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SHORT REPORT

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Pathogenic variants in *SOX11* mimicking Pitt-Hopkins syndrome phenotype

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Abstract

Pitt-Hopkins syndrome (PTHS) is a rare neurodevelopmental disorder characterised by severe intellectual disability (ID), distinctive facial features and autonomic nervous system dysfunction, caused by *TCF4* haploinsufficiency. We clinically diagnosed with PTHS a 14 $^{6/12}$-year-old female, who had a normal status of *TCF4*. The pathogenic c.667del (p.Asp223MetfsTer45) variant in *SOX11* was identified through whole exome sequencing (WES). *SOX11* variants were initially reported to cause Coffin-Siris syndrome (CSS), characterised by growth restriction, moderate ID, coarse face, hypertrichosis and hypoplastic nails. However, recent studies have provided evidence that they give rise to a distinct neurodevelopmental disorder. To date, *SOX11* variants are associated with a variable phenotype, which has been described to resemble CSS in some cases, but never PTHS. By reviewing both clinically and genetically 32 out of 82 subjects reported in the literature with *SOX11* variants, for whom detailed information are provided, we found that 7/32 (22%) had a clinical presentation overlapping PTHS. Furthermore, we made a confirmation that overall *SOX11* abnormalities feature a distinctive disorder characterised by severe ID, high incidence of microcephaly and low frequency of congenital malformations. Purpose of the present report is to enhance the role of clinical genetics in assessing the individual diagnosis after WES results.

KEYWORDS
neurodevelopmental disorders, Pitt-Hopkins syndrome, *SOX11*, whole exome sequencing

1 | INTRODUCTION

Pitt-Hopkins syndrome (PTHS) (OMIM #610954) is a rare neurodevelopmental disorder caused by sequence variants or deletions of *TCF4*, located at 18q21.2 (TCF4, OMIM *602272). Clinically, it is characterised by severe intellectual disability (ID) with absent speech, a distinctive facial phenotype, postnatal microcephaly, epilepsy, autonomic nervous system dysfunction, mainly breathing and intestinal mobility alterations, ophthalmologic anomalies and high risk of autism.[1] Differential diagnosis of PTHS includes a number of neurodevelopmental

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disorders with severe ID and microcephaly, mainly Mowat-Wilson, Rett, and Angelman syndromes.[2] Of note, BAFophies, a group of conditions caused by pathogenic variants in genes coding for the subunits of the BAF complex, are not usually mentioned in the differential diagnosis of PTHS. Coffin-Siris syndrome (CSS, OMIM #135900), which is considered the paradigm of BAFopathies, appears to differ from PTHS. Main clinical manifestations in CSS include moderate developmental delay, hypotonia, coarse facial appearance, hirsutism, hypoplastic/absent fifth distal phalanges, growth restriction, hearing loss and multi-organ malformations.[3]

CSS has been associated with *ARID1B* variants in most patients and *ARID1A*, *SMARCB1*, *SMARCA4*, *SMARCE1*, *ARID2*, *DPF2*, *MARCC2*, *SMARCD1* variants in fewer. Notably, *SOX11* variants were described to cause CSS,[4] leading to consider that the BAF complex and *SOX11* interact in a common pathway. However, with the increasing number of cases described, clinical manifestations of *SOX11* patients appear to differ from CSS. Supporting this clinical evidence, methylation of blood DNA in *SOX11* patients has recently been reported not to match the classic BAFopathy episignature.[5]

Here we describe a patient with a loss-of-function variant in *SOX11* who had a clinical presentation fully consistent with PTHS, and we review the data of patients with *SOX11* mutations reported in the literature.

2 | METHODS

2.1 | Clinical report

Our patient is a 14 $^{6/12}$-year-old female of Italian ancestry, second child of healthy non-consanguineous parents. Her older brother is healthy. Pregnancy was uneventful until 38 weeks, when the delivery occurred by caesarean section due to foetal bradycardia. Measures at birth were reported normal. The mother did not take any medications during or shortly prior to pregnancy or while breastfeeding the baby. The patient experienced motor delay and could walk unsupported at 20 months. She was diagnosed with severe developmental delay during the second year of life. She suffered from a unique episode of febrile seizures as a child. Sleep apnoea, hand stereotypies, constipation and ataxic gait are referred from early infancy on. A friendly behaviour is described, along with a tendency towards isolation. Brain MRI and CT scan of heart and kidneys gave normal results.

We first saw her at age 5 $^{8/12}$ years. Height (H) was 103 cm (−2.2 SD), weight (W) 12.7 kg (−3 SD) and occipital-frontal circumference (OFC) 45.7 cm (−3.8 SD). Distinctive facial features were noted, including high and squared forehead, pencilled eyebrows, up slanted palpebral fissures, wide nasal bridge, wide mouth with tented and M-shaped upper lip, full cheeks, cup-shaped auricles and tapered fingers. Additional clinical manifestations included strabismus and sleep disturbances.

Genetic investigations firstly included NGS analysis of *TCF4*, *CNTNAP2*, *NRXN1*, *UBE3A*, *SLC9A6*, *MECP2*, *CDKL5*, *FOXG1*, *MEF2C*, *ZEB2*,*ATRX*; MLPA analysis of *TCF4*, *FOXG1* and *MECP2*; MS-MLPA analysis of region 15q11q13, conventional karyotyping and array-CGH, resulted all normal. A tentative diagnosis of PTHS was made, clinically.

FIGURE 1 Frontal and lateral view of our patient at age 14 $^{6/12}$ years. [Colour figure can be viewed at wileyonlinelibrary.com]

She underwent a new clinical evaluation at age 14 $^{6/12}$ years. H was 135 cm (−4 SD), W 29 Kg (−4 DS), and OFC 47.7 cm (−4 DS). The same facial dysmorphisms were noted, slightly worsened with age (Figure 1).

She presented with ataxic gait and poor motor coordination. She is currently nonverbal. A formal IQ assessment could not be done, however ID was unequivocally severe. She was enrolled in the research program for Undiagnosed Diseases supported by Telethon Foundation.

3 | GENETIC ANALYSES

Array-CGH analysis on DNA from peripheral blood cells was performed by means of the commercial Agilent 2×244 kit (following manufacturer's instructions).

Conventional karyotyping was performed by R(RBG) banding on metaphases by peripheral blood lymphocytes according to standard procedures.

MLPA analysis was performed by SALSA kit P075-A1 lot.0909 for *TCF4* and *FOXG1* and SALSA kit P015-F1 lot.0315 for *MECP2* (MRC Holland, Amsterdam, the Netherlands).

MS-MLPA of the 15q11q13 region was performed following manufacturer's instructions.

The whole exome of the proband and the mother (father not available) was enriched using the SureSelect QXT Target Enrichment system (Agilent Technologies, Santa Clara, CA, USA), according to the manufacturer's instructions. The libraries were then sequenced on the NovaSeq 6000 Sequencing System (Illumina Inc., San Diego, CA, USA) making use of NovaSeq 6000 S4 Reagent Kit (300 cycles) (IlluminaInc., San Diego, CA, USA), generating 150 bp-long paired-end reads. The average exome coverage of the target bases of at least 100X with 90% of the bases covered by at least 40 reads. Read

TABLE 1 Schematic representation of the phenotype of the seven published patients with *SOX11* pathogenic variants and PTHS diagnostic score ≥6.

Patient # (see Table S1)		**1**	**4**	**5**	**10**	**18**	**29**	**32**
Reference		Present study	Okamoto et al	Hempel et al #1	Hempel et al #8	Al-Jawahiri et al #8	Diel	Wakim
Genomic variant		c.667del p.Asp223Metfs*45	c.305C>T p.Ala102Val	2p25 (4291420-6905655)x1	c.359C>A p.Pro120His	c.259T>C p.Trp87Arg	c.251G>T p.Gly84Val	c.146T>A p.Ile49Asn
4 pts (at least three of seven)	Narrow forehead							
	Thin lateral eyebrows							
	Wide nasal bridge/ridge/tip							
	Flared nasal alae							
	Full cheeks/prominent midface							
	Wide mouth/full lips/cupid bow upper lip							
	Thickened/overfolded helices							
2 pts	Severe ID with absent speech							
2 pts	Breathing anomalies							
1 pt	Myopia							
1 pt	Constipation							
1 pt	Slender fingers/abnormal palmar creases							
1 pt	Unstable gait							
	PTHS CLINICAL SCORE	10	6–10	6–11	6–11	6–8	7–9	7–11

Note: Dark grey square: present; light grey square: not reported; white square: absent. The clinical diagnostic criteria for PTHS are based on Zollino et al report.[1]

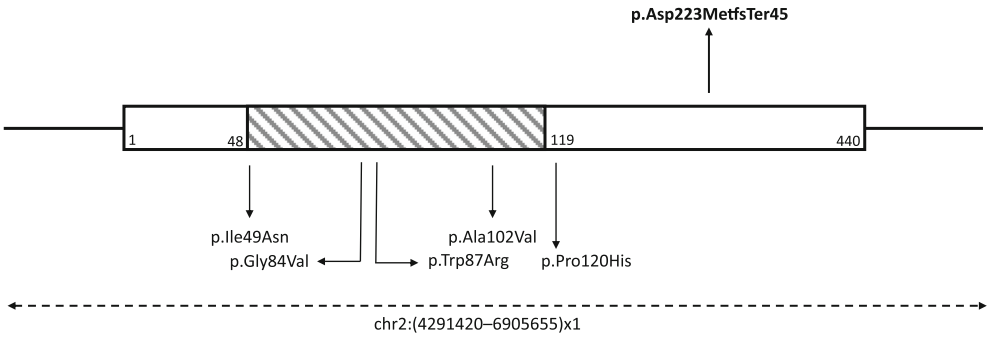

FIGURE 2 Schematic representation of *SOX11* variant in patients with PTHS clinical score ≥6. Stop-gain variant of our proband is shown above; missense variants are shown below. The striped box indicates the high-mobility group domain; the dotted line indicates the whole-gene deletions in patient 5 (see Table S1).

processing and variant calling were performed using VarGenius pipeline.[6] Sanger Sequencing validation was performed.

4 | RESULTS

4.1 | Genetics

WES in the proband showed the NM_003108.4: c.667del (p.Asp223MetfsTer45) variant in *SOX11*. The variant was absent in the mother and was classified as likely pathogenic according to the ACMG guidelines.

4.2 | Revision of *SOX11* patients reported in the literature

Literature deals with a total of 82 subjects with pathogenic variants in *SOX11*, including complete gene deletions (14%), missense (74%) and loss-of-function (12%) variants.[4,5,7–19] Detailed clinical information and clinical pictures were available for 32/82 subjects, including our patient. We found that 17/32 patients (53%) presented with facial characteristics consistent with PTHS. Of them, 7/17 also had severe ID with absent speech, while the remaining 10 presented with moderate ID and preserved language ability. Thus, both the facial and the neurodevelopmental phenotype was consistent with PTHS in 7/32 subjects (22%) (Table S1; Table 1). In spite of the limited number of patients, it is worth noting that frequencies of missense, loss-of-function variants and whole gene deletion in this group (Figure 2) are 72% (5/7), 14% (1/7) and 14% (1/7), respectively, overlapping those of all reported *SOX11* patients.

Regardless of facial dysmorphisms, the frequency of the most significant clinical features – reported in at least 40 patients, with the exception of hypertrichosis – was assessed; results are presented in Table S2. Severe ID is recorded in 11/43 patients (26%), mild to moderate ID in 22/43 (53.5%); microcephaly in 22/48 (46%); growth restriction in 15/43 (35%); sensorineural hearing loss in 12/48 (25%). Hypertrichosis is described in 6/18 (33%). Hypogonadic hypogonadism was evaluated in 12 subjects, 10 of whom tested positive.

We compared the clinical manifestations of patients with *SOX11* variants with those of a large series of patients with mutations in either *ARID1B*, the most common mutated gene in typical CSS,[20] and *TCF4*, causative of PTHS (Figure 3).

5 | DISCUSSION

We describe here a patient with clinical presentation highly consistent with PTHS, in whom a pathogenic variant in *SOX11* was detected by WES. Clinical features consistent with PTHS were severe ID, the typical facial dysmorphisms, breathing anomalies, ataxic gait with poor motor coordination, constipation, strabismus and stereotypical features. By reviewing literature data of *SOX11* patients with evaluable pictures and detailed clinical description, we found that 7/32 (22%), including our patient, had a clinical presentation overlapping PTHS. Of note, additional 10 patients exhibited the PTHS facial dysmorphisms, but they all had a significantly less severe cognitive impairment.

PTHS is a rare condition, and, accordingly, the clinical diagnosis mostly depends on the centre-specific experience. An international consensus statement has recently been reported[1] not only to avoid the bias of the observer's expertise, but especially for the benefit of reliable diagnosis and management of PTHS patients. This consensus statement is also focused on clinical diagnostic criteria for PTHS; by standardised phenotypic analysis of a great number of patients with a proven mutation in *TCF4*, the most distinctive clinical manifestations were selected, including the most typical facial characteristics, leading to define a clinical score system for PTHS diagnosis. A clinical score >9 is proposed to indicate a convincing diagnosis of PTHS, requiring molecular testing; a score between 6 to 8 to suggest *TCF4* molecular analysis and a score <6 to allow for definitive exclusion of PTHS. Based on that, the clinical score of our patient was 10. The previously described six patients we found with a likely PTHS phenotype had a clinical score of 6. However, this score is potentially higher, considering that some highly sensitive clinical signs, namely myopia, constipation, slender fingers and unstable gait, were not evaluated in these six patients. The remaining 10 subjects with a PTHS phenotype limited to the facial dysmorphisms all scored 4.

Thus, clinical manifestations of a considerable number of subjects with pathogenic variants in *SOX11* fall in the spectrum of PTHS.

In addition, by comparing clinical manifestations of patients reported in the literature with *SOX11* or *ARID1B* variants, we

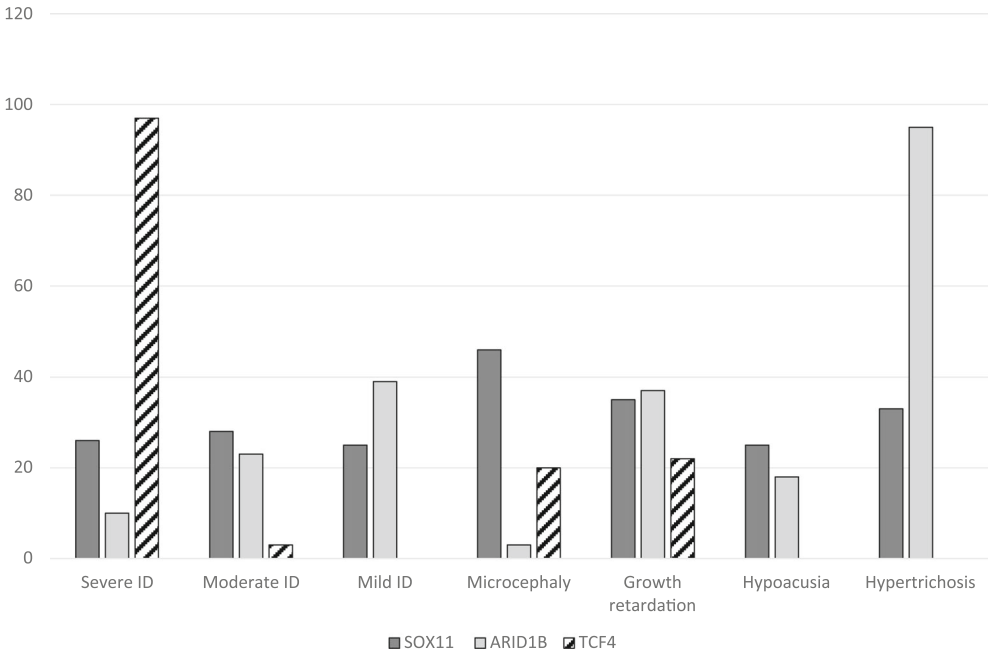

FIGURE 3 Histograms show the comparison of clinical manifestations between patients with *SOX11*, *ARID1B* and *TCF4* variants.

observed that on average *SOX11* mutations cause a distinguishable phenotype characterised by severe ID with high incidence of microcephaly, which differs from CSS, as already demonstrated. Yet, a CSS phenotype can be still noticed in a subset of *SOX11* patients (Figure 3, Table 1 and Table S2).

The molecular bases underlying the clinical diversity of the *SOX11*-associated disorders are still unknown. Remarkably, loss of functions variants located in the only coding exon of *SOX11* might reasonably escape nonsense-mediated mRNA decay, leading to consider that the underlying pathomechanisms could include not only haploinsufficiency but also dominant negative or gain-of-function effects. However, functional studies are needed to validate this hypothesis.

It must be specified that the purpose of these considerations is not to create or disprove clear-cut categories among the highly heterogeneous neurodevelopmental disorders, but to enhance the role of clinical genetics in assessing the precise diagnosis and the precise prognostic evaluation in individual patients, especially when WES results are obtained before a diagnostic hypothesis can be raised clinically.

AUTHOR CONTRIBUTIONS

Domizia Pasquetti and Federica Francesca L'Erario are involved in manuscript writing, literature revision and in creating tables and patient figures. Daniela Orteschi performed array-CGH. Pietro Chiurazzi and Paolo Alfieri contributed to patient case and performed repeated clinical evaluation of the patient. Arianna Panfili and Elena Sonnini contributed to manuscript revision, literature revision and in creating tables and patient figures. TUDP Study Group performed ES analysis. Manuela Morleo and Vincenzo Nigro performed interpretation and validation of ES results. Marcella Zollino was responsible for the study design, is involved in manuscript writing and supervised all the activities.

FUNDING INFORMATION

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/cge.14414.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

ETHICS STATEMENT

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of the Department of Life Sciences and Public Health of Catholic University of Roma, Italy.

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SUPPORTING INFORMATION

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

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