Characterization of the SRD5A3-CDG Clinical Spectrum

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Abstract

We aimed to characterize the clinical spectrum of patients diagnosed with SRD5A3-CDG, a subtype of congenital disorders of glycosylation (CDG) due to variants in the steroid 5a-reductase type 3 (SRD5A3) gene. It presents with multi-systemic involvement including neurological disability, dermatologic abnormalities, and ophthalmological defects. We conducted a cross-sectional study of children (n=6, ages 4-16 years) with a confirmed diagnosis of SRD5A3-CDG (c.57G>A, p.W19X). Families completed a detailed medical history questionnaire, two quality of life measures, and an adaptive behavior scale. Prevalent clinical features in our cohort included visual impairment (6/6), developmental delay (6/6), nystagmus (5/6), retinal dystrophy (4/6), and hypotonia (3/6). The Vineland Adaptive Behavior Scales demonstrated deficits across all functional domains (Composite Mean 36.17 ± 26.88), although one child did not show significant deficits. The QI-Disability Form demonstrated a mean total score of 64.8 (±12.7), and the PedsQL-Family Impact Module demonstrated a mean total score of 56.5 (±31.5). Vineland composite scores did not correlate with levels of disability captured by the QI-Disability Form (Pearson Correlation range -0.63 to +0.69, p>0.05 on all subscales). Ultimately, despite genotypic homogeneity, there is notable variability in adaptive functioning and quality of life among affected children that does not correlate with age.

Keywords

Congenital disorder of glycosylation, SRD5A3, developmental delay, visual impairment, quality of life.

Introduction

Congenital Disorders of Glycosylation (CDGs) are a rapidly growing family of metabolic disorders that involve defects in generating and attaching glycans to proteins and lipids. There are over 160 CDGs divided into six categories, over 40 of which involve defects in multiple glycosylation pathways[1]. One example is SRD5A3-CDG caused by variants in steroid 5 alpha-reductase type 3 (*SRD5A3*). First discovered in 2010, *SRD5A3* is transcribed to produce dolichols through the reduction of the alpha-isoprene unit of polyprenols, a process necessary for the synthesis of dolichol-linked monosaccharides and the N-glycosylation oligosaccharide precursor[2-3]. N-glycosylation is an essential post-translational modification of specific asparagine residues on most membrane-bound and secreted proteins produced by eukaryotic cells. This post-translational processing of proteins affects cell-cell interactions, cell-matrix interactions, and intracellular signaling[4].

There are over twenty unique variants associated with SRD5A3-CDG including nonsense (e.g., p.Trp107X, p.Trp102X, p.Trp19X), missense (e.g., p.Pro307Arg, p.Pro315Ser), and deletion/insertion (e.g., Gln96delinsX). Patients present with ophthalmological defects (e.g., visual impairment, nystagmus, retinal disease), developmental delay, hypotonia, skin disease, cerebellar defects, and intellectual disability[5-12]. Brain magnetic resonance imaging typically shows cerebellar hypoplasia or atrophy. However, variable findings such as demyelination, small basal ganglia, punctate white matter lesions, thick corpus callosum, colpocephaly, malrotation of the hippocampus, and a thin cervical cord have also been reported[1,11-12].

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The genetic landscape of CDGs is rapidly expanding, as is the phenotypic spectrum associated with each subtype. A thorough understanding of the genotypic and phenotypic spectrum of each CDG is needed to improve clinical care and prepare for future clinical trials. In this cross-sectional study, we characterized the clinical spectrum of disease in a cohort of unpublished patients with SRD5A3-CDG and assessed standardized measures of adaptive functioning and quality of life. We hypothesize that hypotonia and nystagmus are the most prevalent symptoms across patients in the SRD5A3-CDG cohort.

Methods

We conducted a single-center cross-sectional study of SRD5A3-CDG. Participants were recruited in partnership with the Sappani Foundation and Cure SRD5A3. The diagnosis of SRD5A3-CDG was confirmed via genetic report showing bi-allelic pathogenic variants. Participants completed a medical history questionnaire, the PedsQL Family Impact Module (PedsQL-FIM), the QI-Disability, and the Vineland Adaptive Behavior Scales, 3rd Edition (VABS).

Medical History Questionnaire

Caregivers completed an electronic medical history questionnaire by REDCap survey. The medical history questionnaire included questions on demographics (e.g., age, race, sex), family history (e.g., neurological disease), birth history (e.g., birth weight, complications), diagnoses related to SRD5A3-CDG (e.g., visual impairment, developmental delay), developmental milestones (e.g., head control, babbling), current and past therapies (e.g., physical therapy, occupational therapy, speech therapy), and current and past medications. Medical history forms were reviewed with the family by the study team (VD) upon completion. Families also had the option to provide photos of affected children (front and profile, Figure 1).

Standardized Questionnaires

All participants completed two quality of life measures and an adaptive behavior scale. Quality of life measures (PedsQL FIM and QI-Disability) were administered by the study team (VD) by phone or videoconference to one parent from each family. The VABS was administered by interview and scored by a pediatric neuropsychologist (DH).

The PedsQL-FIM measures the self-reported quality of life of caregivers and other family members of children with chronic illness. It is comprised of 36 items scored on a 5-point Likert scale in the following domains: physical functioning, emotional functioning, social functioning, cognitive functioning, communication, worry, daily activities, and family relationships. Higher scores are indicative of better functioning and less negative impact. The QI-Disability form measures the quality of life of children and adolescents with chronic illness. It is comprised of 32 items scored on a 5-point Likert scale within the following domains: health and well-being, feelings and emotions, family and friends, activities and the outdoors, and daily life. For both quality-of-life measures, the computation of scale scores is the mean of each section, and the mean of the scale scores is the total score.

The VABS is a standardized assessment of adaptive functioning. The overall level of adaptive function for each patient is reflected in the Adaptive Behavior Composite (ABC) score which is based on scores from four adaptive behavior composite domains: Communication, Daily Living Skills, Socialization, and Motor Skills. The Communication domain is a measure of how well each patient listens and understands, expresses themselves through speech, and reads and writes. The Daily Living Skills domain assesses each patient's ability to perform practical, age-appropriate activities of living. The Socialization domain reflects each patient's level of function in social situations. Finally, the Motor Skills domain reflects each patient's ability to perform age-appropriate motor functions such as walking and writing and is only reliable for participants under 8 years of age[13]. Where available, VABS age-equivalent scores for subdomains are reported.

Statistics

Given the small sample size for this study, descriptive statistics and nonparametric tests were used for comparisons and correlations. Pearson correlation coefficient was run to assess the relationship between the Vineland ABC score and each of the following variables: age, FIM mean total score, QI disability total score, and each QI disability section score. Additionally, Vineland domain subscale raw scores for each participant were summed and plotted versus age.

Results

Demographics

We enrolled six participants of Asian descent. There were two males and four females with a mean age of 10.17 years (± 4.79, range 4-16). Three of the six participants were siblings (one male and two females), and the remaining three participants were singletons. All participants were homozygous for the nonsense variant c.57G>A, p.W19X (Table 1).

Medical History Questionnaire

All six participants had developmental delay and visual impairment. Five of the six (83.3%) had nystagmus, 4/6 (66.7%) had retinal dystrophy, and 3/6 (50%) had hypotonia. Other clinical features included movement disorder (2/6, 33.3%), weakness (2/6, 33.3%), optic disk or nerve hypoplasia (2/6, 33.3%), abnormal skin pigmentation (2/6, 33.3%), seizures (1/6, 16.7%), and sleep problems (1/6, 16.7%). No participants had ichthyosis or eczema (Figure 2).

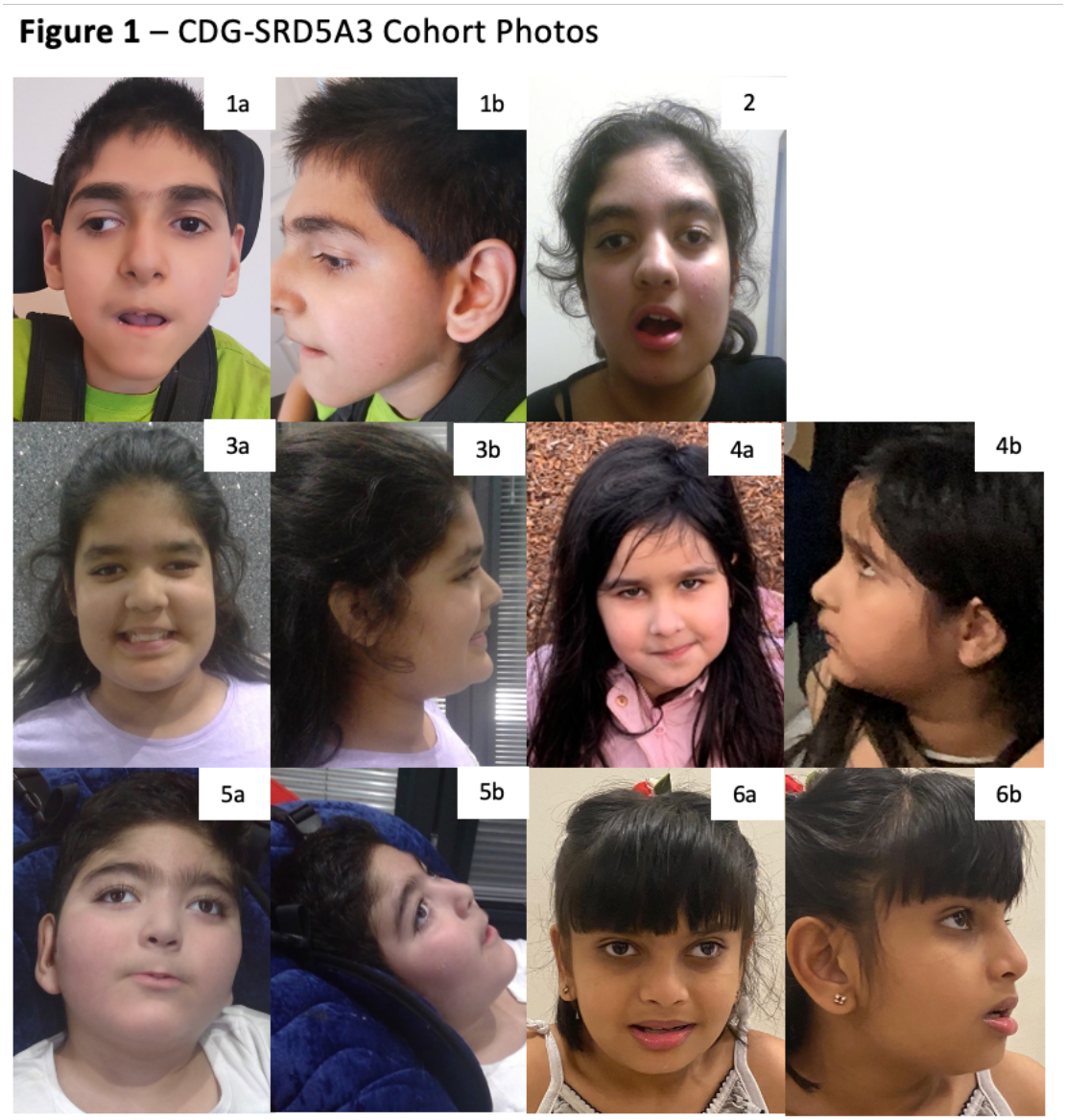

Figure 1. Abnormal craniofacial features associated with CDG-SRD5A3 include strabismus (1, 2, 3, 5, and 6), brachycephaly, microcephaly, hairy forehead (5), arched eyebrows (1, 2, 5), hypertelorism, bulbous nose (1, 2, 6), broad nasal bridge (5), depressed nasal bridge (1, 3, 4), short upturned nose, smooth philtrum (1, 2, 3, 5, 6), large mouth, thin upper lip (1, 5), and abnormal ears (5).

Table 1. Demographic and genotypic makeup of our cohort. Participants 2, 3, and 5 are siblings. Participants 1, 4, and 6 are singletons. All are Asian and have the same genotype.

Participants	Demographics			Mutation	
	Gender	Age (yr)	Ethnicity	Coding DNA	Protein
1	M	16	Asian	c.57G>A	p.Trp19X
2	F	15	Asian	c.57G>A	p.Trp19X
3	F	11	Asian	c.57G>A	p.Trp19X
4	F	6	Asian	c.57G>A	p.Trp19X
5	M	4	Asian	c.57G>A	p.Trp19X
6	F	9	Asian	c.57G>A	p.Trp19X

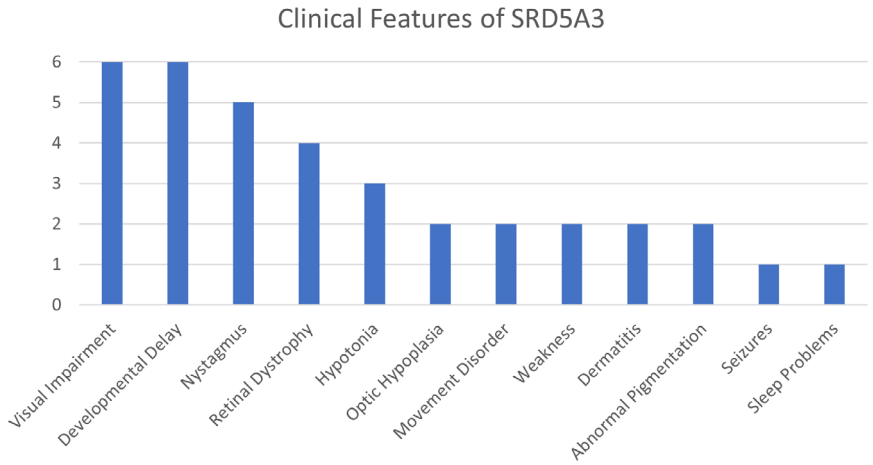

Figure 2. Clinical Features of this SRD5A3-CDG cohort. The most common features are visual impairment, developmental delay, nystagmus, and retinal dystrophy.

Four of the six participants (66.7%) achieved the gross motor milestones of head control (mean 8 months, range 4-12 months), rolling (mean 8.25 months, range 6-12 months), independent sitting (mean 13.25 months, range 8-24 months), and walking (mean 30 months, range 18-48 months) without regression. Of these four, 75% (3/4) are toilet trained (mean 48 months, range 36-60 months) and can speak in at least 2-word phrases (mean 54 months, range 36-90 months). The 9-year-old participant is working on toilet training and has not yet attained babbling or speech. Of the remaining two participants, the 16-year-old child never fully attained gross motor skills, is not toilet trained, and lost his ability to babble at 10 months. The 4-year-old child never attained gross motor milestones or speech due to severe movement disorder and dystonia (Table 2).

Table 2. Motor and language developmental milestones of this SRD5A3-CDG cohort. Two participants did not achieve any motor milestones. Only one participant was able to communicate in sentences. One participant exhibited developmental regression of language skills (lost babbling).

Domain	Milestone	Mean age in months (range in months) n
Motor	Head Control	8 (4-12) 4
	Rolling	8.25 (6-12) 4
	Independent Sit	13.25 (8-24) 4
	Walking	30 (18-48) 4
Language	Babbling	48 (36-60) 3
	First Word	40 (24-72) 3
	2-word Phrase	54 (36-90) 3
	Sentences	60 (60) 1

All participants have engaged in or are currently engaged in speech, occupational, and physical therapy. One-third (2/6) are currently engaged in applied behavioral analysis, and one child is engaged in vision therapy. For two-thirds (4/6) participants, no medications were listed as helpful or unhelpful. Lansoprazole was reportedly effective in managing reflux in one participant. Azithromycin was used for lower respiratory tract infection prophylaxis in one participant. Other medications reported as ineffective in managing symptoms of SRD5A3-CDG included trihexyphenidyl and baclofen for motor symptoms and clonidine, diazepam, and melatonin for sleep and behavioral problems. There are no known drug allergies reported in this cohort.

Standardized Questionnaires

The PedsQL-FIM demonstrated a group mean total score of 49.1 (±30.8). The family with three affected children demonstrated the greatest disability on this measure with a mean of 29.4 (±4), while the mean total score for families with one affected child was 81.8 (±15.4), (Table 3). The group mean total score on the QI-Disability was 64.8 (±12.7). Of the functional domains, participants had the highest mean score on positive emotions (71.2±16.6) and lowest mean score on leisure and outdoors (50.8±26.9), (Table 3).

The group mean composite scores across all domains on the VABS were ≥3 standard deviations (SD) below the standardized mean of 100 in four participants. The child with the highest scores on the VABS was <1 SD below the standardized mean on the Communication composite and <2 SD below the standardized mean on the Daily Living Skills and Socialization composite scores, suggesting that communication was a relative strength. In contrast, four of the remaining five participants demonstrated a relative weakness in communication. A composite Motor Skills score was calculated for the three participants <8-years old and was a relative strength for one. There was no significant correlation between the VABS ABC score and the FIM mean total score, the QI disability total score, and each QI disability section score (Table 3, Figure 3).

The VABS age-equivalent scores for all communication subdomains were under the age of 4-years 8-months for five participants aged 4 to 16 years old. The 11-year-old participant had communication subdomain scores ranging from 6-years 3-months to 15 years with a relative strength in receptive (15-years 0-months) and expressive (11-years 9-months) abilities. The VABS age-equivalent scores for all daily living skills subdomains were under the age of 3-years 1-month for five participants aged 4 to 16 years. The 11-year-old participant demonstrated age-equivalent subdomain scores ranging from 5-years 7-months to 7 years 7-months. The VABS age-equivalent scores for all socialization subdomains were 3 years for five participants aged 4 to 16 years. The 11-year-old participant demonstrated subdomain scores ranging from 3-years 8-months to 4-years 10-months. Finally, the VABS age-equivalent scores for all motor skills subdomains were approximately 2 years old for four participants aged 4 to 16 years. The remaining two participants aged 6 years and 11 years demonstrated subdomain scores ranging from 2-years 6-months to 5-years 1-month. Of note, the children aged 4 and 16 years old had gross motor and fine motor subdomain scores equivalent to a neonate. The children aged 6 and 11 years old had gross motor and fine motor subdomain scores approximately equivalent to a 3-year-old and 4- to 5-year-old, respectively (Table 3, Figure 3). There was no significant correlation between the VABS ABC score and age.

Table 3. Vineland Adaptive Behavior Scales domain and composite scores, PEDsQL total scores, and QI disability total scores. Participants 2, 3, and 5 are siblings.

	Adaptive Behavior Composite	VABs Communication	VABs Daily Living Skills	VABs Socialization	VABS Motor	PedsQL Total	QI Disability Total
1	20	20	20	20	N/A	89.58	50.98
2	27	20	20	38	N/A	25.00	72.23
3	76	87	74	75	N/A	31.94	81.67
4	58	46	64	61	70	65.27	59.43
5	36	24	47	36	20	31.94	54.17
6	32	20	41	32	20	93.75	76.4
Mean (SD)	41.5 (21.24)	36.17 (26.88)	44.33 (22.22)	43.67 (20.34)	36.67 (28.87)	56.25 (30.84)	65.81 (12.66)

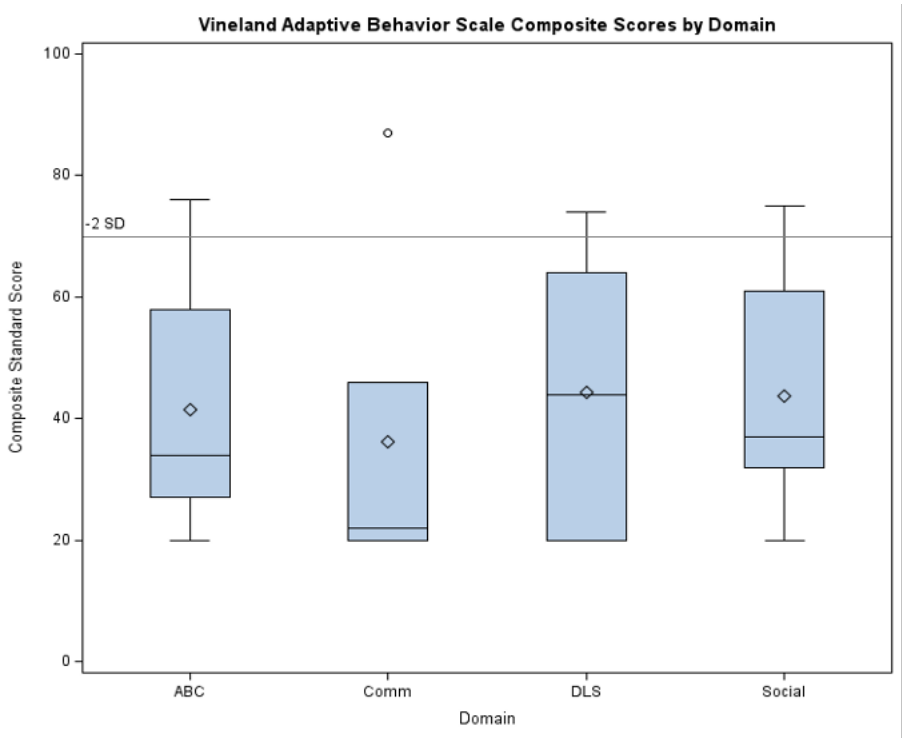

Figure 3. Vineland ABC and scale scores by domain.

Discussion

SRD5A3-CDG is a rare genetic disorder resulting in a defect of the N-glycosylation pathway of post-translational protein processing that leads to neurological disability and functional impairment. Systematic studies of this disorder are limited, and no prior studies have explored the utility of quality-of-life measures or adaptive behavior questionnaires. Characterization of the genotype, clinical phenotype, and quality of life is key to understanding the natural history of this CDG subtype and preparing for future precision therapy clinical trials.

The *SRD5A3* c.57G>A, (p.W19X) variant, seen in all members of this cohort, has been described in children of Turkish, South Asian, Pakistani, Indian, Kurdish, and Emirati descent with the highest prevalence among those of Asian descent [1,5-11]. This is consistent with our study where all participants were of Asian descent. In this small sample, developmental delay and visual impairment were the most prevalent features followed by nystagmus and hypotonia. The predominance of these features is consistent with prior reports of individuals with the p.W19X mutation[1,5-11], where nystagmus and visual impairment were the most common features, followed by hypotonia. Developmental delay was universal within our small sample, but there was considerable variability in the timing of milestone achievement ranging from on time to months to years depending on the milestone. Additionally, two participants never attained the ability to roll or sit up, one of whom demonstrated a loss of babbling at 10 months of age. This suggests that though developmental delay is common, the developmental trajectory of each patient may be variable, and regression appears to be rare. Notably, the two participants with the most severe developmental delay were both male, while the remaining four participants, all female, achieved gross motor milestones through walking. This could suggest increased severity for males with the p.W19X variant, but this is a very small sample. Furthermore, other cases of males with this variant show attainment of independent ambulation[7-8].

The results of the PedsQL FIM showed that there is a notable impact on quality of life with a mean total score greater than 3 SD below the standardized mean. However, this score was driven primarily by the family with three affected children, suggesting that having more children with complex medical needs negatively impacts the quality of life of the family. This finding must still be interpreted with caution as other potential confounders such as impact of the home environment, parental backgrounds, or social support should be considered. Similarly, the QI-Disability questionnaire, which measures the quality of life of the individual, demonstrated a mean total score >2 SD below the standardized mean indicating significant impairment. There was a high degree of variability within the cohort which suggests additional environmental or genetic factors are exerting an effect in combination with the Trp19X mutation. Overall, participants had the highest scores in displaying positive emotions and the lowest scores in engaging in outdoor activities. This may suggest that individuals with SRD5A3-CDG tend to have positive behaviors but struggle with more physical activities, possibly due to comorbid hypotonia and motor impairment.

Within our small sample, all participants demonstrated impairments in adaptive functioning, although there was phenotypic variability, even among the three related participants. The child with the highest Vineland scores was 11 years old (ABC scores within 1-2 SD below the standardized mean) and demonstrated age-equivalent scores in receptive and expressive communication greater than their chronological age. This child has two siblings who are more severely affected with Vineland ABC scores greater than 4 SD below the standardized mean. All three siblings presented with nystagmus, visual impairment, retinal dystrophy, and developmental delay. However, there was some clinical heterogeneity within the siblings; the 9-year-old also had a movement disorder and sleep problems, and the 15-year-old also had hypotonia, weakness, and dermatitis. The most impaired participant (16 years old) scored six SD below the standardized mean and demonstrated age-equivalent scores well below their age in all domains. Ultimately, a larger sample size is needed to adequately assess the progression of age-equivalent skills.

Comparing the sum of VABS raw scores by age suggests that levels of adaptive functioning do not correlate with age. There was no significant correlation between the Vineland ABC mean score with age, with the FIM mean score, with the QI Disability mean total score, and with the QI disability mean section scores. It appears that the perceived impact of the disorder on the affected children or impact of the caregiver-burden does not closely match the objectively measured adaptive functioning. However, our ability to detect a relationship between adaptive functioning and quality of life is limited by the small sample size as well as the family structure of the cohort with half the participants being related and living in the same household. Furthermore, this was a homogenous sample with all Asian individuals with the same genotype (Trp19X) which limits generalizability of these results to the larger SRD5A3-CDG population.

Conclusion

Though this is a small cohort, the clinical features are consistent with previously reported cases of SRD5A3-CDG and support the inclusion of this rare disorder on the differential of any patient presenting with visual impairment, developmental delay, nystagmus, retinal dystrophy, or hypotonia. Despite genotypic and ethnic homogeneity, there is notable variability in adaptive functioning and quality of life among affected children that does not correlate with age in this small sample size. However, there was a negative impact on the quality of life of the individual patient as well as the family, suggesting the effects on perceived

disability and caregiver burden should be considered when developing holistic treatment plans. As precision therapies are being developed, the deficits in adaptive functioning and negatively impacted quality of life scores, as measured by the QI-Disability form, pose promising clinical outcome measures that appear to capture disability in the cohort and could be responsive to intervention in a future clinical trial. To further support this conclusion, larger studies with longitudinal data collection are needed.

Ethics Approval and Consent to Participate

This study was approved by the University of Texas Southwestern IRB (STU-2020-0636).

Data Sharing Statement

Written informed consent was obtained from all patients/families to reproduce the data, figures, and images in this manuscript.

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