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Poole, R.L.; Bijlsma, E.K.; Houge, G.; Jones, G.; Mikstiene, V.; Preiksaitiene, E.; ... ; Tatton-Brown, K.

The *PHF21A* neurodevelopmental disorder: an evaluation of clinical data from 13 patients

Rebecca L. Poole[a], Emilia K. Bijlsma[b], Gunnar Houge[c], Gabriela Jones[d], Violeta Mikštienė[e], Eglė Preikšaitienė[e], Louise Thompson[a] and Katrina Tatton-Brown[f,g]

Potocki–Shaffer syndrome (PSS) is a rare neurodevelopmental disorder caused by deletions involving the 11p11.2-p12 region, encompassing the plant homeodomain finger protein 21A (*PHF21A*) gene. *PHF21A* has an important role in epigenetic regulation and *PHF21A* variants have previously been associated with a specific disorder that, whilst sharing some features of PSS, has notable differences. This study aims to expand the phenotype, particularly in relation to overgrowth, associated with *PHF21A* variants. Analysis of phenotypic data was undertaken on 13 individuals with *PHF21A* constitutional variants including four individuals described in the current series. Of those individuals where data were recorded, postnatal overgrowth was reported in 5/6 (83%). In addition, all had both an intellectual disability and behavioural issues. Frequent associations included postnatal hypotonia (7/11, 64%); and at least one afebrile seizure episode (6/12, 50%). Although a recognizable facial gestalt was not associated, subtle dysmorphic features were shared amongst some individuals and included a tall broad forehead, broad nasal tip, anteverted nares and full cheeks. We provide further insight into the emerging neurodevelopmental syndrome associated with PHF21A disruption. We present some evidence that *PHF21A* might be considered a new member of the overgrowth-intellectual disability syndrome (OGID) family.

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[a]South East of Scotland Clinical Genetics Service, Western General Hospital, Edinburgh, UK, [b]Department of Clinical Genetics, Leiden University Medical Centre, Leiden, The Netherlands, [c]Department of Medical Genetics, Haukeland University Hospital, Bergen, Norway, [d]Nottingham Clinical Genetics Service, Nottingham City Hospital, Nottingham, UK, [e]Department of Human and Medical Genetics, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University, Vilnius, Lithuania, [f]St George's University of London and [g]South West Thames Regional Genetics Department, St George's University Hospitals NHS Foundation Trust, London, UK

Correspondence to Katrina Tatton-Brown, BMBCh MD, South West Thames Regional Genetics Department, St George's University Hospitals NHS Foundation Trust, London SW17 0QT, UK
Tel: +0208 725 0572; e-mail: k.tattonbrown@nhs.net

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Introduction

The plant homeodomain finger protein 21A (*PHF21A*) gene, at chromosome position 11p11.2, encodes the protein PHF21A, also known as BHC80 (Hakimi *et al*., 2002). This protein is a component of the BRAF35/histone deacetylase complex, known as BHC, which has an important role in the repression of neurone-specific genes (Iwase *et al*., 2004). The BHC acts via both histone deacetylation and histone demethylation, the latter alongside the KDM1A complex (or Lysine Specific Demethylase 1-Corepressor of REST, LSD1-CoREST), to catalyse the demethylation of mono- and di-methylated histone H3 lysine 4 (H3K4me1/2) (Lee *et al*., 2005).

Potocki–Shaffer syndrome (PSS) (OMIM 601224) is a rare neurodevelopmental disorder caused by a range of deletions that involve the 11p11.2-p12 region and encompass the *PHF21A* gene (Potocki & Shaffer, 1996; Labonne *et al*., 2015). The characteristic PSS phenotype includes enlarged biparietal foramina, multiple exostoses, intellectual disability, brachycephaly, microcephaly, genitourinary anomalies, strabismus, nystagmus, epilepsy and tapering fingers. Characteristic facial features include a broad and tall forehead, a downturned mouth, a prominent nasal bridge and a short upturned nose with a broad tip and hypoplastic alae nasi (Shaffer *et al*., 1993; Bartsch *et al*., 1996; Swarr *et al*., 2010; Montgomery *et al*., 2013; McCool *et al*., 2017; Trajkova *et al*., 2020).

More recently, frameshift, nonsense and missense *PHF21A* variants, which are predicted to disrupt/alter the normal function of PHF21A, have been shown to cause a specific disorder that shares some features of PSS but has notable differences. To date, 10 unrelated individuals with a neurodevelopmental disorder and constitutional *PHF21A* variants have been reported in two separate case series (Hamanaka *et al*., 2019; Kim *et al*., 2019). Clinical features shared with PSS include intellectual disability, behavioural problems (including autism spectrum disorder), epilepsy and tapering fingers. However, individuals

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with constitutional *PHF21A* variants were recognised to have macrocephaly, whereas microcephaly had been observed in PSS. Other features typical of PSS were notably absent from the single gene *PHF21A* cohort, including enlarged biparietal foramina and multiple exostoses, supporting the authors' conclusion that these features were caused by *ALX4* and *EXT2* respectively, also in the PSS deleted region (Hamanaka *et al*., 2019; Kim *et al*., 2019).

Overgrowth [defined as height and/or head circumference at least two standard deviations (SDs) above the mean (Tatton-Brown *et al*., 2017)] has not yet been described in any of the reports of PSS. However, of the five previously reported individuals with intragenic *PHF21A* variants where both height and head circumference were described, three individuals were overgrown (Case 3, Hamanaka *et al*., 2019; and Patients 1 and 2, Kim *et al*., 2019).

The current series of four individuals, including one previously reported individual (Case 3, Hamanaka *et al*., 2019), were recruited via Clinical Genetics centres in the UK and the Netherlands. We combined data from these four individuals with data from nine other previously reported individuals. On the basis of the evaluation of data from a total of 13 individuals with *PHF21A* variants, we aim to define the phenotype associated with disruption of *PHF21A* and in particular, investigate whether overgrowth is a key characteristic of this emerging neurodevelopmental disorder.

Methods

Three individuals with constitutional *PHF21A* variants were identified via the Deciphering Developmental Disorders study (04/MRE05/50). Data from one of these three individuals (Patient 1) had previously been reported (Case 3, Hamanaka *et al*., 2019). A further individual was recruited from the UK and had previously undergone diagnostic genetic testing at the Center for Human Genetics and Laboratory Diagnostics, Martinsried, Munich, Germany. Individuals were eligible for inclusion in the study if a likely pathogenic or pathogenic *PHF21A* variant had been identified in lymphocyte- or saliva-derived DNA and no additional pathogenic or likely pathogenic single gene/copy number variants had been identified. All *PHF21A* variants were reported with reference to the Matched Annotation from National Centre for Biotechnology Information and European Molecular Biology Laboratory- European Bioinformatics Institute select canonical transcript NM_001352027.3 and were identified through whole exome sequencing (Wright *et al*., 2015). Three out of the four variants were shown to have arisen *de novo* and the inheritance of one variant was unknown (Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/CD/A22*). The *PHF21A* variants were classified using the American College of Medical Genetics and Genomics framework (Richards *et al*., 2015) and Association for Clinical Genomic Science best practice guidelines (Ellard *et al*., 2020) with evidence summarised in Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/CD/A22*.

Consent for publication was obtained from all individuals and consent to publish photographs was requested from all and obtained from two individuals. Phenotypic data were collected through a standardised proforma and clinic review by at least one of the study authors. Anthropometric data included birth and postnatal head circumference, height and weight measurements. *Z* scores were calculated with reference to the UK 1990 and the UK-WHO Child Growth Standards (Freeman *et al*., 1995; Cole *et al*., 1998).

Intellectual disability was defined according to developmental milestones and the level of educational support required in childhood. In general, a child with a mild intellectual disability had delayed developmental milestones and attended mainstream school. A child with a moderate intellectual disability attended a special educational needs school or required significant support in mainstream school. A child with a severe intellectual disability attended a special educational needs school and struggled with speech and language, and daily activities.

Results

Patient 1 (Decipher ID 328685)

Patient 1 is a 9.5-year-old boy from Norway, previously reported as Case 3 by Hamanaka *et al*. (2019). He was born at 39 weeks' gestation following an uncomplicated pregnancy, with a birth weight of 3.8 kg (0.5 SD) and a head circumference of 36 cm (0.9 SD). There were no neonatal health complications. He walked age-appropriately at 18 months; however, fine motor and language development was delayed. At 9.5 years of age, he struggled with his handwriting and, whilst bilingual, he had delayed expressive language, with specific difficulties with articulation. No difficulties in social development were reported; however, he was delayed in activities of daily living such as dressing independently. He received extra help at school for a mild intellectual disability and attention deficit. He had a large appetite, prompting reviews with a dietician.

There was no known significant family history.

On examination, he had mild hypotonia, with some difficulties with balance and coordination. Facial photographs were not available but mild dysmorphic facial features were reported, including hypertelorism, a broad nasal bridge and downturned corners of the mouth. His growth parameters at 8 years of age were as follows: head circumference 57.2 cm (2.1 SD); weight 47.5 kg (3.2 SD); and height 143 cm (2.8 SD) (Table 1). Further data on serial growth parameters are shown in Supplementary Table 2, Supplemental digital content 2, *http://links.lww.com/CD/A23*.

Table 1 Summary of all reported cases showing genetic and phenotypic data, including most recent growth parameters and presence of overgrowth

Nucleotide change	Protein consequence	Intellect. disability	Birth weight/ SD	Postnatal growth/SD					Over-growth[a]	Brain MRI scan	Postnatal hypotonia	Behavioural problems	Additional features	Reference
				Age/year	Weight	Height	Head circumference	BMI						
c.657_658insAA[c] c.660_661insAA[b,d]	**p.(Pro220AsnfsTer48)/p.(Pro221AsnfsTer48)**	**Mild**	**0.5**	**8.0**	**3.2**	**2.8**	**2.1**	**2.9**	**Yes**	**Normal**	**Yes**	**ADHD**	**Difficulties with balance and coordination; large appetite**	**Hamanaka *et al.* (2019, Case 3)/ Current series, Patient 1**
c.706C>T[d]	**p.(Arg236Ter)**	**Mild**	**1.5**	**11.0**	**3.4**	**2.7**	**2.1**	**3.1**	**Yes**	**Small dilated caval septum**	**Yes**	**Anxiety; aggressive behaviour; hyperactivity; immature**	**Hypermobility; constipation; large appetite; one café au lait; afebrile tonic clinic seizure; tapering fingers**	**Current series, Patient 3**
c.959_967delinsTTACA[d]	**p.(Gln320LeufsTer53)**	**Mild**	**1.3**	**3.7**	**ND**	**ND**	**1.4**	**ND**	**ND**	**Arachnoid cyst**	**No**	**Anxiety; ADHD**	**Naevus flammeus; fetal finger pads**	**Current series, Patient 2**
c.1220dupC[c]	p.(Glu408ArgfsTer3)	Severe	1.0	3.0	2.0	1.0	ND	2.0	ND	ND	Yes	ND	Infantile spasms – West syndrome; metopic ridge/suture	Hamanaka *et al.* (2019, Case 1)
c.1285G>A[c]	p.(Gly429Ser)	Unclass	0.7	2.0	2.1	2.6	1.3	0.9	Yes	Normal	Yes	Motor agitation; frequent screams	Infantile spasms, EEG showed hypsarrythmia; myopia	Kim *et al.* (2019, Patient 2)
c.1471dupT[c]	p.(Cys491LeufsX81)	Moderate	0.7	17.8	3.4	−0.9	ND	3.5	ND	Normal	No	ADHD; bipolar disorder; ASD	Recurrent ear infections; obstructive sleep apnoea	Kim *et al.* (2019, Patient 5)
c.1738C>T[c]	p.(Arg580Ter)	Unclass	ND	5.0	ND	ND	1.5	ND	ND	ND	ND	Irritability; hyperactivity; self-harming; autistic traits	Metopic ridge/suture	Hamanaka *et al.* (2019, Case 2)
c.1738C>T[c]	p.(Arg580Ter)	Mild	ND	ND	ND	ND	ND	ND	ND	Normal	ND	ADHD	Multiple generalised tonic-clonic seizures; hip dysplasia	Kim *et al.* (2019, Patient 4)
c.1738C>T[c]	p.(Arg580Ter)	Moderate	2.2	5.3	1.6	0.4	0.9	2.0	No	Normal	No	Anxiety	Recurrent ear infections; constipation	Kim *et al.* (2019, Patient 6)
c.1741C>T[d]	**p.(Arg581Ter)**	**Moderate**	**−0.8**	**8.5**	**1.5**	**0.2**	**ND**	**1.8**	**ND**	**Normal**	**Yes**	**Under investigation for ASD and ADHD**	**Constipation, two episodes of eye-rolling, normal EEG; one café au lait; pes planus**	**Current series, Patient 4**
c.1955delC[c]	p.(Pro652LeufsX104)	Mild	1.3	11.0	2.0	2.2	3.1	1.4	Yes	Normal	Yes	Anxiety, ADHD	Focal epilepsy with complex partial seizures; repetitive movements and hand wringing; immature social skills	Kim *et al.* (2019, Patient 1)
c.1956delT[c]	p.(Pro652ProfsX104)	Unclassified[e]	0.0	ND	ND	ND	ND	ND	ND	Normal	Yes	Anxiety; aggressive behaviour; crying	Seizures – eye blinking and eye-rolling, EEG- confirmed seizure activity precipitated by eye closure, occurring diffusely over occipital region; sleep disturbance	Kim *et al.* (2019, Patient 3)
c.204delA[c]	p.(Gln675ArgfsX81)	Moderate	−0.8	18.0	2.7	−1.8	2.0	3.3	Yes	Normal	No	Anxiety; OCD; one episode of disinhibited behaviour	Binge eating; large appetite; skin picking lesions; periodic echolalia	Kim *et al.* (2019, Patient 7)

Patients in the current study are shown in bold.

ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; CT, computed tomography; EEG, electroencephalogram; OCD, obsessive-compulsive disorder.

[a]Overgrowth defined as height and/or head circumference at least two SDs above the mean.

[b]Reported on different transcripts.

[c]Reported on transcript NM_001101802.1.

[d]Reported on Matched Annotation from NCBI and EMBL-EBI (MANE) select transcript NM_001352027.3.

[e]Intellectual disability present but severity not reported.

He had an advanced skeletal age of 3 years and 6 months, at a chronological age of 2 years and 8 months (Tanner and Whitehouse). A brain MRI scan at 4 years of age was normal. Trio whole exome sequencing identified a de-novo *PHF21A* frameshift variant, c.660_661insAA p.(Pro221AsnfsTer48) (Table 1 and Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/CD/A22*).

Patient 2 (Decipher ID 384482)

Patient 2 is a 5.5-year-old boy from the Netherlands. He was born at 38 + 6 weeks gestation following an uncomplicated pregnancy. His birth weight was 4.15 kg (1.3 SD). He developed jaundice in the neonatal period, which resolved without specific therapy. He had a mild intellectual disability and behavioural problems, which included hyperactivity, a short attention span and an anxiety disorder including fear of loud noises. There was no history of seizures.

There was no known significant family history.

On examination, he had a tall broad forehead with a nevus flammeus, hypertelorism, almond-shaped eyes, a small right ear with an overfolded helix and a tented upper lip (Fig. 1a). He had foetal finger pads. At 2.6 years, his height was 97 cm (1.3 SD) and at 3.3 years his weight was 18 kg (1.5 SD). His head circumference at 3.7 years was 52 cm (1.4 SD) (Table 1). Further data on serial growth parameters are shown in Supplementary Table 2, Supplemental digital content 2, *http://links.lww.com/CD/A23*.

An incidental finding of a small arachnoid cyst was reported on a brain MRI scan that was otherwise normal. Trio whole exome sequencing identified a de-novo *PHF21A* frameshift variant, c.959_967delinsTTACA p.(Gln320LeufsTer53) (Table 1 and Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/CD/A22*).

Patient 3 (Decipher ID 301795)

Patient 3 is an 11-year-old girl from the UK. She was born at 38 weeks following an uncomplicated pregnancy via an emergency caesarean section for reduced foetal movements. Her birth weight was 3.67 kg (1.5 SD). She had no major problems in the neonatal period. She was noted to have an innocent heart murmur on auscultation and was reported to have had normal echocardiography by her mother. Her development was delayed from the first year of life. She sat without support at 19 months, crawled at 22 months, and walked independently at 24 months. Her first words were at 3 years of age. She had an anxiety disorder and additionally exhibited aggressive behaviours, hyperactivity and immaturity for her age. She was frequently hungry/thought about food. She was often constipated and had had one afebrile tonic-clonic seizure at 8 years of age, which was attributed to a possible vasovagal event.

There was no known significant family history.

On examination at 4 years of age, she had joint laxity and hypotonia, with flat foot and calcaneovalgus foot deformity. She had a café au lait macule on her buttock and no other pigmentary or vascular anomalies. Facial features included a tall broad forehead, almond-shaped eyes and a broad nasal tip with anteverted nares (Fig. 1b). Her growth parameters at 11.1 years were head circumference 56.8 cm (2.1 SD); height 163 cm (2.7 SD); and weight 80.9 kg (3.4 SD) (Table 1). Further data on serial growth parameters are shown in Supplementary Table 2, Supplemental digital content 2, *http://links.lww.com/CD/A23*.

A brain MRI scan at 5.8 years of age demonstrated a dilated caval septum and no other abnormality. A de-novo *PHF21A* stop-gain variant, c.706C > T p.(Arg236Ter) was identified through trio whole exome sequencing (Table 1 and Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/CD/A22*).

Patient 4

Patient 4 was an 8.5-year-old girl from the UK. She was born at 40 + 3 weeks following an uncomplicated pregnancy, with a birthweight of 3.09 kg (–0.8 SD). There were no known antenatal or neonatal complications. She had a moderate intellectual disability and was under investigation for possible autism spectrum disorder and attention deficit hyperactivity disorder. She was described as emotionally/socially unaware with poor concentration, and repetitive and sensory behaviours. She had hypotonia and constipation. As a young child, she was investigated for two episodes of eye-rolling and had a normal electroencephalogram. There have been no further episodes since the age of 6 years old.

There was no known significant family history.

On examination, she had flat foot and one café au lait macule on her lower back. She had some subtle dysmorphism with busy eyebrows medially and a broad nasal tip. Head circumference at 6 years and 4 months of age was 49.5 cm (–2.4 SD) but no subsequent head circumference measurements were available. Height at 8.5 years was 131.3 cm (0.2 SD) and weight was 36 kg (1.5 SD) (Table 1). Further data on serial growth parameters are shown in Supplementary Table 2, Supplemental digital content 2, *http://links.lww.com/CD/A23*.

Patient 4 had a brain MRI scan at age 6 years of age, which was reported as normal. Diagnostic testing by the Centre for Human Genetics and Laboratory Diagnostics, Germany, identified a stop-gain *PHF21A* variant, c.1741C > T p.(Arg581Ter) (Table 1 and Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/CD/A22*). The inheritance of the variant is unknown.

Discussion

This descriptive case series of four individuals, including one previously reported individual (Case 3, Hamanaka *et al.*, 2019), brings the total number of individuals with heterozygous *PHF21A* variants to 13 and provides further insight into this emerging neurodevelopmental syndrome. We have combined and evaluated data from these 13 individuals to expand the *PHF21A*-associated phenotype. Of interest, we provide some evidence that *PHF21A* might be considered the newest member of the growing family of genes that can cause an overgrowth-intellectual disability (OGID) syndrome.

Overgrowth, defined as height and/or head circumference at least two SDs above the mean (Tatton-Brown and Weksberg, 2013) was reported in five of the six (83%) individuals for whom growth data were available (Table 1). Two of these individuals were tall/macrocephalic; two were just tall and one was just macrocephalic. Birthweight, used as a proxy for prenatal growth, was normal in 10/11 (91%) individuals (Table 1). A raised BMI of at least two SDs above the mean was present in 6/9 (67%) of individuals of whom two also had tall stature, suggesting weight is unlikely to be the driver of the overgrowth (Table 1).

An intellectual disability was reported in all 13 individuals and was mild in 5/10 (50%); moderate in 5/10 (50%); severe in 1/10 (10%) and unclassified in three individuals. Additional phenotypic associations (derived from data reported in at least 11 individuals) included behavioural problems in 12/12 (100%), of which anxiety was the most frequently reported behavioural issue; postnatal hypotonia in 7/11 (64%); and at least one afebrile seizure episode was mentioned in 6/12 (50%). (Table 1).

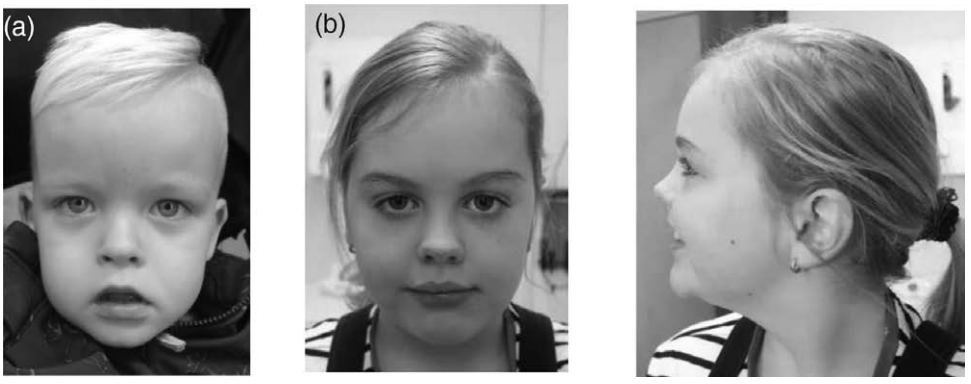
Where available, published clinical photographs were reviewed for a total of eight individuals (Patients 2 and 3 from the current study, Case 1 in Hamanaka *et al.* and Patients 1–4 and 6 in Kim *et al.*). We were unable to fully assess the eyes of two of these individuals. There was not a recognisable gestalt associated with constitutional *PHF21A* variants; however, subtle shared dysmorphic features amongst some individuals included frontal bossing, a tall, broad forehead, anteverted nares, broad nasal tip and full cheeks.

PSS, caused by the deletion of *PHF21A* and varying numbers of neighbouring genes, is a well recognised neurodevelopmental disorder including some features that overlap with the neurodevelopmental disorder associated with *PHF21A* intragenic variants (*PHF21A* neurodevelopmental disorder). Whilst complete growth data are not available, overgrowth does not appear to be a feature of PSS; rather microcephaly was reported in 3/6 (50%) of individuals (Swarr *et al.*, 2010) and growth retardation in 5/10 (Trajkova *et al.*, 2020). Given that 11/12 variants reported in this current series are predicted to result in loss of protein through triggering nonsense-mediated RNA decay, it is surprising that overgrowth should not be a feature of both conditions.

This work supports previous conclusions that disruption of the *PHF21A* gene causes or at least contributes to intellectual disability in individuals with PSS (Kim *et al.*, 2012; Montgomery *et al.*, 2013; Labonne *et al.*, 2015; McCool *et al.*, 2017). *PHF21A* has a high pLI (probability of loss of function intolerance) score of 1.0, indicating it is intolerant to loss of function variation. It is possible that overgrowth is caused by the deletion of *PHF21A* in PSS but is offset by other deleted genes in the PSS region, for example, *EXT2* and *ALX4*, or the greater genomic insult of a large deletion. However, further work is required to explore this and confirm that overgrowth is a major feature of the *PHF21A*-neurodevelopmental disorder.

PHF21A is a histone methyltransferase (with H3K36 specificity) associated with transcriptional repression. Given this role, it would be interesting to undertake episignature mapping to identify possible DNA methylation episignatures,

Fig. 1



(a) Facial appearance of Patient 2 aged 3 years and (b) Patient 3 aged 9.6 years. Facial features include frontal bossing with a tall, broad forehead, mild hypertelorism, eversion of the lateral lower eyelid, full cheeks, almond-shaped eyes and a broad nasal tip with anteverted nares.

both for individuals with PHF21A-related neurodevelopmental disorder and PSS. The epigenetic regulator genes, including *NSD1*, *EZH2*, *DNMT3A*, *EED*, *CHD8* and *HIST1H1E*, are a major cause of the OGID syndromes and are associated with detectable DNA methylation episignatures (Aref-Eshghi *et al*., 2020). Current, albeit limited data, indicate that *PHF21A* may be the newest member of the epigenetic regulator OGID syndrome genes.

Our assessment of the phenotype associated with *PHF21A* disruption in the current series of four individuals, and integration with reported cases, provides further evidence for an association with a distinct neurodevelopmental disorder and highlights an emerging association with intellectual disability, behavioural problems, anxiety, hypotonia, a large appetite, characteristic facial features and possible overgrowth. Our findings are in keeping with previous work highlighting disruption of epigenetic regulation as a key mechanism of overgrowth with intellectual disability (Tatton-Brown *et al*., 2017).

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Conflicts of interest

There are no conflicts of interest.

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