



Pitt-Hopkins Syndrome: A Review of Current Literature, Clinical Approach, and 23-Patient Case Series

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Abstract

Pitt-Hopkins syndrome (PTHS) is a rare, genetic disorder caused by a molecular variant of *TCF4* which is involved in embryologic neuronal differentiation. PTHS is characterized by syndromic facies, psychomotor delay, and intellectual disability. Other associated features include early-onset myopia, seizures, constipation, and hyperventilation-apneic spells. Many also meet criteria for autism spectrum disorder. Here the authors present a series of 23 PTHS patients with molecularly confirmed *TCF4* variants and describe 3 unique individuals. The first carries a small deletion but does not exhibit the typical facial features nor the typical pattern of developmental delay. The second exhibits typical facial features, but has attained more advanced motor and verbal skills than other reported cases to date. The third displays typical features of PTHS, however inherited a large chromosomal duplication involving *TCF4* from his unaffected father with somatic mosaicism. To the authors' knowledge, this is the first chromosomal duplication case reported to date.

Keywords

developmental delay, autism, intellectual disability, genetics, seizures, pediatric, ophthalmology, behavior

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Pitt-Hopkins syndrome (PTHS; MIM #610954) is a rare neurodevelopmental disorder caused by a pathogenic variant of the *TCF4* gene found on chromosome 18q21.2.¹⁻⁴ The syndrome was first described in 1978 in 2 unrelated individuals who shared similar characteristics of dysmorphic facial features, developmental delay, clubbed fingers, and an abnormal breathing pattern.⁵ It was presumed to be an autosomal recessive disorder until 2007 when the *TCF4* gene, (MIM #602272) was identified, supporting an autosomal dominant inheritance pattern secondary to haploinsufficiency of *TCF4*.¹⁻³ Transcription factor 4, the protein product of *TCF4*, is a basic helix-loop-helix E-protein believed to be involved in early brain development and neuronal differentiation.^{1-4,6-10} The exact prevalence of PTHS is unknown. Estimates by Rosenfeld et al suggest a population frequency of 1:34,000 to 1:41,000 based on chromosomal microarray data from their commercial lab, although there are believed to be fewer than 500 confirmed cases worldwide.^{4,11}

Cases are phenotypically similar to other syndromic, neurodevelopmental disorders such as Angelman syndrome (MIM #105830), Rett syndrome (MIM #312750), Mowat-Wilson syndrome (MIM #235730), and ATR-X syndrome (MIM #301040).¹²⁻¹⁵ Studies have revealed a molecular variant in

TCF4 in 2% of patients clinically diagnosed with Angelman syndrome and in 1 of 81 children clinically diagnosed with Rett syndrome.^{16,17} In addition, there is an autosomal recessive condition involving variants in *CNTNAP2* and *NRXN1* causing Pitt-Hopkins-like syndrome 1 (PTHLS1; MIM #610042) and Pitt-Hopkins-like syndrome 2 (PTHLS2; MIM #614325). Clinically, PTHLS1 and PTHLS2 patients present with similar phenotypes to PTHS patients, however may have milder delays in motor development.¹⁸⁻²¹

Although there is no cure for PTHS, studies are underway to identify and target the molecular pathways affected by *TCF4* pathogenic variants. Clinical management of PTHS should include surveillance for common comorbidities and interventions to address symptoms, though there are currently no clinical trials to guide treatment. The University of Texas

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Southwestern Medical Center in collaboration with Children's Health Dallas and the Pitt-Hopkins Research Foundation have established a specialty clinic to care for this rare population. The authors aim to describe the series of patients cared for in this clinic and compare the frequencies of phenotypic traits previously reported in the literature to those observed in their patient population. In addition, they aim to discuss the therapeutic interventions and subspecialty care utilized in the authors' population of PTHS patients.

Methods

Searches of the PubMed database (<http://www.ncbi.nlm.nih.gov/pubmed>) were performed to collect all articles involving the characterization of PTHS, genetics of PTHS, or animal models of PTHS. Keywords used included PTHS, *TCF4*, 18q deletion, 18q monosomy, and 18q21. Seventy-five articles were reviewed, and 58 were included in the following literature review. Relevant primary literature, review articles, research letters, and letters to the editor available in English were included. Publications on Pitt-Hopkins-like syndrome, schizophrenia, and involvement of *TCF4* in the innate immune system and gastric mucosa were excluded. Case reports published prior to 2007 were also excluded as the molecular diagnosis was not confirmed. The frequencies of commonly described phenotypic characteristics from the available publications are reported herein.

Retrospective clinical data were collected on a cohort of 23 patients with a molecular diagnosis of PTHS referred to the UT Southwestern/Children's Health Center for Autism and Developmental Disabilities. Genetic test results were reviewed in the medical record, and reported genotypes were confirmed in the University of California, Santa Cruz Genome Browser (<https://genome.ucsc.edu/index.html>) using the appropriate human genome build (18 or 19) corresponding to that which was available in the genetic report. Reports indicated that *TCF4* transcript variant 1 (NM_001083962.1) was used for all patients except for patient 21, in whom *TCF4* transcript variant 3 (NM_001243226.2) was used. Clinical data were collected in a de-identified database and the frequency of specific phenotypic characteristics were calculated and reported herein. Therapeutic interventions utilized in this cohort are also discussed, some of which are off-label use. In addition, a clinical diagnostic score was assigned to each patient based on the proposed scoring rubrics by Marangi et al and Whalen et al.^{22,23} If data were unavailable, a subscore of zero was assigned. Informed consent for publication of photographs was obtained. The study received exempt status from the UT Southwestern Medical Center Institutional Review Board.

Review of Clinical Phenotype

The authors reviewed 25 case reports and case series published in the literature from 2007 to 2016, and found 282 cases reported in total.^{1-3,8,11-13,17,22-38} Most included only 1 or 2 cases except for 3 larger studies including de Winter et al (n = 101), Whalen et al (n = 33), and Hasi et al (n = 27).^{23,29,37} The frequencies of commonly reported features are reported herein.

PTHS is commonly described to have certain characteristic facial features (116/131, 89%) described as "coarse" with up-slanted palpebral fissures, beaked nasal bridge, prominent ears, and a broad mouth with exaggerated "Cupid's Bow" appearance of the philtrum. A single palmar crease (65/109, 60%), persistent fetal finger pads (34/75, 45%), postnatal growth restriction including short stature (48/125,

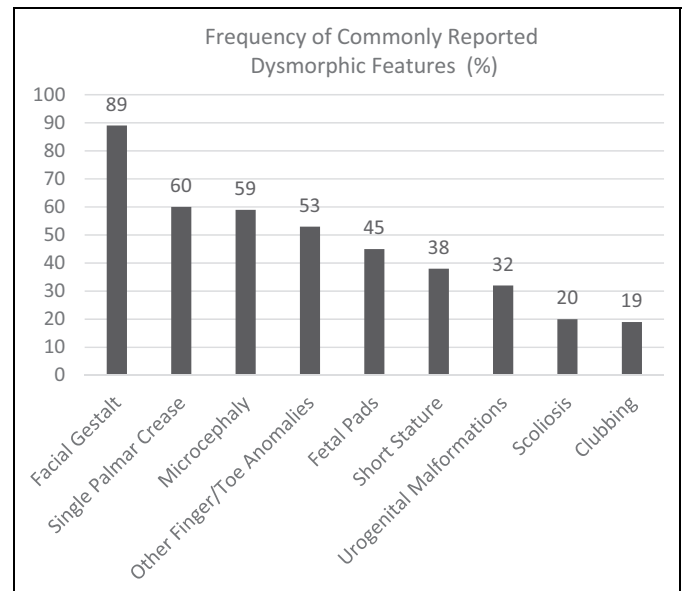


Figure 1. Graph depicting the rates of commonly reported dysmorphic characteristics as reported in the published cases.

38%), and microcephaly (85/144, 59%) are also commonly seen.³⁹ Other finger and toe anomalies including over-riding toes, syndactyly, and polydactyly have also been described (52/98, 53%). Less commonly, clubbing (10/54, 19%) and scoliosis (18/91, 20%) are described. See Figure 1 for graphical representation of these rates of commonly reported dysmorphic features. Figure 2 depicts the facial features and Figure 3 depicts fetal pads, flat feet, and overriding toes that were seen in the authors' cohort. Photos were provided by the authors' participating families.

Uniformly, individuals with PTHS have global developmental delay and intellectual disability, often coming to attention in the first year of life.³⁹ Twenty-two of the 25 case reports reviewed mention some degree of psychomotor delay; many not ambulatory until after age 3 years and most nonverbal.^{1-3,8,11-13,17,22-28,31-36,38} Prior publications describe moderate to severe intellectual disability in 131 cases, however neurocognitive data was not included in the publications. In a prospective study of 10 participants with PTHS (ages 32 to 289 months), a standardized battery of testing revealed a mental developmental age equivalent ranging from 3.5 to 15 months and a gross motor age equivalent ranging from 4 to 19 months of age.⁴⁰ The test instruments used included the Bayley Scales of Infant Development, Autism Diagnostic Interview-Revised, Vineland Adaptive Behavior Scales, and Developmental Behavior Checklist.⁴⁰ Eight of the 10 participants met criteria for a diagnosis of autism spectrum disorder, however the Autism Diagnostic Interview-Revised is only validated for children and adults with a mental age-equivalent of 2 years or older.⁴⁰ A happy disposition (82/94, 87%) and stereotypies including flapping, hand-wringing, and rocking (83/107, 78%) are common, but aggression can be seen in nearly half of individuals (32/67, 48%). Sleep disturbances including insomnia or frequent nocturnal awakenings are less commonly reported in the literature (7/39, 18%).

Approximately 38% (93/242) have seizures. Seizure semiology is quite variable including generalized tonic-clonic, atonic, focal onset with both motor and nonmotor onset, as well as infantile spasms rarely.^{8,11,16,27,28,31,33,36} There is not a characteristic electroencephalogram (EEG) signature associated with this syndrome. Seizures are

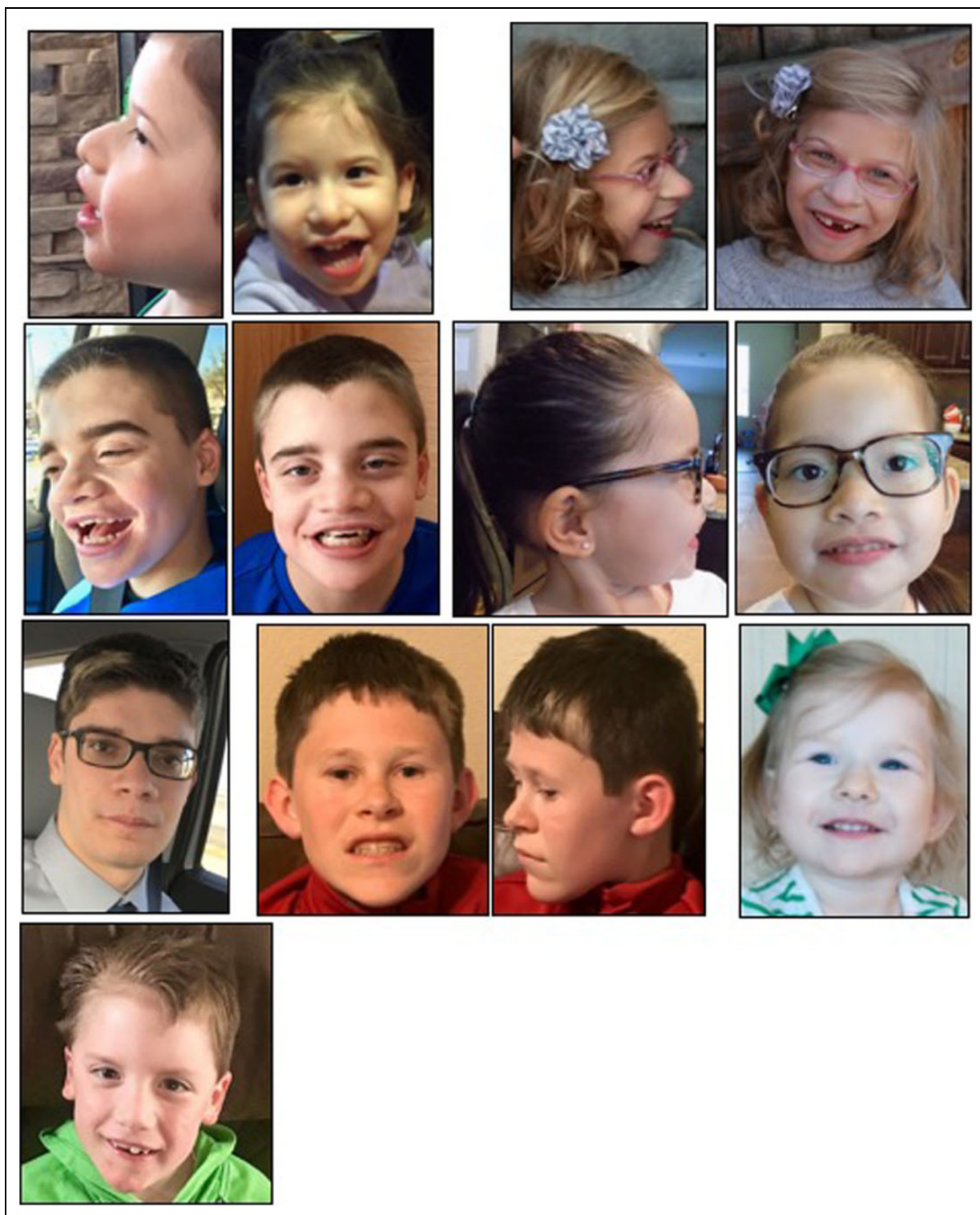


Figure 2. Photographs demonstrating the facial gestalt commonly seen in PTHS: broad nasal bridge with bulbous tip, wide mouth with Cupid's bow philtrum, and prominent ears.

not typically intractable, but there is not a specific antiseizure medication which has been shown to be more effective than others. Antiseizure medications should be chosen based on current recommendations and guidelines in the management of epilepsy. Figure 4 depicts a graphical representation of the above frequency data.

Nearly half (119/249, 48%) exhibit a paroxysmal breathing pattern of hyperventilation with or without subsequent apnea, similar to the pattern seen in Rett and Joubert syndromes.⁴¹ It is typically described as rapid, heavy breathing and often followed by a period of breath holding that can be long enough to induce cyanosis or loss of



Figure 3. Photographs demonstrating the fetal pads, flat feet, and overriding toes.

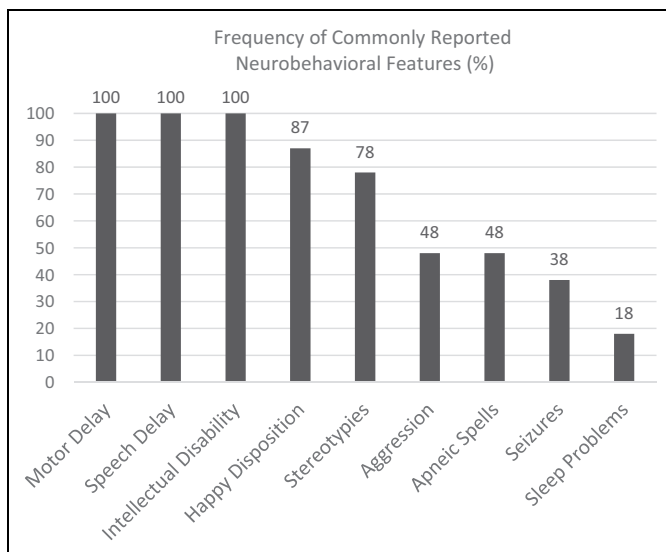


Figure 4. Graph depicting rates of the neurodevelopmental and behavioral traits described in the published cases.

consciousness, however precise definitions regarding the periodicity or duration of these spells are not clearly stated in the literature. Onset of breathing abnormalities is typically during early childhood, from 3 to 7 years, and is believed to be a behavioral manifestation of emotional states, as spells only occur during wakefulness and have no ictal electrographic correlate on EEG.^{42,43} The pathophysiology of the abnormal breathing spells remains unknown, but some hypothesize

they are due to aberrant neuronal development of the autonomic nervous system or medullary breathing control centers, as demonstrated in the mouse model.^{6,41} Therapeutic interventions for breathing problems including mood-stabilizing agents such as neuroleptics, selective-serotonin reuptake inhibitors, and antiseizure medication as well as acetazolamide have been utilized with variable success. Acetazolamide, a common first-line agent, is a diuretic that blocks reuptake of bicarbonate in the kidneys, thereby leading to a metabolic acidosis and theoretical stimulation of the central chemoreceptors to indirectly increase the respiratory drive.^{42,44} Verhulst et al report on 2 individuals with PTHS and apneic spells who were given acetazolamide 250 mg daily and demonstrated objective improvements in the apnea-hypopnea index and mean SpO₂ after 4 weeks of therapy.⁴⁴ Gaffney reports similar results in a patient who exhibited a 70% reduction in apneic spells by parental report while on acetazolamide.⁴² Alternatively, Maini et al demonstrated objective improvements in the apnea-hypopnea index, mean SpO₂, and reduction in frequency by parental report after 7 months of therapy with valproic acid in a patient who failed diazepam.⁴³

Early onset myopia (110/207, 54%) and strabismus (114/234, 49%) were reported in approximately half of individuals with PTHS, and may relate to abnormal retinal development as demonstrated in the zebrafish and fruit fly models.^{45,46} Families commonly reported chronic constipation (168/241, 70%), often present from infancy. Constipation can be severe, and cases of Hirschsprung's disease (1/64, 2%) as well as intestinal malrotation (5/27, 19%) have been reported.^{3,29,32} Slowed gastrointestinal transit times were demonstrated in a mouse model, suggesting a potential role of *Tcf4* in the development of the enteric nervous system.⁴⁷ Many are chronically managed with laxatives and stool softeners. See Figure 5 for a

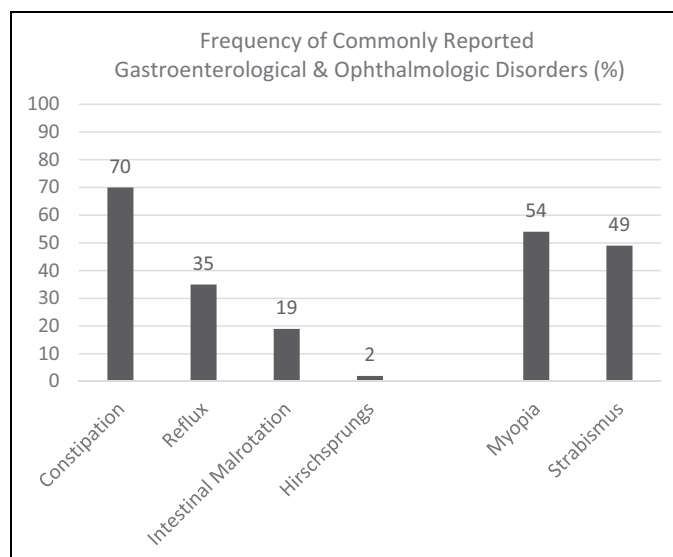


Figure 5. Graph depicting the rates of the associated gastroenterological and ophthalmologic disorders commonly reported in published cases of PTHS.

graphical representation of the rates of associated GI and ophthalmologic disorders.

Though *TCF4* is believed to be involved in neuronal differentiation, there are no consistent, major structural abnormalities seen on brain imaging. The most commonly reported findings include dysplasia of the corpus callosum^{1,24,25,48} and bulging of the caudate heads.¹² Small hippocampi, temporal lobe white matter hyperintensities, delayed myelination patterns, and hypoplasia of the cerebellar cortex and vermis have also been described.^{1,8,11,24,27} Global cerebral atrophy with widening of the sulci and ventriculomegaly may also be seen in PTHS patients.¹² Diffusion tensor imaging was found to be normal in 1 case report.⁴⁵ Figure 6 depicts magnetic resonance images from the authors' cohort highlighting the dysplastic corpus callosum, bulging caudate, global atrophy, and nonspecific T2 hyperintensities.

Whalen et al and Marangi et al independently proposed a clinical diagnostic score to aid in the medical decision making regarding which patients should be considered for *TCF4* testing (See Table 1 for details of each scoring rubric).^{22,23} On the Whalen et al scale, a score of 15 or greater should prompt testing if older than 3 years of age, 10 or greater if under 3 years of age. The Marangi et al rubric, a score of greater than or equal to 10 out of a possible 16 should prompt testing for PTHS. In the de Winter et al cohort with molecularly confirmed PTHS, a score was calculated for 47 participants based on each model and found 8 of the items were present in at least 75% of the participants including: severe intellectual disability (47/47, 100%), severe speech impairment (15/15, 100%), walking >3 years/severe motor delay <3 years (44/47, 94%), constipation (40/47, 85%), protrusion mid/lower face (36/47, 77%), broad nasal bridge or convex nasal ridge (44/45, 98%), large mouth (37/47, 79%), and everted vermillion of lower lip (37/36, 80%).³⁷ Genetic testing for PTHS would have been indicated in 17% (8/47) and 62% (29/47) based on the Whalen et al score and Marangi et al score, respectively. The scores were diagnostic in 9% (4/47) of the participants based on the Marangi et al score. De Winter et al conclude that a more precise diagnostic criteria and detailed phenotyping are still needed.³⁷

Cases

Rather than describing each of the 23 cases in narrative detail, the authors have chosen to provide overall frequency data and focus on 3 cases that stand out as either phenotypically or genotypically different from previously reported cases in the literature (see Table 2 for details). To the authors' knowledge, this is the fourth largest cohort of novel patients reported to date. Overall, rates of commonly reported features were similar in the authors' population when compared to the previously published cases except for a higher frequency of myopia and sleep disturbances in the authors' population. See Figure 7 for a graphical representation of this data.

All the patients demonstrate some degree of developmental delay, and all but 1 of the cases demonstrate the characteristic facial features, as shown in Figure 2. Sixteen of the 23 patients were ambulatory at the time of evaluation, and all but 2 (patients 12 and 21) had a wide-based ataxic gait. The average age at ambulation was 4.6 years with a range of 1.3 to 10 years. All patients, except for Patient 12, who was speaking in sentences by age 7 years, had severe language delays. Eight were babbling at the time of evaluation but did not have any discrete words. The authors reviewed school assessment reports for all 16 children for whom records were available. The most commonly used measures of functioning focused on adaptive and early developmental skills and included the Vineland Adaptive Behavior Scales–2nd Edition, the Adaptive Behavior Assessment System–II, the Developmental Profile 3, and the adaptive scales from the Behavior Assessment System for Children–2nd Edition. Aside from Patient 12, all children in this cohort fell below the first percentile for age across measured domains, such as communication, cognitive, social, daily living, motor skills and overall composites of adaptive functioning. They consistently fell in the severely impaired range at or near the floor of these measures. Of note, these measures were based on parent/caregiver report, and direct assessment of these children with standardized measures of developmental ability was rare.

Abnormal breathing spells were present in 45% (10/22) of the cohort, and stereotypies present in 90% (18/20) of the cohort. Sleep disturbances including difficulties falling asleep or frequent nocturnal awakenings were reported in 12 of 22 patients (88%). Of the 17 patients who underwent formal visual acuity testing, 15 (88%) had early-onset myopia and 12 of 16 (75%) had strabismus. Constipation was reported in 19 of 23 patients (83%). Over one-third (8/23, 35%) of patients had at least 1 lifetime seizure, however only 4 of the 8 patients with a history of seizures were taking antiseizure medications at the time of evaluation. Patient 18 was taking levetiracetam monotherapy, Patient 4 taking levetiracetam and oxcarbazepine, Patient 11 taking lamotrigine and oxcarbazepine, and Patient 9 taking oxcarbazepine and topiramate. In addition, 7 of the patients were taking amantadine for behavioral problems including anxiety and aggression. Families attributed improvements in focus, diminished hyperactivity, decreased frequency of abnormal breathing spells, as well as more rapid developmental progression to amantadine. The authors note this is anecdotal information that has not been systematically evaluated in this population.

Approximately half (11/23) of the authors' cohort were found to have a copy number variant, while the remainder had sequence variants that were classified as pathogenic. All but 3 of the patients were referred to the authors' clinic with the confirmed molecular diagnosis, so indication for genetic testing was not readily available. The remaining 3 patients were internal referrals diagnosed by commercial sequencing panel with an a priori suspicion for PTHS. Only 1 of the 4 patients with a full gene deletion was ambulatory and all were nonverbal at the

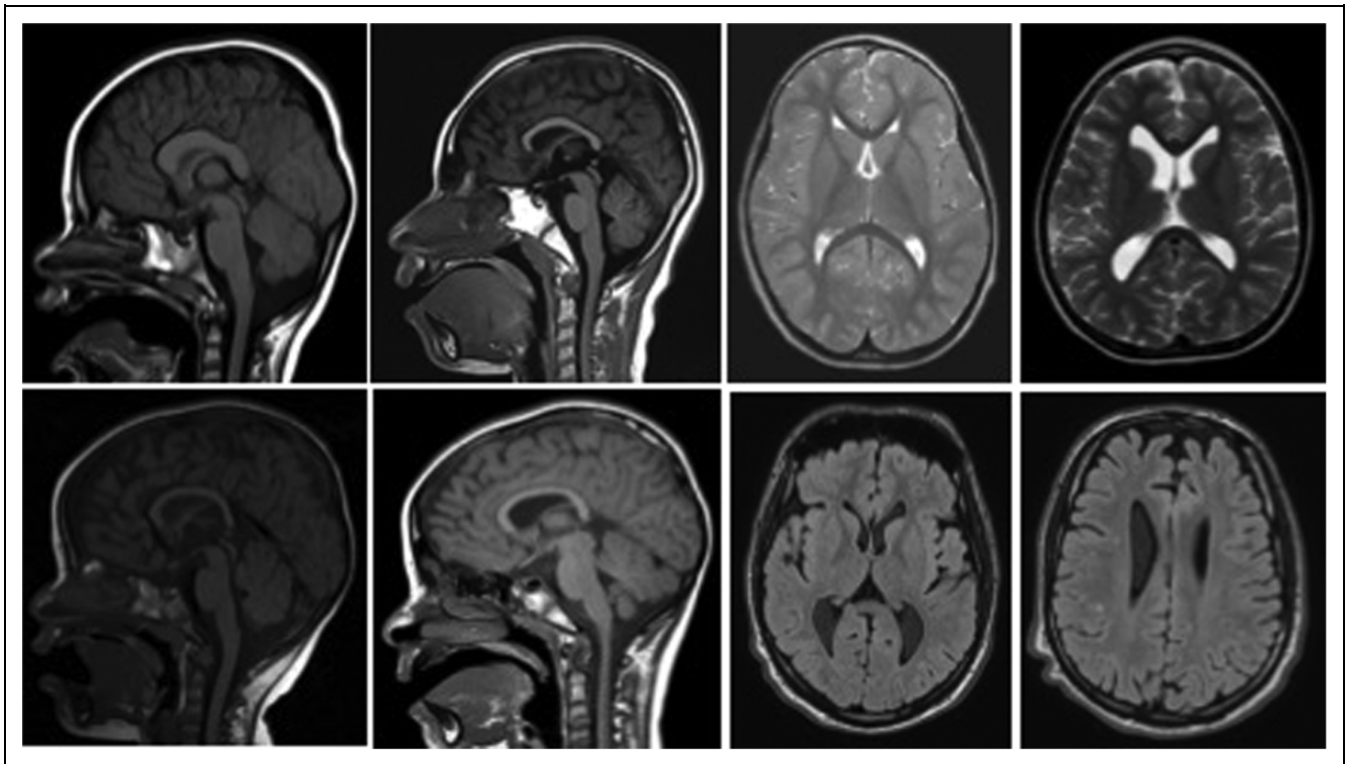


Figure 6. Sagittal T1 magnetic resonance imaging (MRI) scans (left) and axial T2 (top right) and FLAIR (bottom right) MRI Scans depicting common anomalies seen in PTHS including dysplasia of the corpus callosum, bulging caudate, global atrophy, and scattered T2 hyperintensities. Images are from the authors' cohort at UTSW Medical Center/Children's Health Center for Autism and Developmental Disabilities.

time of evaluation. However, 2 of these nonambulatory patients were under the age of 3 years at the time of evaluation, and therefore younger than typical onset of ambulation for PTHS. None of the patients with a frameshift variant had seizures, though most (4/6) of this subgroup were on a medication for behavior such as risperidone, amantadine, or Vayarin. Clinically meaningful conclusions of genotype-phenotype correlations are limited secondary to the small sample sizes of the subgroups.

Patient 5 carries a 201-kB duplication encompassing exons 4 to 8 on the *TCF4* variant 1 (NM_001083962.2), and to the authors' knowledge is the first case with a duplication of this size to be reported. The duplication was found on chromosomal microarray, inherited from an unaffected father who carries a somatic mosaicism of the same variant. Developmentally, the patient was rolling by 3 months, sitting at 10 months, and pulling to stand at 20 months. He was not yet ambulatory on his initial evaluation at 2 years 3 months. He was described to have a happy disposition without aggression, anxiety, or apneic spells. There was neither reported constipation nor seizure-like activity, and his vision had not yet been evaluated. Based on his facial features and developmental-behavioral profile, he seems phenotypically consistent with a diagnosis of PTHS, though this molecular variant has not been reported as causative in other PTHS patients.

Patient 12 carries a single base-pair deletion in the penultimate exon of *TCF4* and, to the authors' knowledge, is the highest functioning patient described to date. He presented at the age of 9 years with developmental delay and mildly dysmorphic facial features. He was rolling at 6 months, sitting at 8 months, and walking by 15 months. He babbled at 8 months and spoke his first word at 14 months. He had 5 words at 2 years, 2-word phrases at 4 years, and full sentences by 7 years. He struggled with low frustration tolerance, sleep disturbance,

and chronic constipation. His chromosomal microarray was normal in 2013, but was later diagnosed with PTHS by whole exome sequencing in 2016. Of note, his visual acuity is normal, and he has never demonstrated any spells of abnormal breathing or seizure-like activity. In his clinical neuropsychological testing, his full-scale intelligence quotient (IQ, Stanford Binet Intelligence Scales, 5th edition) was 57, and he met criteria for autism spectrum disorder as well as attention-deficit/hyperactivity disorder. He is thriving in the special education classroom and continues to gain new skills.

Patient 21 is a boy with a 148-kb deletion involving exons 1 and 2 of the *TCF4* variant 3 (NM_001243226), which was found on chromosomal microarray. His phenotype is unique in that he lacks the typical facial features associated with most cases of PTHS and his motor delays were less prominent. He was ambulatory by 18 months of age with a normal gait pattern, but exhibits severe language delay, nonverbal at the age of 8 years 8 months. He carries a diagnosis of autism spectrum disorder and severe intellectual disability. He had frequent stereotypies of hand flapping and rocking, but no sleep problems, constipation, vision impairment, or dysmorphic facial features.

Discussion

PTHS is a rare neurodevelopmental disorder that is likely underdiagnosed secondary to lack of familiarity with this syndrome and underutilization of genetic testing. As understanding of rare syndromes grows it is reasonable to consider genetic testing in individuals lacking a clear underlying etiology for developmental delay. According to the most recent American Academy of Neurology and Child Neurology Society practice

Table 1. Clinical Diagnostic Tools Proposed by Whalen et al and Marangi et al.

Whalen et al clinical diagnostic score		Marangi et al clinical diagnostic score	
Frequent features	Positive points	Frequent features	Positive points
Deep set eyes	1	Moderate to severe intellectual disability	2
Protrusion of mid and/or lower face	1	Absent speech	2
Marked nasal root	1	Severe speech impairment with more than 10 words vocabulary and/or capacity to form 2-3 word sentences	1
Broad/beaked nasal bridge	1	Normal growth parameters at birth	1
Flared nostrils	1	Postnatal microcephaly or progressive slowing down of head circumference	1
Large mouth	1	Epilepsy/EEG abnormalities	1
Tented upper lip/prominent Cupid's bow	1	Ataxic gait/motor incoordination	1
Everted lower lip	1	Breathing abnormalities: hyperventilation fits or apnea episodes	1
Walking >3 years or severe motor delay <3 years	2	Mild to severe constipation	1
Ataxic gait	1	Brain MRI abnormalities (corpus callosum hypoplasia, enlargement of the ventricles, and thin hindbrain)	1
Absent language (or <5 words)	2	Ophthalmologic abnormalities (strabismus, myopia, and astigmatism)	1
Stereotypic movements of the head \pm hands	2	Typical PTHS facial features	4
Hyperventilation	1	Facial features only partially consistent with PTHS	2
Hypotonia	1	Maximum score = 16	
Smiling appearance	1	≥ 10 should prompt testing for PTHS	
Anxiety/agitation	1		
Strabismus	1		
Unusual features	Negative points		
Microcephaly ≤ 3 SD	-2		
Overgrowth	-1		
Visceral malformations	-1		
Loss of purposeful hand skills	-1		
Maximum score = 20			
>15 indication for <i>TCF4</i> screening			
10-15 consider <i>TCF4</i> screening if <3 years			
<10 no indication for <i>TCF4</i> screening			

Abbreviations: EEG, electroencephalogram; MRI, magnetic resonance imaging; PTHS, Pitt-Hopkins syndrome.

guidelines, routine cytogenetic testing, such as a chromosomal microarray, is recommended in the evaluation of a child with global developmental delay that is static, is nonprogressive, and lacks a clear etiology.⁴⁹ Approximately half of the patients in the authors' cohort required second or third tier genetic testing with whole exome sequencing or commercially available panels to establish a molecular diagnosis of PTHS, as initial testing with chromosomal microarray was nondiagnostic. According to the American College of Medical Genetics and Genomics, whole exome sequencing can be considered when there is likely to be a high degree of genetic heterogeneity associated with a condition such that whole exome sequencing analysis of multiple genes is more practical than single gene testing.⁵⁰ In a recent study of 57 undiagnosed neurology patients, whole exome sequencing had a diagnostic yield of 49.1%.⁵¹ An estimated cost analysis of whole exome sequencing in pediatric neurology patients found that whole exome sequencing, when used in place of other second tier testing modalities, can result in lower long-term costs and expedited

diagnosis.⁵² Furthermore, the cost of whole genome sequencing has decreased substantially since discovery, now costing less than \$1500 by some estimates.⁵³

As with autism and intellectual disability in general, there are specific comorbidities commonly seen in PTHS patients that, if managed appropriately, may improve the quality of life for patients and their families. In brief, individuals with PTHS should be evaluated for constipation, myopia, strabismus, spells of abnormal breathing, seizures, and sleep disturbances in addition to management of their developmental delays with appropriate therapies including speech, occupational, and physical therapy. Though treatment is only supportive at this time, a multidisciplinary team approach is valued in more complex cases with multiorgan system involvement to routinely assess and manage the challenges these patients and families face. The American Academy of Pediatrics defines children with medical complexity as those with multiple significant chronic health problems that affect multiple organ systems and result in functional limitations, high health care need or

Table 2. Detailed Genotype and Phenotype of the Authors' Cohort, Organized by type of Pathogenic Variant.

Patient	Genotype	Genetic test	Age at evaluation	Age at ambulation	Language	HV and apnea	Stereotypies	Sleep disturbance	Myopia	Strabismus	Constipation	Seizures	Current medications	Marangi score	Whalen score
Full gene deletions															
3	4.2 Mb, ~16 genes	CMA 2016 (buccal)	1y 10m	–	–	–	+	–	+	–	+	–	–	12	17
2	6.757 Mb, ~20 genes	CMA 2015	2y 9m	–	–	+	+	–	+	+	+	–	–	12	17
17	7.6 Mb, ~40 genes	CMA 2011	6y 2m	6.5y	–	–	+	+	+	+	+	–	Amantadine, vitamin D, Dulcolax, iron, Senna, hydroxyzine	12	18
8	25 Mb, ~100 genes	CMA 2012	28y 7m	–	–	–	UN	–	+	UN	+	+	h/o CBZ	10	13
Partial gene deletions															
21	148 kb—exons 1 and 2, ^a novel	CMA 2015	8y 8m	1.5y	Babble 24m	–	+	–	UN	UN	+	–	–	5	5
4	20 kb—exons 4 and 5	CMA 2012	5y 4m	5y	Babble 6m	–	+	–	+	+	–	+	OXC, LEV	12	17
14	188 kb—exons 4 to 8	CMA 2014	3y 3m	2.5y	Babble 20m	–	+	+	+	+	+	–	MiraLAX	12	16
19	100 kb—exons 4 to 8, de novo	CMA 2011	6y 5m	3.5y	–	+	+	–	+	+	+	–	Amantadine, MiraLAX, glycopyrrolate, lansoprazole	12	20
15	138 kb—exons 5 to 6, similar reported x1	CMA 2014	2y 11m	2.5y	Babble 11m	–	+	+	UN	UN	+	+	(GTCx1) MiraLAX	11	14
11	94 kb—exons 5 to 11	CMA 2010	10y	4y	–	+	+	+	+	+	+	+	Amantadine, LTG, Hydroxyzine, OXC, Vayarin	13	16
7	3.8 kb—exons 18, 19, and part of 20	CMA 2016	1y 8m	–	Babble 12m	+	UN	+	+	+	–	–	MiraLAX, lansoprazole	10	16
Frameshift molecular variants															
16	c.680_682delinsT, Trp227LeufsX29 in exon 10, novel	Epilepsy Panel 2012	12y 8m	9y	Babbled 9m	+	+	–	UN	UN	–	–	Acetazolamide, risperidone	13	19
13	c.457_461del in exon 12, de novo, novel	WES 2013	18y 11m	3.5y	–	–	+	+	+	–	+	–	Vayarin	13	16
22	c.1031delA in exon 13, de novo, novel	WES 2016	10y 5m	9y	–	+	+	–	UN	UN	+	–	Clonidine, risperidone	13	16
23	c.1239dupT in exon 15, novel	Rett/Angelman syndrome Panel 2016	3y	3y	–	+	+	+	+	+	+	–	Magnesium, amantadine	11	18
1	c.1414delG in exon 16, reported x1	Autism Panel 2015	3y 4m	–	Babble 24m	UN	UN	–	+	+	+	–	Risperidone, melatonin, amantadine	8	9
12	c.1933delG in exon 19, de novo, novel	WES 2015	12y 5m	1.3y	Sentences 7y	–	+	+	–	–	+	–	Melatonin, MiraLAX	9	11

(continued)

Table 2. (continued)

Patient	Genotype	Genetic test	Age at evaluation	Age at ambulation	Language	HV and apnea	Stereotypies	Sleep disturbance	Myopia	Strabismus	Constipation	Seizures	Current medications	Marangi score	Whalen score
Missense molecular variants															
6	c.1739G>A, Arg->Glu in exon 18, de novo, reported x2	WES 2014	10y 2m	10y	–	+	+	+	+	+	+	+	Seroquel	14	19
10	c.1738C>T, Arg->Try in exon 18, de novo, reported x6	WES 2015	2y 3m	–	–	–	+	+	+	+	+	–	–	12	16
18	c.1650-2 A>G in intron 17 leading to splice site variant, novel, c.1650-2 A>C reported x1	Rett/Angelman syndrome Panel 2015	3y	3.5y	–	+	+	+	+	+	+	+	LEV, glycopyrolate, lactulose, MiraLAX, risperidone, melatonin, esomeprazole, CBD oil	15	20
Nonsense molecular variants															
9	c.1037C>G in exon 13, de novo, novel	WES 2016	37y 10m	3.5y	–	+	+	UN	UN	UN	+	+	Amantadine, OXC, TPM, melatonin, myoinositol, CBD oil, levothyroxine, Mg, Kava, Petadolex	12	16
20	c.1174 A>T in exon 15, novel	TCF4 Sequence 2015	7y 6m	5y	–	–	–	–	–	+	+	+	Pyridoxine, clonidine, amantadine	12	16
Duplications															
5	201 kb including exons 4 to 8, mosaic father, novel	CMA 2016	2y 4m	–	Babble 12m	–	–	+	UN	UN	–	–	Melatonin	9	14
Total n (%)															
10/22 (45) 18/20 (90) 12/22 (55) 15/17 (88) 12/16 (75) 19/23 (83) 8/23 (35)															

Note is made of novel variants and inheritance pattern where available. Abbreviations: CMA, chromosomal microarray; WES, whole exome sequencing; CBD, carbamazepine; OXC, oxcarbazepine; LEV, levetiracetam; LTG, lamotrigine; TPM, topiramate; BP, base pair; IS, infantile spasms; UN, data unavailable at the time of chart review.

*Patient 21 used TCF4 transcript variant 3 while the remainder of patients' genotypes were based on TCF4 transcript variant 1.

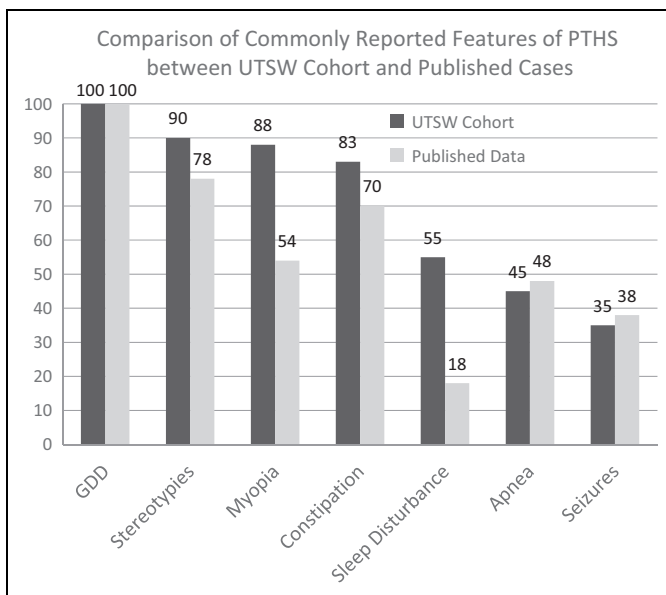


Figure 7. Graph depicting the rates of common clinical findings in the authors' cohort of PTHS patients compared to the rates of previously published cases. GDD, global developmental delay.

utilization, and often the need for or use of medical technology.⁵⁴ The American Academy of Pediatrics identifies this population as being at high risk for adverse medical, developmental, psychosocial, and family outcomes.⁵⁴ As such, PTHS patients should be considered medically complex given the high prevalence of multiorgan system dysfunction including brain, eyes, lungs, and intestines. Evaluations by pediatric-trained neurologists, ophthalmologists, pulmonologists, and gastroenterologists would provide the necessary team-based approach, which is recommended by the American Academy of Pediatrics in caring for medically complex children.^{54,55} Additional services from speech and language pathologists, physical and occupational therapists, social work, nursing, and school-based resources are also commonly needed. The American Academy of Pediatrics defines team-based care as a health care model that endorses the partnership of children and families working together with 1 or more health care providers and other team members across multiple settings to identify, coordinate, and address shared goals that meet the needs of the whole child in order to (1) maximize the health and functioning of the patient and family unit and (2) provide proactive care.⁵⁵ It is the authors' belief that by applying a team-based approach to the care of PTHS patients, they may improve the quality of life of the patient and family unit, though research in this field of pediatrics is limited.⁵⁵ Furthermore, as knowledge of the pathophysiology of *TCF4* variants deepens, specific treatments directed at the underlying molecular abnormality or other downstream targets may confer even more benefits and hopefully reverse the phenotype. Promising preclinical data on the use of histone de-acetylation inhibitors in mouse models of PTHS have shown normalization of long-term potentiation, increased vocalizations, and improvements in learning and

memory.⁵⁶ This study suggests that deficits associated with *TCF4* haploinsufficiency can be effectively treated, even in the postnatal period.

The ability to clinically diagnose PTHS is quite limited as evidenced by the numerous patients described in the literature as a different clinical syndrome, only to find out that the molecular diagnosis differs from the clinical diagnosis. In the authors' cohort, patients 1, 5, 12, and 21 testing for PTHS would not have been recommended based on the clinical diagnostic scores, supporting the de Winter et al conclusion that the available clinical diagnostic scoring tools are limited.³⁷ The lack of prospective, quantitative phenotyping or natural history studies in this genetically identified syndrome leaves us with only clinical observation to describe the features to date. In addition, the scarcity of patients increases the risk that patients are included in multiple publications, limiting the conclusions that may be drawn from data collected in a nonstandardized manner. Thus, the authors feel it is much more reliable to approach the disorder with a genetic diagnosis first, followed by standardized clinical assessment and treatment of symptoms. In this cohort, the authors describe 3 cases offering atypical genotypes and phenotypes. It is the authors' hypothesis that Patient 12 has a milder phenotype secondary to the location of his pathogenic variant in the penultimate exon, potentially yielding a more functional protein product, similar to a patient with a translocation involving *TCF4* described by Kalcheuer et al.^{57,58} Conversely, Patient 21 presents with profound cognitive and language deficits, but is lacking the other common clinical characteristics of PTHS. His deletion is small and may only impact the functioning of 1 of the longer *TCF4* transcript variants, thus creating a different phenotype as many of the other *TCF4* transcript variants do not include the region encompassed by this deletion.^{10,23} Given the clinical features of Patient 5, it is the authors' hypothesis that his duplication is disrupting the function of *TCF4*, though a large duplication such as his has not been described previously. As the authors have done here, many previously published case reports have described novel genotypes or phenotypes, suggesting there is still room to expand upon the commonly accepted phenotype associated with PTHS. Future studies that systematically study the cognitive, behavioral, and neuropsychological profiles in an objective, quantitative, prospective manner along with the natural history of PTHS are needed in order to identify potential clinical biomarkers and outcome measures for testing future novel therapeutic interventions.

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Author Contributions

KG contributed to the study design, data acquisition, data analysis, and drafting and revisions of the manuscript. CN contributed to the study design, data analysis, and drafting and revisions of the manuscript.

MM contributed to data acquisition and manuscript revisions. PE contributed to data analysis and manuscript revisions. PC contributed to study design, data acquisition and analysis, and manuscript revisions. SG contributed to study design, data acquisition, and manuscript revisions. All authors gave final approval for submission.

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Ethical Approval

The study received exempt status from the institutional review board, and photographs are published with consent of the legal guardians.

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