REVIEW

Diagnosis and management in Pitt-Hopkins syndrome:
First international consensus statement

Marcella Zollino¹,² | Christiane Zweier³ | Ingrid D. Van Balkom⁴,⁵ | David A. Sweetser⁶ |
Joseph Alaimo⁷ | Emilia K. Bijlsma⁸ | Jannine Cody⁹ | Sarah H. Elsea⁷ | Irina Giurgea¹⁰ |
Marina Macchiaiolo¹¹ | Robert Smigiel¹² | Ronald L. Thibert¹³ | Ingrid Benoist¹⁴ |
Jill Clayton-Smith¹⁵ | Channa F. De Winter¹⁶ | Stijn Deckers¹⁷ | Anusha Gandhi⁷ |
Sylvia Huisman¹⁸ | Dagmar Kempink¹⁹ | Frea Kruisinga¹⁸ | Vittoria Lamacchia²⁰ |
Giuseppe Marangi¹,² | Leonie Menke¹⁸ | Paul Mulder⁴,⁵ | Ann Nordgren²¹ |
Alessandra Renieri²⁰ | Sue Routledge²² | Carol J. Saunders²³ | Agnieszka Stembalska²⁴ |
Hans Van Balkom²⁵ | Sandra Whalen¹⁰ | Raoul C. Hennekam¹⁸ |

¹Fondazione Policlinico Universitario A.Gemelli, IRCCS, UOC Genetica
²Università Cattolica Sacro Cuore, Istituto di Medicina Genomica, Roma, Italy
³Institute of Human Genetics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
⁴Jornx Department of (Youth) Mental Health and Autism, Lentis Psychiatric Institute, Groningen, The Netherlands
⁵Rob Giel Research Centre, Department of Psychiatry, University Medical Center Groningen, Groningen, The Netherlands
⁶Division of Medical Genetics and Metabolism, Massachusetts General Hospital for Children, Boston, Massachusetts
⁷Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas
⁸Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands
⁹Department of Pediatrics, University of Texas Health Science Center at San Antonio, San Antonio, Texas
¹⁰Sorbonne Université, INSERM, UMR_S 933, Assistance Publique Hôpitaux de Paris, Département de Génétique Médicale, Hôpital Trousseau, Paris, France
¹¹Rare and Genetic Diseases Unit, Bambino Gesù Children’s Hospital, Rome, Italy
¹²Department of Pediatrics, Division of Pediatrics and Rare Disorders, Wroclaw Medical University, Wroclaw, Poland
¹³Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts
¹⁴Dutch Pitt-Hopkins Syndrome Foundation, Vlaggenschip, Oosterhout, The Netherlands
¹⁵Manchester Centre for Genomic Medicine, St Mary’s Hospital, and Division of Evolution and Genomic Sciences School of Biological Sciences, University of Manchester, Manchester, UK
¹⁶Organisation for Individuals with Intellectual Disabilities, Trajectum, Zwolle, The Netherlands
¹⁷Department of Pedagogical Sciences, Radboud University Nijmegen, Nijmegen, The Netherlands
¹⁸Department of Pediatrics, Academic Medical Centre, Amsterdam UMC, Amsterdam, The Netherlands
¹⁹Department of Orthopedic Surgery, Sophia Children’s Hospital, UMCR, Rotterdam, The Netherlands
²⁰Department of Medical Genetics, University of Siena, Siena, Italy
²¹Karolinska Center for Rare Diseases, Karolinska University Hospital, Stockholm, Sweden
²²Pitt Hopkins UK, Ilford, UK
²³Center for Pediatric Genomic Medicine, Children’s Mercy Hospital, Kansas City, Missouri
²⁴Department of Genetics, Wroclaw Medical University, Wroclaw, Poland
²⁵Behavioral Science Institute, Radboud University Nijmegen, Nijmegen, The Netherlands

ABBREVIATIONS: ACMG, American college of Medical Genetics; bHLH, basic helix-loop-helix; MLPA, multiplex ligation-dependent probe amplification; MRI, magnetic resonance imaging; NGS, next generation sequencing; PCR, polymerase chain reaction; PPI, proton pump inhibitor; PTHS, Pitt-Hopkins syndrome; R, recommendation; TCF4, transcription factor 4.

Marcella Zollino, Christiane Zweier, Ingrid Van Balkom, and David A. Sweetser should be considered joint first authors.
Pitt-Hopkins syndrome (PTHS) is a neurodevelopmental disorder characterized by intellectual disability, specific facial features, and marked autonomic nervous system dysfunction, especially with disturbances of regulating respiration and intestinal mobility. It is caused by variants in the transcription factor 4 (TCF4). Heterogeneity in the clinical and molecular diagnostic criteria and care practices has prompted a group of international experts to establish guidelines for diagnostics and care. For issues, for which there was limited information available in international literature, we collaborated with national support groups and the participants of a syndrome specific international conference to obtain further information. Here, we discuss the resultant consensus, including the clinical definition of PTHS and a molecular diagnostic pathway. Recommendations for managing particular health problems such as dysregulated respiration are provided. We emphasize the need for integration of care for physical and behavioral issues. The recommendations as presented here will need to be evaluated for improvements to allow for continued optimization of diagnostics and care.

**KEYWORDS**

autonomic dysfunction, diagnostic criteria, guidelines, molecular diagnostic pathway, Pitt-Hopkins syndrome, syndromic behavior, TCF4

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### 1 | INTRODUCTION

Pitt-Hopkins syndrome (PTHS) (MIM #610954) is a neurodevelopmental disorder with physical, cognitive, and behavioral characteristics, caused by deletions or variants in the TCF4 gene located at 18q21.2 and encoding transcription factor 4 (TCF4, MIM #602272). The condition is named after the Australian physicians David Pitt and Ian Hopkins who described two unrelated affected individuals in 1978. Reliable prevalence figures have not been published but based on the number of known affected individuals in the United Kingdom and the Netherlands prevalence is estimated as one in 225,000 to 300,000 (joint unpublished experience). A group of experts recognized that there was variability in practices in various countries with respect to diagnostics and management of individuals with PTHS, and formed an International PTHS Consensus Group. Data obtained from a literature review using PubMed searches starting at October 28, 2017, with key words "Pitt Hopkins," "PTHS," "Pitt-Hopkins," and "PTHS." The 120 available publications were evaluated critically, and previously unpublished data from consensus group members were added. Subsequently, we used a modified Delphi consensus to draft paragraphs on all major topics, and reach conclusions, which were discussed in a face-to-face meeting on May 25, 2018. The results were presented to the participants of the First PTHS World Conference (Sassenheim, the Netherlands May 25-27, 2018). This allowed substantial input of families and other caregivers of 51 individuals with PTHS, and led to a series of recommendations that are presented here (a detailed Methodology is available in the Supporting Information).

### 2 | CLINICAL DIAGNOSTIC CRITERIA

#### 2.1 | Definition

Currently, mutations in only a single gene (TCF4) are known to cause PTHS. It could be argued that the diagnosis should be made based on the molecular findings and clinical criteria are no longer needed. However, there are still individuals with a phenotype that cannot be distinguished from PTHS and in whom no mutation can be found. Furthermore, there are individuals with a variant in TCF4, but with a phenotype that differs markedly from the PTHS phenotype, and this has major consequences in counseling patients and families, especially as increasingly the first study in an individual with intellectual disability is next generation sequencing (NGS). We concluded there is still need for reliable clinical criteria.

Two sets of clinical diagnostic criteria have been published. Both sets are based on the presence, and sometimes the absence, of various signs and symptoms, and can be useful. However, when the two sets of criteria were used in retrospect in the largest series of individuals with PTHS published until now, it was evident that these could not yet be considered sufficiently precise to be used as diagnostic criteria. Therefore, a redefinition is needed.

To determine sensitivity of signs and symptoms, we gathered data on a series of 100 individuals with PTHS known to the present authors and in whom the clinical diagnosis was molecularly confirmed (Table 1; illustrated in Figure 1). We used the scored features as available in the files, to avoid a bias. Signs present in at least 75% were accepted as being sufficiently characteristic of the condition to be used to assess sensitivity, plus the breathing anomalies whose frequency varies markedly according to age. To determine specificity, we reasoned that the two entities that resemble PTHS most, that is, Angelman syndrome and Rett syndrome, should be reliably discernable from PTHS based on clinical features proposed. We gathered the same data as in individuals with PTHS in a series of 50 individuals with either Angelman or Rett syndrome, including only molecularly confirmed individuals (Table 1). Results indicated that the facial signs specifically allow distinction from Angelman syndrome and Rett syndrome.
We defined the clinical diagnostic criteria for PTHS by first proposing a group of features termed cardinal features, which we consider to be characteristic for PTHS, and which are highly specific (Table 2; Figure 2), and second a group of features termed supportive features, which should raise suspicion of a PTHS diagnosis, but are less specific. Subsequent discussion of these criteria allowed consensus for the clinical diagnostic criteria, based on the presence of cardinal and supportive features: if an individual has a score of 9 or higher, the diagnosis of PTHS can be clinically confirmed (R1). This score can only be reached if at least two of the three cardinal features are present. A score of 6 to 8 including the presence of the facial characteristics indicates a suspicion for PTHS and needs further confirmation by molecular testing.

We have tried to obtain an impression of the sensitivity of the criteria by applying these to the set of 100 individuals used to define the diagnostic criteria and a second set of 50 molecularly confirmed individuals with PTHS, not used to define the criteria. We then compared these scores to those of a set of 50 individuals with Angelman syndrome and 50 with Rett syndrome (Table S1, Supporting Information). All individuals with PTHS in both groups scored 6 or higher, indicating none would have been missed as having PTHS based on clinical criteria (complete sensitivity). Results show that none of the individuals with Angelman and Rett syndromes fulfilled the criteria for the clinical diagnosis of PTHS, and three of the individuals with Angelman syndrome and none of the individuals with Rett syndrome fulfilled the criteria for possible PTHS, indicating that specificity was very high, but not complete. An additional nine individuals with Angelman syndrome reached a total score of 6 to 8 but did not fulfill the criterion of the presence of facial characteristics, further indicating that the facial morphology represents the most specific criterion of PTHS. This is in agreement with our joint clinical experience that in rare patients, the

<table>
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<tr>
<th>HPO term</th>
<th>Signs</th>
<th>PTHS1 Number</th>
<th>PTHS2 Number</th>
<th>AS Number</th>
<th>Rett Number</th>
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<tr>
<td></td>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
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<td>Narrow forehead</td>
<td>83/100</td>
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<td>34/49</td>
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<td>91/100</td>
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<td>46/50</td>
<td>92</td>
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<td>72/100</td>
<td>72</td>
<td>47/50</td>
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<td>Full cheeks/prominent midface</td>
<td>81/100</td>
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<td>46/50</td>
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<td>50/50</td>
<td>100</td>
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<td>59/93</td>
<td>59</td>
<td>37/48</td>
<td>77</td>
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<td></td>
<td>Development</td>
<td></td>
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<td>0010864</td>
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<td>98/100</td>
<td>98</td>
<td>48/50</td>
<td>96</td>
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<td>0001344</td>
<td>Very limited or absent speech</td>
<td>89/100</td>
<td>89</td>
<td>46/50</td>
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<td>0002066</td>
<td>Gait ataxia</td>
<td>57/89</td>
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<td>0002194</td>
<td>Delayed gross motor development</td>
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<td>50/50</td>
<td>100</td>
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<td></td>
<td>Autonomic dysregulation</td>
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<td>Any breathing anomalies</td>
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<td>47</td>
<td>36/49</td>
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<td>Intermittent hyperventilation</td>
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<td>40</td>
<td>34/49</td>
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<td>38</td>
<td>25/49</td>
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<td>70/93</td>
<td>75</td>
<td>45/49</td>
<td>92</td>
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<td></td>
<td>Visual anomalies</td>
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<td>Myopia</td>
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<td>Strabismus</td>
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<td>19/50</td>
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<td>Neurological/behavioral features</td>
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<td>0000253</td>
<td>Microcephaly</td>
<td>17/97</td>
<td>18</td>
<td>11/47</td>
<td>23</td>
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<tr>
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<td>40/100</td>
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<td>15/47</td>
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<td>39</td>
<td>7/42</td>
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<td>43</td>
<td>13/42</td>
<td>31</td>
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<tr>
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<td>20</td>
<td>13/49</td>
<td>27</td>
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<td>0002376</td>
<td>Regression</td>
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<td>1</td>
<td>5/50</td>
<td>10</td>
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<td></td>
<td>Hand features</td>
<td>61/80</td>
<td>76</td>
<td>38/50</td>
<td>76</td>
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<tr>
<td>0001238</td>
<td>Slender fingers</td>
<td>40/80</td>
<td>50</td>
<td>23/50</td>
<td>46</td>
</tr>
<tr>
<td>0000954</td>
<td>Single transverse palmar crease</td>
<td>35/72</td>
<td>49</td>
<td>25/48</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Hand washing movements</td>
<td>6/100</td>
<td>6</td>
<td>5/47</td>
<td>10</td>
</tr>
<tr>
<td>0000733</td>
<td>Other stereotypic hand movements</td>
<td>63/96</td>
<td>66</td>
<td>24/50</td>
<td>48</td>
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</tbody>
</table>
discrimination between Angelman syndrome and PTHS based on clinical criteria can be extremely difficult, especially at a young age. However, to more reliably determine specificity and sensitivity, a prospective study will be needed (Box 1).

2.2 | Severity scores

A major issue for families is an indication of the severity of an entity at the time of diagnosis. Until now, no severity score for PTHS has been published. We suggest that a set of criteria that determine severity of PTHS should be established in close collaboration with the families gathered in the support groups as families can indicate best which physical, cognitive, and behavioral issues influence the life of affected individuals and their families most. Ideally, such criteria should be stratified according to the nature of the genetic cause (R2).

![FIGURE 1](A) Facial phenotype of eight individuals with molecularly confirmed Pitt-Hopkins syndrome. Ages are 15, 20 months, 8, 10, 15, 16, 18, and 31 years, respectively. (B) Major facial signs in Pitt-Hopkins syndrome, used for the clinical diagnostic criteria

**Recommendations**

R1 The clinical diagnosis of PTHS is based on a combination of signs and symptoms (Table 2): the clinical diagnosis can be confirmed if a score of 9 or higher is reached, and a score of 6 to 8 including the presence of the facial characteristics indicates a suspicion for PTHS and needs further confirmation by molecular testing. A++
BOX 1

VOTING PROCESS OF THE PARTICIPANTS OF THE CONSENSUS GROUP FOR THE RECOMMENDATIONS

All participated and the following options were available for the voting:
A. Evidence or general agreement allow full agreement with the recommendation
B. Evidence or general agreement are in favor of the recommendation
C. Evidence or general agreement are weak for the recommendation
D. There is not enough evidence or general agreement to agree with the recommendation

Depending on the proportion of votes received, the strength of each recommendation was calculated and indicated as:
+ 26%-49% of the votes
++ 50%-69% of the votes
+++ 70% or more of the votes

R2 A set of criteria to indicate the severity of PTHS should be developed in collaboration with families. A++

3 | MOLECULAR DIAGNOSTIC CRITERIA

PTHS is caused by heterozygous loss-of-function variants or hemizygosity leading to haploinsufficiency of TCF4, which encodes a basic helix-loop-helix (bHLH)-TCF4. TCF4 is located on 18q21.2, spanning 443 kb, and encodes for at least 18 alternative transcripts (Table S2, Supporting Information). These isoforms have a different length, but all share a C-terminal region of 489 amino acids (Figure S1). NM_001083962.1, constituted by 20 exons, is the transcript most commonly used as reference in the scientific literature dealing with PTHS-associated variants. To date, there are more than 140 different TCF4 aberrations reported in literature, including chromosomal translocations, large deletions, intragenic deletions, and truncating/probably gene disruptive or missense variants. Additionally, common single nucleotide variants in TCF4 have been reported as susceptibility factors for schizophrenia, Fuchs corneal dystrophy, and primary sclerosing cholangitis. TCF4 should not be confused with TCF7-like 2 (TCF7L2) encoding a protein also named TCF4 (T cell factor 4).

3.1 | TCF4 function

TCF4 belongs to the family of bHLH transcription factors or E-proteins, which are characterized by a broad expression pattern. TCF4 is known to be involved in B- and T-cell development, in epithelial-mesenchymal transition and in neurodevelopment. Its bHLH domain mediates interaction with DNA and formation of both homodimer and heterodimer with other classes of HLH proteins that are tissue specific or lack the basic DNA-binding domain. PTHS causing mutations in TCF4 were shown to impair interaction with ASCL1, another bHLH transcription factor involved in noradrenergic neuronal development. Impaired interaction with the ASCL1-PHONY-RET pathway has been hypothesized to explain at least some of the PTHS symptoms such as hyperbreathing (Figure 2A).

3.2 | Chromosome imbalances including TCF4

Intersitial deletions of 18q including TCF4 and ranging from about 1.2 up to 12 Mb have been reported in individuals with a PTHS phenotype indistinguishable from the phenotype in patients with intragenic TCF4 aberrations. Deletion size and number of additionally deleted genes within that range have no obvious impact on phenotype or clinical outcome. We concur with the diagnosis of PTHS in individuals with such deletions (Figure 2B). Larger and terminal deletions with a size up to 25 Mb have been reported in individuals with less typical phenotypes including only some aspects of PTHS. These large deletions should be considered contiguous gene syndromes, as other genes might contribute to the phenotype as well and should rather be termed “18q deletion syndrome” to which the exact breakpoints should be added (Figure 2B). This also applies to large deletions that are either present as mosaics or result from a ring chromosome.

Several other structural chromosomal aberrations such as balanced translocations disrupting TCF4 have been reported. The phenotype in these individuals varied, and the diagnosis of PTHS should only be accepted if the phenotype fulfills the clinical criteria (see Section 2.1).

TABLE 2 Clinical diagnostic criteria for PTHS

<table>
<thead>
<tr>
<th>Cardinal</th>
<th>Supportive</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Face (at least three of seven)</td>
<td>1. Myopia</td>
</tr>
<tr>
<td>a. Narrow forehead</td>
<td>2. Constipation</td>
</tr>
<tr>
<td>b. Thin lateral eyebrows</td>
<td>3. Hand (slender fingers and/or abnormal palmar creases)</td>
</tr>
<tr>
<td>c. Wide nasal bridge/tip</td>
<td>4. Unstable gait</td>
</tr>
<tr>
<td>d. Flared nasal alae</td>
<td>each 1 point</td>
</tr>
<tr>
<td>e. Full cheeks/prominent midface</td>
<td></td>
</tr>
<tr>
<td>f. Wide mouth/full lips/cupid bow upper lip</td>
<td></td>
</tr>
<tr>
<td>g. Thickened/overfolded helices</td>
<td>4 points</td>
</tr>
<tr>
<td>2. Severe intellectual disability with absent or limited (&lt;5 words) speech</td>
<td>2 points</td>
</tr>
<tr>
<td>3. Breathing regulation anomalies (intermittent hyperventilation and/or apnea)</td>
<td>2 points</td>
</tr>
</tbody>
</table>

Clinical diagnosis of Pitt-Hopkins syndrome.
Score ≥ 9. Molecular confirmation indicated.
Possible clinical diagnosis of Pitt-Hopkins syndrome.
Presence of facial characteristics + additional criteria, either cardinal or supportive, totaling a Score of 6-8. This score warrants TCF4 molecular analysis.
Insufficient clues for the presence of Pitt-Hopkins syndrome.
Score < 6. No further studies specifically for PTHS indicated. Further studies for other etiologies indicated.
**FIGURE 2**  Functions of TCF4. (A) Within the basic region of its bHLH domain, TCF4 binds to E-box motifs in promoter regions of transcriptional target genes. It forms homodimer and heterodimer, for example, with other bHLH domain proteins such as ASCL1 which is involved in regulation of the noradrenergic system via the ASCL1-PHOX2B-RET pathway. Mutations in this pathway are associated with breathing phenotypes and Hirschsprung disease. (B) The long arm of chromosome 18 (UCSC genome browser) with location of TCF4 in 18q21.2. Deletions within the region represented by the dark blue bar are associated with a typical PTHS phenotype. Larger deletions including TCF4 and expanding into the regions represented by the middle blue bars are associated with a less typical phenotype but with severe ID and other clinical aspects of PTHS. (C) Schematic drawing of TCF4 with non-coding (light gray), coding (dark gray), and bHLH domain encoding (black) exons. Above the scheme, different aberrations associated with a PTHS or PTHS-like phenotype are depicted, below the scheme are aberrations associated with mild intellectual disability. Sequence variants or deletions affecting exons represented by the dark blue bar cause typical PTHS, those in exons represented by the middle blue bar are associated with a more variable PTHS-like phenotype with severe intellectual disability, and variants located in regions represented by the light blue bar are associated with mild and/or non-specific intellectual disability. *, truncating variants; orange circles, missense variants; #, frameshifting variants with protein elongation; magenta circle: in-frame inclusion of an amino acid; black circles with lines: translocations; red lines, deletions; blue line, duplication.

### 3.3 | TCF4 variants

Probably gene disruptive or truncating variants represent the majority of sequence variants in TCF4 found in PTHS and comprise splice site, nonsense, and frameshift variants. They are mostly distributed between exons 7 and 19 of TCF4 and, with few exceptions, are unique. Two frameshift variants in exon 19 were predicted to result in elongation of the protein, possibly also resulting in loss of function. Pathogenic missense variants are identified in about 20% of patients and cluster in the highly conserved bHLH domain, encoded by exon 18. Several amino acids within this domain are recurrently affected (Figure 2C). Only two de novo missense variants outside the bHLH domain have been reported.\(^{15,30}\) Intragenic deletions involving one or several exons of TCF4, predicted to cause a shift in the reading frame, have been identified in ~12% of published cases.\(^{3,19,31-33}\) One partial duplication of several exons has been reported.\(^{22}\) Gene disruptive deletions/variants affecting exons 9 to 19 and missense variants in exon 18 (bHLH domain encoding) are probably to result in PTHS. No convincing genotype-phenotype correlations within this latter group have been observed.

### 3.4 | TCF4 variants and non-PTHS phenotype

Several TCF4 variants associated with non-specific mild intellectual disability have been described, as well as variants associated with more severe intellectual disability and a limited number of PTHS characteristics. These variants probably include gene disruptive/truncating mutations, a non-frameshift insertion of an amino acid, translocations, and partial gene deletions.\(^{22,26,29,33-37}\) Some of these variants segregated in families together with mild intellectual disability.\(^{29,36}\) A recent study reevaluated the clinical phenotype of 10 patients with non-specific ID without clinical suspicion of PTHS, in whom a TCF4 variant was identified by high-throughput sequencing.\(^{37}\) In retrospect, five had typical PTHS, three were clinically classified as possible PTHS and two did not resemble PTHS. In absence of a phenotype fulfilling the clinical diagnostic criteria, individuals should not be diagnosed as having PTHS based solely on an identified variant in TCF4 (R3).

The milder or more non-specific phenotype associated with those TCF4 variants is only partially explained so far. While individuals with variants affecting exons 9 to 19 usually have typical PTHS, individuals with variants in exons 1 to 4 have non-specific mild intellectual...
disability and individuals with variants affecting exons 7 to 8 present with moderate to severe intellectual disability and sometimes have some of the characteristics of PTHS (Figure 2B). Variants in exons 9 to 19 affect all known functional protein isoforms, while variants in upstream exons might spare variable subsets of isoforms. This may explain the phenotypic differences and the milder signs and symptoms associated with N-terminal variants. The nature of variants may also explain the phenotype, as a variant in the splice acceptor of exon 17, predicted to result in an in-frame inclusion of one amino acid, or a splice variant in splice donor of exon 12, which might be leaky, were associated with non-specific mild or moderate intellectual disability.

### 3.6 | Pattern of inheritance

Variants in TCF4 underlying typical PTHS usually occur de novo. Recurrence risk for sibs of affected individuals is therefore generally low. Germ line or low-grade parental mosaicism has been reported in four instances, representing 2% to 3% of published cases. Additionally, our joint experience in 273 individuals with molecularly confirmed PTHS indicates five recurrences in siblings without a detectable (mosaic) TCF4 variant in the parents. Therefore, we confirm an empiric recurrence risk of up to 2% (R4). To our knowledge, no individual with typical PTHS has reproduced. Several TCF4 variants with milder phenotypes, not fulfilling the diagnostic criteria of PTHS, have been segregating in an autosomal dominant pattern. In these families, recurrence risk is 50%.

### 3.7 | Molecular genetic testing

Currently, the first-tier test in any individual with intellectual disability is evaluation of a chromosomal imbalance using chromosomal microarray analysis. As chromosomal imbalances represent a significant proportion of PTHS-causing aberrations, we suggest this approach in
individuals with severe ID and facial characteristics suspected of having PTHS. If the clinical phenotype is compatible also with Angelman syndrome, we recommend methylation analysis, either subsequently or in parallel (e.g., multiplex ligation-dependent probe amplification (MLPA) or polymerase chain reaction) of the Angelman syndrome locus. If NGS testing is available, the most effective second-tier test is exome sequencing or panel sequencing, as there are several clinical entities that resemble PTHS that can be assessed in this single analysis. Large-scale unbiased NGS studies showed pathogenic TCF4 variants in ~0.7% of tested individuals with ID without a previous clinical suspicion of PTHS.27 If NGS availability is limited or absent, or if the clinical suspicion of PTHS is very strong, targeted analysis by Sanger sequencing of TCF4 and deletion/duplication testing by MLPA is the alternative second tier (Figure 3). Classic karyotyping to check for a balanced translocation should be considered if studies yield negative results and clinical suspicion is high.

Variants identified in TCF4 should be evaluated and reported according to American College of Medical Genetics (ACMG) criteria and with regard to the respective patient’s clinical phenotype (R5). Deletions up to 12 Mb, probably gene disruptive/truncating variants (including frameshift intragenic deletions) in exons 9 to 19 and recurrent missense variants in the bHLH domain can be considered pathogenic if the phenotype fits. Parental testing in these cases is not required to make the diagnosis in the index patient, but is recommended to confirm de novo occurrence of the variant. Variants located in the N-terminal exons or being atypical in their nature (e.g., in-frame aberrations, some splice variants, missense variants outside the bHLH domain, translocations, duplications) should be interpreted cautiously as reported TCF4 variants exist that are associated with phenotypes other than PTHS. Evaluating the clinical phenotype and consulting databases containing previously reported variants are useful in such interpretations. Unusual splice variants or unusual intragenic aberrations might require mRNA analysis to further investigate their consequences. Mosaicism has been reported for large 18q deletions (>12 Mb)24 (own experience in 6/103 tested patients). There is no indication so far that mosaicism for smaller and intragenic TCF4 variants is particularly frequent. Obviously, mosaicism should be taken into consideration if there are clinical clues such as pigment anomalies or asymmetry.

Recommendations

R3 TCF4 variants can cause PTHS but can also cause other intellectual disability associated phenotypes which should not be labeled PTHS. A+++  
R4 Empirically, after the birth of an individual with molecularly confirmed PTHS, a recurrence risk of 2% should be given. A++  
R5 Interpretation of variants in TCF4 require consideration of the phenotype of the tested individual, pattern of inheritance of the phenotype and the variant, earlier experience with the variant, and nature and localization of the variant, using ACMG criteria. A+++  

4 | PRENATAL MOLECULAR DIAGNOSIS

Classic PTHS typically has a low recurrence risk, empirically being around 2% (see Section 3.6). In the absence of a family history of PTHS, it is unprobably that the syndrome will be diagnosed by prenatal fetal ultrasonography, as PTHS is not associated with characteristic congenital abnormalities.

As in all disorders usually caused by de novo variants, germ line mutations cannot be excluded and prenatal diagnostic tests should be offered to families with a previous affected child (R6). Reliable prenatal diagnostic testing can be offered if the genetic alteration in the index patient is known. Testing can be performed through either chorionic villous sampling, amniocentesis, or pre-implantation genetic testing after in vitro fertilization, using single gene sequencing or deletion testing, depending on the genetic alteration in the earlier affected child.

Non-invasive cell-free fetal DNA multigene screening that includes TCF4 may allow identification of de novo variants also in families without a previous affected child. Samples of biological parents would be essential for the interpretation of a large number of variants detected this way, and often pathogenicity will be difficult to prove. In our opinion, meaningful use in daily practice is very limited at present, and prenatal screening or testing for PTHS outside of a known familial mutation, remains challenging (R7). If such testing is offered, pre-test counseling should include careful discussions of reliability and informative value of results, as well as ethical issues.

Recommendations

R6 Prenatal testing should be offered to families in which the diagnosis of PTHS in the index patient is molecularly confirmed. A+++  
R7 Prenatal testing for PTHS outside of a known familial genetic alteration remains challenging due to the current difficulty in interpreting reliably all variants that will be obtained. Use of this type of testing as a screening method is not recommended at the present time. A+++  

5 | GASTROENTEROLOGY

Early hypotonia in infants with PTHS may lead to feeding issues, which are monitored with infant feeding assessments and generally resolve with age. Feeding difficulties such as gagging, food refusal, and ritualized eating may occur but in general, many individuals are described as excellent eaters.4

Gastrointestinal disturbances are common in children and adults with PTHS and include constipation (80% and 70%, respectively), gastroesophageal reflux disease (38%), and burping (29%).4,5 Hyper-breathing may lead to air swallowing with subsequent excessive burping and pain due to abdominal swelling,4,6 and was present in 22 of 47 individuals with PTHS present at the World Conference in 2018. In one patient, a gastrosomy was placed to let air escape several times a day, which resolved her severe complaints (L.M., unpublished observation). Food intolerances in this group of 47 individuals did not occur more frequently than in the general population.

Although Hirschsprung disease is often considered in PTHS, it is very rare, having been reported in a single individual only.4,6 Constipation is frequent and is typically present lifelong and severe.4,6 In a study of PTHS mouse models, those with the deletion mimicking TCF4 haploinsufficiency in humans exhibited decreased upper GI and distal colon velocities.45 Data on bowel passage velocities are lacking. We hypothesize that the impaired gut motility may be caused by a
defective regulation through the autonomic nervous system. Other gut problems include pyloric stenosis and malrotation.5

The treatment for constipation is similar as for the general population (R8).48 Behavioral modification such as regular toilet sitting for a set period after every meal and utilizing positive reinforcement through a reward system is also helpful. Effective management involves careful evaluation using constipation diaries, the Bristol stool form scale, and the section C of the Questionnaire on Pediatric Gastrointestinal Symptoms (R9).49

Gastroesophageal reflux management is similar as for the general population.50 Proton pump inhibitors form the first-line treatment. Individuals with PTHS respond well to these if medication is given in sufficiently high doses (omeprazole 0.7-3.5 mg/kg/day; for maintenance, usually half the dose is needed) (R10).51

Recommendations

R8 The commonly occurring marked and chronic constipation in individuals with PTHS should be monitored and evaluated through a diary or dedicated questionnaires. A+++  
R9 Constipation in individuals with PTHS should be treated as in the general population, including behavioral modification strategies. A++  
R10 Gastroesophageal reflux in individuals with PTHS should be treated as in the general population. Anti-reflux medications need to be used on their maximum dosage. A++

6 | RESPIRATION

Disturbed regulation of respiration is one of the cardinal criteria of PTHS. It is most probably part of the general dysautonomia that occurs in PTHS and which might also manifest as dilated pupils with sluggish response to light, instability of temperature, decreased distal circulation, constipation, or urinary retention.4,16 The age of onset of respiration problems is variable. We gathered data on 256 molecurally confirmed individuals and found that 123 (48%) had hyperbreathing which started at a mean age of 6.1 years (3 months, 37 years).2-4,15,16,18,19,22,23,30 This frequency may be influenced by a publication bias, but the true frequency of a disturbed respiration may well be higher, as affected individuals may have been reported at an age where they may not yet have developed this phenomenon. When stratified according to age, the incidence of respiration problems was 20% before 2 years of age, 23% between 3 and 5 years, 22% between 6 and 10 years, 69% between 11 and 15 years, and present in over 90% of older individuals.2 Rarely, initial hyperbreathing disappeared over a longer period of time.3,4 There is no correlation between genotype and the occurrence of hyperbreathing.22

The typical breathing pattern consists of rapid breathing, both regular and irregular, followed by stopping of the breathing. Duration is usually 2 to 5 minutes. It may occur several times per hour to a few times per year. The spells are not reported during sleep.52 Apneas and hyperbreathing may also occur independent of each other. Periods of hyperbreathing may be triggered by excitement, stress, or anxieties but may occur without discernible precursor. A period of apnea may be followed by cyanosis and rarely loss of consciousness. Oxygen saturation may be decreased during a spell of abnormal breathing.53 We are not aware of any instance of fatal asystole provoked by a spell of apnea (R11). The breathing abnormalities may precede or follow the start of epilepsy, but only infrequently is a spell followed immediately by a seizure.54 Many affected individuals develop clubbing of fingers within a few years after the start of the breathing irregularities. In 9 of 49 individuals with PTHS in whom the hands were evaluated during the 2018 PTHS World Conference clubbing was present. Some affected individuals were reported with clubbing preceding the hyperbreathing, but most probably the hyperbreathing had gone unnoticed in these individuals.19 Other secondary phenomena are excessive burping (28%) and swelling of the abdomen (20%).4,48 Breathing spells may cause anxieties in affected individuals and appear quite concerning, but many are seemingly not disturbed and remain comfortable. Others do stop activities, some sit down to prevent a fall, and in a minority loss of consciousness occurs. In a limited number of affected individuals, irregular breathing at night3,4,18 and catathrenia (end-inspiratory apnea and expiratory groaning during sleep)55 has been reported. Parasomnias were reported in 10 of 47 attendees of the 2018 PTHS World Conference. Although polysomnographies were not available for evaluation, it has been postulated that the breathing problems at night may also have a different cause and be obstructive in nature (R.C.H., personal observations) (R12).

Verhulst et al53 reported two individuals with PTHS and marked spells of hyperbreathing which decreased in number and duration when using acetazolamide. A similar effect was reported in a single other individual.56 Acetazolamide is a carbonic anhydrase inhibitor and is used in acute mountain sickness.57 It may act through induction of a metabolic acidosis not only by decreasing bicarbonate reuptake in the kidneys but also by directly affecting central chemoreceptors.58,59 A major side effect may be low potassium levels which has been a reason to stop the medication in several individuals with PTHS (R.C.H., unpublished observations). In individuals without PTHS, other medications such as triazolam and zolpidem have been used for central sleep apnea60,61 but effectiveness must be expected to be low due to the different origin of the respiratory problems in individuals with PTHS.62 In a mouse model of Rett syndrome, sarizotan has been shown to reduce the incidence of apnea and hyperbreathing,63 and a clinical trial is now underway. If successful it may hold promise for the breathing problems in PTHS.

Recommendations

R11 It should be explained to caregivers that spells of hyperbreathing, despite being disturbing to witnesses, are unlikely to be harmful. A++/B+ (equal votes).  
R12 If breathing disturbances occur at night, polysomnography should be considered in individuals with PTHS to exclude obstructive sleep apnea. A+++/B++ (equal votes)

7 | SENSES

7.1 | Vision

Structural ocular abnormalities are uncommon in individuals with PTHS. Tear duct blockage occurred in 12 of 101 individuals assessed.6
and other abnormalities reported in single individuals include enophthalmia,\textsuperscript{16} small optic nerves,\textsuperscript{19} and macular degeneration.\textsuperscript{3}

Functional impairments are common. Refractive errors are present in 64% of individuals, consisting of myopia in 52% and hypermetropia in 22%. Myopia is typically severe (>6 dpt) and children usually need glasses before 2 years of age.\textsuperscript{18} Strabismus was reported in 44% of individuals.\textsuperscript{2,4,14,18,19,22,29,30,52,54,64} Nystagmus occurs in 14% of individuals with PTHS.\textsuperscript{2,4,18,19,64} Dilated pupils with a sluggish response to light have been reported in three individuals.\textsuperscript{56}

As visual impairments are common, once the clinical diagnosis of PTHS is suspected, the child needs to be referred for ophthalmological evaluation, with ongoing surveillance thereafter (R13). Management protocols as for the healthy population can be followed for management of visual problems in individuals with PTHS.

7.2 | Hearing

Hearing loss is found in 10% of individuals with PTHS\textsuperscript{4} and is typically conductive.\textsuperscript{4,26} Given that speech delay is a universal feature in individuals with PTHS, it is prudent to perform hearing evaluations on all, to ensure that speech development is not hampered by poor hearing (R14). Informative evaluations can be performed without the necessity of cooperative feedback such as optoacoustic emission and auditory evoked potential.

7.3 | Other senses

In a questionnaire study, 4 of 101 individuals with TCF4 variants were reported to be hypersensitive to smell, and two individuals seemed to have an inability to smell.\textsuperscript{4} Detailed evaluations of smell in groups of individuals with PTHS are lacking.

Recognizing and dealing with pain is challenging in individuals with PTHS due to their limited ability to communicate verbally and their seemingly different way of reacting to pain. There is anecdotal evidence that children with PTHS are more bothered by minor painful stimuli such as a small scrape or cut, while in contrast they seem less bothered by major painful events such as post-surgical pain. Possibly this is related to the involvement of TCF4 in pain signalling as showed in the mouse.\textsuperscript{65} Tools such as the FLACC have been developed to aid in the recognition and assessment of pain in children with cognitive limitations,\textsuperscript{56} and their use in children with PTHS is advocated (R15). Disturbed filtering and processing of external and internal sensory stimuli are possibly due to sensorimotor gating issues in PTHS\textsuperscript{67,68} (See Section 13).

Recommendations

R13 Every child with PTHS should be evaluated for visual impairment once the diagnosis has been established; subsequent surveillance is indicated. A+++

R14 Hearing should be evaluated in every individual with PTHS at regular intervals. A+++

R15 Care providers should be aware of the various manifestations of pain in individuals with PTHS and specific tools to assess pain are recommended. A+++
fingers do not appear to cause major problems. The mobility in the thumbs may be decreased, less developed or absent distal flexion crease of the thumbs is present in 50% of affected individuals, and anykloses of the thumbs have been reported, but occur infrequently (present in a single affected individual of the PHTS World Conference). More generalized camptodactyly has been reported in five individuals with a microdeletion and in a single individual with a TCF4 variant.

Major problems occur frequently in the feet, which are almost invariably slender. A flat foot deformity, generally flexible, is often noted, but pes cavus also occurs. In 25%, there is a pes planovalgus deformation, and overlapping toes are not uncommon. Scoliosis has been reported in 18% of individuals and can arise during puberty but also at younger ages. In single individuals, kyphosis, pectus excavatum, and decreased mobility in a knee have each been described.

Minor limb anomalies do not require therapeutic interventions but the shape and function of the feet and ankles often require special footwear, inserts, or orthotics. In selected cases, surgical procedures may be beneficial, for example, flat foot reconstruction.

There is no study available on the results in larger groups of individuals on the management of scoliosis. Our joint experience indicates that management should be as for the general population. An individual evaluation with a regular spinal follow up might be warranted, taking into consideration the variable muscle tone.

Recommendations

**R19** Flat feet and valgus positioning in individuals with PHTS often require special footwear, inserts, or orthotics. Surgical correction may be necessary if walking remains impaired. A++

**R20** Individuals with PHTS should have their spine checked regularly from an early age. A++

**R21** Management of scoliosis in individuals with PHTS follows management in the general population. A++

### 10 | PEDIATRIC MEDICAL FOLLOW-UP

Most affected children present in the first year of life with hypotonia and developmental delay. Motor skills are delayed with approximately 30% of children walking unaided at 3 to 5 years of age, and 75% at 6 to 10 years of age. Those who walk independently often have a wide-based, unsteady and somewhat ataxic gait (see Section 8). Some individuals may walk only with assistance, while others do not acquire independent walking skills. Of those individuals unable to walk alone, some achieve independent mobility by using a manual wheelchair, including navigating through doors (S.D., personal observations). Speech is typically significantly delayed, with many individuals remaining non-verbal. Up to 55% of individuals speak single words before 10 years of age, with only a minority using whole sentences (<10%). Of the 47 individuals present during the 2018 PHTS World Conference 39 used 0 to 5 words, two 10 to 20 words, and six were able to use short sentences. Few individuals develop dressing or toileting skills, with up to 20% of individuals being toilet trained for urine between 11 and 15 years of age.

Growth parameters at birth are usually within the normal range, intrauterine growth retardation has been observed in 8% of newborns. Post-natal height drops below –2 SD in about 30% of individuals, as does head circumference in 25%, resulting in an OFC between –3 and –2 SD in approximately half of the individuals. No major dental anomalies have been reported, and teething and shedding of teeth occur at a normal age. Increased spacing of teeth is common. It is prudent to have children with PHTS evaluated regularly (usually once per 6 months) by a dentist as children with developmental disabilities are more probably to have unmet dental needs.

Eruption (erupting) (28%), reflux (38%), and constipation (80%) are common in children (see Section 5). Behaviors during feeding include gagging, choking, and not chewing properly. Some individuals refuse food, or have very strict rituals during feeding. In general, many individuals are described as excellent eaters. A cleft palate occurs only rarely, a highly arched palate is common. Drooling is seen in 80% of individuals, usually more prominent in young children, and teeth grinding occurs in 29%. Recurrent respiratory infections (otitis media, tonsillitis, bronchitis) and urinary tract infections have been reported in one-third of affected individuals, occurring mainly in childhood. Immunological disturbances are sporadically reported and include low IgA, IgM, and IgG levels. Of 47 affected individuals at the 2018 PHTS World Conference immunological testing was performed in seven, and abnormalities in immune-globulin levels were found in three. Vaccinations should be given according to national schemes (R23). TCF4 is involved in fetal B lymphocyte development in mice, and immunological anomalies may be expected in individuals with PHTS.

Visceral malformations are uncommon (2%), and ultrasound of the heart and kidneys are only indicated in case of suggestive symptoms (R24). Urogenital problems consist of cryptorchidism (33%), fusion or underdevelopment of labia majora, and underdeveloped internal genitalia. Present (limited) data indicate that puberty develops at a typical age and pace.

The pediatrician, preferably one with experience in PTHS, should play a central role in the clinical care for children with PTHS by undertaking surveillance of health problems, coordinating multidisciplinary care, and overseeing the social support system surrounding the child (R25).

Recommendations

**R22** Individuals with PHTS should undergo regular dental assessments. A++

**R23** Vaccinations should be given to every child with PTHS according to national guidelines. A++

**R24** Ultrasound of heart and kidneys are indicated in children with PHTS only if suggestive signs or symptoms are present. A++

**R25** Every child with PTHS needs regular follow-up, preferably by a pediatrician familiar with PHTS. A++

### 11 | ADULT MEDICAL FOLLOW-UP

Adult height is mildly below the expected target height in 18% of patients. There is no report of related endocrine issues (growth
hormone deficits; thyroid dysfunction) to explain this. Some individuals tend to become somewhat overweight with time, but excessive weight gain is not a major problem overall in PTHS. Mild microcephaly was reported in 23.5% of adults.\textsuperscript{3,4,14,18,19,30,76} Facial characteristics in adults are similar to those in children, as the change in facial gestalt is limited after infancy.

Feeding problems are uncommon in adults with PTHS: problems with drinking and swallowing solid foods were each reported in 8% of individuals.\textsuperscript{4} Constipation is common and occurs in 70% of adult individuals (see Section 5).\textsuperscript{3,4,14,18,19,30} Gastroesophageal reflux is present in one-third of adults and typically responds well to adequate anti-reflux medication.\textsuperscript{4}

Frequent musculoskeletal signs in adults are pes planus or valgus (~50%), overriding toes (28%), scoliosis (25%), and limited thumb mobility (~25%).\textsuperscript{4} Monitoring for these signs is indicated as orthopedic shoes or other orthotic devices, physiotherapy, or other specific treatments may be needed (R26). In individuals with limited mobility, physiotherapy is indicated to prevent contractures.

Frequent infections are not common; however, urinary tract infections in particular may go unrecognized or manifest as unusual behavior changes in adults and are important to keep in mind (unpublished observations) (R27).

Teeth remain widely spaced in adults with PTHS, bruxism occurs, and drooling is frequent. Prognathism may develop and lead to mastication difficulties. Improving adequate oral motor skills by a speech therapist may be helpful in children and adults (R28). Dental pain may be difficult to indicate for an individual with PTHS, and in case of unexplained behavioral changes, dental evaluation is indicated.

Genital anomalies (cryptorchidism, small penis, abnormal clitoris, or labia) are described in 30% of individuals. Adult males should be checked for cryptorchidism, as this may have been overlooked previously. If present, management is as in the general population (R29).

To date, few older patients have been reported with PTHS; thus, it is difficult to accurately predict life span. Thirty-six adults with molecularly confirmed PTHS have been reported.\textsuperscript{3,4,14,18,19,23,30,33,76} Most of them are young adults (~35 years). Published data\textsuperscript{77} and our joint experience indicate expected life span to be typical. In a questionnaire study of 101 individuals, the oldest participant was 32 years, with an excellent physical condition.\textsuperscript{4} One of the original patients reported by Pitt and Hopkins\textsuperscript{4} died at 19 years of age due to pneumonia. Another patient was found to have a Hodgkin lymphoma and died at age 29 years. We have knowledge of three other individuals who developed malignancies: Hodgkin lymphoma, medulloblastoma, and rhabdomyosarcoma (in a child). It is uncertain whether there is a relation between the malignancies and PTHS. No other individuals with malignancies have been described in the literature. Data on cardiovascular functioning, osteoporosis, and dementia in adults with PTHS are not available.

Recommendations

R26 Special shoes or braces to correct foot anomalies should be considered to improve stability and mobility of individuals with PTHS. A++

R27 Behavior changes in individuals with PTHS may be caused by pain due to unrecognized physical causes and should lead to careful physical exams for constipation, infections and dental problems. A++

R28 Speech therapy may be indicated in individuals with PTHS for oral issues such as drooling. A++

R29 Cryptorchidism in males with PTHS should be checked for, and if present should be treated following standards for the general population. A+++
utensus and ovaries have also been reported.\textsuperscript{3,4,15,17,19,30,67} No data are available on fertility in either males or females.

Sexual education should be proposed according to the level of emotional and cognitive functioning.\textsuperscript{82} Contraceptive options for females with intellectual disability are available in several countries; if unavailable recommendations as for the general population should be followed (R32). Suppression of menses using contraceptives should be considered in some individuals who show marked difficulties in dealing with menses. Screening for cervical and breast cancer as well as prostate cancer should be performed according to national standards.

**Recommendations**

R30 Individuals with PTHS and their families require lifelong care, preferably provided by a multidisciplinary healthcare team. A+++  
R31 Preparations for transition of care should be initiated from a pubertal age on. Transition should include early and careful transfer of the individual’s medical and social information. A+++  
R32 Sexual education appropriate to the level of emotional and cognitive functioning should be offered, and contraception management should follow standards for individuals with intellectual disability, or if unavailable, for the general population. A+++  

### 13 | COGNITION AND BEHAVIOR

#### 13.1 | Cognition

TCF4 is necessary for neurodevelopment and it plays an important role in cognition and behavior.\textsuperscript{68,83} Individuals with PTHS often have disrupted sensorimotor gating,\textsuperscript{67,68} indicating disturbed filtering of external and internal stimuli. Adequate filtering facilitates management of the more relevant information, preventing information overload, and encouraging mental and behavioral integration.

Identifying suitable assessment tools for the PTHS population is difficult, but all individuals with PTHS cognitively assessed through standardized measures in previous publications showed moderate to severe intellectual disability.\textsuperscript{4,47,78} Reported developmental ages in PTHS range from 9 to 36 months (mean 14.5 months) in a series of 101 individuals (mean age 9 years; median age 8 years).\textsuperscript{4} Unpublished data on 13 individuals with PTHS (mean age 15.84 years; range 2.56-30.84 years) indicated that a wide variability is present in cognitive features, with the mean developmental age determined with the Vineland Screen is 1.42 years (range 0.24-4.24 years; S.D., personal observations). Almost all individuals in this study sample were aware of action reaction; about 1.42 years (range 0.24-4.24 years; S.D.) self-injurious behaviors and anxiety (R31). Physical and occupational therapy are recommended for development of motor coordination.\textsuperscript{67} Communication and language capacities should always be assessed and interpreted in light of these interwoven connections.\textsuperscript{78,86}

Individuals with PTHS have mild to severe motor learning impairments and often engage in stereotypic and repetitive movements such as hand clapping and flapping, repeated hand to mouth movements, head shaking, head banging, body rocking, washing, finger crossing, and rubbing toes together.\textsuperscript{4,47,78,85} Motor milestones and self-care skills are delayed (see Section 10). Very few develop independent daily living skills such as dressing or toileting.\textsuperscript{4} Unpublished observations in 13 individuals showed that 10 were able to actively help with dressing, and six were able to unzip their coats or pants (S.D., personal observations). Skills may still develop at older ages, however.\textsuperscript{4} Loss of previously acquired hand skills has been reported rarely.\textsuperscript{30} Following initial diagnosis of PTHS, developmental assessments to determine appropriate services and educational strategies are necessary (R33) (see also Section 10).

### 13.2 | Language and communication

PTHS patients typically have problems with verbal memory and language development.\textsuperscript{68} Kennedy et al\textsuperscript{68} showed that Tcf4 haploinsufficient mice have deficits in social interaction, ultrasonic vocalization, repulse inhibition, and spatial and associative learning and memory. Loss-of-function mutations in Tcf4 lead to the near-complete lack of language acquisition. Language acquisition is virtually absent in most PTHS individuals.\textsuperscript{4,31,47,67,78,83,85} Up to 55% of individuals express only single words before 10 years of age, and indeed many have little to no expressive language throughout their lifespan (R34). Two studies characterized expressive language in PTHS individuals and showed that although in this group few individuals (9%-10%) produce whole sentences, communicative intent can be unclear, and qualitative impairments may exist, such as immediate or delayed echolalia and stereotyped utterances.\textsuperscript{47,78} Every individual with PTHS should be directly assessed for level of communication and possible existing barriers to increase effective communication potential (R35). Developmentally appropriate communication strategies, such as speech therapy and augmentative and alternative communication support should be considered.\textsuperscript{67} No studies specific for individuals with PTHS using these communication strategies are available.

Other interventions include special education services to focus on the development of life skills and behavioral modification targeting self-injurious behaviors and anxiety (R36). Physical and occupational therapy are recommended for development of motor coordination.\textsuperscript{67} Communication and language capacities should always be assessed and interpreted in light of these interwoven connections.\textsuperscript{78,86}

#### 13.3 | Behavior

Most children with PTHS are described as amiable and exhibit lovable behaviors, but many also engage in hair pulling, temper tantrums, inappropriate laughing, hyperextending limbs, and throwing, banging on, or kicking objects.\textsuperscript{4,47,78} A “smiling appearance” was reported in 51%.\textsuperscript{4} Self-injurious behaviors such as pinching, pressing, and hitting oneself are also observed along with high levels of self-absorption and difficulties engaging socially.\textsuperscript{4,78} The behavioral phenotype is further characterized by anxiety, agitation, repetitive behaviors, and autism spectrum disorder (ASD).\textsuperscript{47,67,78} Difficulties in filtering and processing...
sensory input increase the risk of under- or overstimulation and may lead to maladaptive behaviors. On the other hand, at the PTHS World Conference, an overwhelming majority of parents indicated their child with PTHS enjoyed musical experiences, and anecdotally parents mentioned using music to improve their child’s difficult moods. Assessing the sensory processing profile in the individual with PTHS is necessary to facilitate interventions to prevent under- and/or overstimulation (R37).

13.4 | Anxiety and agitation

Anxious, agitated, and/or aggressive behaviors were previously reported in more than one-third of individuals with PTHS; frustration from limited communicative capabilities may lead to these behavioral problems (R38). Aggression and shouting are often associated with (unrecognized) pain or other sensory or somatic issues. Aggression and shouting are often associated with changes in routine (see also Section 7). The onset of puberty can intensify these behaviors (R.L.T., D.A.S., personal observations).

13.5 | Repetitive behaviors/stereotypies

The majority of individuals with PTHS studied show intense and frequent repetitive movements or mannerisms (eg, flapping, twisting, waving or flicking hands or fingers repetitively, body rocking). They also show repetitive handling of toys or objects, fascinations with specific objects, and repetition of the same activities. Repetitive behaviors may intensify further when anxiety is present, or when sensory and environmental issues remain unresolved.

13.6 | Autism spectrum disorder

Deficits in social and communication interaction skills combined with patterns of repetitive behavior, as well as impairments in adaptive skills are prominent in individuals with PTHS. Few studies have implemented direct in-person assessments of autism characteristics, although various studies have reported on language development. Insistence on sameness and on behavioral patterns of repetitive behaviors and stereotypies such as hand clapping and flapping, head banging, body rocking, or finger mannerisms are variable, occur within different contexts, and cannot be explained by the associated degree of intellectual disability and/or developmental delay. Therefore, careful behavioral observations and autism-specific assessments of social functioning are warranted to judge whether deficits in social-communication skills and behavioral patterns are in excess of what could be expected for the developmental level. If applicable, a separate diagnosis of comorbid ASD is helpful to inform specific interventions and prevent overstimulating and/or under-stimulating the individual with PTHS (R39).

13.7 | Pharmacotherapy

Persistent maladaptive behavior can be very distressing and is a relevant treatment target. Possible underlying physical, mental, and environmental issues leading to problematic behaviors should be identified through careful functional assessments and addressed first through behavioral therapy and environmental changes. If these strategies prove insufficient, pharmacologic intervention should be considered. Evidence for the efficacy of psychotropic medication in individuals with PTHS is limited, however, and placebo-controlled studies are not available. Still, in a survey on medication during the PTHS World Conference 28 families reported on current and previous medication types, treatment targets, and side effects: sleep problems were addressed with melatonin and/or neuroleptic medication (gabapentin; irritability, agitation, and hyperactive behaviors were targeted with methylphenidate and clonidine, and a benzodiazepine (lorazepam) had been prescribed for agitation. Antipsychotic agents, pipamperon and promethazine, were used to target challenging behavior. These antipsychotics should be carefully monitored, evidence for efficacy is limited and long-term use may result in significant adverse effects such as weight gain, hypertension and diabetes. Overall, parents reported satisfaction with medications prescribed and noted few significant side effects, but no single medication was found to be extraordinarily effective. Generally recommended prescribing practice includes starting at low doses and titrating slowly to best efficacy, monitoring health before starting and during pharmacotherapy, evaluating regularly to decide on stopping/continuing medication while incorporating evidence from direct observations by caregivers (R40).

Recommendations

R33 Every individual with PTHS should be directly assessed for levels of cognitive and social-emotional development and communication. A++

R34 Most individuals with PTHS are nonverbal. Every effort should be made to explore additional methods of communication including augmented communication techniques. A+++ R35 Additional developmental and educational support should be provided to individuals with PTHS to incite and accommodate their maximum cognitive and educational potential, taking into account their invariably present cognitive and communicative impairments. A+++ R36 Special education strategies should focus on learning skills to enhance daily life skills and to modify anxious and/or self-injurious behaviors. A+++ R37 Assessment of sensory processing profile in individuals with PTHS informs interventions to prevent under- and/or overstimulation. A++ R38 Precursors to anxiety, agitation or aggression may remain underappreciated in individuals with PTHS due to severe communication deficits, and detailed face-to-face assessments and observations in the environment of the individual are needed. A++ R39 A separate clinical diagnosis of ASD should be considered in each individual with PTHS. If applicable, ASD specific interventions should be employed to stimulate development. A++ R40 No specific medication is known to be generally effective in individuals with PTHS and behavioral problems, and prescribing practices as in the general population should be followed. A++

14 | CONCLUSIONS

The present recommendations aim to improve diagnostics and to serve caregivers and families in their care to individuals with PTHS. The diagnostic pathways are deliberately formulated in such a way
that they can be applied universally, irrespective of the access to modern technologies, and recommendations are meant to be cost effective, avoiding unnecessary procedures. We realize that local circumstances such as medicolegal environments may dictate adaptations of the recommendations. Together with the various national PTHS support groups we aim to initiate prospective audits to expand the evidence base for each recommendation, allowing further ameliorations (Box 2).

BOX 2

MAJOR RESEARCH ISSUES FOR INDIVIDUALS WITH PITT-HOPKINS SYNDROME

- What is the natural history of Pitt-Hopkins syndrome in adults and older individuals?
- Breathing anomalies: what are the long-term consequences of breathing anomalies, both physically and cognitively? What is the prevalence of obstructive sleep apnoea? Can breathing anomalies be decreased if needed?
- Seizures: are seizures primary or consequences of breathing anomalies?
- Other symptoms caused by autonomic nervous system dysregulation: what is the exact pathogenesis? If needed, can consequences (especially drooling and constipation) be influenced?
- Immune system: what are the consequences of PTHS variants causing Pitt-Hopkins syndrome for immunological functioning, including reactions to vaccination?
- Motor functioning: what is the pathogenesis of the foot position anomalies? Can physical therapy, drugs or surgical procedures effectively influence these anomalies?
- Communication: what are the communication abilities? Are there biomarkers that predict these abilities? Which approach best increases communicative abilities?
- Behaviour: what are the specific characteristics of autism or autism spectrum disorder in individuals with Pitt-Hopkins syndrome? In which way do factors such as autonomic dysregulations, food or other environmental factors influence behaviour? Is it possible to address behavioural difficulties effectively through psychotherapy, contextual adjustments and/or drugs if needed?
- Genotype – phenotype correlations
- Molecular characteristics: can a functional study be developed that indicates with sufficient certainty causality of a Pitt-Hopkins phenotype? Can the mRNA derived from the wild type allele be stabilized in vitro? Does this lead to increased protein formation and if so, does this influence the consequences of haplotype insufficiency for TCF4 in animal models?

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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.

CONFLICTS OF INTEREST

Nothing to declare.

REFERENCES


84. Rannals MD, Page SC, Campbell MN, Gallo RA, Mayfield B, Maher BJ. Neurodevelopmental models of Transcription Factor 4 deficiency converge on a common ion channel as a potential therapeutic target for Pitt Hopkins syndrome. Rare Diseases. 2016;5:e1220468.


SUPPORTING INFORMATION

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