Molecular Syndromology

Novel Insights from Clinical Practice

Mol Syndromol 2022;13:543–550
DOI: 10.1159/000524844

Received: July 23, 2021
Accepted: April 30, 2022
Published online: June 7, 2022

SBIDDS Syndrome: A New Spoke of the Epigenetic Machinery Wheel

Sebastiano Aleo[a] Lidia Pezzani[a, b] Donatella Milani[a] Laura Pezzoli[b]
Paola Marchisio[a, c] Maria Iascone[b]

[a]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milano, Italy; [b]Laboratorio di Genetica Medica, ASST Papa Giovanni XXIII, Bergamo, Italy; [c]Università degli Studi di Milano Statale, Milano, Italy

Established Facts

- Mendelian disorders of the epigenetic machinery (MDEM) exhibit several overlapping clinical features that are likely due to common abnormalities at the epigenomic level, which lead to downstream convergence at the transcriptomic level.
- Germline biallelic mutations of *PRMT7* (OMIM *610087) are causative of an ultra-rare neurodevelopmental disease named SBIDDS syndrome (short stature, brachydactyly, intellectual developmental disability, and seizures; OMIM #617157).
- *PRMT7* is the only monomethylating arginine methyltransferase.

Novel Insights

- Some clinical features of SBIDDS remind those seen in other MDEM, such as tendency to being overweight, short stature, and limb anomalies.
- Among new reported clinical features, hypogonadism could be underestimated in SBIDDS and in MDEM in general.
- Auricular tags and pits may represent key features in SBIDDS syndrome.

Keywords
Epigenetic machinery · WES · *PRMT7* · SBIDDS syndrome

Abstract

Introduction: Mendelian disorders of the epigenetic machinery are a growing group of disorders exhibiting several overlapping clinical features that are probably due to common abnormalities at the epigenomic level, which lead to downstream convergence at the transcriptomic level. ***Case presentation:*** Here, we report a new case of short stature, brachydactyly, intellectual developmental disability, and seizures (SBIDDS) syndrome with a severe ocular phenotype and hypogonadism. ***Conclusion:*** Similarities and connections with other mendelian disorders of the epigenetic machinery are highlighted, confirming SBIDDS' enrolment as a new spoke of the epigenetic machinery wheel.

S.A. and L.P. contributed equally to this work.

Karger@karger.com
www.karger.com/msy

Correspondence to:
Donatella Milani, donatella.milani@policlinico.mi.it

Karger

Introduction

Being able to quickly adapt to different environmental conditions is key to survival for every biological system, including the cell. Post-translational modifications (PTMs) are essential mechanisms that eukaryotic cells use to modulate protein functions and coordinate their signalling networks to the changing environment and include phosphorylation, acetylation, methylation, and ubiquitination [Duan and Walther, 2015]. Frequent targets of PTMs are histones. Germline mutations in genes encoding histone machinery molecules have recently been linked to mendelian disorders of the epigenetic machinery (MDEM), an emerging group of complex diseases that are often characterized by facial dysmorphisms, intellectual disability (ID), developmental delay, growth alterations, and a pletora of other abnormalities [Fahrner and Bjornsson, 2019].

Among histone machinery proteins, methyltransferases transfer a methyl group from S-adenosylmethionine to the side chains of lysines and arginines on histone tails. So far, the only monomethylating arginine methyltransferase is *PRMT7*, which participates in gene regulation, stem cells biology, and cancer pathogenesis [Jain and Clarke, 2019]. SBIDDS (short stature, brachydactyly, intellectual developmental disability, and seizures; OMIM #617157) is an ultrarare autosomal recessive syndrome caused by mutations in *PRMT7* (OMIM *610087) [Akawi et al., 2015; Kernohan et al., 2017; Agolini et al., 2018; Birnbaum et al., 2019; Valenzuela et al., 2019] (Fig. 1).

Here, we report a newly diagnosed case of SBIDDS syndrome with a remarkable ocular phenotype and hypogonadism, and we highlight the clinical similarity of SBIDDS with other MDEMs, confirming its enrolment as a new spoke of the epigenetic machinery wheel.

Material and Methods

Case Report

The proband was the only son of a non-consanguineous couple. Family history revealed 2 female maternal cousins with mild ID and a neonatal death of a paternal uncle who died soon after birth by an unknown cause. Pregnancy was complicated by intrauterine growth restriction; fetal distress and premature membrane rupture resulted in a caesarean section at 37 weeks of gestation.

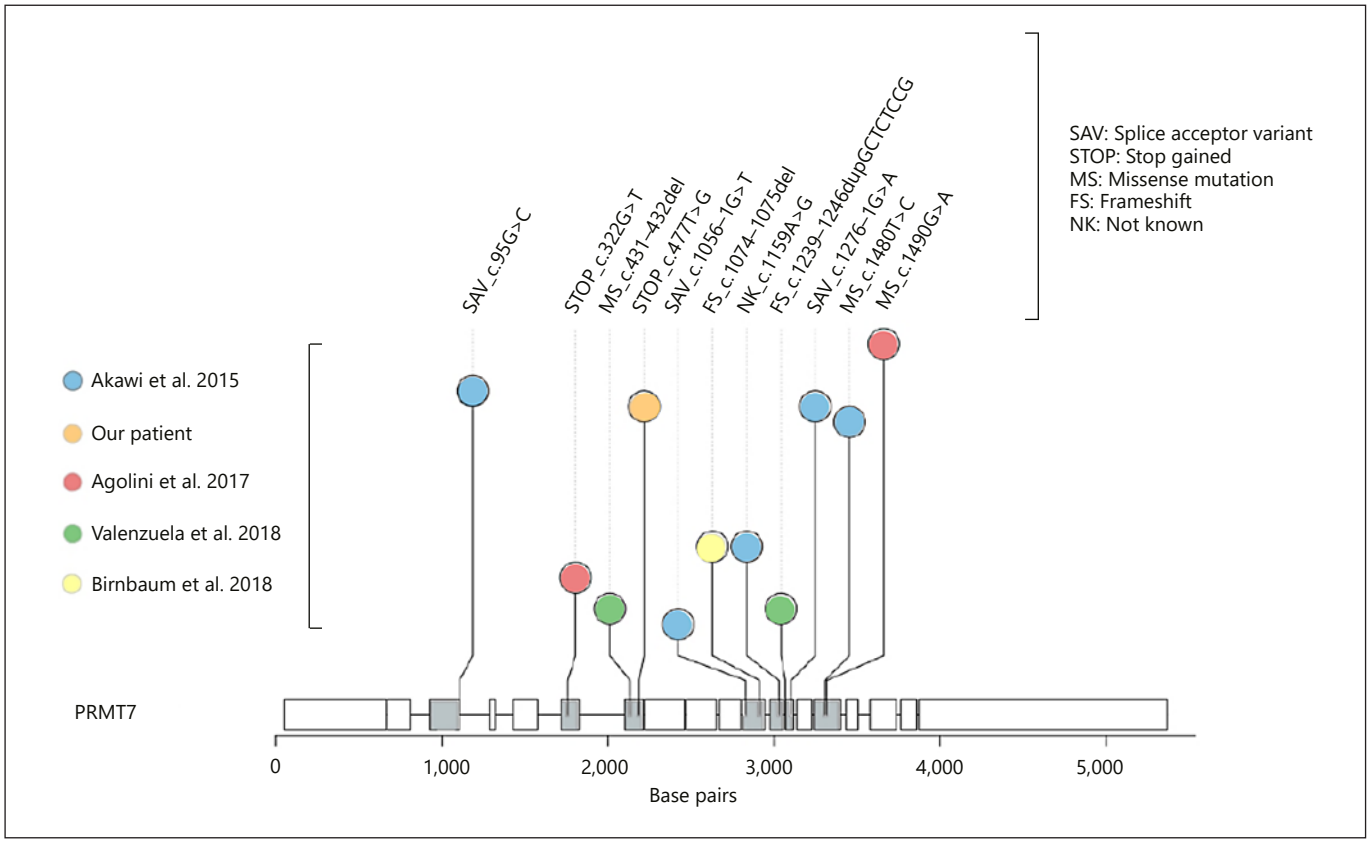

Fig. 1. *PRMT7* variants in reported SBIDDS patients.

Birth weight was 2,150 g (3rd centile), while length and occipitofrontal circumference were not reported.

At birth he had right cryptorchidism, mild tricuspid and mitralic insufficiency, bilateral hydroureteronephrosis, and monolateral ocular persistent fetal vasculature (PFV) with retro-lental fibroplasia. Brain MRI only showed left microphthalmia.

During the first year of life, developmental delay was noted, with sitting being achieved at 12 months of age. Neurological examination reported hypotrophic lower limbs with absent osteotendinal reflexes and global hypotonia. Autonomous walking was accomplished at the age of 4, while speech remains absent. At 3 years, partial epileptic seizures were diagnosed and at 7 years celiac disease. Shortly before our assessment at 16 years of age, a neuropsychological and neuro-ophthalmological examination were performed showing severe ID with a global IQ of 32 (Leither-R scale) and low retinal function. Upon physical examination, he was short (130.5 cm, −5.38 SDS), brachycephalic (OFC of 50.8 cm, −4.12 SDS), and weighed 43.5 kg (−2.61 SDS). He had a short neck, upslanted palpebral fissures, left blepharoptosis and microphthalmia, long eyelashes, small nose with hypoplastic nostrils, long philtrum, large upper incisors, high-arched palate, large ears with a bilateral posterior helix pit, central obesity with hypotrophic lower limbs, dorsal kyphosis, and clino-brachydactyly of fingers. Furthermore, feet appeared flat and narrow with a bilateral hallux valgus, and brachydactyly of III, IV, and V toes (Fig. 2). The presence of hypogenitalism prompted the request for a hormonal assessment which revealed hypogonadotropic hypogonadism, low insulin growth factor (IGF1) levels, and normal thyroid function.

CGH-array analysis was normal. Trio-WES analysis was then performed.

Methods and Results

After informed written consent, genomic DNA was extracted from peripheral blood samples using a standard procedure. Trio WES with DNA samples of the patient and his healthy parents was performed as described before [Pezzani et al., 2018]. Briefly, the exonic and flanking splice junction regions of the genome were captured using the Clinical Research Exome v.2 kit (Agilent Technologies, Santa Clara, CA, USA). Sequencing was done on a NextSeq500 Illumina system with 150 bp paired-end reads. Reads were aligned to human genome build GRCh37/UCSC hg19 and analyzed for sequence variants using a custom-developed analysis tool [Pezzani et al., 2018]. Additional sequencing technology and variant interpretation protocol have been previously described [Pezzani et al., 2018].

Coverage on target for the index was ≥10× for 98.1% with a mean coverage of 227×.

Trio-WES analysis revealed a previously unreported homozygous non-sense variant NM_019023.5: c.477T>G; (p.Tyr159ter) in exon 7 of *PRMT7* (Fig. 1). Both parents were found to be heterozygous carriers of the variant.

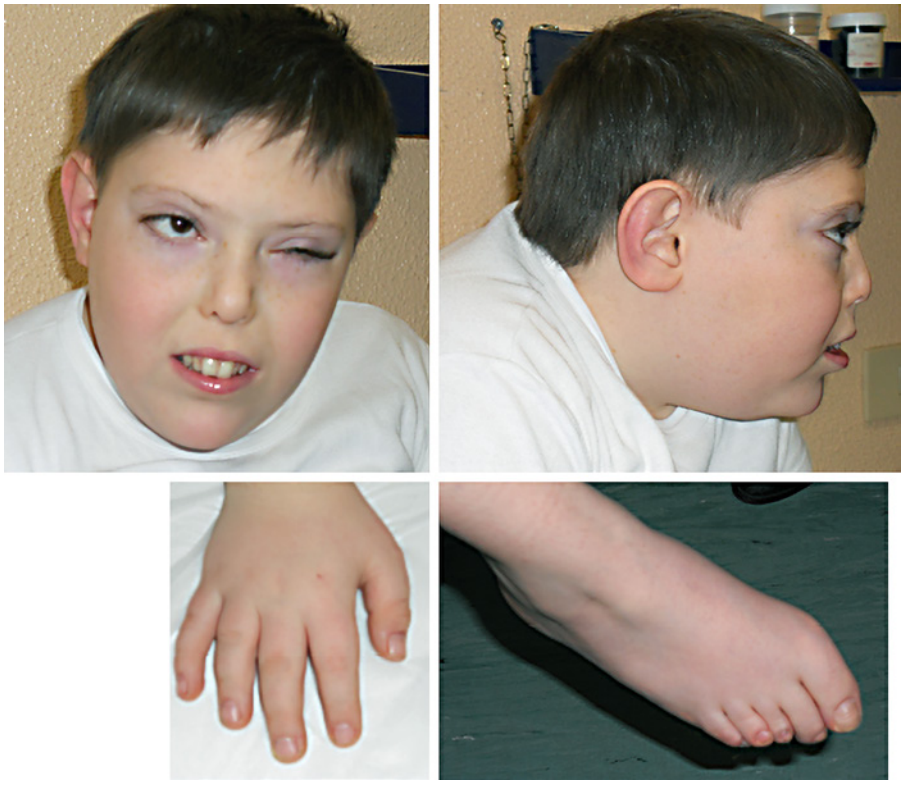

Fig. 2. Somatic features of our patient. Short neck, upslanted palpebral fissures, left blepharoptosis and microphthalmia, long eyelashes, small nose with hypoplastic nostrils, long philtrum, large upper incisors, high-arched palate, large ears with a bilateral posterior helix pit, clino-brachydactyly of fingers, flat and narrow feet with a bilateral hallux valgus, and brachydactyly of III, IV, and V toes.

Mol Syndromol 2022;13:543–550
DOI: 10.1159/000524844

Table 1. Reported SBIDDS patients

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Patient	Our case	Akawi et al. [2015] Pt1 (272790)	Akawi et al. [2015] Pt2 (272789)	Akawi et al. [2015] Pt3 (281373)	Akawi et al. [2015] Pt4 (270360)	Akawi et al. [2015] Pt5 (304331)	Akawi et al. [2015] Pt6 (304327)	Kernohan et al. [2017] Pt1	Agolini et al. [2018] Pt1	Agolini et al. [2018] Pt2	Agolini et al. [2018] Pt3	Valenzuela et al. [2019] Pt1	Birnbaum et al. [2019] Pt1	Birnbaum et al. [2019] Pt2
Sex	M	F	F	F	F	F	F	M	M	M	F	F	M	M
Parental origin	Italian	na	na	na	na	na	na	Afghanistan	Italian	Tunisian	Tunisian	Caucasian	Jewish Bucharian	Jewish Bucharian
PRMT7 variants	c.477T>G; p.(Tyr159ter)	c.1276-1G>A c.1480T>C; p.(Trp494Arg)	c.1276-1G>A c.1480T>C; p.(Trp494Arg)	c.95G>C; p.(Arg32Thr) c.1159A>G; p.(Arg387Gly)	c.95G>C; p.(Arg32Thr) c.1056-1G>T	c.95G>C; p.(Arg32Thr) c.1056-1G>T	c.95G>C; p.(Arg32Thr); c.1056-1G>T	Chr16:68,345,747-68,361,056, hg19 (15.309 bp del)	c.322G>T; p.(Glu108Ter)	c.1490G>A; p.(Arg497Gln)	c.1490G>A; p.(Arg497Gln)	c.431_432del c.1239_1246dup-GCTCTCCG	c.1074_1075delAG; p.(Arg385fs)	c.1074_1075delAG; p.(Arg385fs)
Zygosity	Homozygous	Compound heterozygous	Compound heterozygous	Compound heterozygous	Compound heterozygous	Compound heterozygous	Compound heterozygous	Homozygous	Homozygous	Homozygous	Homozygous	Compound heterozygous	Homozygous	Homozygous
Prenatal findings	IUGR	na	na	na	na	na	na	IUGR, polyhydramnios, absent stomach bulb	IUGR	No	No	IUGR, polyhydramnios	IUGR, short limbs, microftalmia, juvenile pilocytic astrocytoma	IUGR, short limbs
Gestation weeks	37	41	41	40	41	38/40	38/40	38/40	35	39+6	40	38+2	–	35+5
Birth weight, SDS	−3.9	−2.22	−2.4	−1.3	−1.6	−2.5	na	−2.0	−3.4	−1.3	−1.7	−2.2	–	−4.0
Birth length, SDS	na	na	na	na	na	na	Nana	−2.0	−2.0	−1.0	−1.3	−2.3	–	na
Birth OFC ,SDS	na	−1.66	na	na	na	na	na	−4.0	−3.1	−0.7	−1.2	−0.7	–	−1.5
Age at last evaluation, years	18	27	35	22	14	9	6	8	3.5	21	15	2	–	1.6
OFC, SDS	−4.12	na	na	−2.5	1.6	−2.4	−2.7	−4	<−2	−0.4	−0.2	−1.8	–	−1.7
Height, SDS	−5.38	−1.98	na	−2.8	−1.4	−2	−2.9	−2	<−2	−1.9	−2.8	−2.2	–	−4
Weight, SDS	−2.61	3.3	2.22	na	1.8	0.8	−2.7	−1.3	<−2	2.2	1.5	−2.2	–	−4
Obesity	Yes (truncal)	Yes (truncal)	Yes (truncal)	No	Yes (truncal)	Yes	No	No	No	Yes	Yes	No	–	No
Motor delay	Yes	Yes	Yes	Yes	Yes	Mild	Yes	Yes	Yes	Yes	Mild	Yes	–	Yes
Speech	Absent	na	Delayed	na	Delayed	Delayed	Delayed	Delayed	Absent	Delayed	Delayed	Delayed	–	Delayed
Cognitive disability	Severe	Learning disability	Learning disability	Moderate	Mild	Mild	Mild	Severe	Severe	Severe	Moderate	Mild	–	Moderate
Behavioural issues	No	No	No	No	No	Anxiety	No	No	No	Autoaggressive behavior	No	No	–	No
Epilepsy	Yes	Yes	No	No	No	No	Yes	Yes	No	Yes	Yes	No	–	No
Neuromuscular features	Hypotonia, muscular hypotrophy, neuropathy	No	Hypotonia	Hypotonia	Hypotonia	Hypotonia, fatigue	Hypotonia	Hypotonia	Hypotonia	Hypotonia	Hypotonia	Hypotonia	–	Hypotonia
Neuroimaging	Normal	na	na	na	na	ns	na	Thick CC, delayed myelination, tethered cord	Cerebellar cyst	Thin CC, cerebellopontine angle lipoma	Normal	Normal	–	Dysmorphic lateral ventricles, subtle periventricular calcifications, delayed myelination, low cord L3-L4, excessive number of sacral vertebrae
Eyes	Left microftalmia, PFV	Normal	Normal	Coloboma	Unilateral ptosis, strabismus, astigmatism	Strabismus, astigmatism	Strabismus, astigmatism	Normal	Dacryostenosis	Normal	Strabismus	Normal	–	Strabismus
Hearing impairment	No	Yes	No	Yes	No	No	No	No	No	No	Yes[a]	Yes	–	Yes
Heart	Tricuspid and mitral insufficiency	Normal	Cardiomyopathy	na	na	na	na	na	Normal	Normal	na	Normal	–	Normal

Mol Syndromol 2022;13:543–550
DOI: 10.1159/000524844

Table 1 (continued)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Urogenital defects	Ureteral dysplasia, VUR, hypogenitalism, right cryptorchidism	na	Renal insufficiency	No	No	Antenatal cystic dysplastic kidney	No	Kidney hypoplasia, VUR, right cryptorchidism	No	Cryptorchidism	na	No	–	Criptorchydism, penile chordee, unilateral mild hydrouretero-nephrosis
Endocrine defects	Hypogonadotropic hypogonadism	Pseudohypo-parathyroidism	Pseudohypo-parathyroidism	No	No	na	na	na	No	na	na	No	–	na
Skin	Dry skin	na	na	Dry skin	Dry skin	na	na	na	Dry skin	Dry skin	Dry skin	Normal	–	na
Dysmorphic features	Upslanted palpebral fissures, left blepharoptosis, long eyelashes, small nose, hypoplastic nostrils, long philtrum, large upper incisors, high-arched palate, short neck	Epicanthus, wide nasal bridge, prominent forehead, hypertelorism	Malar flattening, depressed nasal bridge	na	Short palpebral fissures, short upturned nose, flat mid face	Short palpebral fissures, short upturned nose	Short palpebral fissures, short upturned nose	Sparse hair, brachycephaly, short forehead, deep-set eyes, flat nasal bridge, broad nasal root and tip, square shaped chin, short neck	High forehead, hypertelorism, anteverted nares, smooth philtrum, thin upper lip vermilion, thick everted lower lip, mild prognathism, short neck	High forehead, hypertelorism, deep-set eyes, anteverted nares, long philtrum, thick vermilion of the lips, short neck	High forehead, hypertelorism, deep-set eyes, anteverted nares, long philtrum, thick vermilion of the lips, short neck	Sparse hair, high forehead, deep-set eyes, short palpebral fissures, short upturned nose ,malar flattening	–	Frontal bossing, upslanting palpebral fissures, small nose, depressed nasal bridge
Ears	Large ears, auricular pit	No	No	Preauricular ear tag	No	No	No	No	Large ears, preauricular skin tag	No	Preauricular skin tag	Preauricular skin tag	–	No
Hands	Brachydactyly, clinodactyly	Short III-IV-V metacarpals	Brachydactyly of V finger, short metacarpal	Short V meta-carpal	Abnormality metacarpal bones	Brachydactyly	Abnormal metacarpal bones	Brachydactyly and webbing 2-3-4 fingers bilateral, broad thumbs proximally inserted	Brachydactyly	Brachydactyly, short metacarpal bones	Brachydactyly	Brachydactyly, bilateral–single palmar crease	–	na
Feet	Hallux valgus, flat feet, brachydactyly of III-IV right toes and IV left toe	Short metatarsal bones	Short IV meta-tarsal	Short metatarsal bones	Short metatarsal bones	Short metatarsal bones	Short metatarsal bones	Normal	na	Brachydactyly	Brachydactyly	na	–	na
Other	Celiac disease, kyphosis	Blue sclerae	Sleep apnea, abnormal dental eruption, hypertension	–	–	Bilateral cholesteatomas	Joint hypermobility	Feeding difficulties, gastroesophageal reflux, laryngomalacia, pilonidal dimple	Laryngomalacia dysmetric lower limbs, feeding difficulties, dysphagia, decreased bone mineral density, bilateral absence of patella	Delayed bone age, kyphosis	–	Venous malformation	–	Interrupted inferior vena cava pectus excavatum

na, not available; IUGR, intrauterine growth retardation; SDS, standard deviation score; CC, corpus callosum; PFV, persistent fetal vasculature. [a]*CDH23* pathogenic variant.

Discussion

SBIDDS syndrome is an ultrarare neurodevelopmental disorder with only 13 cases described thus far (Table 1) [Akawi et al., 2015; Kernohan et al., 2017; Agolini et al., 2018; Birnbaum et al., 2019; Valenzuela et al., 2019]. The involved gene is *PRMT7* which could be considered part of the histone machinery. Some of the described clinical features actually remind of those seen in MDEM. For example, Rubinstein Taybi syndrome (RSTS, OMIM #180849, #613684) shows a peculiar growth characterized by generalized delay during infancy, followed by a tendency to overweight, similar to SBIDDS, with resulting truncal obesity. Interestingly, patients reported as not being overweight were all younger than 6 years, thus not excluding the possibility of a weight increase later on [Kernohan et al., 2017; Agolini et al., 2018; Birnbaum et al., 2019; Valenzuela et al., 2019]. The concurrent presence of celiac disease in our patient could have additionally delayed the onset of obesity. Of note, *Prmt7* appears to be critical for maintenance of muscle mass in aging, and *Prmt7*-deficient mice exhibit age-related obesity and hyperglycaemia due to a muscle fiber-type switch from oxidative to glycolytic muscle metabolism [Jeong et al., 2016]. Intriguingly, *Chrysanthemi zawadskii* var. *latilobum*, a perennial herb that is widely used as a traditional medicine in Korea and China, seems to ameliorate obesity-induced skeletal muscle atrophy in mice via regulation of PRMTs and therefore could be the base for the development of new therapeutic approaches [Yoo et al., 2020].

Another shared feature is ID with delay/absence of speech. Of note, *PRMT7* suppression seems to reduce both mRNA and the levels of the protein SHANK3 in hippocampal CA1 pyramidal cells [Lee et al., 2020]. *SHANK3* haploinsufficiency in humans causes Phelan-McDermid syndrome (OMIM #606232), which is characterized by ID, autism spectrum disorder, and severe speech delay. The fact that both SBIDDS and Phelan-McDermid syndrome share an important speech delay hints to a regulation of *SHANK3* by *PRMT7*.

The majority of MDEM show hands and feet abnormalities, such as broad thumbs and halluces (RSTS, Wiedemann-Steiner syndrome [WDSTS, OMIM #605130]), clinodactyly, and brachydactyly. Similarly, SBIDDS patients have brachydactyly/clinodactyly. Analysing the photos of reported patients, we identified what looked like broad thumbs in 2 cases [Birnbaum et al., 2019; Valenzuela et al., 2019]. In addition, radiographic images of Agolini's patient seems to have a wide distal phalanx of the thumb [Agolini et al., 2018].

These features all somehow remind of MDEMs. Furthermore, there are other signs also associated with epigenetic machinery defects. For example, both SBIDDS and MDEM frequently manifest various ocular defects. The ocular phenotype displayed by our patient is unusually severe. PFV is the result of a failed regression of the hyaloid vascular system during foetal development, mainly driven by endothelial apoptosis. Although PFV is usually an isolated finding, a genetic basis may well be present [Prakhunhungsit and Berrocal, 2020]. PRMTs like *PRMT7* may play an important regulatory role in the involved pathways [Affara et al., 2007], and it could be then involved in persistent hyperplastic primary vitreous pathogenesis as well as in that of the venous malformation in the case of Valenzuela et al. [2019]. Further studies will be needed to verify it.

Similarly, our patient's hypogonadotropic hypogonadism (HH) is interesting. *PRMT7* is in fact expressed in the hypothalamus, pituitary gland, and in other important endocrinological structures such as thyroid and parathyroids, and 2 patients suffered from pseudohypoparathyroidism [Akawi et al., 2015]. *PRMT7* could contribute to the normal functioning of these organs but may not be crucial. However, *Prmt7* is abundantly expressed in male germ cells, and deletion of this gene resulted in germ cell number reduction [Chen et al., 2020]. It should be noted that hypogonadism is a well-known feature of some MDEM [Borjeson et al., 1962; Wilson et al., 1991], and an additional number of MDEM actually seems to show pubertal anomalies; i.e., a diminution of the pubertal growth spurt in Kabuki syndrome (OMIM #147920, 300867) and in RSTS is observed [Schott et al., 2016: Beets et al., 2014]. Detailed and thorough studies, however, are currently lacking. Considering that pubertal endocrinological features in syndromic children are often overlooked, the prevalence of hypogonadism could be underestimated.

Other notable features are reported in only a few cases of SBIDDS syndrome and in MDEM. Dry skin, for example, is a non-specific and generally under-reported feature that has been described in SBIDDS and in *RAI1* associated Smith-Magenis syndrome (SMS, OMIM #182290) [Edelman et al., 2007]. Tethered cord and sacral dimples have been described by Kernohan et al. [2017] and in RSTS, Kabuki, and Sotos syndrome (OMIM #117550) [Ajmone et al., 2018; Kuzucu et al., 2020; Mu-

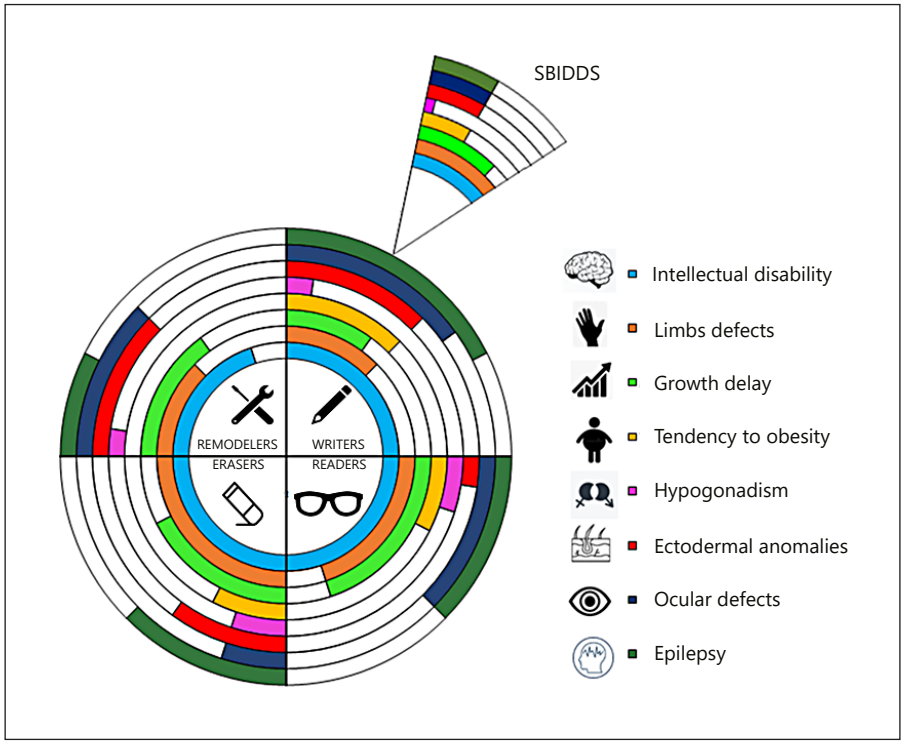

Fig. 3. Graphical representation of overlapping clinical features between MDEMs and SBIDDS. The coloured segments show the proportion of MDEMs with clinical features reported in SBIDDS patients, while the separate slice represents the proportion of SBIDDS patients having a specific clinical sign.

roi et al., 2021], and the absence of the patellar bone in the case report of Agolini et al. [2018] and in Say-Barber-Biesecker-Young-Simpson syndrome (SBBYSS, OMIM #603736) [Lemire et al., 2012].

Taken together, these elements support SBIDDS as a new spoke of the epigenetic machinery wheel (Fig. 3).

Conversely, a better comparison of published SBIDDS patients' features allowed to note the common presence of sparse eyebrows and highlighted that auricular tags and pits are present in roughly half the cases (Table 1). Both these features are unusual in MDEM; while facial dysmorphisms are non-specific, pits/tags may represent a key feature and they could be included in the condition's name: Brachydactyly, Auricular abnormalities, Short stature, Seizures, and Intellectual disability syndrome (BASSI syndrome).

MDEM are emerging as a growing group of mendelian disorders caused by pathogenic variants in epigenetic regulators and exhibiting several overlapping clinical features, which are probably the consequence of common abnormalities at the epigenomic level, which lead to downstream convergence at the transcriptomic level. We can consider SBIDDS syndrome as a new form of MDEM. The mechanisms of disease causation are still unknown for the most part, and no genotype-phenotype correlations have been ascertained to date [Agolini et al., 2018]. In principle, however, proximal mutations are predicted to result in a global loss of Prmt7 protein and in a more severe phenotype, as in our patient, in patient 1 reported by Agolini et al. [2018], and in the patient reported by Kernohan et al. [2017]. Future studies should also be aimed at understanding *PRMT7* functions and interactions. This data, coupled with a better definition of the associated clinical phenotype thanks to new SBIDDS reports, will then help improve our knowledge on the complex genetic basis of this disease and of MDEM in general.

Acknowledgments

The authors are grateful to the parents of the patient for their cooperation. This study has been generated within the European Reference Network on Rare Congenital Malformations and Rare Intellectual Disability (ERN-ITHACA).

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and approved by the Ethics Committee Milano Area 2 (Protocol code: PED-

CARE-2018). Written informed consent was obtained from the parents of the patient for publication of the details of his medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have no funding sources to declare.

Author Contributions

S.A., L.P., and D.M. were involved in conception and design of the study and writing of the manuscript. L.P. and M.I. were involved in laboratory experiments and data interpretation. L.P. and D.M. were involved in genetic counseling and patient evaluation. D.M., P.M., and M.I. revised the manuscript and made substantial scientific contributions. All authors read and approved the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

Affara M, Dunmore B, Savoie C, Imoto S, Tamada Y, Araki H, et al. Understanding endothelial cell apoptosis: what can the transcriptome, glycome and proteome reveal? Philos Trans R Soc Lond B Biol Sci. 2007;362(1484):1469–87.

Ajmone PF, Avignone S, Gervasini C, Giacobbe A, Monti F, Costantino A, et al. Rubinstein-Taybi syndrome: New neuroradiological and neuropsychiatric insights from a multidisciplinary approach. Am J Med Genet B Neuropsychiatr Genet. 2018;177(4):406–15.

Akawi N, McRae J, Ansari M, Balasubramanian M, Blyth M, Brady AF, et al. Discovery of four recessive developmental disorders using probabilistic genotype and phenotype matching among 4,125 families. Nat Genet. 2015;47(11):1363–9.

Agolini E, Dentici ML, Bellacchio E, Alesi V, Radio FC, Torella A, et al. Expanding the clinical and molecular spectrum of PRMT7 mutations: 3 additional patients and review. Clin Genet. 2018;93(3):675–81.

Beets L, Rodríguez-Fonseca C, Hennekam RC. Growth charts for individuals with Rubinstein-Taybi syndrome. Am J Med Genet A. 2014;164A(9):2300–9.

Birnbaum R, Yosha-Orpaz N, Yanoov-Sharav M, Kidron D, Gur H, Yosovich K, et al. Prenatal and postnatal presentation of PRMT7 related syndrome: Expanding the phenotypic manifestations. Am J Med Genet A. 2019;179(1):78–84.

Borjeson M, Forssman H, Lehmann O. An X-linked, recessively inherited syndrome characterized by grave mental deficiency, epilepsy, and endocrine disorder. Acta Med Scand. 1962;171:13–21.

Chen M, Wang Y, Lin L, Dong F, Wu H, Bao S, et al. PRMT7 is involved in regulation of germ cell proliferation during embryonic stage. Biochem Biophys Res Commun. 2020;533(4):938–44.

Duan G, Walther D. The roles of post-translational modifications in the context of protein interaction networks. PLoS Comput Biol. 2015;11(2):e1004049.

Edelman EA, Girirajan S, Finucane B, Patel PI, Lupski JR, Smith ACM, et al. Gender, genotype, and phenotype differences in Smith-Magenis syndrome: a meta-analysis of 105 cases. Clin Genet. 2007;71(6):540–50.

Fahrner JA, Bjornsson HT. Mendelian disorders of the epigenetic machinery: postnatal malleability and therapeutic prospects. Hum Mol Genet. 2019;28(R2):R254–64.

Jain K, Clarke SG. PRMT7 as a unique member of the protein arginine methyltransferase family: A review. Arch Biochem Biophys. 2019;665:36–45.

Jeong HJ, Lee HJ, Vuong TA, Choi KS, Choi D, Koo SH, et al. Prmt7 Deficiency Causes Reduced Skeletal Muscle Oxidative Metabolism and Age-Related Obesity. Diabetes. 2016;65(7):1868–82.

Kernohan KD, McBride A, Xi Y, Martin N, Schwartzentruber J, Dyment DA, et al. Loss of the arginine methyltranserase PRMT7 causes syndromic intellectual disability with microcephaly and brachydactyly. Clin Genet. 2017;91(5):708–16.

Kuzucu P, Türkmen T, Börcek AÖ. First report of tethered cord syndrome in a patient with Sotos syndrome. BMC Pediatr. 2020;20(1):183.

Lee SY, Vuong TA, So HK, Kim HJ, Kim YB, Kang JS, et al. PRMT7 deficiency causes dysregulation of the HCN channels in the CA1 pyramidal cells and impairment of social behaviors. Exp Mol Med. 2020;52(4):604–14.

Lemire G, Campeau PM, Lee BH. KAT6B Disorders. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 2012.

Muroi A, Enokizono T, Tsurubuchi T, Tsukada K, Ohto T, Ishikawa E. Association of Kabuki syndrome and tethered cord syndrome: a report of three cases and literature review. Childs Nerv Syst. 2021;37(4):1339–43.

Pezzani L, Marchetti D, Cereda A, Caffi LG, Manara O, Mamoli D, et al. Atypical presentation of pediatric BRAF RASopathy with acute encephalopathy. Am J Med Genet A. 2018;176(12):2867–71.

Prakhunhungsit S, Berrocal AM. Diagnostic and Management Strategies in Patients with Persistent Fetal Vasculature: Current Insights. Clin Ophthalmol. 2020;14:4325–35.

Schott DA, Blok MJ, Gerver WJ, Devriendt K, Zimmermann LJ, Stumpel CT. Growth pattern in Kabuki syndrome with a KMT2D mutation. Am J Med Genet A. 2016;170(12):3172–9.

Valenzuela I, Segura-Puimedon M, Rodríguez-Santiago B, Fernández-Alvarez P, Vendrell T, Armengol L, et al. Further delineation of the phenotype caused by loss of function mutations in PRMT7. Eur J Med Genet. 2019;62(3):182–5.

Wilson M, Mulley J, Gedeon A, Robinson H, Turner G. New X-linked syndrome of mental retardation, gynecomastia, and obesity is linked to DXS255. Am J Med Genet. 1991;40(4):406–13.

Yoo A, Jang YJ, Ahn J, Jung CH, Seo HD, Ha TY. Chrysanthemi Zawadskii var. Latilobum Attenuates Obesity-Induced Skeletal Muscle Atrophy via Regulation of PRMTs in Skeletal Muscle of Mice. Int J Mol Sci. 2020;21(8):2811.