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TELO2-related syndrome (You-Hoover-Fong syndrome): Description of 14 new affected individuals and review of the literature

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Abstract

You-Hoover-Fong syndrome (YHFS) is an autosomal recessive condition caused by pathogenic variants in the *TELO2* gene. Affected individuals were reported to have global developmental delay, intellectual disability, microcephaly, dysmorphic facial features, ocular involvement including cortical visual impairment, strabismus, cataract and rotatory nystagmus, movement disorder, hypertonia and spasticity, balance disturbance and ataxia, and abnormal sleep pattern. Other features reported include poor growth, cleft palate, cardiac malformations, epilepsy, scoliosis, and hearing loss. To date, 12 individuals with YHFS have been reported in the literature. Here we describe 14 new individuals with YHFS from 10 families. Their clinical presentation provides additional support of the phenotype recognized previously and delineates the clinical spectrum associated with YHFS syndrome. In addition, we present a review of the literature including follow-up data on four previously reported individuals with YHFS.

KEYWORDS
developmental delay, microcephaly, syndromic intellectual disabilities, TELO2, YHFS, You-Hoover-Fong syndrome

1 | INTRODUCTION

You-Hoover-Fong syndrome (YHFS) is an autosomal recessive condition caused by pathogenic variants in the *TELO2* gene, which has a critical role in checkpoint responses to cellular stress. The protein product of *TELO2* also interacts with each of the six-mammalian phosphatidylinositol-3-kinase-related kinase (PIKK) genes (*ATM*, *ATR*, *DNA-PKcs*, *mTOR*, *SMG1*, *TRRAP*) and prevents their rapid degradation. Additionally, two specific Telo2-interacting genes, *TTI1* and *TTI2*, associate with *TELO2* to create a TELO2-TTI1-TTI2 complex (TTT) that serves as a PIKK-specific chaperone for Hsp90 (Takai et al., 2007). In the absence of a normal TTT complex, PIKKs are poorly folded and proteolyzed, thereby reducing their levels (Hurov et al., 2010).

All of the affected individuals with TELO2-related syndrome recognized thus far have been observed to have global developmental delay, intellectual disabilities, and microcephaly. Other common features include facial dysmorphism, ocular involvement including strabismus, cortical visual impairment, cataracts and rotatory nystagmus, sleep disorder, movement disorders, hypertonia and spasticity, balance disturbance, and ataxia. Some other features have been occasionally reported include poor growth, cleft palate, scoliosis, cardiac malformations, epilepsy, and hearing loss. As whole-exome sequencing (WES) becomes more widely used, more individuals are being diagnosed with this condition thus providing more opportunity to understand the natural history of YHFS. Here we describe the clinical and molecular features of 14 new individuals from 10 families diagnosed with YHFS. In addition, we present a review of the literature including follow-up data on four previously reported individuals with YHFS.

2 | MATERIALS AND METHODS

2.1 | Human subjects research and data collection and management

This study was approved by the Institutional Review Board of Johns Hopkins University and was conducted in accordance with institutional standards. Families included in this research study provided oral consent for participating in the study and written consent to review the clinical medical records. The study participants included the clinical individuals diagnosed with YHFS and seen for initial or ongoing care within the medical genetics clinic at Johns Hopkins and individuals referred by their physicians from other institutions in the United States and other countries. Further recruitment was done through GeneDx, a large commercial laboratory, which contacted the submitters of samples found to harbor pathogenic variants *TELO2* and connected us with the physicians/families who were interested to be part of the study. Later, we included affected individuals whose families learned about the study through peer recruiting and were interested to be part of the research study. Inclusion criteria for this study required the presence of biallelic pathogenic variants in *TELO2* for individuals at any age who were diagnosed with YHFS.

The study is a retrospective and cross-sectional description of the phenotype. The clinical information was collected by interviewing families and reviewing the clinical medical records of the individuals. We designed our own comprehensive data collection form (available upon request from the authors) and we collected and stored the data in a REDCAP database administered by the Data Informatics Services Core (DISC) of the Johns Hopkins Biostatistics Center (Harris et al., 2009).

We used CDC age-specific developmental milestones to quantify development (https://www.cdc.gov/ncbddd/actearly/milestones/index.html). We also used Denver II Development Screening Test to compare the individuals' performance for various age-appropriate tasks in our cohort to the performance of other children the same age. Items that could be completed by 90% of typically-developing children but failed by individuals in our cohort are referred to as delays (Frankenburg, 1992 & 1992). Regarding growth, we used Pedi-Tools based on the WHO child growth standards to determine the Z-score of length/height, weight and head circumference (Chou et al., 2020).

3 | RESULTS

3.1 | Molecular analysis

We identified nine novel pathogenic variants in TELO2 in our cohort from the previously unreported 14 individuals from 10 families, bringing the total to 19 pathogenic variants in TELO2 gene (Figure 1). We identified biallelic TELO2 variants in all individuals diagnosed with YHFS (Figure 1 and Table S1). These variants were mostly missense and scattered throughout the gene. The most frequent variant in our cohort is p.Gly131Asp present in six individuals (12% of the total variants). All of our individuals were diagnosed between the ages of 15 months to 16 years, except for one individual diagnosed at 3 weeks of age due to confirmed molecular diagnosis in his older brother. Of the 18 individuals included in our cohort, 12 were male (67%), ranging in age from 2 months to 24 years old at the time of enrollment or last known clinical encounter. One individual in our cohort was deceased at age of 8 years.

A summary of the key clinical manifestations of the 14 new individuals, updated clinical information on 4 previously reported individuals and 8 additional individuals from the medical literature are presented in

Family (F); Patient (P)	DNA variant	Protein variation
F1; P1	partial gene del, c.1826G>A	del 1.6kb in 16p13.3 p. Arg609His
F2; P2	c.392G>A c.1100G>T	p.Gly131Asp p.Cys367Phe
F3; P3	c.2159A>T c.392G>A	p.Asp720Val p.Gly131Asp
F4; P4, 5	c.1842+G>A c.2296G>A	IVS15+G>A p.Val766Met
F5; P6, 7	c.1207C>T c.2275C>G	p.Arg403ter p.Arg759Gly
F6; P8	c.392G>A c.1772T>G	p.Gly131Asp p.Val591Gly
F7; P9	c.392G>A c.394 C>T	p.Gly131Asp p.Arg132Trp
F8; P10, 11	c.2159A>T c.1772T>G	p.Asp720Val p.Val591Gly
F9; P12	c.2226G>A c.2312T>C	p.Thr742= p.Leu771Ser
F10; P13, 14	c.59_63delCGTC T, c.392G>A	p.Ser20PhefsX20 p.Gly131Asp
F11; P15, 16, 17	c.1100G>T c.2159A>T	p.Cys367Phe p.Asp720Val
F12; P18	c.1100G>T c.2296G>A	p.Cys367Phe p.Val766Met
F13; P19	c.779C>T c.1826G>A	p.Pro260Leu p.Arg609His
F14; P20	c.2159A>T c.514C > T plus c.2034+1G>A	p. Asp720Val p.Gln172ter plus IVS16+1G > A
F15; P21, 22	c.1750dupA c.2312T>C	p.Thr584Asnfs*42 p.Leu771Ser
F16; P23, 24	c.1100G>T c.1216G>A	p.Cys367Phe p.Gly406Ser
F17; P25, 26	c.1826G > A homozygous	p.Arg609His

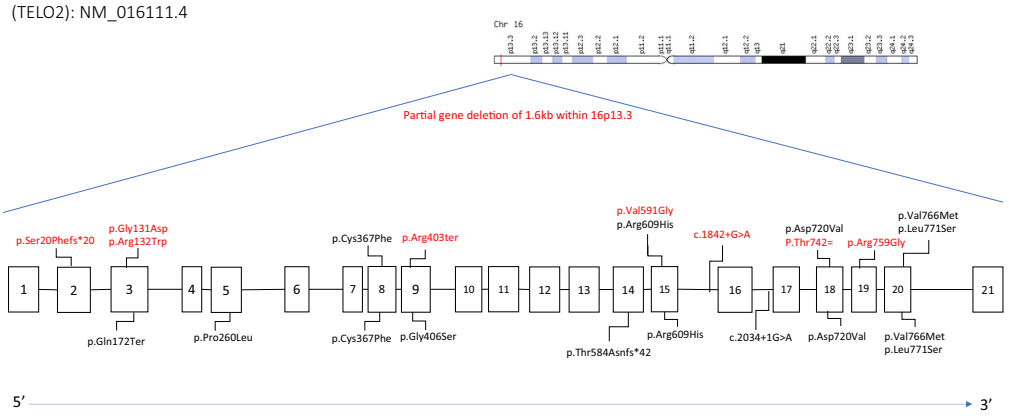

FIGURE 1 All reported TELO2 pathogenic variants. Variants identified in this study are shown above the figure with novel variants identified in this study in red. Below the figure all TELO2 pathogenic variants reported in the literature are shown.

Table 1 and Figure 2. Complete clinical and molecular details of all individuals with YHFS are presented in Table S1 and Appendix S1.

3.2 | Pregnancy and perinatal period

Pregnancy and perinatal complications have not been clearly described previously for YHFS. Prenatal complications were an almost constant finding in this cohort (16/18). Intrauterine growth restriction was the most frequent complication ($n = 8$) during pregnancy, followed by decreased fetal movements and preeclampsia ($n = 4$) each, and oligohydramnios ($n = 3$). Prematurity was identified in six individuals with gestational age range from 34 to 36 weeks. Seventy-two percent were delivered vaginally and 28% had caesarean section; 60% of these due to fetal distress. APGAR scores were reportedly below 7 in 6 of 14. Birth weight ranged from 1.59 kg (delivered at 38 weeks) to 3.71 kg, with an average birth weight of 2.46 kg in 18 individuals. The mean birth weight Z-score was -1.9 ± 1.36 (-4.6 to 1) with 44% within 0 to -2 standard deviations (*SD*), 28% within -2 to -3 *SD*, and 22% below -3 *SD* of the mean birth weight of a 40-week (term) gestation newborn. Nine individuals required neonatal intensive care unit admission for a range of 1 day to 6 weeks. The most common reason for prolonged newborn hospitalization were feeding issues (7/9), hypoxia with need for oxygen therapy (5/9), hypotonia (3/9), and birth defects such cleft lip/palate, cardiac and vascular anomalies (3/9). Less common were seizures, jaundice, and infection in one individual each. Out of 17, 14 individuals passed their newborn hearing screening. Seventy-eight percent of the parents had concerns about prolonged poor feeding since birth, which was associated with hypotonia in 43% of the time. However, further investigations were initiated at age of 6 months in 50% of the individuals, while the rest of the affected individuals had delayed work-up until the age between 9 months and 2.5 years.

3.3 | Neurologic complications and brain imaging

The most commonly reported neurological abnormalities were hypotonia in 15 of 18, hypertonia and spasticity in 10 of 18, abnormal movement in 15 of 18 which include constant non-purposeful movement of the extremities, jerking movement, persistent startle reflex, head drop, body stiffness, tremor, chorea, and dystonia. Ataxia or gait problems were noted in 13 out of 17 individuals, and a diagnosis of epilepsy was made in 1 individual. Our cohort is consistent with previous reports where microcephaly was identified in 18/18. One individual (P3) in our cohort was borderline microcephalic. She received growth hormone treatment between ages of 4–11 years. Documented head circumference at 3 years was at the 1st percentile with minimal growth to the 4th percentile in comparison with her weight (34th–36th percentile) and height (10th–17th percentile) around 10 years of age.

In our cohort, out of 16 individuals who underwent neuroimaging, 12 individuals reported some form of brain abnormalities identified by MRI or CT including white matter abnormality ($n = 11$), thin or hypoplastic corpus callosum ($n = 7$), and prominent ventricles or ventriculomegaly ($n = 9$). Other brain abnormalities including hypoplasia of the bilateral optic nerves, diminished pituitary gland volume, and maldevelopment of the left cochlea and vestibular canal along with empty sella were identified in one individual each.

TABLE 1 Summary of the clinical manifestations of the individuals in our cohort and affected individuals from literature.

Category	Issues	This study affected, *n*/total eligible, *n*	From literatures[a] affected/data available, *n*[b]	Combined
Neurological	ID	15/15[c]	7/7	22/22
Brain	DD	17/18	7/7	24/25
	Hypo−/hypertonia	17/18	3/3	20/21
Anomalies[d]	Microcephaly	18/18	8/8	25/26
	Abnormal movement	15/18	4/6	19/24
	Ataxia	13/17[e]	4/4	17/21
	Epilepsy	1/18	3/8	4/26
	Abnormal EEG	2/11[f]	2/3	4/14
	Abnormal white matter	11/16	1/3	12/19
	Dilation of the ventricles	9/16	0/3	9/19
	Abnormal corpus callosum	7/16	0/3	7/19
Gastrointestinal	Feeding problems	18/18	2/2	20/20
	Failure to thrive	18/18	2/2	20/20
	GERD/vomiting	15/18	ND	15/18
	Constipation	10/18	ND	10/18
	Drooling	10/17[g]	ND	10/18
	G-tube	9/18	ND	9/18
	Dysmotility	7/18	ND	7/18
	Aspiration	4/18	ND	4/18
Behavioral	Autistic Features	16/17[e]	1/1	17/18
	Sleeping problems	16/18	5/6	21/24
	Self-injurious behavior	14/17[e]	ND	14/17
	Short attention span/ADHD	11/17[e]	1/1	12/18
	Aggressive behaviors	6/17[e]	1/1	7/18
	Laughter outburst	8/17[e]	4/4	12/21
	Anxiety	6/17[e]	ND	6/17
	Obsessive–compulsive behaviors[c]	5/17[e]	ND	5/17
Ocular	Strabismus	13/18	4/7	17/25
	Astigmatism	7/18	ND/7	7/25
	Cortical visual impairment	5/18	1/7	6/25
	Hypermetropia/Myopia	4/18	2/7	6/25
	Rotatory nystagmus	2/18	1/7	3/25
	Cataract	2/18	3/7	5/25
	Retinitis pigmentosa	2/18	1/7	3/25
	Optic nerve hypoplasia	1/18	ND/7	1/25
Craniofacial features	Ankyloglossia	11/18	1/6	12/24
	Lacrimal duct blockage	6/18	1/6	7/24
	Tented/thin upper lip	5/15[h]	1/6	6/21
	High arched palate	4/15[h]	0/6	4/21
	Ears abnormalities	3/15[h]	1/6	4/21
	Forehead (prominent/narrow/wide)	3/15[h]	2/6	5/21
	Hypertelorism	3/15[h]	1/6	4/21
	Cleft palate	2/18	2/6	4/24
	Macroglossia	2/15[h]	1/6	3/21

TABLE 1 (Continued)

Category	Issues	This study affected, *n*/total eligible, *n*	From literatures[a] affected/data available, *n*[b]	Combined
	Smooth philtrum	1/15[h]	1/6	2/21
Musculoskeletal	Joint laxity	9/18	0/6	9/24
	Kyphosis/Scoliosis	7/18	3/6	10/24
	Joint contracture	5/18	2/6	7/24
	Small hands/feet	5/18	4/6	9/24
	Syndactyly	5/18	0/6	5/24
	Brachydactyly	4/18	2/6	6/24
	clinodactyly	3/18	5/6	8/24
	Pectus deformities	3/18	0/6	3/24
	Pes planus	3/18	0/6	3/24
	Torticollis	3/18	0/6	3/24
	Femoral anteversion	3/18	0/6	3/24
	Broad thumbs	2/18	0/6	2/24
	Vertebral deformity	1/18	1/6	2/24
Skin and nails	Eczema	13/18	ND	13/18
	Translucent skin	7/18	ND	7/18
	Dark circles under eyes	6/18	ND	6/18
	Easy Bruising	5/18	ND	5/18
	Nail hypoplasia	4/18	2/2	6/20
	Recurrent skin infection	2/18	ND	2/18
	Brittle hair	2/18	ND	2/18
Immunological	Recurrent infection/severe sepsis	11/18	1/1	12/19
	abnormal laboratory	7/18	ND	7/18
	Allergic rhinitis	5/18	ND	5/18
	Asthma	3/18	ND	3/18
	EoE	3/18	ND	3/18
	PANDAS	2/8	ND	2/18
	Crohn's disease	1/18	ND	1/18
	FUO	1/18	ND	1/18
	Food anaphylaxis	1/18	ND	1/18
Hematological	Anemia	11/18	1/1	12/19
Endocrine	Hypo−/hyperthyroidism	5/18	0/1	5/19
	Bone age (delayed/advanced)	3/18	ND	3/18
	Vitamin D deficiency	2/18	1/1	3/19
	Growth hormone deficiency	2/18	ND	2/18
	DMI	1/18	ND	1/18
	Irregular period	1/18	ND	1/18
Cardiac[i]	MVP/MVR	3/10	0/6	3/16
	PFO	3/10	0/6	3/16
	VSD	2/10	0/6	2/16
Dental	Cavities	4/17[e]	ND	4/17
	Overcrowded teeth	2/17[e]	ND	2/17
	Enamel fractures	1/17[e]	ND	1/17
	Hypodontia	1/17[e]	ND	1/17
	Permanent teeth loss	1/17[e]	ND	1/17

(Continues)

TABLE 1 (Continued)

Category	Issues	This study affected, *n*/total eligible, *n*	From literatures[a] affected/data available, *n*[b]	Combined
	Teeth nerves damage	1/17[e]	ND	1/17
Vascular[i]	DAA	2/10	0/6	2/16
	Vascular ring	2/10	0/6	2/16
	Coarctation of aorta	1/10	0/6	1/16
	Port wine stain	1/18	ND	1/18
Renal/ genitourinary	Small kidneys	3/18	0/2	3/20
	Hypogenitalism	2/18	1/2	3/20
	Bilateral hydrocele	1/18	0/2	1/20
	Cryptorchidism	1/18	0/2	1/20
	Hypospadias	1/18	0/2	1/20
	Cordea	0/18	1/2	1/20
	Duplicated collecting system	0/18	1/2	1/20
Hearing loss		3/18	2/6	5/24

Abbreviations: ADHD, attention deficit hyperactive disorder; DAA, double outlet aortic artery; DD, developmental delay; DMI, type I diabetes mellitus; Echo, echocardiogram; EEG, electroencephalogram; EoE, eosinophilic esophagitis; FUO, fever of unknown origin; GERD, gastroesophageal reflux disorder; ID, intellectual disability; MVP/MVR, mitral valve prolapse/mitral valve regurgitation; ND, not described; PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PFO, patent foramen ovale; VSD, ventricular septum defect.

[a]Ciaccio et al., 2021; Del-Prado-Sánchez et al., 2020; Moosa et al., 2017; You et al., 2016.

[b]$n = 8$ unless not described in the literature.

[c]Diagnosis is not applicable for three individuals due to age.

[d]Out of 16 individuals who had brain images.

[e]Not applicable for one individuals.

[f]Patients who had EEG.

[g]Data are not available for one individual.

[h]Data are not available for three individuals.

[i]Out of 10 individuals who had an Echo.

3.4 | Development

The parents were asked about the age when their child/children achieved specific developmental milestones (Table 2 and Figure 2c). One individual was 2 months old at the time of the interview, so many advanced milestones were not applicable to him. Global developmental delay was present in almost 100%, however, 12 individuals eventually learned to walk; eight walked unsupported by 18 months to 4.5 years and four walked with support by average age of 36 months. Language development, fine motor, and self-care skills are significantly affected. Nine individuals have no speech. Of those with at least one word to communicate, the average age of first word was 23 months, with a range of 9 months to 2.5 years. One individual could speak in short sentences at age of 13 years and 9 months. Out of 17, 13 individuals rely completely on a care provider for dressing/undressing and the rest need some assistance. Twelve individuals depend on a care provider to feed, and five can use spoon or fork with assistance. Out of individuals over 5 years of age, 4/14 were partially toilet-trained while the rest were incontinent.

Out of the 18 individuals, 5 individuals had developmental regression. In one individual (P4) the developmental regression was noted at 6 months of age as he stopped rolling, sitting, and making sounds. He received physical therapy at that time, and he was able to regain his lost motor milestones. However, parents noted recurrent episodes of regression in his development after illnesses. His sister (P5) also had episodes of language and social skills regression after infection. The mother of P2 noted gross motor regression of unclear etiology around age 7 years when he started to need assistance in climbing into bed, climbing stairs, and running. He also stopped playing with toys and preferred to chew on them. Affected individual P8 had social skills regression (stopped waving). In another individual (P18), speech and gross motor regression was noted at age of 12 months but she was able regain her lost milestones around ages of 14–20 months. Stereotypical repetitive behaviors and other autistic features were described by the parents in 16 of 17 individuals; however, autism spectrum disorders were officially diagnosed in only 9 individuals.

3.5 | Gastrointestinal

Gastrointestinal involvement was observed in all 18 of our individuals as feeding problems (e.g., poor appetite, chewing and swallowing difficulties and food aversion) and failure to thrive (FTT). The age of the diagnosis of FTT ranged from 2 months to 2 years. Other common problems include gastroesophageal reflux disease (78%), chronic constipation (56%), drooling (59%), gastrostomy (50%), and vomiting (33%). While four individuals had episodes of aspiration pneumonia,

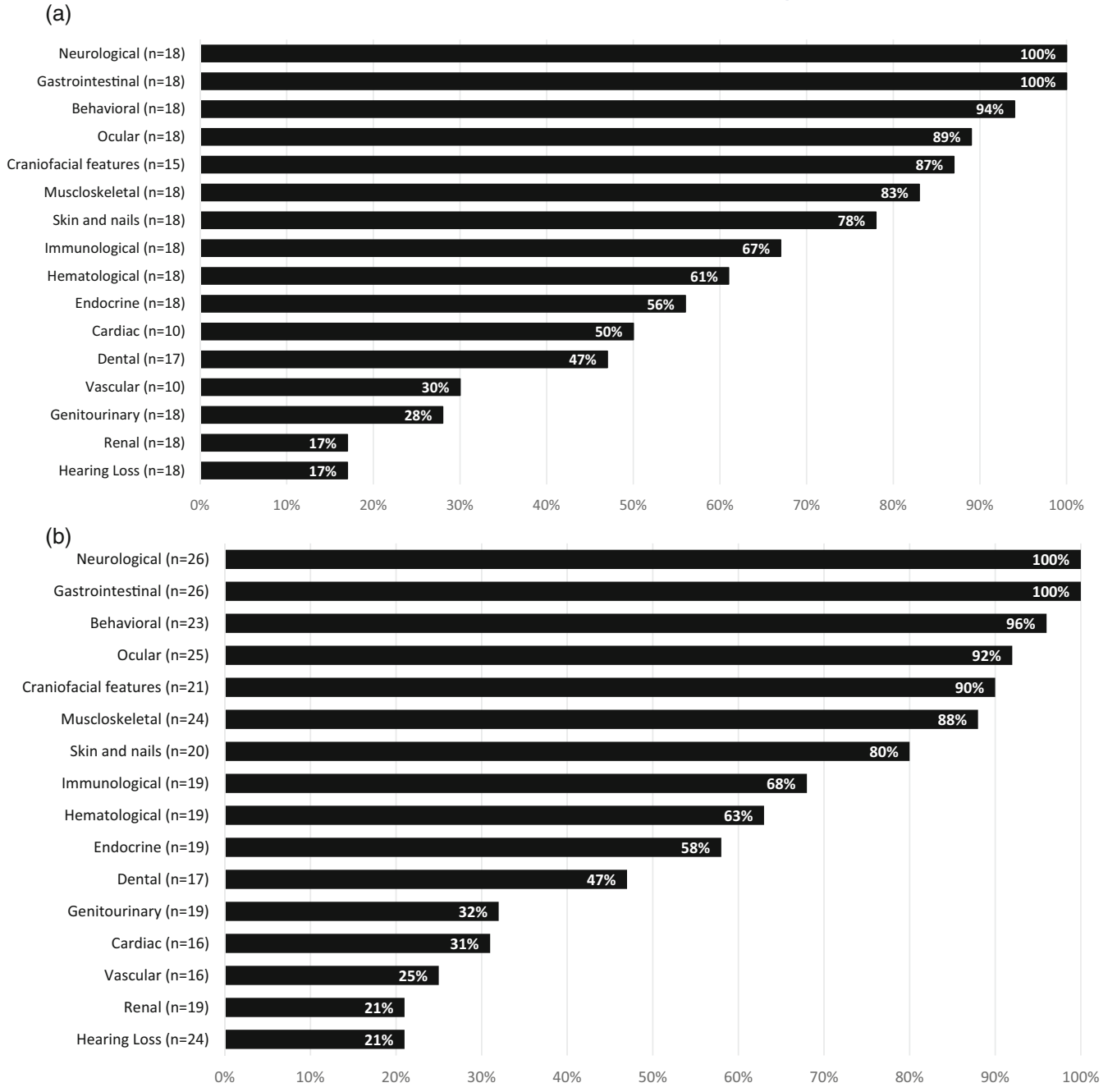

FIGURE 2 (a) Summary of the clinical manifestations of the individuals in our cohort. (b) Summary of the clinical manifestations of all reported individuals. (c) Percentage of developmental milestones achieved in the individuals in our cohort.

two individuals also had frequent choking episodes. Seven individuals are diagnosed with dysmotility and one individual suffered from chronic pseudo-intestinal obstruction associated with feeding pain syndrome that required exclusive parenteral nutrition. Hepatopathy is noted with elevated transaminase in five individuals, but no evidence of synthetic dysfunction.

3.6 | Behavioral issues

Behavioral problems were noted frequently in our cohort including self-injurious behaviors (14/17), laughter outbursts (8/17), aggressive behaviors, anxiety, and chewing on objects in 6 of 17 each. Short attention span was repeatedly described by the parents (11/17) however, only 4 had an official diagnosis of ADHD. Other less common behaviors noted were obsession in five individuals, skin picking, tantrum attack, and pica in two individuals each, and tics in one individual. Sleep problems are common (16/18) in individuals with YHFS including frequent awakening at night (67%), disruptive night behaviors such as periods of laughter, awake screaming/laughing during the night (58%), difficulties in initiating sleep (50%), and irregular sleep–wake cycles (38%). Further, sleeping-related restlessness was identified in two individuals and myoclonus in one.

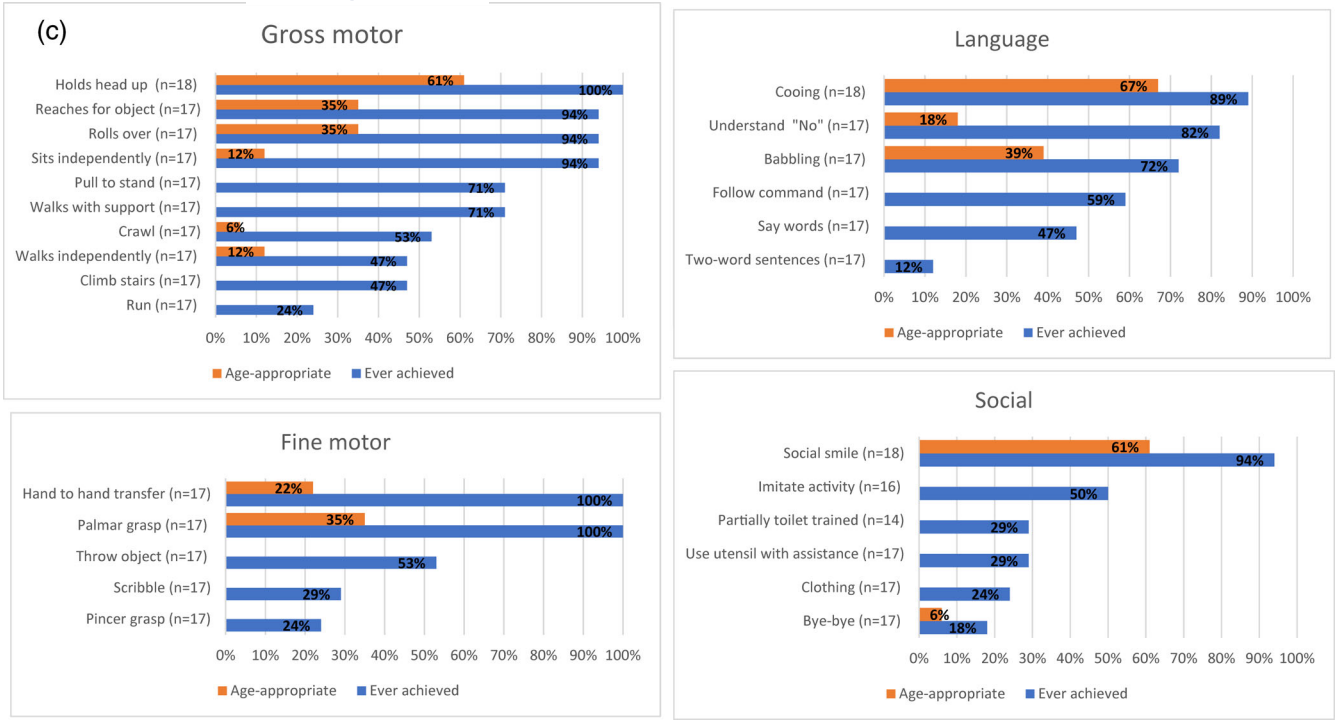

FIGURE 2 (Continued)

3.7 | Ocular involvement

All of the individuals had at least one detailed ophthalmological exam. Ophthalmological anomalies were noted in 16 individuals (89%) with strabismus observed in (72%), astigmatism observed in (39%) cortical visual impairment in (28%), hypermetropia/myopia in (22%), rotatory nystagmus in two individuals, and oculogyric movement in one individual. Optic nerve hypoplasia and small optic nerve were noted in one individual each.

3.8 | Craniofacial features

Specific facial dysmorphisms were not consistent. The most recognized features included ear findings ($n = 5$); high arched palate ($n = 4$), and three individuals each with narrow forehead, hypertelorism, and tented upper lip. The most common congenital craniofacial anomalies included ankyloglossia in 11 individuals (61%), lacrimal duct blockage in 6 individuals and cleft palate in 2 individuals.

3.9 | Musculoskeletal

Musculoskeletal problems were observed in the majority of our cohort (15/18) including kyphosis/scoliosis (39%), pectus deformities, torticollis, and pes planus (17% each). Joint laxity was observed frequently in our cohort (50%) and joint contractures were also noted in 28%. Other minor anomalies included syndactyly and small hands/feet (28% each), brachydactyly (22%), clinodactyly (17%), and broad thumbs (11%). Less common musculoskeletal problems include femoral anteversion in two individuals, and bilateral acetabular dysplasia in one individual. In one individual (P6), muscle biopsy showed lipid overload in muscular fibers, and decreased activity of complex I in the mitochondrial respiratory chain.

3.10 | Skin and nails

In the skin and nails, abnormalities were seen in 14/18 including eczema in 72%, translucent skin (39%), dark circles under eyes (33%), easy bruising (28%), and nail hypoplasia (22%). Recurrent skin infection, and brittle hair were noted in two each.

3.11 | Immunology and hematology

In 12 of 18 individuals some form of immunological problem was identified ranging from recurrent infection (56%) to severe sepsis (28%) which led to death in one individual. Further, five individuals were diagnosed with allergic rhinitis and three individuals with asthma, three individuals were either diagnosed or suspected to have eosinophilic esophagitis, and two individuals were diagnosed with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). One individual each has Crohn's disease, cyclic fever of unknown origin (FUO), and food allergies with anaphylaxis. In regard to abnormal immunological laboratory findings, abnormal white blood cell count and/or differential were identified in three individuals including intermittent

TABLE 2 Age of developmental milestones attainment in patients from our cohort.

A. Gross motor skills				
	Ever achieved	**Age-appropriate**	**Range**	**Average age**
Holds head up ($n = 18$)	100%	61%	2–24 months	5 months
Rolls over ($n = 17$)	94%	35%	4 months–6.3 years	10 months
Reaches for object ($n = 17$)	94%	35%	4–6 years 4 months	15 months
Sits independently ($n = 17$)	94%	12%	6 months–6.5 years	21 months
Crawl ($n = 17$)	53%	6%	7 months–3 years	18.9 months
Pull to stand ($n = 17$)	71%	0.00%	12 months–3 years	21.9 months
Walks with support ($n = 17$)	71%	0.00%	18 months–4 years	34 months
Walks independently ($n = 17$)	47%	12%	14 months–4.5 years	26 months
Climb stairs ($n = 17$)	47%	0.00%	NR	NR
Run ($n = 17$)	24%	0.00%	NR	NR
B. Fine motor skills				
	Ever achieved	**Age-appropriate**	**Range**	**Average age**
Palmar grasp ($n = 17$)	100%	35%	3 months–2 years	7.4 months
Hand to hand transfer ($n = 17$)	100%	22%	6 months–5 years	21 months
Pincer grasp ($n = 17$)	24%	0.00%	>2–8 years	4.5 years
Scribble ($n = 17$)	29%	0.00%	18 months–5 years	3.8 years
Throw object ($n = 17$)	53%	NR	NR	NR
C. Language skills				
	Ever achieved	**Age-appropriate**	**Range**	**Average age**
Cooing ($n = 18$)	89%	67%	2–12 months	2.9 months
Babbling ($n = 17$)	72%	39%	6 months–1.5 years	8 months
Understand "No" ($n = 17$)	82%	18%	12 months–5 years	27 months
Follow command ($n = 17$)	59%	0.00%	NR	NR
Say words ($n = 17$)	47%	0.00%	9 months–2.5 years	23 months
Two-word sentences ($n = 17$)	12%	0.00%	NR	NR
D. Social skills				
	Ever achieved	**Age-appropriate**	**Range**	**Average age**
Social smile ($n = 18$)	94%	61%	2 months–2 years	3 months
Imitate activity ($n = 16$)	50%	0.00%	2–4 years	3 years
Bye-bye ($n = 17$)	18%	6%	9 months–4 years	–
Use utensil with assistance ($n = 17$)	29%	0.00%	11.5–3 years	8.65 years
Clothing ($n = 17$)	24%	0.00%	5.75–13.75 years	10.3 years
Partially toilet trained ($n = 14$)	29%	0.00%	5–11.6 years	7.8 years

leukopenia, intermittent lymphopenia, low absolute lymphocytes, and neutropenia. Two individuals have positive ANA, and one individual each has elevated IgA, not detectable VZV Ig, abnormal CD4, and antibody anti-neutrophilic polynuclear positive (anti-CD16, specificity HNA1a). The most common hematological finding was anemia in 11 individuals (61%). Iron studies in 5 individuals suggested iron deficiency anemia, and 6 individuals received iron supplements which improved the anemia, although 3 of the treated individuals showed fluctuation in the level once the supplement discontinued. In five individuals, anemia required no treatment.

3.12 | Endocrine

The endocrine features in our individuals (10/18) included hypothyroidism ($n = 4$) and two individuals each with delayed bone age, growth hormone (GH) deficiency, hypoglycemic episodes during illnesses, and vitamin D deficiency. In one individual GH deficiency required treatment while the other entered puberty with no treatment. Other endocrine problems identified in only one individual included type I diabetes mellitus, subclinical hyperthyroidism, irregular periods, and advanced bone age.

3.13 | Other features

Cardiac and vascular involvement have been described in early case series. We had no report of major cardiac or vascular anomalies observed in our new individuals affected with YHFS. Minor cardiac anomalies were identified including patent foramen ovale and mitral valve prolapse. Dental problems were identified in eight individuals (47%) including multiple cavities in four individuals and overcrowded teeth in two individuals. Other problems identified in one individual each included multiple enamel fractures, front teeth nerves damaged, loss of some of the permanent teeth, and congenitally missing teeth.

Renal and genitourinary problems were not commonly reported in our cohort and previous reports. In our cohort, small kidneys were reported in three individuals, and hypogenitalism (i.e., small penis) was reported in two individuals. One individual each had cryptorchidism, hypospadias, and bilateral hydrocele. Audiological evaluation indicated hearing loss in three individuals; one with sensorineural hearing loss, and one with mixed hearing loss.

4 | DISCUSSION

Here we present data on 14 newly reported individuals with YHFS, which brings the total to 26 reported individuals (Ciaccio et al., 2021; Del-Prado-Sánchez et al., 2020; Moosa et al., 2017; You et al., 2016). In addition to the previously described features, our cohort expands the clinical spectrum of YHFS to include previously unreported clinical findings such as endocrine abnormalities, immunological issues, and structural brain abnormalities. We further expand the clinical features in a variety of organ systems including gastrointestinal, ocular, and musculoskeletal. Our cohort further provides follow-up data for four individuals reported previously including the two oldest individuals providing information regarding survival into adulthood. (Complete clinical and molecular details of all individuals with YHFS are presented in Table S1 and Appendix S1.)

All individuals with YHFS recognized in our cohort and in the literature have global developmental delays as an essential feature in diagnosing YHFS. We defined the extent of the developmental delays more precisely and determined the average developmental trajectory and current capabilities. The findings in our cohort demonstrate that communication and ambulation is possible in these individuals, highlighting the importance of thorough developmental assessments and initiation of proper therapies and provision of assistive devices for communication. The prevalence of abnormal tone beginning in infancy and the movement disorders and ataxia in individuals with YHFS highlights these findings as recurring and possibly distinguishing features of YHFS.

Multiple behavioral concerns and abnormal sleeping patterns recognized in almost all of the individuals with YHFS had significantly reported negative effects on their families. Individuals have benefited from medications such as guanfacine, risperidone in conjunction with either amitriptyline or clonidine in two individuals, and olanzapine to alleviate agitation and aggressive behaviors and to help with sleeping. Melatonin alone or combined with either gabapentin or risperidone was used to treat sleeping problems in five individuals. The clinical outcome was satisfactory, and parents reported improve in the quality of their sleep in 80% of the individuals. Further, behavioral therapy was beneficial when initiated in three individuals. These finding support that neuropsychology assessment in older children is warranted.

In our cohort, one individual had a seizure disorder, which is a feature reported previously in three individuals with YHFS (Moosa et al., 2017; You et al., 2016) suggesting that seizures may be more common than in the general population based on Centers for Disease Control estimates of seizure prevalence of 1.2% in the U.S. population. Structural brain anomalies were noted in 12 individuals in our cohort, which was a previously unreported feature in YHFS, except for one case reported by Ciaccio et al. (2021) with unusual symmetric hyperintensity and swelling of cortical spinal tracts. Ophthalmological anomalies were commonly noted in our cohort and in previous reports with strabismus observed most frequently, followed by astigmatism and cortical visual impairment. From the previous cases (Del-Prado-Sánchez et al., 2020; Moosa et al., 2017) along with our cohort, five individuals had cataracts and three had retinitis pigmentosa. Further, in our cohort minor renal and genitourinary anomalies were identified, as well in previous cases, including hypogenitalism with chordae (You et al., 2016) and kidneys with a duplicated collecting system (Moosa et al., 2017).

Another relevant finding in our cohort involved poor growth which is commonly noted in the neonatal period and persists through childhood. Aside from feeding issues, intrauterine growth restriction was reported frequently (44%) in pregnancy which implies that growth deficiency may begin prenatally in these children. Interestingly, diet modification in three individuals showed objective improvement in behaviors, developmental status, and abnormal movement. The parent of two siblings noted improvement in the behaviors and resolution of abnormal movement and ataxia when gluten, soy, sugar, and high carbohydrate foods are eliminated from their diet along with starting mitochondrial supplements. In the third individual, use of maldextrin-containing formula led to worsening GI symptoms and he developed abnormal somatic movements. Once this formula was discontinued, parents noted improvement in the child's behavior and energy status, and he began to acquire new milestones. These observations from our cohort were measured objectively by the parents and no cell-line studies were done to support these observations. However, the metabolism of glucose supply carbons to the TCA cycle utilized by mitochondria to generate energy is directly regulated by mTORC1. Studies have suggested that the disassembled and inhibited Tel2-Tti1-Tti2 (TTT)-RUVBL1/2 complex could block mTORC1 activation leading to ATP depletion (Kim et al., 2013). We propose the need for close monitoring by dietitian especially after any diet modification in individuals with YHFS to detect any worsening symptoms while ensuring adequate caloric intake.

The clinical and laboratory data from our cohort suggest that immunological problems could be a part of the YHFS. The immune pathophysiology could be due to the role of the TTT complex to

TABLE 3 Tests and evaluations to consider for patients with YHFS[a].

System/concern	Evaluations to consider	Comments
Neurological	Baseline evaluation by neurology	If clinically indicated
	Brain MRI and EEG	
Eyes/ears	Ophthalmological evaluation	To ensure adequate vision and hearing for optimize development
	Audiological evaluation	
Cardiac	Baseline evaluation by cardiologist	For structural cardiac defect, vascular malformation
	Echo	
Gastrointestinal/ feeding	Gastroenterology/nutrition/feeding team evaluation Assess longitudinal growth	At baseline and throughout lifespan
Musculoskeletal	Physical exam for skeletal anomalies that may require an orthopedist	Evaluate for joint hyperextensibility/contracture, pes planus, and scoliosis
Development	Comprehensive developmental assessment including speech, motor, social, academic	At baseline and throughout lifespan to access early intervention and special education
Psychiatric/ behavioral	Neuropsychiatric evaluation	Evaluate for ASD, attention issues, anxiety, OCD, and aggression
Sleep	Screen for sleep disorders, apnea	At baseline and as medically indicated
Hematological	CBC	Baseline and as medically indicated
Endocrine	Free T4, TSH	Baseline and as medically indicated
	Screening for hypoglycemia	If medically indicated
	Screen for growth hormone deficiency	After 2 years of age, as medically indicated
	25(OH) vitamin D	Baseline and as medically indicated
Immunological	Immunological evaluation	Assess if recurrent infections
		CBC with diff, immunoglobulins, T cell subsets, vaccine titers if clinically indicated
Family support and resources	Social work involvement for caregiver support	At baseline and as medically indicated

Abbreviations: ASD, autism spectrum disorder; CBC, complete blood count; Echo, echocardiogram; EEG, electroencephalogram; EEG, electroencephalogram; Hx, history; MRI, magnetic resonance imaging; OCD, obsessive–compulsive disorder; OT, occupational therapy; PT, physical therapy; ST, speech therapy; TSH, thyroid stimulating hormone.
[a]The table content is statement of opinion based on the clinical findings from the patients from the cohort and literature.

control protein stability of PIKKs, including the interaction with *mTOR* gene that plays a role in various cellular processes including T-lymphocyte activation and differentiation (Delgoffe et al., 2009), (Delgoffe et al., 2011). For that, children with YHFS who suffered from recurrent infection may benefit from an assessment by an immunologist. Further study is needed to define the extent and prevalence of immunopathology in individuals with YHFS.

Our study has expanded the phenotype and genotypes recognized to be associated with YHFS, thereby facilitating the diagnosis of future patients and guide patient care. With this information, we hope multiple healthcare problems can be anticipated, recognized earlier and appropriate care can be established with a multidisciplinary team including neurologists, psychiatrists, gastroenterologists and dietitians, ophthalmologists, orthopedists, endocrinologists and therapists for physical, occupational and speech to optimize the care for this rare disease (Table 3). There is still a need for continuous research to understand further the natural history of YHFS to improve medical care for these individuals and be prepared for potential disease-specific treatment trials in the future.

AUTHOR CONTRIBUTIONS

Daniah Albokhari synthesized the clinical data, drafted the initial manuscript, and revised the manuscript. Michelle M. Morrow and Timothy Blake Palculict critically reviewed and revised the manuscript. Amanda Barone Pritchard, Adelyn Beil, Candace Muss, Caleb Bupp, Dorothy K. Grange, Geoffroy Delplancq, Jennifer Heeley, Melissa Zuteck, Paul Kuentz, and Julie E. Hoover-Fong provided clinical evaluations, critically reviewed, and revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Timothy Blake Palculict and Michelle M. Morrow are employees of GeneDx, Inc. Julie E. Hoover-Fong is a consultant for BioMarin, Pfizer, Ascendis, QED, and InnoSkel. Julie E. Hoover-Fong is a site principal investigator (PI) for clinical trials for BioMarin, Therachon, Pfizer, and QED.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

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

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