	8.9%
No	N/A	93.4%	91.1%
Child Referred for ASD Diagnosis[1]			
Yes	N/A	4.2%	12.2%
No	N/A	95.8%	87.8%
Child Race			
American Indian or Alaska Native	2.6%	1.3%	0.0%
Asian	7.7%	3.9%	2.2%
Black or African American	0.0%	0.0%	2.2%
Native Hawaiian or Other Pacific Islander	0.0%	0.0%	0.0%
White	87.9%	93.4%	93.3%
Other	0.0%	1.3%	2.2%
Child Ethnicity			
Hispanic or Latino	17.9%	3.9%	8.9%
Not Hispanic or Latino	82.1%	96.1%	91.1%
% of Time Spent in Classroom with TD Peers			
School specifically for Children with DD	33.3%	3.9%	6.7%
Homeschooled/Other Alt. Learning Environment	2.6%	5.3%	6.7%
1-39%	17.9%	30.3%	42.2%
40-79%	5.1%	26.3%	22.2%
80-99%	5.1%	26.3%	13.3%
Entire Day	35.9%	7.9%	8.9%
Hearing Problems			
Yes	7.7%	13.2%	13.3%
No	92.3%	86.8%	86.7%
Vision Problems			
Yes	17.9%	9.2%	13.3%
No	82.2%	90.8%	86.7%

ASD = Autism spectrum disorder; DS = Down syndrome; WS = Williams syndrome

[1] This question was only displayed to respondents who did not note that their child had an ASD diagnosis

Table 3. ASRS and ABAS-3 descriptive statistics

	ASD Mean (SD) ASRS n = 39 ABAS-3 n=39	**DS Mean (SD) ASRS n = 76 ABAS-3 n=73**	**WS Mean (SD) ASRS n = 38 ABAS-3 n=32**	**F-Statistic**	**p-value**
ASRS Total Score	71.74 (5.04)	58.96 (7.79)	65.24 (6.03)	47.21	**<.001***†‡
Social Communication	68.74 (6.94)	55.93 (9.25)	60.84 (8.69)	28.78	**<.001***†‡
Unusual Behaviors	67.00 (8.96)	61.79 (8.303)	65.53 (6.42)	6.11	**<.01***‡
Self-Regulation	63.85 (5.45)	54.88 (7.62)	63.26 (5.83)	32.134	**<.001***‡
ABAS-3 GAC	71.97 (5.04)	71.27 (12.42)	65.50 (11.19)	2.73	.069
Conceptual Domain	74.49 (15.16)	69.18 (12.04)	66.03 (10.77)	4.42	**<.05**†
Social Domain	70.92(11.40)	82.27 (14.09)	77.06 (11.97)	9.76	**<.001***
Practical Domain	75.13 (16.74)	70.86 (12.65)	63.76 (11.31)	6.36	**<.01**†‡

*DS group significantly different from ASD group after using Games-Howell method to correct for multiple tests †WS group significantly different from ASD group after using Games-Howell method to correct for multiple tests ‡DS group significantly different from WS group after using Games-Howell method to correct for multiple tests; ASRS = Autism Spectrum Ratings Scale; ABAS-3 = Adaptive Behavior Assessment System, Third Edition; GAC = General Adaptive Composite; ASD = Autism spectrum disorder; DS = Down syndrome; WS = Williams syndrome

Table 4. Multiple regression using sex, age, adaptive behavior, & diagnosis, to predict ASRS total score

Predictor Variable	R	R^2	Beta	Sample Statistic[a]
Autism Spectrum Rating Scales Total Score				
Overall Model	.70	.50		27.18**
Sex			-.02	-.29
Age			-.01	-.15
ABAS-3 General Adaptive Composite			-.30	-4.80**
Group (DS) [†]			-.75	-9.89**
Group (WS) [†]			-.34	-4.46**

*$p < .05$; **$p < .001$

[a] Sample statistic = F for overall models, t for individual predictors; [†]Diagnosis was dummy coded, with ASD as the reference group; ABAS-3 = Adaptive Behavior Assessment System, Third Edition; DS = Down syndrome; WS = Williams syndrome

Table 5. ASRS treatment subscale analyses

Scale	Screen Negative Mean (SD) DS n=59 WS n=17	Screen Positive Mean (SD) DS n=17 WS n=19	Autism Mean (SD) n=39	F statistic	P value
Adult Socialization					
Down syndrome	62.29(5.80)	65.65(9.04)	67.53(6.02)	8.02	**<.001**†
Williams syndrome	60.41(6.11)	64.68(6.47)		14.63	**<.01**†
Attention					
Down syndrome	52.32(6.53)	55.50(12.35)	60.41(4.66)	14.88	**<.001**†
Williams syndrome	59.88(4.86)	62.16(6.06)		1.06	.35
Atypical Language					
Down syndrome	65.86(7.90)	71.24(9.89)	71.49(8.82)	6.09	**<.01**†
Williams syndrome	67.64(6.64)	71.32(8.79)		1.34	.27
Behavioral Rigidity					
Down syndrome	60.12(8.91)	66.41(11.71)	71.10(7.74)	17.82	**<.001***†
Williams syndrome	61.18(8.80)	68.00(6.83)		9.65	**<.001***†
Peer Socialization					
Down syndrome	60.73(7.55)	66.76(12.52)	71.03(6.71)	17.23	**<.001***†
Williams syndrome	63.41(6.04)	68.79(8.85)		6.67	**<.001**†
Sensory Sensitivity					
Down syndrome	56.02(8.02)	63.12(9.62)	74.44(7.85)	59.06	**<.001***†‡
Williams syndrome	60.00(7.27)	70.79(5.57)		23.80	**<.001***†
Social Emotional Reciprocity					
Down syndrome	52.35(7.63)	58.56(9.32)	66.38(5.54)	43.40	**<.001***†‡
Williams syndrome	54.88(5.89)	63.63(7.71)		20.30	**<.001***†
Stereotypy					
Down syndrome	56.93(9.63)	65.82(11.79)	70.69(7.27)	26.87	**<.001***†
Williams syndrome	58.94(5.95)	66.73(7.32)		16.65	**<.001***†

*Screen negative and screen positive significantly different at .05 level; †Screen negative and autism groups significantly different at the .05 level; ‡Screen positive and autism groups significantly different at the .05 level