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Challenging Behaviors in Toddlers and Preschoolers with Angelman, Prader-Willi, and Williams Syndromes

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Abstract

Children with neurogenetic syndromes (NGS) experience comorbid challenging behaviors and psychopathology. We examined challenging behaviors in 86 toddlers and preschoolers across three NGS (Angelman syndrome [AS], Prader-Willi syndrome [PWS], and Williams syndrome [WS]) and 43 low-risk controls (LRC), using the Child Behavior Checklist for Ages 1½–5. Challenging behavior profiles differed across NGS, with generally elevated behaviors in AS and WS, but not PWS, relative to LRC. Withdrawn and autism spectrum symptoms were particularly elevated in AS. Although several profiles were similar to those previously reported in older children and adults, we also observed inconsistencies that suggest non-linear developmental patterns of challenging behaviors. These findings underscore the importance of characterizing early challenging behaviors to inform atypical phenotypic development and targeted intervention.

Keywords

challenging behavior; early childhood; Angelman syndrome; Prader-Willi syndrome; Williams syndrome; Child Behavior Checklist

Children with neurogenetic syndromes (NGS) often experience comorbid challenging behaviors and psychopathology (Hodapp and Dykens 2007), which substantially impact family functioning and parental mental health (Reilly et al. 2015; Waite et al. 2017). However, few studies have examined the emergence of challenging behaviors in toddlers and preschoolers with NGS (Åkefeldt and Gillberg 1999; Fidler et al. 2006; Glenn and Cunningham 2007; Hahn et al. 2014; Klaassen et al. 2013; Klein-Tasman and Lee 2017), with prior studies focusing on one NGS in isolation, calling to question the specificity of

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Compliance with Ethical Standards

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

challenging behavior profiles to individual NGS versus features shared across phenotypes (e.g., developmental delays). The present study addressed this need by examining challenging behaviors in young children across three NGS associated with intellectual disability – Angelman syndrome (AS), Prader-Willi syndrome (PWS), and Williams syndrome (WS) – and those with no known developmental concerns. Our primary goal was to establish early childhood challenging behavior profiles for each NGS, thus identifying syndrome-specific differences that may inform early, targeted intervention and advance understanding of complex relationships between genes, behavior, and development.

Establishing early challenging behavior profiles across NGS offers a number of practical benefits for improved clinical care. First, given higher rates of challenging behaviors in NGS than low-risk groups, clarifying early profiles across NGS may yield insights on their developmental course and onset, enabling targeted treatments in early development (Hodapp et al. 2003). Second, prior work has demonstrated non-linear associations between early behavioral responsivity and later challenging behaviors in NGS such as fragile X syndrome (FXS), where under-reactive infants subsequently showed hyper-responsive patterns (Baranek et al. 2008; Roberts et al. 2012). Thus, early and later challenging behavior profiles in NGS may be different, either due to delayed onset or non-linear trajectories. Identifying such discontinuities may help families and practitioners orient to syndrome-specific developmental expectations and inform etiology by identifying critical periods of change and vulnerability. Finally, as NGS are caused by distinct genetic mechanisms, contrasting challenging behavior profiles across young children with NGS, who are more naïve to intervention than older children and adults, may inform broad genetic underpinnings of challenging behaviors, advancing potential biological treatments and theoretical understanding of the dynamic aspects of emergent outcomes (Karmiloff-Smith 2009).

Table 1 provides an overview of AS, PWS, and WS. Although these NGS are all broadly associated with challenging behaviors in later development, the specific nature of symptoms varies across groups and ages. We aimed to characterize challenging behaviors in toddlers and preschoolers with AS, PWS, and WS by (a) identifying challenging behaviors in each NGS by comparing general profiles and rates of clinically significant behaviors between low-risk controls (LRC) and each NGS, (b) informing specificity of challenging behaviors in NGS by examining cross-syndrome similarities and differences, and (c) contextualizing domain-level differences through exploratory item-level analyses. We broadly expected children with NGS to display greater challenging behaviors than LRC. We also hypothesized that challenging behaviors would be greatest in AS and lowest in PWS. For our exploratory analyses, we expected items obtusely related to developmental delays, motor issues, and speech problems to be elevated across NGS.

Methods

Participants

Participants were drawn from the Purdue Early Phenotype Study, an ongoing longitudinal study of phenotypic development in low-incidence NGS. Families were recruited nationally through web-based parent support groups, social networks, and syndrome research registries. The current sample included 129 mothers who reported that their child had been

diagnosed with AS ($n = 30$), PWS ($n = 22$), or WS ($n = 34$); the remaining 43 were LRC. Age and sex were similar across groups (age: Kruskal-Wallis $H = 0.45$, $p = .931$; sex: $\chi^2(3) = 4.05$, $p = .256$). Table 2 provides additional demographic information. Genetic disorders reported by mothers were verified through genetic or medical records for the majority of children with NGS (64%; AS: 57%; PWS: 86%; WS: 56%). AS subtypes included maternal deletion (77%), paternal uniparental disomy (10%), and *UBE3A* gene mutations (7%), while PWS subtypes included paternal deletion (64%) and maternal uniparental disomy (36%), which were representative of the genetic mechanisms underlying these NGS (Alexander 2016; Greydanus et al. 2016).

Measure

The present study focused on the Child Behavior Checklist for Ages 1½–5 (CBCL), a 100-item parent-report measure for assessing challenging behaviors in young children (Achenbach and Rescorla 2000). The CBCL has good test-retest reliability, construct and criterion validity (Rescorla 2005), and has been used in research involving young children with NGS (Klein-Tasman and Lee 2017; Tonnsen et al. 2015). Parents rate each item on a 3-point scale to indicate if it is not true (0), somewhat or sometimes true (1), or very true or often true (2) of their child. Individual item scores are aggregated into seven narrowband scales: emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems, and aggressive behavior. The first four and last two narrowband scales are combined to form broadband internalizing and externalizing scales, respectively. The total problems scale is constructed by summing all item scores. Five Diagnostic and Statistical Manual of Mental Disorders (DSM)-oriented scales are derived: depressive, anxiety, autism spectrum, attention deficit/hyperactivity, and oppositional defiant problems. Scores are categorized into normal, borderline, and clinical ranges, with higher scores representing greater challenging behaviors.

Statistical Analyses

We used nonparametric statistical analyses suited for non-normally distributed and small samples. We first evaluated preliminary associations between challenging behaviors and both age and sex using Spearman's correlation and Wilcoxon rank-sum tests, respectively. We then contrasted challenging behavior raw scores and proportions of scores in borderline or clinical ranges across group pairs using Wilcoxon rank-sum and Fisher's exact tests, respectively. Each pairwise comparison included separate analyses for all 15 CBCL scales, with Holm-Bonferroni correction to address multiple comparisons. Finally, we examined group differences in the proportions of children with challenging behaviors at the item level using Fisher's exact tests. Effect sizes were reported using point biserial correlation and phi coefficient (Fritz et al. 2012), with .1, .3, and .5 interpreted as small, medium, and large effects, respectively (Cohen 1992).

Results

Descriptive and Preliminary Analyses

Table 3 summarizes raw scores and qualitative categories across CBCL scales and groups. Across the sample, age was positively associated with total, internalizing, and externalizing

problems (total: $r_s = .24$, $p = .007$; internalizing: $r_s = .22$, $p = .016$; externalizing: $r_s = .28$, $p = .002$). Challenging behaviors did not differ by sex (total: $Z = 0.98$, $p = .323$, $r_{pb} = .09$; internalizing: $Z = -0.26$, $p = .794$, $r_{pb} = -.02$; externalizing: $Z = 1.35$, $p = .179$, $r_{pb} = .12$).

Atypicalities in Challenging Behaviors

Figure 1 depicts challenging behavior profiles for narrowband and DSM-oriented scales and Table 4 details pairwise comparisons. Children with AS displayed greater total problems than LRC, largely driven by internalizing problems. For narrowband scales, children with AS exhibited atypically elevated somatic complaints, withdrawn behavior, and attention problems. They also exhibited greater depressive, autism spectrum, and attention deficit/hyperactivity problems, and fewer oppositional defiant problems. The proportions of children with AS with scores in borderline or clinical ranges were higher than those of LRC for attention ($p < .001$, $\phi = .61$), depressive ($p = .012$, $\phi = .40$), and autism spectrum ($p = .030$, $\phi = .36$) problems only.

Children with PWS generally displayed similar levels of challenging behaviors to LRC, with the exception of greater withdrawn behavior and autism spectrum problems, and fewer sleep and anxiety problems. The proportions of children with PWS with scores in borderline or clinical ranges were similar to those of LRC for all 15 CBCL scales, $ps > .412$, $-.28 < \phi s < .21$.

Children with WS displayed greater total problems than LRC, driven by both internalizing and externalizing problems. For narrowband scales, children with WS exhibited atypically elevated somatic complaints, withdrawn behavior, and attention problems. They also exhibited greater depressive, autism spectrum, and attention deficit/hyperactivity problems. The proportion of children with WS with scores in borderline or clinical ranges was higher than that of LRC for attention problems only, $p = .001$, $\phi = .47$.

Cross-syndrome Comparisons of Challenging Behaviors

Across NGS, children with PWS had the least challenging behaviors, with significantly lower total problems than both AS and WS groups. However, the challenging behaviors driving these differences differed at the broadband level, with PWS and AS differing in internalizing problems, but PWS and WS differing in externalizing problems. At the narrowband level, children with PWS exhibited fewer sleep, attention, depressive, and attention deficit/hyperactivity problems than those with AS and WS, while children with AS displayed greater withdrawn behavior and autism spectrum problems than those with WS.

Most Frequent Challenging Behaviors in Neurogenetic Syndromes

Table 5 presents the five most frequent challenging behaviors in each NGS. Four behaviors were common to all three NGS. Fisher's exact tests revealed that two items, *acts too young for age* and *speech problem*, occurred frequently across NGS but infrequently in LRC, suggesting that these items likely were not syndrome-specific and were instead broadly associated with developmental disorders. In contrast, *chews on things that aren't edible* was specific to AS and WS, while *gets into everything* was applicable to most children, including LRC.

Discussion

The present study aimed to characterize challenging behaviors in toddlers and preschoolers with AS, PWS, and WS. To our knowledge, this study is the first to examine early childhood challenging behaviors across multiple NGS concurrently, laying the foundation for understanding the specificity of challenging behaviors during a critical developmental period. Our results indicated that early challenging behavior profiles are distinct across NGS. Children with AS and WS had atypically elevated scores for several CBCL scales while those with PWS and LRC had similar levels of challenging behaviors; cross-syndrome comparisons further revealed nuanced differences between AS and WS in terms of greater withdrawn behavior and autism spectrum problems in AS. At the item level, we observed a range of specificity of individual challenging behaviors, from non-syndrome-specific items that broadly differentiated NGS from LRC to more syndrome-specific items that varied across NGS. Notably, although early challenging behavior profiles differed across NGS, not all profiles in our early-childhood sample mapped onto well-established challenging behavior profiles previously observed in older children and adults. These findings underscore the importance of cross-syndrome research and characterization of early challenging behaviors – distinct from later childhood and adulthood – to appreciate the complex dynamics of atypical phenotypic development (Karmiloff-Smith 2009).

As expected, our NGS sample exhibited broadly higher rates of challenging behaviors than LRC, particularly in the AS and WS groups, with a number of patterns congruent with profiles previously reported in older children with NGS. For example, all NGS groups displayed greater withdrawn and autism spectrum problems than LRC, with markedly elevated rates in AS. These high rates of autism-related symptoms in our toddler and preschool-aged sample are consistent with high rates of autism in older children with NGS, particularly in AS (Betancur 2011; Zafeiriou et al. 2013). However, it is notable that other challenging behaviors were less consistent with established child and adult phenotypes. Young children with WS, for example, had similar levels of anxious/depressed and anxiety problems as LRC, despite anxiety being a prevalent psychiatric diagnosis in WS during middle childhood (Leyfer et al. 2006). Similarly, young children with PWS did not display early indicators of known challenging behaviors such as compulsive behaviors, sleep problems, and temper tantrums (Dimitropoulos et al. 2006; Maas et al. 2010; Tunnicliffe et al. 2014). Thus, although a subset of expected challenging behaviors appeared to be present at young ages, others were not detected in our sample.

The relative absence of such challenging behaviors at young ages may reflect developmental, phenotypic, or measurement issues. Developmentally, it is likely that a subset of challenging behaviors will naturally emerge later in development, consistent with previous work documenting lower base rates of challenging behaviors in young children with NGS (Abel and Tonnsen 2017; Dimitropoulos et al. 2001; Leyfer et al. 2006) and the later onset of psychopathology such as anxiety (21 years; de Lijster et al. 2017) and attention-related disorders (7–9 years; Kessler et al. 2007) in non-syndromic populations. This possibility is supported by the generally low proportions of scores in borderline or clinical ranges in both NGS and LRC groups. Importantly, low rates of challenging behaviors in early childhood suggest potential for preventive opportunities, leveraging the

multidirectional effects that genes, environment, and behavior play in shaping developmental outcomes (Karmiloff-Smith 2009). It is also possible that despite generally low severity across groups, our NGS and LRC groups may be exhibiting different pre-symptomatic trajectories, as has been previously demonstrated in NGS such as FXS. A number of studies has reported developmental shifts between hypo- and hyper-responsivity in FXS and related disorders (Baranek et al. 2008; Low Kapalu and Gartstein 2016), with more hypo-reactive infants demonstrating greater challenging behaviors subsequently (Roberts et al. 2012). Future longitudinal work is critical to teasing apart these possibilities, which could inform etiology and natural history of challenging behaviors in NGS as well as optimal strategies for intervening and monitoring symptoms in early development.

Characteristics of our measurement approach may also have resulted in lower rates of reported challenging behaviors in our sample. Although parents are generally accurate reporters of child problem behaviors (Glascoe and Dworkin 1995), behavior rating scales such as the CBCL feature a number of inherent limitations that could have affected our findings. First, informants may experience greater difficulty in rating internalizing than externalizing problems because, by definition, the former involves more self-directed and subjective states and perceptions (Whitcomb 2018). Second, different informants may offer diverse perspectives on early challenging behaviors, such as parents and teachers being more sensitive to internalizing and externalizing problems in preschoolers, respectively (Hinshaw et al. 1992). Finally, items on the CBCL may be less sensitive to prodromal psychopathology symptoms in NGS. Indeed, our item-level analyses suggested a number of challenging behaviors commonly endorsed across NGS but not in LRC, potentially reflecting that shared developmental and genetic characteristics, such as developmental delays, speech concerns, and motor issues, may drive item responses and result in inadequate item invariance across groups (Borsboom 2006). Given the widespread use of the CBCL in NGS samples, further psychometric work is needed to examine the factor structure and validity of the CBCL for NGS, which will add to the nascent literature on its psychometric properties as applied to populations with developmental disorders (Medeiros et al. 2017; Pandolfi et al. 2009).

The early-emerging, differential patterns of challenging behaviors we observed among NGS support a number of potential clinical implications. First, our findings provide preliminary evidence that parent-reported challenging behaviors offer a feasible method for detecting early emerging features of challenging behaviors in NGS. Second, it is notable that many of these challenging behaviors are sub-threshold in terms of clinical norms, which have not been developed for NGS groups. Thus, in the context of longitudinal surveillance, measures such as the CBCL, while helpful in identifying early deviations in developmental trajectories and tracking symptom changes, may be refined by establishing clinical norms of expected behaviors within specific NGS and other high-risk groups. Finally, previous studies have demonstrated that behaviors need not exceed clinical thresholds before preventive efforts could be initiated; for example, behaviorally inhibited preschoolers at risk for anxiety disorders showed lower levels of anxiety symptoms and disorders if their parents received a six-session intervention program involving parenting skills, cognitive restructuring, and exposure hierarchies (Rapee et al. 2010), and a 12-session parent-mediated social communication intervention reduced the severity of prodromal autism symptoms in infants at high familial risk for autism (Green et al. 2017). Thus, it is possible that the emerging

patterns of challenging behaviors we detected in our high-risk NGS sample may be similarly leveraged to inform preventive efforts in NGS populations.

Further research is needed to address limitations of the present study such as the cross-sectional and parent-report nature of the data, lack of information on cognitive functioning, and small sample sizes common to studies of NGS. For example, although all of our NGS groups are characterized by developmental delays, which could be challenging to accurately measure in young children with NGS (Soorya et al. 2017), it is possible that variability in cognitive skills may have contributed to observed cross-syndrome differences. In addition to replicating our findings in larger samples, future work should incorporate multi-informant, multi-method, and naturalistic approaches to holistically understand challenging behaviors in young children with NGS. Longitudinal and prospective studies will also be valuable to understand the developmental trajectories of these challenging behaviors, as they are well suited to deal with the significant heterogeneity across individuals and detect potentially subtle changes in challenging behaviors of young children as well as their correspondence with later challenging behaviors. This work is critical to informing syndrome-specific preventive treatments to optimize outcomes for children with NGS and their families.

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Figure 1.

Mean *T* scores of Child Behavior Checklist narrowband scales (a) and DSM-oriented scales (b) for each neurogenetic syndrome and low-risk controls. Error bars represent standard errors. AS = Angelman syndrome; PWS = Prader-Willi syndrome; WS = Williams syndrome; LRC = Low-risk controls.

Table 1

Overview of Angelman, Prader-Willi, and Williams Syndromes

	Angelman Syndrome	Prader-Willi Syndrome	Williams Syndrome
Genetic cause	Loss of expression of maternal ubiquitin protein ligase E3A gene, <i>UBE3A</i> (Greydanus et al. 2016)	Deficient expression of paternal genes on chromosome 15q11-q13 (Alexander 2016)	Deletion of multiple genes on chromosome 7q11.23 (Pereira et al. 2016)
Prevalence	1:10,000 – 1:20,000 (Greydanus et al. 2016)	1:10,000 – 1:30,000 (Alexander 2016)	1:7,500 – 1:20,000 (Pereira et al. 2016)
Key characteristics	Severe cognitive impairment Jerky movements Minimal use of speech Happy demeanor Interest in social interactions (Williams 2010)	Mild cognitive impairment Strengths in visuospatial processing Hypotonia Feeding difficulties Hyperphagia and obesity (Whittington and Holland 2010)	Mild cognitive impairment Strengths in language abilities Cardiovascular anomalies Hypersociability coupled with deficits in perceiving social cues (Morris 2010)
Selected challenging behaviors and psychopathology	Hyperactivity (Clarke and Marston 2000) Sleep disturbances (Abel and Tonnsen 2017; Spruyt et al. 2018) Mouthing and feeding anomalies (Berry et al. 2005; Welham et al. 2015) Aggressive and self-injurious behavior (Larson et al. 2015) Autism spectrum disorder (Bonati et al. 2007)	Excessive daytime sleepiness (Maas et al. 2010) Compulsive and ritualistic behaviors (Dimitropoulos et al. 2006) Temper tantrums (Tunnicliffe et al. 2014) Skin picking (Hustyi et al. 2013) Psychosis (Yang et al. 2013) Disruptive behavior disorders (Shrikri-Tal et al. 2017) Obsessive-compulsive disorder (Shrikri-Tal et al. 2017) Autism spectrum disorder (Dykens et al. 2017)	Sleep difficulties (Abel and Tonnsen 2017; Annaz et al. 2011) Attention problems (Klein-Tasman and Lee 2017) Autism spectrum disorder (Klein-Tasman et al. 2009) Attention-deficit/hyperactivity disorder (Rhodes et al. 2011) Anxiety disorder (Royston et al. 2017)

Table 2

Demographic Characteristics of Participants

	AS (<i>n</i> = 30)		PWS (<i>n</i> = 22)		WS (<i>n</i> = 34)		LRC (<i>n</i> = 43)		Group Equivalence	
	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	Statistic	<i>p</i>
Child characteristics										
Median age (months)	30.5		28.2		31.0		28.7		Kruskal-Wallis	.931
(Interquartile range)	(22.8–41.9)		(24.7–34.8)		(24.6–42.0)		(22.1–39.4)		$H = 0.45$	
Sex										
Male	50.0	15	40.9	9	50.0	17	65.1	28	$\chi^2 = 4.05$	.256
Female	50.0	15	59.1	13	50.0	17	34.9	15		
Race										
White	96.0	24	94.1	16	93.1	27	97.5	39	Fisher's exact	.807
Non-White	4.0	1	5.9	1	6.9	2	2.5	1		
Ethnicity										
Non-Hispanic	100.0	25	94.1	16	93.1	27	97.5	39	Fisher's exact	.477
Hispanic	0.0	0	5.9	1	6.9	2	2.5	1		
Premature birth										
No	83.3	25	72.7	16	91.2	31	100.0	43	Fisher's exact	.002
Yes	16.7	5	27.3	6	8.8	3	0.0	0		
Family characteristics										
Mother's marital status										
Never married	10.0	3	4.6	1	14.7	5	0.0	0	Fisher's exact	.036
Now Married	86.7	26	90.9	20	79.4	27	100.0	43		
Separated/Divorced/Widowed	3.3	1	4.6	1	5.9	2	0.0	0		
Mother's educational attainment										
High school diploma or less	10.0	3	0.0	0	5.9	2	2.3	1	Fisher's exact	.369
Some college/Associate's degree	26.7	8	18.2	4	29.4	10	14.0	6		
Bachelor's degree	20.0	6	45.5	10	32.4	11	39.5	17		
Advanced degree	43.3	13	36.4	8	32.4	11	44.2	19		
Median family income (\$1,000)	97.5		83.5		80.0		94.0		Kruskal-Wallis	.494

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		AS (<i>n</i> = 30)		PWS (<i>n</i> = 22)		WS (<i>n</i> = 34)		LRC (<i>n</i> = 43)		Group Equivalence	
		%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	Statistic	<i>p</i>
(Interquartile range)		(78–125)		(60–150)		(55–110)		(47–135)		<i>H</i> = 2.40	

Note. AS = Angelman syndrome; PWS = Prader-Willi syndrome; WS = Williams syndrome; LRC = Low-risk controls.

Table 3
Descriptive Statistics of Child Behavior Checklist Raw Scores and Qualitative Categories

Scale (Scoring range)	Median (Interquartile Range)				% Clinical Range % Borderline Range			
	AS	PWS	WS	LRC	AS	PWS	WS	LRC
Total problems (0–200)	34.5 (27–54)	24 (16–31)	36.5 (26–48)	21 (13–34)	16.7 13.3	0.0 4.6	17.7 2.9	4.7 2.3
Broadband scales								
Internalizing problems (0–72)	10 (5–14)	4 (2–7)	7.5 (4–12)	4 (1–6)	10.0 16.7	0.0 0.0	14.7 0.0	2.3 2.3
Externalizing problems (0–48)	12.5 (7–17)	7 (5–11)	13 (10–19)	9 (5–13)	10.0 0.0	0.0 0.0	8.8 8.8	2.3 4.7
Narrowband scales								
Emotionally reactive (0–18)	2 (1–4)	0 (0–1)	1 (0–3)	1 (0–3)	0.0 10.0	0.0 0.0	5.9 8.8	0.0 4.7
Anxious/Depressed (0–16)	1 (0–4)	0 (0–1)	1 (0–3)	1 (0–2)	0.0 0.0	0.0 0.0	2.9 2.9	0.0 0.0
Somatic complaints (0–22)	2 (1–4)	0.5 (0–2)	2.5 (1–5)	0 (0–2)	6.7 13.3	4.6 0.0	8.8 17.7	2.3 0.0
Withdrawn (0–16)	4 (3–4)	2 (1–3)	2 (1–3)	0 (0–1)	13.3 10.0	9.1 9.1	8.8 2.9	2.3 0.0
Sleep problems (0–14)	4.5 (2–6)	1 (0–2)	4.5 (3–6)	3 (2–4)	6.7 6.7	0.0 0.0	5.9 5.9	9.3 2.3
Attention problems (0–10)	6 (3–8)	3 (1–4)	5 (3–7)	2 (0–3)	36.7 23.3	0.0 9.1	32.4 11.8	2.3 2.3
Aggressive behavior (0–38)	6 (2–9)	4.5 (3–7)	8.5 (5–14)	7 (4–12)	0.0 3.3	0.0 0.0	5.9 0.0	0.0 0.0
DSM-oriented scales								
Depressive problems (0–20)	3 (2–6)	1 (0–2)	3.5 (2–5)	1 (0–3)	16.7 13.3	0.0 9.1	17.7 5.9	2.3 0.0
Anxiety problems (0–20)	1 (0–4)	1 (0–2)	2.5 (1–4)	2 (1–3)	0.0 3.3	0.0 0.0	5.9 5.9	0.0 0.0
Autism spectrum problems (0–24)	5 (4–7)	3 (2–5)	2.5 (2–4)	1 (0–2)	23.3 3.3	4.6 13.6	8.8 5.9	2.3 0.0
Attention deficit/hyperactivity problems (0–12)	7.5 (5–9)	4 (2–5)	7 (5–9)	3 (2–5)	6.7 10.0	0.0 0.0	11.8 5.9	0.0 0.0

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Scale (Scoring range)	Median (Interquartile Range)				% Clinical Range			
					% Borderline Range			
	AS	PWS	WS	LRC	AS	PWS	WS	LRC
Oppositional defiant problems (0–12)	1 (0–3)	2 (0–3)	2 (1–4)	3 (1–5)	0.0	0.0	5.9	0.0

Note. AS = Angelman syndrome; PWS = Prader-Willi syndrome; WS = Williams syndrome; LRC = Low-risk controls; % Clinical Range = Percentage of participants with *T* scores of 64 or more for total problems and broadband scales or *T* scores of 70 or more for narrowband and DSM-oriented scales; % Borderline Range = Percentage of participants with *T* scores of 60 through 63 for total problems and broadband scales or *T* scores of 65 through 69 for narrowband and DSM-oriented scales.

Table 4

Atypicalities and Cross-syndrome Comparisons of Child Behavior Checklist Raw Scores

Scale	Wilcoxon Rank-Sum Test									
	AS vs. LRC			PWS vs. LRC			WS vs. LRC			r_{pb}
	Z	p	r_{pb}	Z	p	r_{pb}	Z	p	r_{pb}	
Total problems	3.57	<.001	.42	0.30	.766	.04	3.81	<.001	.43	
Broadband scales										
Internalizing problems	4.62	<.001	.54	0.76	.450	.09	3.36	<.001	.38	
Externalizing problems	1.26	.207	.15	-1.03	.304	-.13	2.77	.006	.32	
Narrowband scales										
Emotionally reactive	1.51	.132	.18	-2.20	.028	-.27	0.42	.678	.05	
Anxious/Depressed	0.50	.614	.06	-2.62	.009	-.32	0.58	.563	.07	
Somatic complaints	3.40	.001	.40	0.51	.611	.06	4.63	<.001	.53	
Withdrawn	6.61	<.001	.77	4.44	<.001	.55	5.16	<.001	.59	
Sleep problems	1.86	.063	.22	-3.62	<.001	-.45	1.84	.066	.21	
Attention problems	4.89	<.001	.57	2.05	.041	.25	4.88	<.001	.56	
Aggressive behavior	-1.26	.206	-.15	-2.23	.026	-.28	0.87	.385	.10	
DSM-oriented scales										
Depressive problems	4.34	<.001	.51	0.09	.931	.01	4.21	<.001	.48	
Anxiety problems	-0.67	.502	-.08	-3.49	.001	-.43	0.54	.591	.06	
Autism spectrum problems	6.27	<.001	.73	3.90	<.001	.48	4.10	<.001	.47	
Attention deficit/hyperactivity problems	4.17	<.001	.49	0.55	.584	.07	4.68	<.001	.53	
Oppositional defiant problems	-3.01	.003	-.35	-1.97	.049	-.24	-0.50	.615	-.06	
Cross-syndrome Comparisons										
Scale	Wilcoxon Rank-Sum Test									
	AS vs. PWS			AS vs. WS			WS vs. PWS			r_{pb}
	Z	p	r_{pb}	Z	p	r_{pb}	Z	p	r_{pb}	
Total problems	3.03	.002	.42	0.06	.952	.01	3.19	.001	.43	
Broadband scales										
Internalizing problems	3.54	<.001	.49	1.32	.186	.17	2.42	.016	.32	
Externalizing problems	1.99	.046	.28	-1.11	.267	-.14	3.41	.001	.46	

Atypicalities	Wilcoxon Rank-Sum Test									
	AS vs. LRC			PWS vs. LRC			WS vs. LRC			r_{pb}
	Z	p	r_{pb}	Z	p	r_{pb}	Z	p	r_{pb}	
Narrowband scales										
Emotionally reactive	3.09	.002	.43	0.88	.380	.11	2.33	.020	.31	
Anxious/Depressed	2.38	.017	.33	-0.09	.928	-.01	2.63	.009	.35	
Somatic complaints	2.32	.021	.32	-1.05	.295	-.13	3.27	.001	.44	
Withdrawn	2.81	.005	.39	3.58	<.001	.45	-0.24	.809	-.03	
Sleep problems	4.26	<.001	.59	0.28	.781	.03	4.26	<.001	.57	
Attention problems	3.26	.001	.45	0.55	.583	.07	3.07	.002	.41	
Aggressive behavior	0.81	.419	.11	-1.88	.060	-.24	2.77	.006	.37	
DSM-oriented scales										
Depressive problems	3.72	<.001	.52	0.07	.946	.01	3.57	<.001	.48	
Anxiety problems	1.72	.086	.24	-0.87	.387	-.11	3.04	.002	.41	
Autism spectrum problems	2.82	.005	.39	3.41	.001	.43	-0.24	.810	-.03	
Attention deficit/hyperactivity problems	3.63	<.001	.50	0.24	.807	.03	4.12	<.001	.55	
Oppositional defiant problems	-0.40	.687	-.06	-2.31	.021	-.29	1.50	.134	.20	

Note. p values in bold remain significant after Holm-Bonferroni correction. AS = Angelman syndrome; PWS = Prader-Willi syndrome; WS = Williams syndrome; LRC = Low-risk controls.

Table 5
Top Five Child Behavior Checklist Challenging Behaviors across Neurogenetic Syndromes

Item	AS		PWS		WS		LRC	
	Rank	% Concern	Rank	% Concern	Rank	% Concern	Rank	% Concern
Acts too young for age	1	96.6 ^a	4	72.7 ^b	2	82.4 ^{ab}		11.6 ^c
Speech problem	2	93.3 ^a	1	90.9 ^a	1	91.2 ^a		11.6 ^b
Chews on things that aren't edible	2	93.3 ^a	5	59.1 ^{bc}	2	82.4 ^{ab}		39.5 ^c
Can't concentrate, can't pay attention for long	4	86.7 ^a		45.5 ^b		79.4 ^a		27.9 ^b
Gets into everything	5	83.3 ^a	2	77.3 ^a	2	82.4 ^a		62.8 ^a
Poorly coordinated or clumsy		66.7 ^a	2	77.3 ^a		70.6 ^a		14.0 ^b
Can't stand waiting; wants everything now		69.0 ^a	5	59.1 ^a	2	82.4 ^a		69.8 ^a
Quickly shifts from one activity to another		76.7 ^a	5	59.1 ^{ab}		79.4 ^a		44.2 ^b

Note. AS = Angelman syndrome; PWS = Prader-Willi syndrome; WS = Williams syndrome; LRC = Low-risk controls; % Concern = Percentage of participants who indicated that the item was very true or often true or somewhat or sometimes true of their child.

^{a-c}Values in a row with no common superscripts are significantly different from one another ($p < .05$), based on Fisher's exact tests.