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SHORT REPORT

Expanding the clinical and molecular spectrum of *PRMT7* mutations: 3 additional patients and review

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Protein arginine methyltransferase 7 (PRMT7) is a member of a family of enzymes that catalyze the transfer of methyl groups from S-adenosyl-l-methionine to nitrogen atoms on arginine residues. Arginine methylation is involved in multiple biological processes, such as signal transduction, mRNA splicing, transcriptional control, DNA repair, and protein translocation. Currently, 7 patients have been described harboring compound heterozygous or homozygous variants in the *PRMT7* gene, causing a novel intellectual disability syndrome, known as SBIDDS syndrome (Short Stature, Brachydactyly, Intellectual Developmental Disability, and Seizures).

We report on 3 additional patients from 2 consanguineous families with severe/moderate intellectual disability, short stature, brachydactyly and dysmorphisms. Exome sequencing revealed 2 novel homozygous mutations in *PRMT7*. Our findings expand the clinical and molecular spectrum of homozygous *PRMT7* mutations, associated to the SBIDDS syndrome, showing a possible correlation between the type of mutation and the severity of the phenotype.

KEYWORDS

brachydactyly, intellectual disability, late onset obesity, *PRMT7*, SBIDDS, seizures, short stature

1 | INTRODUCTION

Post-translational modifications (PTMs) are essential mechanisms that eukaryotic cells use to diversify their protein functions and coordinate their signaling networks.[1] Defects in PTMs have been linked to numerous developmental disorders and human diseases, highlighting the importance of PTMs in maintaining normal cellular states. In this study, we report on 3 clinically undiagnosed patients from 2 families (2 males, 1 female). Clinical features included developmental and speech delay combined with dysmorphic features and skeletal defects. Sequence analysis revealed 2 novel homozygous variants in the *PRMT7* gene, encoding a member of the protein arginine N-methyltransferase (PRMTs) family of proteins.[2] PRMTs are enzymes that direct post-translational methylation on targeted arginine residues in eukaryotes and regulate several cellular processes including signal transduction, RNA processing, DNA repair, protein subcellular localization and interactions.[3,4] Among the PRMTs, that generate dimethylarginine, PRMT7 is unique in producing exclusively monomethylarginine products and appears to participate in broad cellular processes under normal and disease conditions, including cancer.[5] Transcriptome analysis of skeletal muscle from wild-type and Prmt7-null mice, showed that 130 distinctive genes involved in skeletal and muscular disorders displayed altered expression in the absence of Prmt7.[6] In addition, PRMT7 plays a role in maintaining the embryonic stem cell stemness[7] and negatively regulates the neuronal differentiation.[8]

Germline *PRMT7* mutations were originally described by Akawi et al in 6 females from 3 families with a novel syndromic intellectual disability condition, characterized by mild intellectual disability, facial dysmorphisms, microcephaly, short stature and brachydactyly.[9] More recently, a male child with severe intellectual disability, seizures and microcephaly, was reported displaying a homozygous deletion

encompassing the transcription start site of *PRMT7* producing a null allele.[10] This disorder is now known as SBIDDS syndrome (Short stature, Brachydactyly, Intellectual Developmental Disability, and Seizures) (OMIM 617157).

The patients reported in this study extend the clinical and mutational spectrum of the *PRMT7*-related disorder, showing a possible genotype/phenotype correlation that can have an impact on clinical management of patients with SBIDDS syndrome.

2 | PATIENTS AND METHODS

2.1 | Family 1

The patient (patient 1) (Figure 1A, 1a–b), a male, was the second child of Italian consanguineous parents (first cousins). A diagnosis of intrauterine growth retardation was made at the 22nd week of gestation. Birth weight was 2050 g (−3.42 SD), length 47 cm (−2.05 SD), occipitofrontal circumference (OFC) 31 cm (−3.13 SD).

Physical examination at 6 months showed all growth parameters below third centile, severe hypotonia, joint laxity, left lower limb shorter than the right, bilateral dacryostenosis, high forehead, hypertelorism, anteverted nares, smooth philtrum, thin upper lip vermilion, thick everted lower lip, mild prognathism, large ears, and cutaneous eczema.

The patient had feeding difficulties, and dysphagia. During the first 3 months of life, the baby had some 'absence' episodes with unremarkable EEGs. Brain magnetic resonance imaging (MRI) showed a cyst containing cerebrospinal fluid localized in the right cerebellopontine angle cistern.

At the most recent assessment, the patient was 3 years and 7 months old. Weight was 11.700 kg, length 90.3 cm, and OFC 47 cm (all <third centile). Developmental milestones were delayed. He had severe intellectual disability accompanied by absent speech and inability to walk. A radiographic skeletal survey showed short hand phalanges, left femur 12 mm shorter than the right, decreased bone mineral density, and bilateral absence of patella (Figure 2, 1a–d). Ophthalmological and audiological examinations, routine biochemical analysis and dosage of thyroid and parathyroid hormones, abdominal ultrasound and 2-dimensional color Doppler echocardiography were normal.

2.2 | Family 2

2.2.1 | Case 1

The patient (patient 2) (Figure 1A, 2a–b), a 21-year-old male, was the first of 2 siblings, born from consanguineous healthy parents of Tunisian origin. Birth weight was 2950 g (−1.32 SD), length 49 cm (−0.98 SD), OFC 34 cm (−0.68 SD). Genetic counseling was requested in the perinatal period because of hypotonia. No feeding problems were noted in the first years of life, while hyperphagia and weight gain have occurred after 15 years of age. Unilateral cryptorchidism was surgically corrected at 4 years old.

Physical examination revealed high forehead, hypertelorism, deep-set eyes, anteverted nares, long philtrum, thick vermilion of the lips, short neck, kyphosis, brachydactyly, and atopic dermatitis.

A radiographic skeletal survey confirmed the brachydactyly of hands and feet with forth and fifth fingers showing markedly reduced metacarpal bones and general short phalanges (Figure 2, 2a-c). Bone age at 17 years of age was delayed. Ocular, hearing assessment, and echocardiogram were normal.

Last evaluation, at 21 years of age, disclosed short stature (160 cm, <third centile, −1.92 SD), overweight (80 kg, 75th centile, +2.23 SD, BMI 31.5), and OFC 54.5 cm (75th centile, −0.41 SD). He had severe intellectual disability, verbal speech limited to a few words, and an autoaggressive behavior. Five seizures were recorded between 4 and 9 years of age. EEG and metabolic screen were normal. Brain MRI revealed a thin corpus callosum and a lipoma in left cerebellopontine angle.

2.2.2 | Case 2

This 15-year-old female (patient 3) (Figure 1A, 3a–b) was the younger sibling of patient 2. Birth weight was 2750 g (−1.72 SD), length 48 cm (−1.31 SD), OFC 33 cm (−1.21 SD). Hypotonia was recorded in the first months of life. No feeding difficulties were noted. Weight gain began after menarche, at 12 years of age. Ocular examination disclosed strabismus, surgically corrected at 4 years old. Audiogram revealed profound sensorineural hearing loss, treated with hearing aids.

At last evaluation, at 15 years of age, growth parameters disclosed short stature (145.5 cm, <third centile, −2.77 SD); overweight (63 kg, 90th centile, +1.54 SD, BMI 30), and OFC 54 cm (50th centile, −0.18 SD). Physical examination revealed the same dysmorphic and cutaneous features observed in her brother, and brachydactyly of hands (Figure 2, 3a–c). Bone age at 8 years was normal. She had moderate intellectual disability and limited verbal speech with poor autonomy for daily life activities. From 6 years of age, she had seizures, which were well controlled with valproic acid (300 mg/daily).

2.3 | Genetic studies

See Appendices S1 and S2 (Supporting information).

3 | RESULTS

3.1 | Family 1

SNP-array analysis in patient 1 identified several long contiguous stretches of homozygosity all over the genome (7.63% of the autosomal genetic material), consistent with a third degree consanguinity and displayed a small microduplication on the long arm of a chromosome 12 (ISCN: arr 12q24.23(118 287 778–118 590 408)×3) which was inherited from the father. Targeted exome sequencing data analysis (Tables S1 and S2), revealed a homozygous private nonsense change, NM_019023.2:c.322G>T, p.(Glu108Ter), in exon 4 of the *PRMT7* gene (Figure 1B). The unaffected parents and the older brother were heterozygous for this mutation.

3.2 | Family 2

Karyotype and high-resolution CGH-array analysis (244 K; Agilent Technologies, Waldbronn, Germany) in patients 2 and 3 were normal.

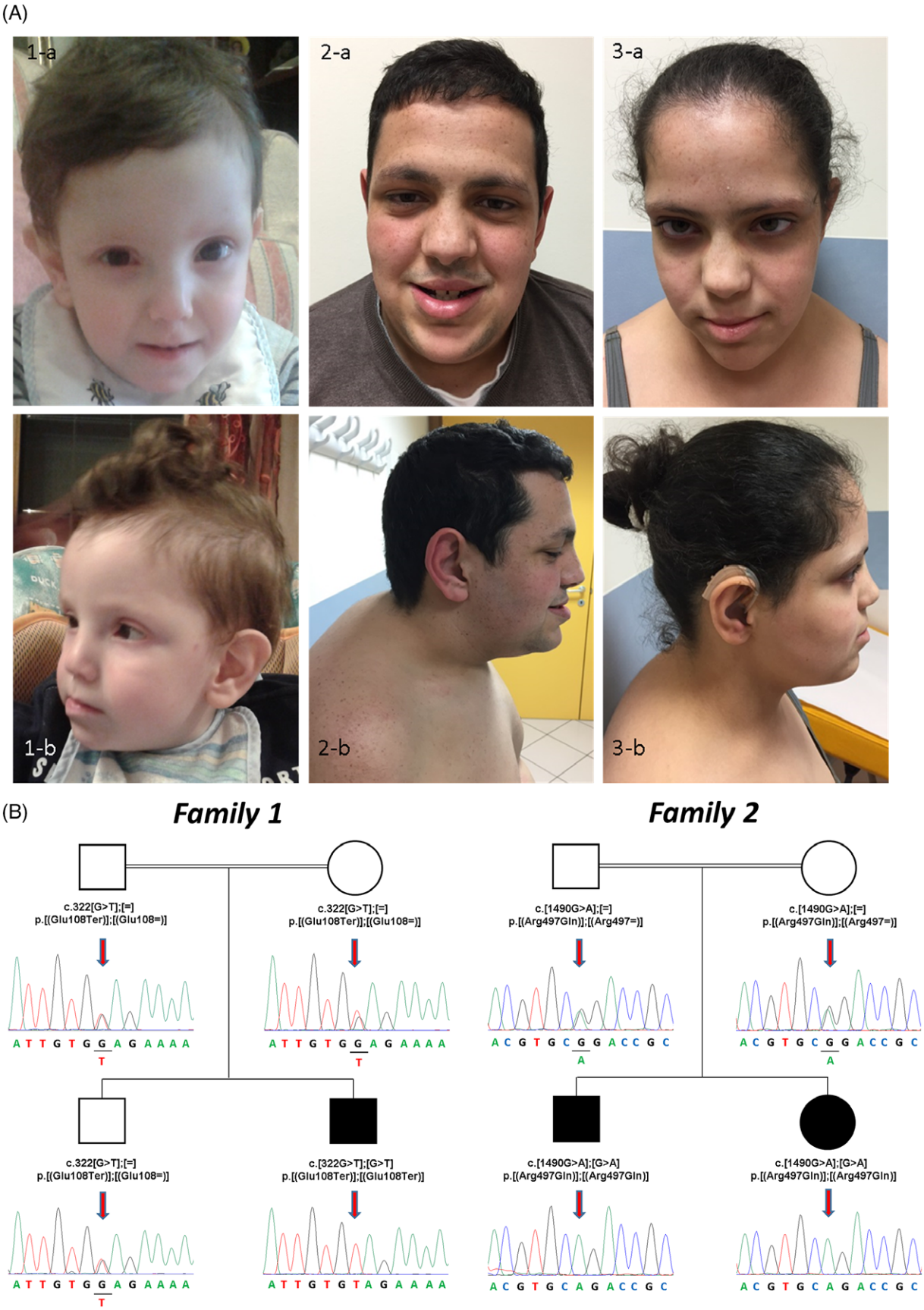

FIGURE 1 A, Craniofacial characteristics of patients with homozygous PRM7T mutations at 1, 21, and 15 years of age, respectively patients 1, 2 and 3: note high forehead, hypertelorism, deep-set eyes, anteverted nostrils, lower everted thick lip, short neck, kyphosis (2-b, 3-b). B, Pedigree and electropherograms of PRMT7 variants identified in the 2 families. [Color figure can be viewed at wileyonlinelibrary.com]

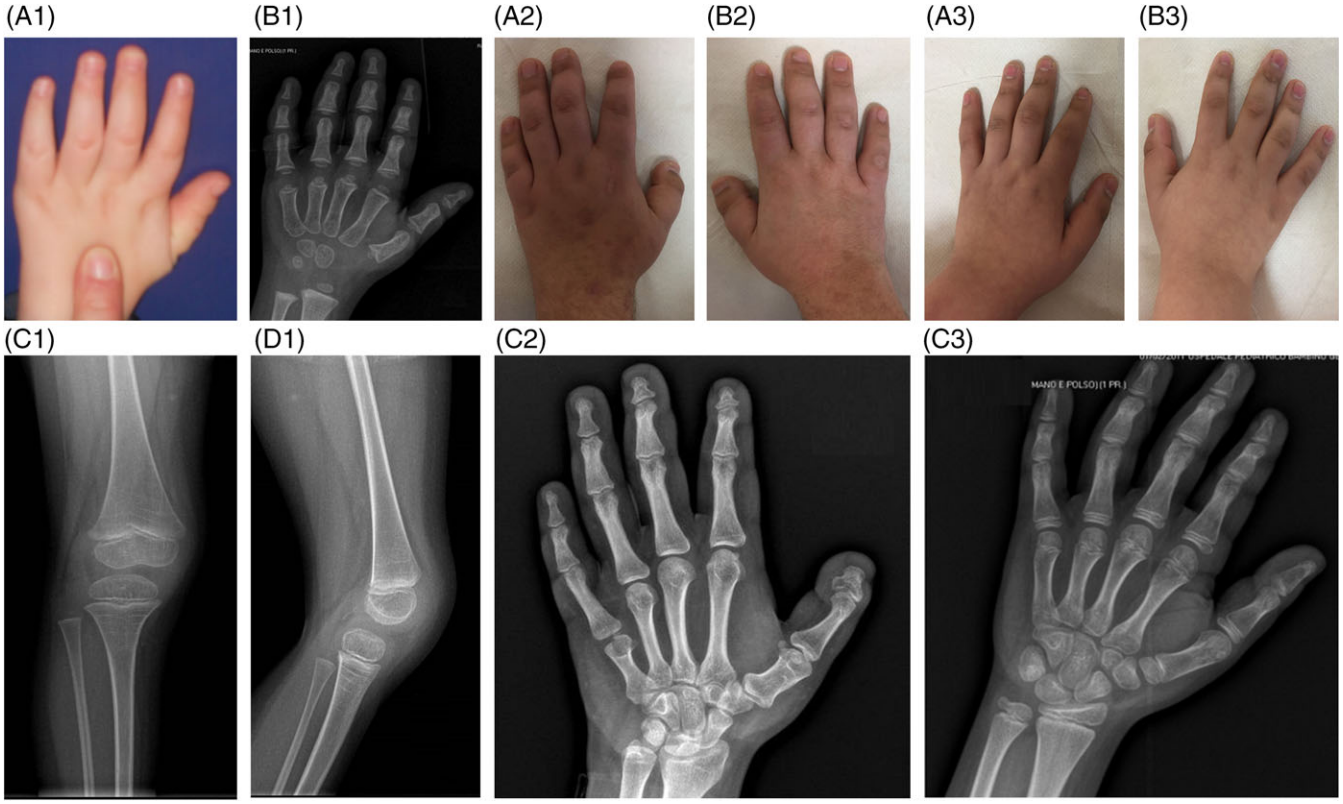

FIGURE 2 Skeletal features of patients 1, 2 and 3, including brachydactyly of hands. Note hypoplasia of the distal phalanges in all patients, with fingers 4 and 5 showing shortened metacarpal bones more pronounced in patient 2 (2-a, 2-b and 2-c). In addition, patient 1 has bilateral absent patella (1-c and 1-d). [Color figure can be viewed at wileyonlinelibrary.com]

Whole exome sequencing, performed in the family quartet, revealed that affected siblings shared the homozygous missense variant NM_019023.2:c.1490G>A, p.(Arg497Gln) in exon 13 of the *PRMT7* gene (Figure 1B). WES data output are summarized in Table S3. This variant, predicted as deleterious and probably damaging respectively by SIFT and Polyphen 2.0, has a global minor allele frequency of 0.000033, as reported in the Exome Aggregation Consortium (ExAC) database. The variant was confirmed by Sanger sequencing and tested for familial segregation. In addition, a homozygous private missense variant NM_022124.5:c.1152C>A, p.(Ser384Arg) in the *CDH23* gene was identified in patient 3. Based on its predicted disruptive impact (CADD score = 26) and the involvement of biallelic *CDH23* mutations in non-syndromic autosomal recessive deafness type 2 - (OMIM 601386), it is likely that this variant may underlie the profound sensorineural hearing loss specifically observed in this patient. Molecular modeling was used to investigate the effects of the p.(Arg497Gln) variant on the PRMT7 protein, showing that this missense substitution may have an impact on normal protein folding (Figures S1 and S2).

4 | DISCUSSION

In this study, we used exome sequencing to investigate the genetic basis of a disorder characterized by global developmental delay associated with dysmorphic facial features and skeletal anomalies in 2 non-related consanguineous families. Sequence analysis identified 2 novel homozygous mutations in the post-translational regulator PRMT7 in both families.

The clinical characteristics of our patients and those previously published are reported in Table 1. All known patients share global developmental and speech delay, although with a variable degree of expression. Severe/moderate intellectual disability was found in our patients as well as in the case reported by Kernohan et al, while mild developmental delay was found in the first reported families.[9] It is possible that the degree of clinical expression is related to specific mutations. In the present series, we hypothesize that the more severe phenotype in family 1 in comparison to that observed in family 2 might be caused by a more deleterious mutation. Indeed, the *PRMT7* nonsense mutation of patient 1, is predicted to result in a truncated protein that lacks approximately 67% of the N-terminal methyltransferase domain and the entire C-terminal methyltransferase domain, probably leading to a global loss of the PRMT7 protein. However, no expression studies were performed. The severe phenotype in our patient 1, presenting a substantial developmental delay and severe feeding difficulties is comparable to that described by Kernohan et al, where a deletion encompassing the transcription start site of the *PRMT7* gene produces a null allele. Interestingly, both these patients share feeding difficulties and poor weight gain, features not found in the other reported cases. Two of our patients (family 2) presented with a late-infancy onset of obesity which should be considered a cardinal feature, since it was recorded in 6/10 PRMT7-mutated patients.

TABLE 1 Clinical features of our SBIDDS patients and those previously published

Clinical features	Akawi et al, 2015[9]						Kernohan et al, 2016[10]	This report			Total
Patients	Pt1	Pt2	Pt3	Pt4	Pt5	Pt6	Pt1	Pt1	Pt2	Pt3	No of patients (%)
Sex	F	F	F	F	F	F	M	M	M	F	7 F/3 M
Mutation (PRMT7)	c.1276–1G > A + p.(Trp494Arg)			p.[(Arg32Thr)]; [(Arg387Gly)]	c.1056-1G > T + p. (Arg32Thr)		15 309 bp; HOM deletion	p.[(Glu108Ter)]; [(Glu108Ter)]	p.[(Arg447Gln)]; [(Arg447Gln)]		
Age at last evaluation (y)	23	19	22	14	9y 7mo	6y 2mo	8	3y 7mo	21	15	
Prenatal growth											
Gestation (weeks)	41	41	40	41	38/40	38/40	38/40	37	39 + 6	40	
Birth weight (g)	2440 (SD −2.22)	2381 (SD −2.37)	2807 (SD −1.26)	2690 (SD −1.73)	2495 (SD −1.67)	NA	2150 (SD −2.77)	2050 (SD −3.42)	2950 (SD −1.32)	2750 (SD −1.72)	
Birth length (cm)	NK	NK	NK	NK	NK	NK	46 (SD −2.06)	47 (SD −2.05)	49 (SD −0.98)	48 (SD −1.31)	
Head circumference (cm)	32.5 (SD −1.6)	NK	NK	NK	NK	NK	30.5 (SD −3.11)	31 (SD −3.13)	34 (SD −0.68)	33 (SD −1.21)	
Postnatal growth											
Weight (kg)	97.6 (SD 3.30)	82.4 (SD 2.22)	NK	68 (SD 1.8)	45 (SD 0.8)	17 (SD −1.5)	20 (SD −3.26)	11.7 (SD −2.14)	80 (SD +2.23)	63 (SD +1.54)	
Height/length (cm)	151.5 (SD −1.98)	NK	146.6 (SD −2.80)	150 (SD −1.4)	132 (SD −2.0)	102 (SD −2.9)	110 (SD −1.93)	90.3 (SD −2.37)	160 (SD −1.92)	145.5 (SD −2.77)	
Head circumference (cm)	NK	NK	52 (SD −2.5)	57 (SD 1.6)	51 (SD −2.4)	49 (SD −2.7)	47.7 (SD −4.7)	47 (SD −1.57)	54.5 (SD −0.41)	54 (SD −0.18)	
Feeding difficulties	No	No	No	No	No	No	Yes GER	Yes GER	No	No	2/10 (20%)
Obesity	Yes	Yes	No	Yes	Yes	No	No	No	Yes	Yes	6/10 (60%)
Developmental delay	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10/10 (100%)
Hypotonia	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/10 (80%)
Sat independently	NK	16 mo	NK	10 mo	14 mo	11 mo	NK	10 mo	12 mo	10 mo	
Walking independently	3–4 y	4–5 y	2–2.5 y	2–2.5 y	4 y	2 y 2/12	6 y	No walking	4 y 6mo	20 mo	
First words	NK	2–2.5 y	NK	18 mo	Delayed	18 mo	Few words	Absent speech	2 y	18 mo	
Cognitive deficits	Learning disability	Learning disability	Special needs school	Mild	Mild	Mild	Moderate/severe	Severe	Severe	Moderate	
Brain abnormalities	No	No	No	No	No	No	Thick CC	Cerebellar cyst	LCPAL, thin CC	No	3/10 (30%)
Seizures/epilepsy	Yes	No	No	1 Febrile convulsion	No	EEG atypical absence	Yes (onset 4 y)	absence, EEG normal	5 episodes	Yes (onset 6 y)	7/10 (70%)
Craniofacial dysmorphism	Yes	NK	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9/9 (100%)
Flat face	Yes	NK	Yes	Yes	Yes	Yes	Yes	Yes	No	No	7/9 (78%)

TABLE 1 (Continued)

Clinical features	Akawi et al, 2015[9]						Kernohan et al, 2016[10]	This report			Total
Prominent forehead	NK	NK	NK	NK	NK	NK	No	Yes	Yes	Yes	3/4 (75%)
Hypertelorism	NK	NK	NK	NK	NK	NK	Yes	Yes	Yes	Yes	4/4 (100%)
Deep-set eyes	Yes	NK	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9/9 (100%)
Flat nose	Yes	NK	No	Yes	Yes	No	Yes	Yes	No	No	5/9 (55%)
Anteverted nostrils	Yes	NK	No	Yes	Yes	No	Yes	Yes	Yes	Yes	7/9 (78%)
Preauricular ear tag	No	No	Yes	No	No	No	No	No	No	Yes	2/10 (20%)
Long philtrum	Yes	NK	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	8/9 (89%)
Thin lips	NK	NK	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8 (100%)
Gingival hypertrophy	NK	NK	NK	NK	NK	NK	Yes	Yes	No	No	2/4 (50%)
Retrognathia	NK	NK	NK	NK	NK	NK	Yes	No	No	No	1/4 (25%)
Skin anomalies	NK	NK	Eczema, soft skin	NK	NK	NK	NK	Eczema	Eczema, ML	Dry skin	4/4 (100%)
Skeletal anomalies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10/10 (100%)
Short neck	NK	NK	NK	NK	NK	NK	Yes	Yes	Yes	Yes	4/4 (100%)
Hand brachydactyly	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10/10 (100%)
Short 4th metatarsal bone	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	NK	NK	7/8 (88%)
Ocular anomalies	Blue sclerae	No	coloboma	Strabismus	Strabismus	Strabismus	No	Dacryostenosis	No	Strabismus	7/10 (70%)
Laryngomalacia	NK	NK	NK	NK	NK	NK	Yes	Yes	No	No	2/4 (50%)
Cryptorchidism	NA	NA	NA	NA	NA	NA	Yes	No	Yes	NA	2/3 (67%)
Other		Sleep apnea					Small kidneys, VUR	Patellar hypoplasia		SHL (*CDH23* mutation)	

Abbreviations: CC, corpus callosum; F, female; GER, gastroesophageal reflux; LCPAL, left cerebellopontine angle lipoma; M, male; ML, multiple lentigines; NA, not applicable; NK, not known; SHL, Sensorineural hearing loss; VUR, vesicoureteral reflux.

Skeletal anomalies are considered a distinct marker of the syndrome together with the neurological involvement. Upper limbs prevalently display brachydactyly of hands and hypoplasia of the distal phalanges, which were present in our patients. In addition, patient 1 had bilateral absent patella that has not been reported in any *PRMT7* mutated patients, so far. Kernohan et al, have shown that cells from patient with SBIDDS display an altered Wnt signaling, whose role in almost all aspects of skeletal development and homeostasis has been well established.[11] Wnt signaling is activated by PRMT1- and PRMT7-mediated methylation of GTPase-activating protein-binding protein 2 (G3BP2)[12] and reduced through the methylation of disheveled homolog 3 (DVL3) by the same PRMTs.[13] Interestingly, whole-body protein arginine methyltransferase *Prmt7*$^{-/-}$ mice, display growth retardation, skeletal defects, brachydactyly of the fifth metatarsal bone and reduced bone mineral content. These features are particularly evident in the patient 1. In addition, *Prmt7*$^{-/-}$ mice has a significant reduction in muscle stem cells function, leading to defects in regenerative capacity upon muscle injury.[6] This cell-intrinsic mechanism could contribute to the hypotonia observed in SBIDDS patients, whose expressivity is likely dependent on the *PRMT7* genotype, and more specifically the presence of null alleles might be associated to a more severe decrease in skeletal muscle tone. This could explain also the feeding difficulties of patient 1 that are generally observed in infants with severe hypotonia.

Early diagnosis of the disease and genotype-phenotype correlation can provide the opportunity to establish coordinated multispecialty management of the patient, focusing on the changing issues through childhood, including anticipatory care for developmental disabilities, orthopedic problems, feeding, and growth difficulties. Further studies are required to delineate the natural history of this disorder.

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Conflict of interest

The authors declare no conflicts of interest.

Ethics approval

Clinical investigations and genetic analyses were approved by the institutional scientific board of Bambino Gesù Children's Hospital.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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