Behavioural, developmental and psychological characteristics in children with germline PTEN mutations

Cummings, K.; Dias, R. P.; Hart, R.; Welham, A.

DOI:
10.1111/jir.13130

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Cummings, K, Dias, RP, Hart, R & Welham, A 2024, 'Behavioural, developmental and psychological characteristics in children with germline PTEN mutations: a carer report study', *Journal of Intellectual Disability Research*. https://doi.org/10.1111/jir.13130

JIDR Journal of Intellectual Disability Research
Published on behalf of mencap and in association with IASSID

Journal of Intellectual Disability Research doi: 10.1111/jir.13130

VOLUME PART 2024

Behavioural, developmental and psychological characteristics in children with germline *PTEN* mutations: a carer report study

K. Cummings,[1,2] R. P. Dias,[3,4] R. Hart[5] & A. Welham[2,6]

1 *Department of Psychological Services, University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK*
2 *Department of Neuroscience, Psychology and Behaviour, University of Leicester, Leicester, UK*
3 *Department of Endocrinology and Diabetes, Birmingham Children's Hospital, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK*
4 *Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK*
5 *Department of Genetics, Liverpool Women's NHS Foundation Trust, Liverpool, UK*
6 *School of Psychology, University of Birmingham, Birmingham, UK*

Abstract

Background *PTEN* is primarily known as a tumour suppressor gene. However, research describes higher rates of difficulties including intellectual disability and difficulties relating to autism spectrum conditions (ASCs) in people with germline *PTEN* mutations. Other psychological characteristics/experiences are less often reported and are explored in this study.

Methods The parents of 20 children with *PTEN* mutations completed an online survey exploring adaptive behaviour, ASC-associated behaviours, anxiety, mood, hypermobility, behaviours that challenge, sensory experiences, quality of life and parental wellbeing. Published normative data and data from groups of individuals with other genetic neurodevelopmental conditions were used to contextualise findings.

Results Overall levels of adaptive behaviour were below the 'typical' range, and no marked relative differences were noted between domains. Higher levels of ASC-related difficulties, including sensory experiences, were found in comparison with 'typically developing' children, with a possible peak in restrictive/repetitive behaviour; ASC and sensory processing atypicality also strongly correlated with reported joint hypermobility. A relative preservation of social motivation was noted. Anxiety levels were found to be elevated overall (and to relate to sensory processing and joint hypermobility), with the exception of social anxiety, which was comparable with normative data. Self-injurious behaviour was common.

Conclusions Results suggest a wide range of possible difficulties in children with *PTEN* mutations, including elevated anxiety. Despite elevated ASC phenomenology, social motivation may remain relatively strong. Firm conclusions are restricted by a small sample size and potential recruitment bias, and future research is required to further explore the relationships between such characteristics.

Keywords anxiety, autism spectrum conditions, behaviour, *PTEN*

Correspondence: Dr Katherine Cummings, Department of Psychological Services, University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK (e-mail: kc.clinpsy@yahoo.com).

Introduction

The *PTEN* (*P*hosphatase and *ten*sin homologue) gene is located in the 10q23 area of chromosome 10 and encodes a dual specificity protein and lipid phosphatase. This antagonises the phosphatidylinositol 3-kinase signalling pathway and inhibits cell growth, survival and migration (Hopkins *et al.* 2014), explaining its role as a tumour suppressor (Li *et al.* 1997; Liaw *et al.* 1997; Song *et al.* 2012). *PTEN* hamartoma tumour syndromes (PHTSs) are a spectrum of syndromes that are associated with germline mutations of the *PTEN* gene, including Cowden syndrome and Bannayan–Riley–Ruvalcaba syndrome (Hobert & Eng 2009). The prevalence of PHTS is estimated to be 1 in 200 000 (Nelen *et al.* 1996), although this is likely to be an underestimate. Major diagnostic criteria for PHTS include an increased risk of developing cancers, hamartomas and macrocephaly (Pilarski *et al.* 2013). Further clinical characteristics are presented by Macken *et al.* (2019) and highlight rarer associations including autoimmune diseases, joint hypermobility, ocular abnormalities and hearing loss.

Research is increasingly expanding its focus from physiological outcomes to explore behavioural and psychological characteristics that may be associated with *PTEN* changes, including exploring the mechanisms of how *PTEN* impacts neurodevelopment (Skelton *et al.* 2020). Estimated prevalence rates of autism spectrum condition (ASC) in people with *PTEN* aberrations vary, with an estimated prevalence of 17% [95% confidence interval (CI): 8–27%] (Cummings *et al.* 2022). Macrocephaly has been linked to brain overgrowth and ASC (Sacco *et al.* 2015). Sensory features have been reported in people with *PTEN* mutations (Butler *et al.* 2005; Busch *et al.* 2019), with higher scores in under-responsive/sensation-seeking and low-energy scales of the Short Sensory Profile, which were more prominent when ASC was present (Busch *et al.* 2019).

Research exploring intellectual ability (as measured by IQ) has provided varying results on the degree of cognitive impairment associated with PHTS. Some studies suggest a higher prevalence rate of intellectual disability (ID) in people with *PTEN* mutations (Lachlan *et al.* 2007; Yehia *et al.* 2019). However, ability appears variable, with Hansen-Kiss *et al.* (2017) reporting a wide IQ range (39–124). A significantly lower full-scale IQ has been found in individuals with a mutation and ASC diagnoses (mean = 65.90) than individuals without an ASC diagnosis (mean = 96.92; Steele *et al.* 2021). Frazier *et al.* (2015) found that the relationship between PTEN protein expression and full-scale IQ was fully mediated by white matter hyper-intensities, corpus callosum volume and total cortical white matter. The relationships between intellectual ability and other characteristics associated with the syndrome remain under-explored.

Behaviours that challenge (BtC), especially self-injurious behaviour (SIB), are known to occur at elevated and differing rates in genetic neurodevelopmental syndromes (Arron *et al.* 2011). 'Disruptive' behaviour along with 'oppositional and anger issues' has been reported in individuals with *PTEN* mutations (McBride *et al.* 2010; Hansen-Kiss *et al.* 2017), although further details of these behaviours are not described. However, Busch *et al.* (2019) suggested that people with *PTEN* mutations and ASC may require less intervention for BtC than individuals with idiopathic ASC. Individuals with *PTEN* mutations (with or without ASC) were more likely to score higher in the externalising problems scale of the Child Behavior Checklist (CBCL) than the general population (Steele *et al.* 2021). However, BtC, specifically SIB, and their relationship to other variables have not been researched in this group.

Children with *PTEN* mutations and ASC have been described as 'happy and passive' (Frazier 2019), and murine models suggest that anxiety-like behaviour may be reduced in animals with *PTEN* mutations (Dey & Chattarji 2022). However, elevated levels of anxiety have also been reported (Hansen-Kiss *et al.* 2017; Balci *et al.* 2018), and in the general population, hypermobility (a clinical characteristic related to PHTS) has been correlated with anxiety and ASC. Empirically, Steele *et al.* (2021) found elevated internalising problems scores (as measured by the CBCL) in those meeting criteria for ASC with *PTEN* mutations at a similar level to the ASC group, with higher rates of difficulties also found in individuals with *PTEN* mutations not meeting ASC criteria compared with the general population. When specifically looking at the anxious/depressed domains, no significant differences were found between people with *PTEN* mutations with or without ASC and people with macrocephaly and ASC. The complex

and variable relationships between *PTEN* mutations and mood are highlighted by Balci *et al.* (2018) who hypothesised the importance of white matter changes in the neuropsychiatric presentation of individuals with PHTS. It is hoped that the current study will begin to elucidate some of these relationships.

While there is a paucity of research on the psychological and developmental phenotype of PHTS, the effects that *PTEN* changes on families are even less explored. Some research suggests that poorer parental wellbeing is related to child psychological and behavioural variables (e.g. BtC and emotional difficulties; Fitzgerald & Gallagher 2021). However, Adams *et al.* (2018) found no differences on anxiety/depression measures between mothers whose children did or did not display BtC. For parents of children with germline *PTEN* mutations, the combined challenges of possible behavioural/psychological difficulties and physical health problems may affect wellbeing, with some parents carrying germline *PTEN* mutations themselves. This study hopes to begin to explore such relationships.

Aims

Research has begun to explore the psychological and developmental characteristics of people with *PTEN* mutations; however, many of these remain poorly defined. This research aims to support a better definition of developmental, psychological and behavioural characteristics of *PTEN* mutations by comparing scores on such measures to normative data. It is hoped that this will help to begin to recognise distinct patterns of characteristics in children with *PTEN* mutations, and therefore, the most appropriate assessments and services can be developed to provide the best care possible.

Methods

Design

This study was designed in consultation with clinicians working with and parents of children with *PTEN* mutations. A cross-sectional design was employed to assess a range of characteristics in children with *PTEN* mutations at a single time-point. The collected data were then compared with published norms and existing data for individuals with ASC or developmental delay where available.

Recruitment and participants

Recruitment took place via the PTENUKI Patient Group. Direct participants were 20 parents of children aged 2–15 years with *PTEN* mutations. The diagnosis was reported by the parent/caregiver, and no further confirmation of the diagnosis was sought by the authors.

Procedure

Ethical review and approval were granted by the School of Psychology Research Ethics Committee at the University of Leicester. Participants expressed interest to the primary researcher, who provided further information and the link to the first survey, which included the information sheet and consent form. Parents/caregivers were able to request a password-protected summary report of the scores.

Measures

A demographic questionnaire was developed to gather information such as age, where the child lives and diagnostic information. Developmental milestones and head size were also collected. To ascertain head size, the survey asked, 'If known, what is the head circumference of the child?'. A follow-up question then asked how old the child was when this measure what taken, which allowed for the calculation of the percentile. Please see Table 1 for a list of the measures used in this study.

Data analysis

Because of the small sample size, it was recognised that the likelihood of type II errors was raised. However, the number of statistical tests also elevates the risk of type I errors. Effect sizes and CIs are therefore reported and emphasised throughout, with null hypothesis significance testing reported (at $P < 0.05$ except where multiple comparisons/correlations were made involving the same measures, in which case Bonferroni corrections were used) but not emphasised (Cumming 2014).

The small sample size made adherence to parametric test assumptions difficult to assess. Bootstrapping with bias-corrected accelerated CIs

Table 1 Details of measures used in the study

Measure name (abbreviation)	Authors	Measure details	Score range and cut-offs
Social Responsiveness Scale, Second Edition (SRS-2)	Constantino & Gruber (2005)	A 65-item scale that measures difficulties associated with 'autism spectrum disorder' (ASD) diagnostic criteria with five sub-scales. A high level of internal consistency is reported across groups (α = 0.95) for the school-age form. The measure identified differences between clinical and non-clinical groups with a large effect size (Cohen's d = 2.7), suggestive of test validity (Constantino & Gruber 2005).	Range: 0–195, *T*-score calculated *T*-score cut-offs: < 59 – no or low symptomology 60–65 – mild 66–75 – moderate >76 – severe
Spence Children's Anxiety Scale (SCAS)	Spence (1998)	Preschool version: 28-item screening tool measuring anxiety in children ages 3–5. Sub-scales: separation anxiety, physical injury fears, social phobia, obsessive–compulsive and generalised anxiety. Construct validity was assessed by correlating scores with the CBCL internalising score, giving Pearson's r = 0.68 ($P < 0.001$; Spence *et al.* 2001). Parent version: 38-item screening tool measuring anxiety in those aged 6–18. An additional sub-scale measuring panic/agoraphobia is present in comparison with the preschool version. Cronbach's alpha ranged from 0.61 to 0.81, and a confirmatory factor analysis provided support for the six inter-correlated factors (Nauta *et al.* 2004). The preschool and parent versions were used in this study and have previously been used in genetic syndrome research (e.g. Crawford *et al.* 2017; Wall *et al.* 2019).	Preschool range: 0–112 Preschool cut-off: a score of 1 SD above the mean Parent range: 0–114 Parent cut-off: a score of 1 SD above the mean
Mood, Interest and Pleasure Questionnaire Short Form (MIPQ-S)	Oliver *et al.* (2019) and Ross & Oliver (2003)	12-item questionnaire containing two sub-scales: mood, and interest and pleasure. It is designed for use with individuals with severe and profound ID and is completed by caregivers. The MIPQ-S has good inter-rater reliability, calculated at r = 0.75 for both sub-scales. The MIPQ-S demonstrated good internal consistency (α = 0.79 for the mood scale and 0.87 for the interest and pleasure scale; Oliver *et al.* 2019).	Range: 0–24 for each scale and 0–48 for total score Mood cut-offs: abnormally low – 15 and abnormally high – 24 Interest and pleasure cut-offs: abnormally low – 6 and abnormally high – 23
Hypermobility Questionnaire – Adapted Beighton Scale	Created for this study based on Beighton *et al.* (1973)	No questionnaire-based measures of hypermobility were available for use in this study; therefore, a new measure was created. It is a 9-point scale based on the Beighton Scale, which explores movements of the little fingers, thumbs, forearms, elbows, knees and trunk. The study presented caregivers with images of hypermobile movements and asked whether, based on previous observation, the child could complete this action. No reliability or validity information has been calculated for this measure.	Range: 0–9 (higher scores indicate increased hypermobility) 3–7 years cut-offs: females – ≥6 and males – ≥5 8+ years cut-offs: females – ≥5 and males – ≥4 2017

Table 1. *(Continued)*

Measure name (abbreviation)	Authors	Measure details	Score range and cut-offs
Challenging Behaviour Questionnaire (CBQ)	Hyman *et al.* (2002)	The CBQ assesses the presence of SIB, aggression towards others and property and stereotyped behaviour in the past month. 'Severity' of SIB is explored through duration, frequency and frequency of restraint. The scale has shown to have good inter-rater reliability (range of kappa = 0.60–0.92) for questions regarding the presence of challenging behaviour. For the severity items, an inter-rater reliability between 0.50 and 0.57 was calculated.	Range: 0–18
Sensory Experiences Questionnaire – v2.1 (SEQ)	Baranek (2013)	37-item measure that assesses sensory difficulties that may be experienced by children. The SEQ provides a total score and sub-scales of hyper-responsiveness, hypo-responsiveness and sensory seeking, which are designated as occurring in social or non-social contexts. The authors reported good internal consistency for the SEQ sub-scales (α = 0.69–0.80). They also provided evidence for construct validity using a known-groups validity study where the measure was able to discriminate between children with diagnoses of ASC and developmental disabilities and individuals without these diagnoses.	Ranges: Total scale – 33–132 Hypo-responsiveness – 6–24 Hyper-responsiveness – 14–56 Sensory seeking – 13–52 Social – 10–40 Non-social – 22–88
Pediatric Quality of Life Inventory 4.0 Short Form 15 (PEDS-QL)	Varni *et al.* (2001)	15-item questionnaire measuring paediatric health-related quality of life by exploring physical, emotional, social and nursery/school functioning. The proxy-report scales (which were used in this study) showed good internal consistency with all α coeffcients exceeding 0.80. Test–retest reliability ranged from 0.68 to 0.79 (Chen *et al.* 2007).	Range: 0–100 with higher scores indicating better quality of life
General Population Version of the Clinical Outcomes in Routine Evaluation (GP-CORE)	Evans *et al.* (2005)	The GP-CORE is a wellbeing measure consisting of 14 items. It was designed as a self-report measure for the general population. Caregivers were required to answer this questionnaire about themselves. High test–retest reliability (0.91) was noted by the authors with strong correlations to measures such as the Clinical Outcomes in Routine Evaluation with No Risk Items (CORE-NR; Evans *et al.* 2005).	Range: 0–56
Vineland Adaptive Behaviour Scale, Third Edition (VABS)	Sparrow *et al.* (2016)	The VABS was used to explore the child's communication, daily living and socialisation skills. An additional sub-scale exploring motor skills is available for those under 10 years. This measure is widely used in research exploring developmental delay as well as genetic conditions. The authors report good internal consistency (range of α = 0.90–0.98).	Range: standard score is generated

ASC, autism spectrum condition; CBCL, Child Behavior Checklist; ID, intellectual disability; SD, standard deviation; SIB, self-injurious behaviour.

was used where possible to address this, and analyses were repeated using non-parametric tests where appropriate.

Where appropriate, scores were compared with published mean normative data from the measures' author(s), data for 'typically developing' (TD) children and/or data for other groups of relevance, using bootstrapped single-sample *t*-tests. Where Cohen's *d* score is presented, a small effect is recognised as 0.2, medium as 0.5 and large as ≥0.8 (Cohen 1988). Repeated measures analyses of variance (ANOVAs) with *post hoc* comparisons were used to explore within-group differences between standardised sub-scale scores, and odds ratios were calculated where appropriate.

Table 2 Demographic characteristics for the children of participants

Characteristic	
Age (years)	
Mean (SD)	8.30 (3.98)
Bootstrapped 95% CI	6.76–9.95
Range	3.26–15.83
Sex	
Male (%)	11 (55)
Female (%)	9 (45)
Head circumference	
Mean percentile (SD)	96.12 (8.41)
Bootstrapped 95% CI	92.11–99
Range	65–99
Ethnicity	
White or White British (%)	19 (95)
White and Black African (%)	1 (5)

The head circumference data presented are the age-adjusted percentile and were missing for three children. The 99th percentile may be representative of the >99th percentile.
CI, confidence interval; SD, standard deviation.

Results

Demographics and medical characteristics

Demographic data for the children of participants are presented in Table 2. Parents were the only caregiver type to complete the survey. Country of residence data was collected from 15 participants, with most participants residing in the UK (n = 11), three in the USA and one in Finland. A known *PTEN* mutation in a relative was noted in 20% (n = 4) of participants and included parents (n = 4) and a sibling (n = 1).

Legal blindness was not reported; however, three had difficulty with hearing (with no neurological deafness). An autoimmune disorder was reported in two participants (type 1 diabetes and juvenile idiopathic arthritis), and two participants had thyroid cancer. A wide variety of medications were prescribed, including sertraline, methylphenidate and melatonin. One participant had an 'attention deficit hyperactivity disorder' diagnosis; eight had a diagnosis of autism spectrum disorder (ASD); and one had a diagnosis of anxiety and obsessive–compulsive disorder.

Adaptive ability, development and intellectual disability

Parents reported that 60% (n = 12) of individuals had been diagnosed with a 'learning disability' or 'developmental delay'. Descriptive statistics for scores on different domains of the Vineland Adaptive Behaviour Scale, Third Edition (VABS) are reported in Table 3.

Table 3 Descriptive statistics for VABS standard scores

Domain	*N*	Mean (SD)	Median	Inter-quartile range	Range
Adaptive Behaviour Composite	20	67.85 (17.74)	65.00	56.00–76.75	34.00–107.00
Communication	20	65.85 (21.92)	63.00	52.25–81.25	22.00–109.00
Daily living skills	20	69.00 (17.98)	67.00	54.50–83.50	37.00–107.00
Socialisation	20	67.10 (19.86)	66.50	52.00–75.75	31.00–110.00
Motor skills	14	68.43 (21.01)	62.50	49.50–90.00	41.00–102.00

The data for the motor skills domain are only presented for 14 participants as this can only be administered to those aged 9 years or younger.
SD, standard deviation; VABS, Vineland Adaptive Behaviour Scale, Third Edition.

For 70% (n = 14) of participants, the VABS Adaptive Behaviour Composite (ABC) score was <70, and the mean ABC score was significantly lower than the population mean (mean difference = −21.50, 95% CI −28.85 to −13.25, $P < 0.001$), with a large effect size (d = 1.27). No significant differences were found across the three main sub-scales ($F_{1.86, 35.28}$ = 1.39, P = 0.262, η_p^2 = 0.15).

All children could walk independently {the mean age of reaching this milestone was 1.87 years [standard deviation (SD) = 0.72]}. Speech was the sole method of communication for 60% (n = 12), with a further 20% (n = 4) also using additional communication methods. The remaining participants (n = 4) were non-verbal or solely used alternative communication methods (age range = 3.26–13.96 years).

Autism spectrum condition characteristics

Social Responsiveness Scale, Second Edition

The mean total T-score for the Social Responsiveness Scale, Second Edition (SRS-2) was 78.5 (SD = 18.56, range: 42–105). Four participants scored in the 'low to no symptomology' range (T-score of 59 or below), five in the 'moderate' range (T-score of 66–75) and 11 in the 'severe' range (T-score over 76). Scores were significantly higher than the normative data across all domains (Fig. 1).

Significant differences were seen between the SRS-2 domains (F(2.88, 54.73) = 5.99, P = 0.002, η_p^2 = 0.24). *Post hoc* testing with Bonferroni corrections indicated that scores on the restrictive interests and repetitive behaviour sub-scale significantly exceeded both the social communication (4.85, 95% CI 0.77–8.93, P = 0.013) and social motivation sub-scales (9.55, 95% CI 2.95–16.15, P = 0.002). These results suggest a relative 'peak' in scores on repetitive/restricted behaviours as compared with social communication-focused domains.

Anxiety

A T-score of 60 has been suggested to indicate elevated levels of anxiety (Spence 2021). This cut-off was exceeded by 50% (n = 10) of participants.

Bootstrapped, single-sample t-tests comparing the Spence Children's Anxiety Scale (SCAS) z-scores with the normative data (mean = 0, SD = 1; Table 4) indicated small, non-significant differences in social

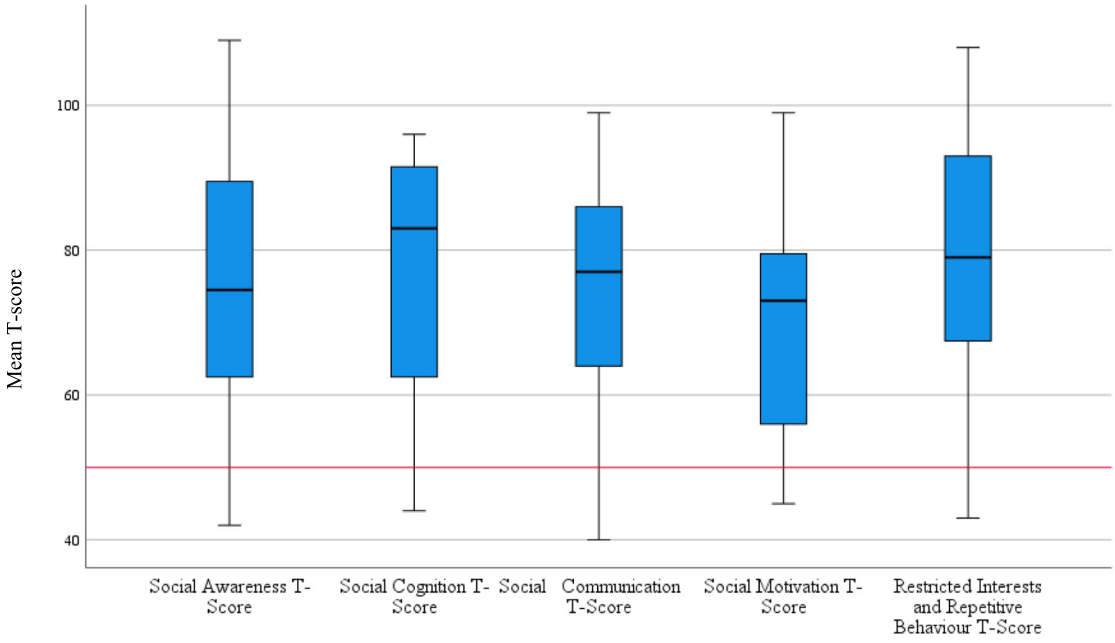

Figure 1. Box plot of Social Responsiveness Scale, Second Edition domain scores. Standardised normative data mean T-score = 50 (red line), standard deviation = 15 for typically developing population.

Table 4 Comparison of SCAS scores between children with a *PTEN* mutation and the normative data

SCAS sub-scale	*N*	Median	Range	Mean/mean difference (SD)	Bootstrapped 95% confidence intervals	Cohen's *d*
Total	20	0.72	−1.44 to 7.57	0.97 (2.19)	−0.01 to 2.12	0.57
Separation anxiety	20	0.50	−1.03 to 3.90	0.70* (1.46)	0.06–1.31	0.56
Social anxiety	20	−0.77	−1.43 to 3.90	0.01 (1.54)	−0.66 to 0.70	0.01
Generalised anxiety	20	0.93	−1.38 to 4.68	0.82* (1.61)	0.16–1.57	0.61
Panic/agoraphobia	12	0.77	−0.09 to 10.92	2.72* (3.86)	0.83–5.05	0.96
Physical injury fears	20	0.29	−1.42 to 6.83	0.69 (1.97)	−0.02 to 1.56	0.44
Obsessive–compulsive	20	0.09	−0.70 to 7.17	0.88 (2.14)	0.01–1.89	0.53

The panic/agoraphobia sub-scale is only in the parent measure and therefore derived from 12 participants. The nature of *z*-scores is such that a score of 0 would indicate no difference from the normative sample and is therefore equal to the mean difference.

*Significant at the 0.05 level.

SCAS, Spence Children's Anxiety Scale; SD, standard deviation.

anxiety compared with normative data. However, normative scores were exceeded with medium effect sizes for total score, separation, generalised and obsessive–compulsive anxiety sub-scales. A large effect size was seen on the panic/agoraphobia sub-scale.

A Friedman test revealed significant differences between sub-scales ($\chi^2(4) = 16.28$, $P = 0.003$), excluding the panic/agoraphobia sub-scale due to the different sample size (this sub-scale is only present on the parent version and not the preschool measure). *Post hoc* analysis with Wilcoxon signed-rank tests was conducted with a Bonferroni correction applied ($\alpha = 0.005$). Substantial (and statistically significant) differences were noted between the social anxiety and generalised anxiety sub-scales ($Z = -3.55$, $P < 0.001$, $r = -0.56$), the social anxiety and obsessive–compulsive sub-scales ($Z = -2.88$, $P = 0.004$, $r = -0.46$) and the social anxiety and separation anxiety sub-scales ($Z = -2.80$, $P = 0.005$, $r = -0.44$), with the social anxiety score being lower in all cases.

Mood and behaviour that challenges

Mood, Interest and Pleasure Questionnaire Short Form

Total scores for the Mood, Interest and Pleasure Questionnaire Short Form (MIPQ-S) ranged from 14 to 45 out of 48 with a mean of 36.05 (SD = 8.44). The mean score for the mood sub-scale was 19.25 (SD = 3.99), and the mean for the interest and pleasure sub-scale was 16.80 (SD = 5.01). The authors of the paper identified scores of 15 and 6 as abnormally low for mood, and interest and pleasure sub-scales, respectively (Oliver *et al.* 2019). Medical interventions or physical illness was reported as having negative effects on mood by four caregivers, with two caregivers reporting that school was a source of distress.

Challenging Behaviour Questionnaire

The Challenging Behaviour Questionnaire revealed that 75% of participants had displayed at least one BtC in the month prior to completing the survey. Forty per cent ($n = 8$) of participants had displayed SIB; 55% ($n = 11$) had displayed physically aggressive behaviour; 35% ($n = 7$) had shown destruction of property or disruption to the environment; and 30% ($n = 6$) had displayed stereotyped behaviour. For those displaying SIB, 'severity' scores ranged from 3 to 9 (mean = 5.88, SD = 2.17).

Hypermobility

Hypermobility had been specifically diagnosed (most often by a paediatrician or physiotherapist, and at a mean age of 2.39 years) in 55% ($n = 11$) of the participants, with two additional respondents stating that they were unsure if a diagnosis had been received. The total mean score on the adapted Beighton Scale was 2.65 (SD = 2.87) out of a total possible 9, with two participants scoring 9 out of 9, indicating

hypermobility in all joints explored. Four participants scored above the relative cut-off (from Singh *et al.* 2017) with three of these participants having been diagnosed with hypermobility.

Sensory features

Total Sensory Experiences Questionnaire – v2.1 (SEQ) scores for each sub-scale were converted to mean scores and compared with data (Baranek 2013) for those diagnosed with ASC and developmental disabilities (DDs) and for TD children (Table 5). Only small effect sizes were seen for differences between the *PTEN* and ASC groups, suggesting similar sensory features across sub-scales. The *PTEN* group scored higher than the TD and DD groups across all sub-scales with medium to large effect sizes across all sub-scales barring sensory seeking.

Quality of life

'Quality of life' was measured using the Pediatric Quality of Life Inventory 4.0 Short Form 15 (PEDS-QL). The mean total score was 55.15 (SD = 17.46) and ranged from 23.33 to 88.33. This was compared with the score of a group of 'TD children with no known health conditions' (Chan *et al.* 2005). The *PTEN* group scored lower on average than the comparison group, with a large effect size (mean difference = 30.94, bootstrapped 95% CI −38.44 to −23.02, $P < 0.001$, $d = 2.11$).

A repeated measures ANOVA indicated no significant differences between the four sub-scales (physical, emotional, social and school/nursery functioning; $F_{2.35,\ 44.71} = 1.55$, $P = 0.221$, $\eta_p^2 = 0.08$).

Relationships between variables

Autism spectrum condition features and ability measure

No participant with an adaptive ability score in the usual range (VABS ABC > 70) had received a diagnosis of ASC. A strong, negative correlation was found between VABS ABC and SRS-2 total *T*-score ($r(18) = -0.83$, bootstrapped 95% CI −0.94 to −0.57, $P < 0.001$; Fig. 2).

Table 5 Mean SEQ scores and comparison with other groups

SEQ sub-scale	*PTEN* (SD) *N* = 20	ASC (SD) *N* = 75	Mean difference (95% CIs)	Cohen's *d*	TD (SD) *N* = 53	Mean difference (95% CIs)	Cohen's *d*	DD (SD) *N* = 44	Mean difference (95% CIs)	Cohen's *d*
Total	2.51 (0.72)	2.58 (0.43)	−0.07 (−0.33 to 0.22)	0.12	1.89 (0.35)	0.62† (0.31–0.97)	1.10	2.11 (0.39)	0.40 (0.09–0.70)	0.69
Hypo-responsiveness	2.51 (0.92)	2.25 (0.72)	0.26 (−0.08 to 0.59)	0.31	1.45 (0.32)	1.06† (0.67–1.47)	1.54	1.74 (0.54)	0.77† (0.38–1.22)	1.02
Hyper-responsiveness	2.59 (0.83)	2.52 (0.51)	0.07 (−0.32 to 0.46)	0.10	1.72 (0.33)	0.87† (0.50–1.24)	1.38	2.04 (0.50)	0.55 (0.21–0.91)	0.80
Social context	2.35 (0.63)	2.32 (0.46)	0.03 (−0.26 to 0.43)	0.05	1.60 (0.28)	0.75† (0.49–1.02)	1.54	1.78 (0.45)	0.57† (0.32–0.81)	1.04
Non-social context	2.62 (0.82)	2.71 (0.50)	−0.09 (−0.44 to 0.26)	0.13	2.10 (0.46)	0.52 (0.19–0.88)	0.78	2.29 (0.49)	0.33 (0.01–0.71)	0.49
Sensory seeking	2.44 (0.97)	2.79 (0.65)	−0.35 (−0.72 to 0.09)	0.42	2.29 (0.67)	0.15 (−0.27 to 0.58)	0.18	2.35 (0.71)	0.09 (−0.32 to 0.56)	0.11

†Significant difference between *PTEN* and comparison group (based on single-sample *t*-tests) after Bonferroni corrections (corrected to 0.003).

ASC, autism spectrum condition; CIs, confidence intervals; DD, developmental disability; SD, standard deviation; SEQ, Sensory Experiences Questionnaire – v2.1; TD, typically developing.

Inter-relationships between hypermobility and autism spectrum condition-related behaviour, sensory processing and anxiety

Large, significant correlations were found between the hypermobility (adapted Beighton) score and total ASC (SRS-2 *T*-score) score ($r(18) = 0.61$, bootstrapped 95% CI 0.22–0.65, $P = 0.005$), and between the hypermobility and sensory processing (SEQ total) scores ($r(18) = 0.73$, bootstrapped 95% CI 0.36–0.90, $P < 0.001$). The correlation between total hypermobility and anxiety (SCAS total *z*-score) was medium in size but not statistically significant ($r(18) = 0.30$, bootstrapped 95% CI −0.28 to 0.88, $P = 0.205$). A medium, positive correlation was noted between sensory processing (SEQ) and anxiety (SCAS) scores ($r(18) = 0.41$, bootstrapped 95% CI 0.04–0.76, $P = 0.071$), suggesting that children with higher levels of anxiety also displayed a higher frequency or intensity of sensory features (see Fig. 2 for critical correlations).

Self-injurious behaviour, mood-related variables, ability, sensory features and autism spectrum condition

Differences between those who displayed SIB in the month preceding the survey ($n = 8$) and those who did not ($n = 12$) were explored using bootstrapped independent *t*-tests (Table 6). Differences between groups in SRS-2 total *T*-score, SEQ mean total score and VABS ABC were statistically significant at 0.05; these effects were all of large size.

Quality of life, autism spectrum condition-related behaviour, mood-related variables and ability

A series of Pearson correlation coefficients with bootstrapping were calculated to explore the relationships between PEDS-QL scores and ASC-related behaviour, anxiety levels, mood, interest and pleasure, and adaptive ability (Table 7 and Fig. 2).

With Bonferroni correction applied, significant negative correlations with large effect sizes remained between the PEDS-QL score, the SRS-2 total *T*-score and the SCAS total *z*-score.

Relationships with parental wellbeing

A series of Pearson correlation coefficients with bootstrapping were run to explore the relationship between parental wellbeing (GP-CORE mean item score) and child characteristics. No relationship was statistically significant, and most were small in size; the largest effect size was noted between the GP-CORE score ($r = 0.29$, $P = 0.216$) and VABS ABC ($r = -0.40$, $P = 0.082$), where the lower the adaptive functioning of the child, the higher the parental distress.

Discussion

This research assessed various psychological and developmental characteristics in a group of 20 children with *PTEN* mutations and tentatively explored the relationships between these characteristics. This may help identify a profile of strengths and difficulties associated with *PTEN* aberrations for children and therefore guide assessment, support and future research.

Similar to the findings of Hansen-Kiss *et al.* (2017), a wide range in ability was noted in the participants (VABS composite scores: 34–107), and 'learning disability' or 'developmental delay' was reported in 60% of participants, which is higher than other studies (e.g. Lachlan *et al.* 2007; Yehia *et al.* 2019). Level of ability correlated with many other variables, and future research should explore the degree to which individuals with *PTEN* mutations and higher levels of ability tend to have fewer difficulties in other areas and the degree to which such individuals may have distinct needs.

A higher prevalence of ASD diagnoses (40%) was noted in the study compared with the estimated prevalence calculated by Cummings *et al.* (2022). Findings suggested a possible relative 'sparing' of social motivation in children with *PTEN* mutations. The relationship between greater levels of ID and higher levels of ASC phenomenology was found to be very strong. There is a known association between ID and ASC in the general population, although the specific relationship between these constructs in different genetic neurodevelopmental syndrome groups remains less well elucidated. It has also been found that the diagnosis of ASC may be significantly reduced or delayed for children with multiple, complex and rare conditions (Sloneem *et al.* 2022) as might be the case for children with *PTEN* mutations. Directions for future research include using a standardised diagnostic test, such as the Autism

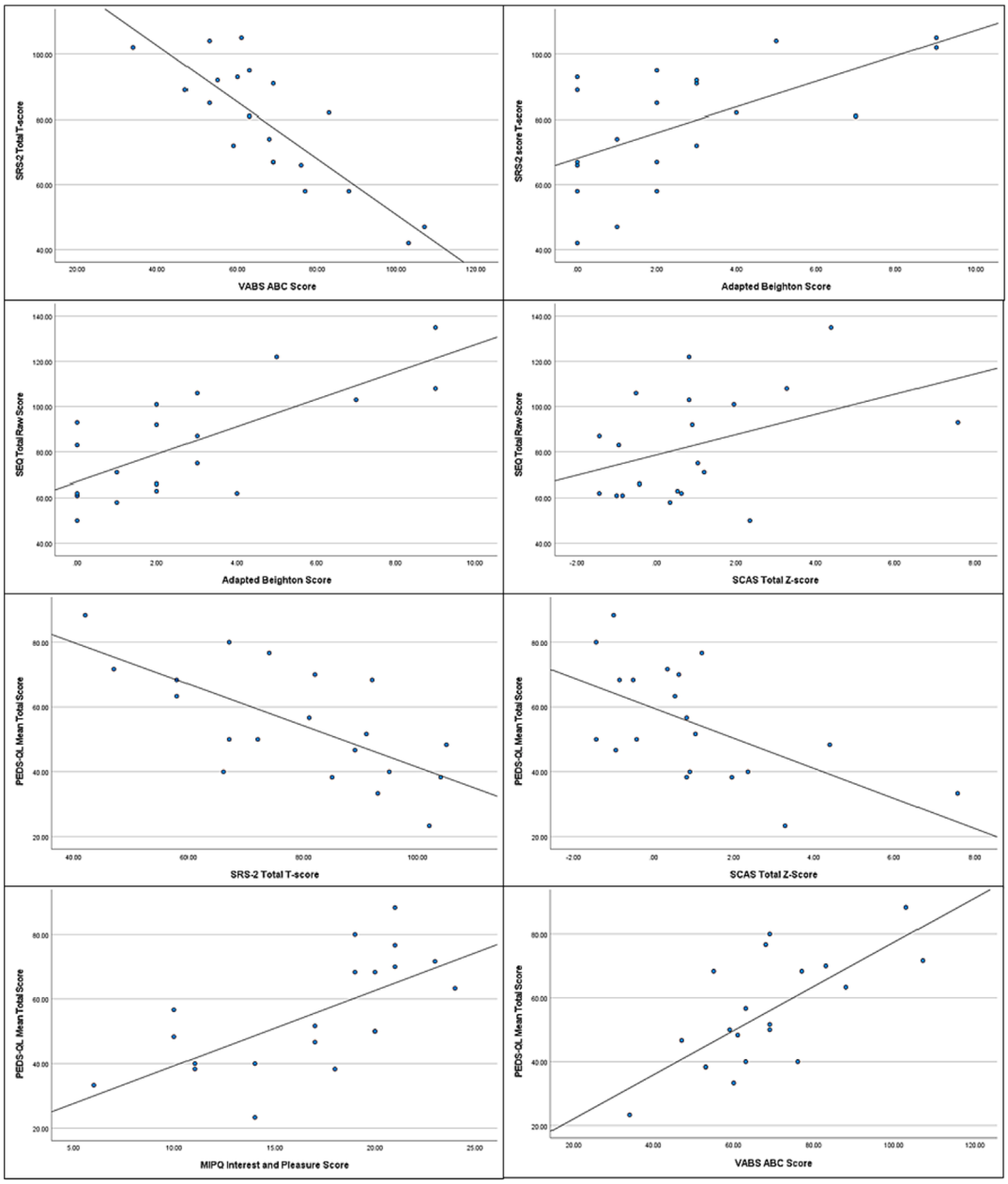

Figure 2. Scatter plots demonstrating relationships between key variables. ABC, Adaptive Behaviour Composite; MIPQ, Mood, Interest and Pleasure Questionnaire; PEDS-QL, Pediatric Quality of Life Inventory 4.0 Short Form 15; SCAS, Spence Children's Anxiety Scale; SEQ, Sensory Experiences Questionnaire – v2.1; SRS-2, Social Responsiveness Scale, Second Edition; VABS, Vineland Adaptive Behaviour Scale, Third Edition.

Diagnostic Observation Schedule, to allow for a clinician-rated measure of ASC symptomology while also allowing the researcher to notice more subtle difficulties not highlighted in questionnaires. Future research should also focus on the prevalence and sequelae of ASC in people with *PTEN* aberrations but without ID.

The present research replicated lower sensory responsiveness levels (Busch *et al.* 2019) in children with PTEN mutations, compared with 'TD' children

Table 6 Differences between those who had and had not displayed SIB

Variable	Mean score of group displaying SIB (SD)	Mean score of group not displaying SIB (SD)	Mean difference (bootstrapped 95% CIs)	Significance (*P* value)	Cohen's *d*
SRS-2 total *T*-score	90.00 (10.11)	70.83 (19.23)	19.17 (6.44–33.08)	0.019	1.25
SCAS total *z*-score	1.77 (2.69)	0.42 (1.69)	1.25 (−0.44 to 3.56)	0.182	0.60
MIPQ-S mood	17.25 (4.83)	20.58 (2.78)	−3.33 (−7.00 to −0.15)	0.065	0.85
SEQ mean total score	2.98 (0.48)	2.20 (0.70)	0.78 (0.18–1.33)	0.013	1.30
VABS ABC	54.13 (10.45)	77.00 (15.67)	−22.88 (−34.94 to −13.15)	0.002	1.72

ABC, Adaptive Behaviour Composite; CIs, confidence intervals; MIPQ-S, Mood, Interest and Pleasure Questionnaire Short Form; SCAS, Spence Children's Anxiety Scale; SD, standard deviation; SEQ, Sensory Experiences Questionnaire – v2.1; SIB, self-injurious behaviour; VABS, Vineland Adaptive Behaviour Scale, Third Edition.

Table 7 Correlations between the PEDS-QL total mean score and other variables

Measure	Pearson's *r*	Bootstrapped 95% CIs	Significance (*P* value)
SRS-2 total *T*-score	−0.68	−0.85 to −0.42	<0.001†
SCAS total *z*-score	−0.58	−0.76 to −0.35	0.007†
MIPQ-S mood	0.38	0.01–0.69	0.101
MIPQ interest and pleasure	0.67	0.47–0.82	0.001†
VABS ABC	0.70	0.39–0.89	<0.001†

†Remain significant following Bonferroni corrections (corrected to 0.01).
ABC, Adaptive Behaviour Composite; CIs, confidence intervals; MIPQ, Mood, Interest and Pleasure Questionnaire; MIPQ-S, Mood, Interest and Pleasure Questionnaire Short Form; PEDS-QL, Pediatric Quality of Life Inventory 4.0 Short Form 15; SCAS, Spence Children's Anxiety Scale; SRS-2, Social Responsiveness Scale, Second Edition; VABS, Vineland Adaptive Behaviour Scale, Third Edition.

or children with a developmental delay (Baranek 2013). Scores in the sensory seeking sub-scale were more consistent with the 'TD' and developmental delay groups (Baranek 2013). Together, these scores may help to explain reports of children with *PTEN* mutations appearing 'passive' (Frazier 2019).

Levels of anxiety, as measured by the SCAS, were elevated in 50% of participants. This is contradictory to anecdotal reports and murine models suggesting that *reduced* anxiety-like behaviour may correlate with *PTEN* mutations (Dey & Chattarji 2022). However, it supports the chart review and some case study findings on elevated anxiety in some with *PTEN* mutations (e.g. Hansen-Kiss *et al.* 2017; Balci *et al.* 2018). Scores varied widely, and therefore, interpretations based on averages may be less helpful and should be read with caution. Furthermore, this sample of children with *PTEN* mutations appears to have disproportionately low levels of ability and high rates of ASC, which may be reflected in the higher levels of anxiety. The social anxiety sub-scale scores were similar to the normative data, which may suggest that social interaction is relatively less problematic for children with *PTEN* mutations. Higher levels of anxiety were moderately correlated with sensory features, reflecting previous research relating sensory sensitivity and anxiety for children with ASC (Uljarević *et al.* 2016). Reduced 'quality of life' (as measured by the PEDS-QL) was noted in the sample as compared with 'TD' children with no known health conditions.

In the present study, 55% of participants reported a hypermobility diagnosis (although, interestingly, only four participants scored above the relative cut-off scores using the adapted Beighton Scale, which may reflect the measure asking parents to rate only on previous observation, potentially underestimating specific joint

involvement). The adapted Beighton Scale score was strongly correlated with ASC phenomenology (consistent with Casanova *et al.* 2020) as well as sensory features, which are noted to be higher in individuals with ASC (Baranek *et al.* 2006).

Analysis exploring differences between those who had (40%) and had not displayed SIB suggested that SIB was strongly associated with sensory processing atypicalities, lower mood, greater ASC phenomenology and lower adaptive ability (as found by Arron *et al.* 2011 in people with Cornelia de Lange syndrome) and moderately related to higher anxiety. While directions of causation were not assessed, there may be important clinical implications to explore. For example, SIB may be used to communicate pain (Hartman *et al.* 2008; Oliver & Richards 2015) and/or may reflect an atypical sensory experience (Symons 2011). Conversely, pain associated with SIB may lead to a lower mood. Future research should explore these complex inter-relationships further, with research focusing on clinically effective interventions to help produce guidelines for clinicians and families. Where SIB is observed clinically, mood and sensory processing should be considered.

Compared with 'TD' children with no known health problems, participants had a lower parent-rated 'quality of life' as measured by the PEDS-QL (Chan *et al.* 2005). Higher PEDS-QL scores were most strongly correlated with higher adaptive ability scores and moderately correlated with ASC-related difficulties, anxiety, mood, and interest and pleasure, indicating that many factors may contribute towards 'quality of life'. While such measures can help indicate where support may need to be directed, care must be taken when interpreting this measure due to assumptions regarding what constitutes a 'high quality of life'.

Interestingly, primarily only small correlations (which were not significant statistically) were noted between parental wellbeing and child behavioural/psychological variables, suggesting that many of these did not greatly impact parental wellbeing in this group. A moderate correlation was found with overall adaptive behaviour, suggesting that the lower the child's ability level, the higher the distress in the parent, contrasting with previous findings that child emotional distress is the most consistent predictor of parental distress (Fitzgerald & Gallagher 2021). However, because of the small sample size, such findings should be interpreted cautiously, with further research looking to confirm these results with a larger sample. Should this pattern be recognised in a larger sample, qualitative techniques such as interviews should be used to explore this relationship in more depth.

Limitations

This study adds to the limited data regarding psychological distress in children with *PTEN* mutations. However, a number of limitations should be noted.

It should be kept in mind that there are many mechanisms by which psychological differences may occur that (due in part to low power) have not been investigated in this study (e.g. the effects of medication). The chosen measures also introduce possible limitations. All were based on informant report rather than direct observation. Where possible, measures were used that could encompass a range of ability levels; however, some of the measures (e.g. the MIPQ-S) may not optimally capture children's experiences. In addition, the measure of hypermobility was adapted anew for the current study, and therefore, the reliability and validity of this measure are unknown. Findings and correlations using this measure should be interpreted with caution with this in mind. Research into a valid measure of parent-reported hypermobility would be beneficial for this area of research. The lack of a single, well-matched comparison group also limits conclusions.

The relatively small sample size of the study is a common limitation in studies of rare genetic syndromes and reduces the statistical power of the findings. Furthermore, participants were recruited via a support charity and associated forums, potentially introducing bias. For these reasons, generalisations and inferences from the findings of this study should be made cautiously with future research looking to replicate these findings with larger sample sizes.

Summary and implications

Key findings include a high prevalence of ASC-related difficulties (which were strongly correlated with level of ability and may feature relatively preserved social motivation), high levels of anxiety (barring social anxiety) and sensory processing differences. Where *PTEN* aberrations are

found or suspected, clinicians and families should be alert to these possible difficulties. Support for BtC and emotional distress may be required for a proportion of children, and sensory processing, mood, ability and ASC should be considered where children display BtC. Therefore, children with *PTEN* aberrations and their families are likely to benefit from having access to a range of professionals (potentially including psychologists and occupational therapists, in addition to medical support).

While these findings provide an overview of characteristics not previously explored in detail in this group, future research should focus on exploring variables in larger samples with direct assessment as well as exploring the relationships between characteristics more fully.

Acknowledgements

The authors would like to thank the participants and their families for giving their time to take part in this research. We would also like to thank the PTENUKI Patient Group for their support in helping us connect with the parents of those with *PTEN* changes.

Conflict of Interest

The authors declare that there is no conflict of interest.

Source of Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Ethics Approval Statement

Ethical review and approval were granted by the School of Psychology Research Ethics Committee at the University of Leicester.

Data Availability Statement

Research data are not shared.

References

Adams D., Clarke S., Griffith G., Howlin P., Moss J., Petty J. *et al.* (2018) Mental health and well-being in mothers of children with rare genetic syndromes showing chronic challenging behavior: a cross-sectional and longitudinal study. *American Journal on Intellectual and Developmental Disabilities* **123**, 241–53.

Arron K., Oliver C., Moss J., Berg K. & Burbidge C. (2011) The prevalence and phenomenology of self-injurious and aggressive behaviour in genetic syndromes. *Journal of Intellectual Disability Research* **55**, 109–20.

Balci T. B., Davila J., Lewis D., Boafo A., Sell E., Richer J. *et al.* (2018) Broad spectrum of neuropsychiatric phenotypes associated with white matter disease in *PTEN* hamartoma tumor syndrome. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics* **177**, 101–9.

Baranek G. T. (2013) *Sensory Experiences Questionnaire (SEQ) Version 2.1 Manual*. University of North Carolina, Chapel Hill, NC.

Baranek G. T., David F. J., Poe M. D., Stone W. L. & Watson L. R. (2006) Sensory Experiences Questionnaire: discriminating sensory features in young children with autism, developmental delays, and typical development. *Journal of Child Psychology and Psychiatry* **47**, 591–601.

Beighton P., Solomon L. & Soskolne C. L. (1973) Articular mobility in an African population. *Annals of the Rheumatic Diseases* **32**, 413–8.

Busch R. M., Srivastava S., Hogue O., Frazier T. W., Klaas P., Hardan A. *et al.* (2019) Neurobehavioral phenotype of autism spectrum disorder associated with germline heterozygous mutations in *PTEN*. *Translational Psychiatry* **9**, 253–9.

Butler M. G., Dasouki M. J., Zhou X., Talebizadeh Z., Brown M., Takahashi T. N. *et al.* (2005) Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline *PTEN* tumour suppressor gene mutations. *Journal of Medical Genetics* **42**, 318–21.

Casanova E. L., Baeza-Velasco C., Buchanan C. B. & Casanova M. F. (2020) The relationship between autism and Ehlers-Danlos syndromes/hypermobility spectrum disorders. *Journal of Personalized Medicine* **10**, 260.

Chan K. S., Mangione-Smith R., Burwinkle T. M., Rosen M. & Varni J. W. (2005) The PedsQL™: reliability and validity of the short-form generic core scales and Asthma Module. *Medical Care* **43**, 256–65.

Chen X., Origasa H., Ichida F., Kamibeppu K. & Varni J. W. (2007) Reliability and validity of the Pediatric Quality of Life Inventory™ (PedsQL™) Short Form 15 Generic Core Scales in Japan. *Quality of Life Research* **16**, 1239–49.

Cohen J. (1988) *Statistical Power Analysis for the Behavioral Sciences*. Routledge Academic, New York, NY.

Constantino J. & Gruber J. (2005) *Social Responsiveness Scale: Manual*. Western Psychological Services, Los Angeles.

Crawford H., Waite J. & Oliver C. (2017) Diverse profiles of anxiety related disorders in fragile X, Cornelia de Lange and Rubinstein–Taybi syndromes. *Journal of Autism and Developmental Disorders* **47**, 3728–40.

Cumming G. (2014) The new statistics: why and how. *Psychological Science* **25**, 7–29.

Cummings K., Watkins A., Jones C., Dias R. & Welham A. (2022) Behavioural and psychological features of PTEN mutations: a systematic review of the literature and meta-analysis of the prevalence of autism spectrum disorder characteristics. *Journal of Neurodevelopmental Disorders* **14**, 1.

Dey R. & Chattarji S. (2022) The same stress elicits different effects on anxiety-like behavior in rat models of *Fmr1*$^{-/y}$ and *Pten*$^{+/-}$. *Behavioural Brain Research* **428**, 113892.

Evans C., Connell J., Audin K., Sinclair A. & Barkham M. (2005) Rationale and development of a general population well-being measure: psychometric status of the GP-CORE in a student sample. *British Journal of Guidance and Counselling* **33**, 153–73.

Fitzgerald J. & Gallagher L. (2021) Parental stress and adjustment in the context of rare genetic syndromes: a scoping review. *Journal of Intellectual Disabilities* **26**, 522–44.

Frazier T. W. (2019) Autism spectrum disorder associated with germline heterozygous *PTEN* mutations. *Cold Spring Harbor Perspectives in Medicine* **9**, 253.

Frazier T. W., Embacher R., Tilot A. K., Koenig K., Mester J. & Eng C. (2015) Molecular and phenotypic abnormalities in individuals with germline heterozygous *PTEN* mutations and autism. *Molecular Psychiatry* **20**, 1132–8.

Hansen-Kiss E., Beinkampen S., Adler B., Frazier T., Prior T., Erdman S. *et al.* (2017) A retrospective chart review of the features of PTEN hamartoma tumour syndrome in children. *Journal of Medical Genetics* **54**, 471–8.

Hartman E. C., Gilles E., McComas J. J., Danov S. E. & Symons F. J. (2008) Clinical observation of self-injurious behavior correlated with changes in scalp morphology in a child with congenital hydrocephalus. *Journal of Child Neurology* **23**, 1062–5.

Hobert J. A. & Eng C. (2009) *PTEN* hamartoma tumor syndrome: an overview. *Genetics in Medicine* **11**, 687–94.

Hopkins B. D., Hodakoski C., Barrows D., Mense S. M. & Parsons R. E. (2014) PTEN function: the long and the short of it. *Trends in Biochemical Sciences* **39**, 183–90.

Hyman P., Oliver C. & Hall S. (2002) Self-injurious behavior, self-restraint, and compulsive behaviors in Cornelia de Lange syndrome. *American Journal of Mental Retardation* **107**, 156–4.

Lachlan K. L., Lucassen A. M., Bunyan D. & Temple I. K. (2007) Cowden syndrome and Bannayan–Riley–Ruvalcaba syndrome represent one condition with variable expression and age-related penetrance: results of a clinical study of *PTEN* mutation carriers. *Journal of Medical Genetics* **44**, 579–85.

Li J., Yen C., Liaw D., Podsypanina K., Bose S., Wang S. I. *et al.* (1997) *PTEN*, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. *Science* **275**, 1943–7.

Liaw D., Marsh D. J., Li J., Dahia P. L. M., Wang S. I., Zheng Z. *et al.* (1997) Germline mutations of the *PTEN* gene in Cowden disease, an inherited breast and thyroid cancer syndrome. *Nature Genetics* **16**, 64–7.

Macken W. L., Tischkowitz M. & Lachlan K. L. (2019) *PTEN* hamartoma tumor syndrome in childhood: a review of the clinical literature. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* **181**, 591–610.

McBride K. L., Varga E. A., Pastore M. T., Prior T. W., Manickam K., Atkin J. F. *et al.* (2010) Confirmation study of *PTEN* mutations among individuals with autism or developmental delays/mental retardation and macrocephaly. *Autism Research* **3**, 137–41.

Nauta M. H., Scholing A., Rapee R. M., Abbott M., Spence S. H. & Waters A. (2004) A parent-report measure of children's anxiety: psychometric properties and comparison with child-report in a clinic and normal sample. *Behaviour Research and Therapy* **42**, 813–39.

Nelen M. R., Padberg G. W., Peeter E. A., Lin A. Y., Helm B. V., Frants R. R. *et al.* (1996) Localization of the gene for Cowden disease to chromosome 10q22-23. *Nature Genetics* **13**, 114–6.

Oliver C. & Richards C. (2015) Practitioner review: self-injurious behaviour in children with developmental delay. *Journal of Child Psychology and Psychiatry* **56**, 1042–54.

Oliver C., Royston R., Crawford H., Moss J., Waite J. & Arron K. (2019) *Informant Assessments of Behaviour and Affect for People with Intellectual Disability (V2)*. The Cerebra Centre for Neurodevelopmental Disorders, Birmingham.

Pilarski R., Burt R., Kohlman W., Pho L., Shannon K. M. & Swisher E. (2013) Cowden syndrome and the *PTEN* hamartoma tumor syndrome: systematic review and revised diagnostic criteria. *Journal of the National Cancer Institute* **105**, 1607–16.

Ross E. & Oliver C. (2003) Preliminary analysis of the psychometric properties of the Mood, Interest & Pleasure Questionnaire (MIPQ) for adults with severe and profound learning disabilities. *British Journal of Clinical Psychology* **42**, 81–93.

Sacco R., Gabriele S. & Persico A. M. (2015) Head circumference and brain size in autism spectrum disorder: a systematic review and meta-analysis. *Psychiatry Research* **234**, 239–51.

Singh H., McKay M., Baldwin J., Nicholson L., Chan C., Burns J. *et al.* (2017) Beighton scores and cut-offs across the lifespan: cross-sectional study of an Australian population. *Rheumatology (Oxford)* **56**, 1857–64.

Skelton P. D., Stan R. V. & Luikart B. W. (2020) The role of PTEN in neurodevelopment. *Molecular Neuropsychiatry* **5**, 60–71.

Sloneem J., Moss J., Powell S., Hawkins C., Fosi T., Richardson H. *et al.* (2022) The prevalence and profile of autism in Sturge–Weber syndrome. *Journal of Autism and Developmental Disorders* **52**, 1942–55.

Song M. S., Salmena L. & Pandolfi P. P. (2012) The functions and regulation of the PTEN tumour suppressor. *Nature Reviews. Molecular Cell Biology* **13**, 283–96.

Sparrow S. S., Cicchetti D. V. & Saulnier C. A. (2016) *Vineland Adaptive Behavior Scales, Third Edition (Vineland-3)*. Pearson, San Antonio, TX.

Spence S. H. (1998) A measure of anxiety symptoms among children. *Behaviour Research and Therapy* **36**, 545–66.

Spence, S. H. (2021) The Spence Children's Anxiety Scale information for researchers and practitioners. Available at: https://www.scaswebsite.com/

Spence S. H., Rapee R., McDonald C. & Ingram M. (2001) The structure of anxiety symptoms among preschoolers. *Behaviour Research and Therapy* **39**, 1293–316.

Steele M., Uljarević M., Rached G., Frazier T. W., Phillips J. M., Libove R. A. *et al.* (2021) Psychiatric characteristics across individuals with *PTEN* mutations. *Frontiers in Psychiatry* **12**, 672070.

Symons F. (2011) Self-injurious behavior in neurodevelopmental disorders: relevance of nociceptive and immune mechanisms. *Neuroscience and Biobehavioral Reviews* **35**, 1266–74.

Uljarević M., Lane A., Kelly A. & Leekam S. (2016) Sensory subtypes and anxiety in older children and adolescents with autism spectrum disorder. *Autism Research* **9**, 1073–8.

Varni J., Seid M. & Kurtin P. (2001) PedsQL™ 4.0: reliability and validity of the Pediatric Quality Of Life Inventory™ Version 4.0 Generic Core Scales in healthy and patient populations. *Medical Care* **39**, 800–12.

Wall C. A., Hogan A. L., Will E. A., McQuillin S., Kelleher B. L. & Roberts J. E. (2019) Early negative affect in males and females with fragile X syndrome: implications for anxiety and autism. *Journal of Neurodevelopmental Disorders* **11**, 22.

Yehia L., Ni Y., Feng F., Seyfi M., Sadler T., Frazier T. W. *et al.* (2019) Distinct alterations in tricarboxylic acid cycle metabolites associate with cancer and autism phenotypes in Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome. *American Journal of Human Genetics* **105**, 813–21.

Accepted 13 February 2024