The adaptive functioning profile of Pitt-Hopkins syndrome

Effie Pearson, Alice Watkins, Chris Oliver, Amna Karim, Jill Clayton-Smith, Alice Welham

PII: S1769-7212(21)00145-2
DOI: https://doi.org/10.1016/j.ejmg.2021.104279
Reference: EJMG 104279

To appear in: European Journal of Medical Genetics

Received Date: 9 November 2020
Revised Date: 14 June 2021
Accepted Date: 22 June 2021


This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Published by Elsevier Masson SAS.
The adaptive functioning profile of Pitt-Hopkins syndrome: Author’s statement

Individual author’s roles are highlighted below using CRediT roles.

**Effie Pearson**: Investigation, Formal analysis, Writing – Original draft

**Alice Watkins**: Investigation, Formal analysis, Writing - Original draft

**Chris Oliver**: Writing – Review & editing, Supervision

**Amna Karim**: Investigation

**Jill Clayton-Smith**: Writing – Review & editing

**Alice Welham**: Conceptualisation, Formal analysis, Writing – Review & editing, Supervision
The adaptive functioning profile of Pitt-Hopkins syndrome

Effie Pearson\textsuperscript{a,b}, Alice Watkins\textsuperscript{a,c}, Chris Oliver\textsuperscript{a}, Amna Karim\textsuperscript{a}, Jill Clayton-Smith\textsuperscript{d}, & Alice Welham\textsuperscript{a,e}.

\textsuperscript{a}School of Psychology, University of Birmingham, Birmingham, UK. \textsuperscript{b}School of Psychology, College of Health \& Life Sciences, Aston University, Birmingham. \textsuperscript{c}UCL Great Ormond Street Institute of Child Health, London, UK. \textsuperscript{d}Manchester Centre for Genomic Medicine, St Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, UK. \textsuperscript{e}Department of Neuroscience, Psychology and Behaviour, University of Leicester, UK.

Dr Effie Pearson is now at Aston University, UK.

Alice Watkins is now at UCL Great Ormond Street Institute of Child Health, London, UK.

Dr Alice Welham is now at University of Leicester, UK.

Correspondence concerning this article should be addressed to: Effie Pearson, School of Psychology, College of Health \& Life Sciences, Aston University, Birmingham, B4 7ET, UK. Email: e.pearson1@aston.ac.uk
Abstract

Background: There are few cohort studies describing the adaptive functioning profile for Pitt-Hopkins syndrome (PTHS). In this study we examine the adaptive functioning profile for PTHS and compare it to Angelman syndrome (AS). Method: Caregivers of 14 individuals with PTHS, 33 with deletion AS and 23 with non-deletion AS, completed the Vineland Adaptive Behavior Scales-II. Results: The profile of adaptive functioning in PTHS was characterised by strengths in socialisation, followed by motor skills, communication then daily living skills. The PTHS group scored significantly lower than the non-deletion AS group on all domains except socialisation and significantly lower than the deletion AS group, for motor skills only. Conclusions: An uneven adaptive behavior profile for individuals with PTHS mirrors that of AS, with implications for assessment and intervention.

Key words: Pitt-Hopkins syndrome, Angelman syndrome, adaptive functioning, behavioral phenotype, intellectual disability, Vineland Adaptive Behavior Scales

Abbreviations: Pitt-Hopkins syndrome (PTHS), Angelman syndrome (AS), autism spectrum disorder (ASD), Vineland Adaptive Behavior Scales (VABS), Social communication questionnaire (SCQ)

Acknowledgements: None to present.

Funding: This research was funded by Cerebra.

Conflict of interest: No conflicts of interest have been declared.
Pitt-Hopkins syndrome (PTHS; OMIM 610954) is a rare genetic neurodevelopmental syndrome caused by deletion or point mutation of the TCF4 gene on chromosome 18q21.2 (Amiel et al., 2007; Brockschmidt et al., 2007; Zweier et al., 2007). The estimated prevalence is between 1:34,000 and 1:41,000 (Rosenfeld et al., 2009), although there are believed to be only 500 confirmed cases worldwide (National Organisation for Rare Diseases, 2018). Clinically, PTHS is associated with severe intellectual disability, an abnormal breathing pattern, a distinctive facial gestalt which evolves over time and high rates of autism spectrum disorder (ASD; Goodspeed et al., 2018; Watkins et al., 2019; Van Balkom et al., 2012). Much of the behavioral description of the syndrome to date has been based on clinical case reports and descriptive studies, with few studies incorporating standardised assessments. There is, therefore, a need for further delineation of the clinical and behavioral profile of PTHS through cohort studies and the use of standardised assessments. This description will allow for greater understanding of the neurodevelopmental profile of PTHS and comparison of similarities and differences with other genetic syndromes.

Adaptive functioning refers to behaviors and skills that enable individuals to function in everyday life, including communication, self-help, social and motor skills and independence. For individuals with PTHS, delays in communication and motor skills have been reported, with absent or minimal speech, impaired motor coordination and ataxia (de Winter et al., 2016; Hasi et al., 2011; Sweatt, 2013; Whalen et al., 2012). In one of the few cohort studies exploring adaptive ability, Van Balkom and colleagues (2012) reported that for a sample of ten, individuals motor skills exceeded cognitive abilities measured by the Bayley Scales of Infant Development (BSID-III; Bayley, 2006) in all participants apart from the youngest. In the same study, the Vineland Adaptive Behavior Scales (VABS; Sparrow et al., 1984) showed relative strengths in daily living skills and communication compared to social skills, for which nine out of the ten participants scored below an overall age equivalence of
20 months. Only the eldest participant scored above this with age equivalence of around 30 months. Other reports from non-specified developmental testing indicate a developmental age equivalence of 14.5 months and a range between 9-36 months in PTHS (de Winter et al., 2016). Furthermore, van Balkom et al. (2012) reported that there seemed to be little progress in adaptive functioning as individuals got older. The literature lacks a comparative approach with individuals with other genetic neurodevelopmental syndromes of similar age and ability, which is considered crucial to furthering the understanding of specific behavioral phenotypes (e.g. Hodapp & Dykens, 2001; Waite et al., 2014).

The need to delineate characteristics associated with PTHS is highlighted by reported similarities with genetic syndromes. Notably, PTHS has significant overlap in characteristics with Angelman syndrome (AS; OMIM 105830), another genetic syndrome, including absent or minimal speech, ataxic gait, a “happy” disposition and epilepsy (Marangi & Zollino, 2015; Tan et al., 2013). Before the improvement in genetic diagnostic techniques such as whole genome sequencing, 2% of individuals who had TCF4 gene alterations associated with PTHS, received a clinical diagnosis of Angelman syndrome (Takano et al., 2010), evidencing the clinical overlap between the two syndromes. This similarity in characteristics warrants investigation as results might inform assessment and intervention.

AS is a rare genetic disorder caused by disrupted genetic information on the maternal copy of chromosome 15q11-13, specifically the UBE3A gene, with an estimated prevalence of between 1 in 12,000 and 20,000 live births (Buckley et al., 1998; Kyllerman, 1995; Petersen et al., 1995). Four different genetic aetiologies of Angelman syndrome have been identified; deletion of UBE3A (65-75% of cases), mutation of UBE3A (5-11% of cases), paternal uniparental disomy (UPD; 3-7% of cases), and imprinting centre defect (3-5% of cases; Clayton-Smith & Laan, 2003; Williams et al., 2010). In addition to the previously mentioned characteristics, other clinical and behavioral features associated with AS are
Adaptive ability in PTHS

severe to profound intellectual disability, feeding problems, sleep disturbance, hyperactivity and short attention span (Clayton-Smith & Laan, 2003; Horsler & Oliver, 2006; Williams et al, 2006). Individuals who have non-deletion aetiologies are reported to present with a milder phenotype than individuals with deletions (Gentile et al., 2010; Lossie et al., 2001; Mertz et al., 2014). However, the profile of relative strengths in social skills compared to daily living, communication and motor skills is found for all genetic causes, albeit with individuals with deletions being more delayed in the development of these skills compared to individuals with non-deletion mechanisms (Gentile et al., 2010).

Despite noted similarities between PTHS and AS, there is a suggestion that the adaptive functioning profiles may be different (Tan et al., 2013). Whilst relative strengths in socialisation are well established in AS, with indications of high sociability in PTHS, adaptive functioning and social and non-social aspects have yet to be examined for individuals with PTHS. Understanding where the syndromes overlap in abilities and where they differ has implications for determining which interventions and educational strategies may be beneficial.

Given the limited literature and absence of comparisons, the aims of this exploratory, cross-sectional study were to: 1) extend previous findings by describing the adaptive profile of PTHS, and 2) compare the adaptive functioning profiles of PTHS and AS.

**Methods**

**Design**

The study was a cross-sectional design and formed part of a larger research project delineating the behavioral phenotype of PTHS (Watkins et al. 2019). Ethical approval was obtained from the Coventry Research Ethics Committee. Anonymised data for the Angelman
Adaptive ability in PTHS syndrome group were provided from a separate, concurrent research project exploring communication (Pearson et al., 2018).

Recruitment and participants

All participants with PTHS were recruited via the Pitt Hopkins UK family support group. Fourteen families responded to invitations and provided informed consent to participate in the research.

Of the 14 participants with PTHS, the mean age was 14.56 years (SD = 9.62), and 42.9% of the sample were male. Of the sample, 11 (78.6%) had genetic confirmation of PTHS from a clinical geneticist, with 7 (50.0%) having TCF4 mutations, 2 (14.3%) had deletion of the TCF4 gene, 1 (7.1%) had translocation and 1 (7.1%) had a sequence repetition. Information on the specific genetic mechanism (deletion, mutation) was not available for three participants, but parents reported genetic confirmation of diagnosis had been received.

Previously collected data from the Wessex Scale (Kushlick et al., 1973) and the Health Questionnaire (Hall et al., 2008) were available for 12 of the 14 participants with PTHS (Watkins et al., 2019) (see table 1). One individual with PTHS had a PEG tube for feeding. All participants with PTHS scored above cut off on a autism screening questionnaire (Social Communication Questionnaire (SCQ); Rutter, Bailey & Lord, 2003).

Table 1. Physical and health characteristics for participants with PTHS (n = 12)

<table>
<thead>
<tr>
<th>Feature</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Blind or almost</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Hearing&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Normal</td>
</tr>
<tr>
<td>Speech&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Partly verbal/verbal</td>
</tr>
<tr>
<td>Mobility&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Partly ambulant/ambulant</td>
</tr>
<tr>
<td>Epilepsy/Seizures&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Ever experienced</td>
</tr>
</tbody>
</table>
Adaptive ability in PTHS

<table>
<thead>
<tr>
<th>Present in past month</th>
<th>3 (25.0%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal difficulties(^b)</td>
<td>5 (41.7%)</td>
</tr>
<tr>
<td>Bowel problems (e.g. obstruction)(^b)</td>
<td>6 (50.0%)</td>
</tr>
<tr>
<td>Skin problems(^b)</td>
<td>4 (33.3%)</td>
</tr>
</tbody>
</table>

*Measured on the Wessex Scale (Kushlick et al., 1973). \(^b\)Measured on the Health Questionnaire (Hall et al., 2008)

The comparison group included 56 individuals with AS, 33 of whom had deletion of 15q11.13 (\(M_{age} = 10.06, \text{SD} = 4.1\)), and 23 participants had non-deletion etiologies (\(M_{age} = 9.43, \text{SD} = 4.14\)); six had UPD, eight had imprinting centre defect, nine had UBE3A mutation. Of the 56 participants, 37 (66.1%) had received genetic confirmation from a clinical geneticist, 15 (26.8%) from a paediatrician and four (7.1%) from a neurologist.

There were no significant differences between the PTHS and AS genetic groups for gender (\(\chi^2 (2) = .375, p = .829\)). A one-way ANOVA indicated age was significantly different between the groups (\(F(2, 67) = 4.002, p = .023\)), although post-hoc t-tests showed no significant differences between the groups: PTHS and non-deletion AS (t(16) = -1.856, \(p = .082\)), PTHS and deletion AS (t(15) = -1.684, \(p = .113\)), non-deletion and deletion AS (t(54) = -.482, \(p = .632\)).

**Procedure**

Data were collected from parent/caregivers who completed the Vineland Adaptive Behavior Scale Second Edition (VABS-II; Sparrow, Cicchetti & Balla, 2005) via telephone. Demographic data were collected as part of wider research studies (Pearson et al., 2018; Watkins et al., 2019) where parent/caregivers completed background information questionnaires.

**Measures**
The VABS-II Interview Form (Sparrow, Cicchetti & Balla, 2005) is a semi-structured interview administered by examiners with parents/caregivers. It assesses adaptive ability across four domains: Communication (sub-domains of receptive, expressive and written), Daily Living Skills (subdomains of personal, domestic and community), Socialisation (subdomains of interpersonal relationships, play and leisure time and coping skills) and Motor Skills (gross and fine). The VABS-II computes standard scores across domains which are then summed to generate an overall Adaptive Behavior Composite (ABC) standard score, with a mean of 100 and a standard deviation of 15. V-scale scores are calculated for subdomains, with a mean of 15 and a standard deviation of 3.

Data analysis

As differences in the developmental and adaptive profile of individuals with either deletion or non-deletion etiologies of Angelman syndrome are well established (Gentile et al., 2010; Sadhwani et al., 2021), the Angelman syndrome sample was split into a deletion and non-deletion group for analysis. Due to the small sample size in the PTHS group, and therefore the difficulty in ascertaining adherence to assumptions of parametric tests, non-parametric tests were used throughout.

To provide descriptions of the adaptive profiles for each of the groups, Friedman tests were used to explore within-group differences between the domain standard scores for both the PTHS and AS groups. Post hoc Wilcoxon signed-rank tests were conducted to identify significant differences between domains. Spearman Rho correlations were used to explore the relationship between VABS-II scores and chronological age in the PTHS group.

To address the second aim of the study, Kruskal-Wallis tests were used to analyse between-group differences in domain standard scores, and ABC standard scores of the VABS-II. Post hoc Mann-Whitney U analyses were conducted to identify significant
differences between genetic groups. Effect sizes \((r)\) were calculated (following Fritz et al., 2012) and considered in relation to Cohen’s (1988) guidelines.

**Results**

*Profile of Adaptive Behavior in PTHS*

Descriptive statistics across domains and subdomains for PTHS can be found in Table 2. The median ABC standard score of individuals with PTHS was 36 (interquartile range = 29.5); this is within the range of a “low adaptive ability level” as classified by Sparrow, Cicchetti & Balla (2005). Across domain standard scores, the observed profile was *Socialisation* > *Motor Skills* > *Communication* > *Daily Living Skills* (Figure 1). There was a significant overall effect of domain for the standard scores of individuals with PTHS \((\chi^2 (3) = 10.9, p = .012)\). Post hoc analysis indicated that standard scores on *Daily Living Skills* were significantly lower than those for *Communication* \((Z = -2.57, p = .010, r = .69, \text{ large effect size})\) and *Socialisation* \((Z = -2.83, p = .005, r = .76, \text{ large effect size})\), while *Communication* scores were also significantly lower than those for *Socialisation* \((Z = -2.93, p = .003, r = .78, \text{ large effect size})\). The motor domain did not differ significantly from any of the other domains.
With regard to subdomain v-scale scores, expressive language and personal subdomains had the lowest median scores, with a v-scale score of 1 for both subdomains. Although, for the personal subdomain, the age equivalence was the highest of all the Daily living skills subdomains (see table 1). There was a significant difference between receptive and expressive subdomains for both v-scale scores ($Z = -6.41, p < .001, r = .69$, large effect size) and age equivalence ($Z = -6.57, p < .001, r = .69$, large effect size), with receptive language scores higher than expressive language.

Table 2. Medians, interquartile ranges (IQR) and ranges for the domains and subdomains of the VABS-II in PTHS (n= 14)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Standard scores/V-scale scores</th>
<th>Age equivalents (in months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>Range</td>
</tr>
<tr>
<td>Communication</td>
<td>38 (29.8)</td>
<td>21-73</td>
</tr>
<tr>
<td>Receptive</td>
<td>4.0 (7.3)</td>
<td>1-11</td>
</tr>
<tr>
<td>Expressive</td>
<td>2.5 (4.0)</td>
<td>1-11</td>
</tr>
<tr>
<td>Writing</td>
<td>5.0 (4.5)</td>
<td>1-10</td>
</tr>
<tr>
<td>Daily living skills</td>
<td>34.5 (28.8)</td>
<td>21-68</td>
</tr>
<tr>
<td>Personal</td>
<td>1.0 (4.3)</td>
<td>1-10</td>
</tr>
<tr>
<td>Domestic</td>
<td>5.5 (6.8)</td>
<td>1-12</td>
</tr>
<tr>
<td>Community</td>
<td>2.5 (3.3)</td>
<td>1-10</td>
</tr>
<tr>
<td>Socialization</td>
<td>46.5 (31.0)</td>
<td>20-90</td>
</tr>
<tr>
<td>Interpersonal relationships</td>
<td>4.5 (7.0)</td>
<td>1-12</td>
</tr>
<tr>
<td>Play and leisure</td>
<td>5.0 (6.3)</td>
<td>1-15</td>
</tr>
</tbody>
</table>
The relationship to age in PTHS

A Spearman’s Rho correlation was conducted to explore the relationship between chronological age and ABC scores for the PTHS group. A significant, strong negative relationship was found between these variables ($r_s = -.96, p < .001$), as shown in figure 2. However, when exploring the relationship between chronological age and mean age equivalence, no correlation was found ($r_s = .27, p = .358$; figure 3), indicating that scores are not significantly associated with age and may remain relatively consistent.

Figure 2. Scatterplot of chronological age and the ABC standard score from the VABS-II
Profile of Adaptive Behavior in AS

For the deletion AS group, the median ABC score was 45 (interquartile range = 17.5) which is in the ‘low adaptive ability’ range. The observed profile across the four domains showed relative strengths in Socialisation and Motor skills compared to Communication and Daily Living Skills, with a significant overall effect between the standard scores ($\chi^2 (3) = 54.4$, $p < .001$). Post hoc analysis indicated that standard scores for Socialisation were significantly higher than scores for Communication ($Z = -4.86$, $p < .001$, $r = .85$, large effect size) and Daily Living Skills ($Z = -4.65$, $p < .001$, $r = .81$, large effect size), and standard scores for Motor Skills were also significantly higher than Communication ($Z = -4.56$, $p < .001$, $r = .79$, large effect size) and Daily Living Skills ($Z = -4.18$, $p < .001$, $r = .77$, large effect size).

The median ABC score for the non-deletion AS group was 53 (interquartile range = 17) which, similar to the other two groups, is in the ‘low adaptive ability’ range. The
observed profile for individuals with non-deletion AS across the four domains was showed relative strengths in *Socialisation* and *Motor skills* compared to *Communication*. A significant overall effect was found between the standard scores ($\chi^2 (3) = 28.0, p < .001$). Post hoc analysis indicated a similar pattern to that in the deletion AS group with standard scores for *Socialisation* significantly higher than scores for *Communication* ($Z = -3.75, p < .001, r = .78$, large effect size) and *Daily Living Skills* ($Z = -3.46, p = .001, r = .72$, large effect size), and standard scores for *Motor Skills* significantly higher than *Communication* ($Z = -3.46, p = .001, r = .72$, large effect size).

*Adaptive behavior profile: between-group comparisons*

The observed profile of the AS groups appeared to display a similar pattern of strengths in *Socialisation* and *Motor Skills* compared to *Communication* and *Daily Living Skills*, with the latter being the weakest domain (figure 1). Whereas for the PTHS group individuals had relative strengths in *Socialisation* and weaknesses in *Daily Living Skills* and *Communication* as can be seen in Figure 1.

Kruskal-Wallis tests indicated significant between-group differences on the *Communication*, *Daily Living Skills* and *Motor Skills* domains, and on the ABC standard score (see Table 3). Post hoc analysis revealed that individuals with PTHS displayed significantly lower standard scores than individuals with non-deletion AS on the *Communication* domain ($U = 92.5, p = .031, r = .35$, medium effect size), *Daily Living Skills* domain ($U = 82.5, p = .013, r = .4$, medium effect size), *Motor Skills* domain ($U = 58.5, p = .001, r = .53$, large effect size) and the ABC standard score ($U = 92.5, p = .031, r = .35$, medium effect size). Individuals with PTHS also showed significantly lower standard scores on the *Motor Skills* domain than those with deletion Angelman syndrome ($U = 128, p = .027, r = .33$, medium effect size). Furthermore, individuals with deletion Angelman syndrome
showed significantly lower standard scores than individuals with a non-deletion aetiology of Angelman syndrome for Communication ($U = 193.5$, $p = .002$, $r = .41$, medium effect size), Daily Living Skills ($U = 215.0$, $p = .006$, $r = .37$, medium effect size), Motor Skills ($U = 113.5$, $p < .001$, $r = .58$, medium effect size) and the ABC standard score ($U = 215.0$, $p = .006$, $r = .37$, medium effect size). However, for all groups, there were no significant between-group differences of the Socialisation domain.
Table 3. Median and interquartile ranges of the domain and ABC sum and standard scores of the VABS, Kruskal-Wallis tests and Post hoc Mann-Whitney U test analyses for PTHS, AS deletion and AS non-deletion groups.

<table>
<thead>
<tr>
<th>Domain</th>
<th>PTHS (n=14)</th>
<th>Deletion AS (n=33)</th>
<th>Non-deletion AS (n=23)</th>
<th>Kruskal-Wallis Tests</th>
<th>Post Hoc analysis</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>IQR</td>
<td>Median</td>
<td>IQR</td>
<td>H     df  p</td>
<td>U   df  Z  p</td>
</tr>
<tr>
<td>Communication</td>
<td>Median</td>
<td>38.0</td>
<td>29.75</td>
<td>42.0</td>
<td>12.0</td>
<td>53.0 15.0</td>
</tr>
<tr>
<td>- Standard Score</td>
<td>IQR</td>
<td>29.75</td>
<td>12.0</td>
<td>53.0</td>
<td>10.00 2  .007</td>
<td>PTHS&lt;ND 82.5 2 2.46 .013 .40 (medium)</td>
</tr>
<tr>
<td>Daily Living Skills</td>
<td>Median</td>
<td>34.5</td>
<td>28.75</td>
<td>40.0</td>
<td>15.0</td>
<td>51.0 22.0</td>
</tr>
<tr>
<td>- Standard Score</td>
<td>IQR</td>
<td>28.75</td>
<td>15.0</td>
<td>51.0</td>
<td>2.00 2  .133</td>
<td>-    -    -    -</td>
</tr>
<tr>
<td>Socialization</td>
<td>Median</td>
<td>46.5</td>
<td>31.0</td>
<td>55.0</td>
<td>18.0</td>
<td>55.0</td>
</tr>
<tr>
<td>- Standard Score</td>
<td>IQR</td>
<td>31.0</td>
<td>18.0</td>
<td>55.0</td>
<td>14.0</td>
<td>14.0</td>
</tr>
<tr>
<td>Motor Skills</td>
<td>Median</td>
<td>41.5</td>
<td>24.0</td>
<td>54.0</td>
<td>5.0</td>
<td>56.0</td>
</tr>
<tr>
<td>- Standard Score</td>
<td>IQR</td>
<td>24.0</td>
<td>5.0</td>
<td>54.0</td>
<td>5.0</td>
<td>56.0</td>
</tr>
<tr>
<td>ABC Standard Score</td>
<td>Median</td>
<td>37.0</td>
<td>32.75</td>
<td>45.0</td>
<td>18.0</td>
<td>53.0</td>
</tr>
<tr>
<td></td>
<td>IQR</td>
<td>32.75</td>
<td>18.0</td>
<td>53.0</td>
<td>17.0</td>
<td></td>
</tr>
</tbody>
</table>

* a 2 datapoints for the deletion AS group were missing for the Motor skills domain
Discussion

This study provides an assessment of the adaptive profile of a group of individuals with PTHS, using a standardised measure and comparisons with individuals in AS. To date, this is one of the first studies of adaptive ability in PTHS using a cohort design, a standardised assessment and a comparative approach.

The profile of domains of adaptive behavior for PTHS was uneven with significant differences between standard scores across domains. Relative strengths in socialisation over communication and daily living skills were evident, with daily living skills the weakest area. Interestingly, this profile contrasts with the pattern of adaptive functioning reported by van Balkom et al. (2012) who found strengths in daily living skills and communication, with relative weaknesses in socialisation. It is unlikely that differences between the adaptive profiles in the two studies could be accounted for by age range and sample size, which are similar. Instead, the discrepancy could reflect measurement differences. The study by van Balkom et al. used an earlier version of the VABS (Sparrow et al., 1984), administered by directly the same child psychiatrist and neuropsychologist. Differences between versions of the VABS are important when comparing adaptive profiles. The VABS-II expanded upon the VABS and was also adapted to reflect cultural and technological changes. Of particular relevance to the comparison to van Balkom et al.’s (2012) study, the VABS-II introduced a number of new items relevant to the developmental period between birth and three years of age, to allow for better differentiation of developmental delays in this period (Sparrow et al., 2005). Given the results of the current study, it is this developmental period that is most relevant for the majority of individuals with PTHS. Therefore, the increased sensitivity of the VABS-II to developmental changes during this period likely accounts for some of the discrepancies in the reported profile between the current study and van Balkom et al.’s
Adaptive ability in PTHS (2012). Additionally, the two studies might have included a differing range of cognitive abilities. However, the current study did not include cognitive testing or additional neurodevelopmental measures and so direct comparison to van Balkom et al.’s (2012) study, in which wider neurodevelopmental testing using the Bayley Scales of Infant Development (BSID-II) was conducted, is limited. To clarify the differences between these two studies, future research requires a larger cohort of individuals with PTHS and wider neurodevelopmental measures alongside measures of adaptive behavior.

In all domains, participants with PTHS displayed lower adaptive functioning compared to individuals with deletion or non-deletion AS. Although the relative strength in socialisation in PTHS mirrors the profile seen in AS caused by deletion or non-deletion aetiologies. This is consistent with reports of high sociability and the putative similarities between the syndrome groups, although in comparison to PTHS individuals with AS reportedly show more pro-social behaviors (Watkins et al., 2019).

Relative strengths in the socialisation domain are interesting in the context of high rates of ASD behaviors for people with PTHS. Indeed, all participants in this study met criteria indicative of ASD on the SCQ, a well-respected screening measure. An understanding of how relatively high socialisation abilities and the difficulties in social interactions associated with ASD relate to one another for those with PTHS awaits study. The raft of problems associated with test sensitivity of ASD measures for individuals with severe intellectual disability are also relevant to the profile of social behavior in PTHS (Moss & Howlin, 2009).

Other aspects of the adaptive functioning profile in PTHS overlap with the profile reported in Angelman syndrome, particularly the dissociation between receptive and expressive language (Jolleff & Ryan, 1993; Williams et al., 2006). The similar profile of
strengths in social skills and receptive language in relation to poor expressive language may result in the emergence of challenging behavior in PTHS, a profile evidenced in Angelman syndrome (Clayton-Smith & Laan, 2003; Tunnicliffe & Oliver, 2011). Indeed, around half of individuals with PTHS (48-54%) are reported to show aggression (de Winter et al., 2018; Watkins et al., 2019) and so intervention for improving expressive communication skills in PTHS might be beneficial, to mitigate some of the risk markers for the emergence of challenging behavior. Given the overlap in characteristics, communication interventions shown to be effective in Angelman syndrome, such as functional communication training (Radstaake et al., 2012) or enhanced natural gestures (Calculator, 2002) may also be appropriate for individuals with PTHS.

For motor skills, the lower scores of the PTHS group were statistically significantly different from both the deletion and non-deletion AS groups, suggesting that motor skills is an area of weakness for people with PTHS in comparison to both aetiologies of AS. However, the age range for the AS groups was lower than the PTHS group. Given that as individuals with AS get older mobility reduces and there is an increase in hypertonicity of limbs (Clayton-Smith, 2001), the difference in motor skills may not have differed if the age ranges between groups were similar. In other areas (overall adaptive functioning, daily living skills and communication), differences between the PTHS group and the non-deletion AS group were statistically significant, but differences with the deletion AS group did not reach statistical significance. So, whilst it may appear there are areas where there is similarity between levels of adaptive behavior for deletion AS and PTHS, low power due to the small number of participants with PTHS means that a lack of statistically significant difference should not be taken to indicate equivalence.

Limitations of this study include the informant-report nature of the data and the relatively low n in the PTHS group (thus reducing power to detect between-group and
Adaptive ability in PTHS

between-domain differences), the unequal group sizes, and the differing age ranges of the
PTHS group and the two AS groups. With regard to the latter point, although no significant
differences were found between the ages of the groups on post-hoc tests, given that adaptive
ability appears to remain relatively consistent with age, standard scores are likely to be lower
for older participants, and a small number in the PTHS group were over 18 years of age.
However, findings were not affected when these individuals were removed from analyses.

Additionally, another limitation is the use of cross-sectional data to explore
trajectories of adaptive functioning. This approach limits the conclusions regarding the nature
of abilities as individuals get older. The collection of longitudinal data is important to report
the natural history of the syndrome and examine the premise that abilities plateau and remain
consistent. This research would also allow for further understanding about whether factors
such as earlier diagnosis of PTHS may influence adaptive ability.

In conclusion, this study found that the adaptive functioning profile of PTHS is
uneven and characterised by relative strengths in socialisation, followed by motor skills and
communication and finally daily living skills. This pattern broadly mirrors the profile seen in
AS, although individuals with PTHS showed lower levels of ability in all areas, particularly
in relation to individuals with non-deletion AS. These similarities suggest that interventions
that are evidenced to be effective in individuals with AS may also be appropriate for
individuals with PTHS. In particular, interventions focusing on increasing expressive
communicative skills are important to try and minimise the emergence of challenging
behavior.
References

Amiel, J., Rio, M., de Pontual, L., Redon, R., Malan, V., Boddaert, N., ... & Colleaux, L. (2007). Mutations in TCF4, encoding a class I basic helix-loop-helix transcription factor, are responsible for Pitt-Hopkins syndrome, a severe epileptic encephalopathy associated with autonomic dysfunction. The American Journal of Human Genetics, 80(5), 988-993. doi: 10.1086/515582


