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CLINICAL REPORT

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Confirmation and further delineation of the SMG9-deficiency syndrome, a rare and severe developmental disorder

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Abstract

Introduction: SMG9 deficiency is an extremely rare autosomal recessive condition originally described in three patients from two families harboring homozygous truncating *SMG9* variants in a context of severe syndromic developmental disorder. To our knowledge, no additional patient has been described since this first report.

Methods: We performed exome sequencing in a patient exhibiting a syndromic developmental delay and in her unaffected parents and report the phenotypic features.

Results: Our patient presented with a syndromic association of severe global developmental delay and diverse malformations, including cleft lip and palate, facial dysmorphic features, brain abnormalities, heart defect, growth retardation, and severe infections. She carried a novel *SMG9* homozygous variant NM_019108.3:c.1177C>T, p.(Gln393*), while her unaffected parents were both heterozygous.

Conclusions: We confirm that bi-allelic truncating *SMG9* variants cause a severe developmental syndrome including brain and heart malformations associated with facial dysmorphic features, severe growth and developmental delay with or without ophthalmological abnormalities, severe feeding difficulties, and life-threatening infections.

KEYWORDS

heart and brain malformation, nonsense mediated decay, SMG9

1 | INTRODUCTION

Pangenomic next generation sequencing (NGS) techniques such as exome and genome sequencing are becoming central in the genetic exploration and diagnosis of patients with nonspecific or ultra-rare diseases which cannot be identified clinically (Lee et al., 2014). SMG9 deficiency is such an ultra-rare and largely unrecognizable developmental disorder, originally described in 2016 by Shaheen and collaborators (Shaheen et al., 2016, p. 9). In this study, the authors investigated two families using autozygocity mapping, linkage analysis and exome sequencing, and identified a homozygous truncating variant in the *SMG9* gene in affected individuals of both families. All three

described patients shared a syndromic developmental disorder characterized by brain and heart malformations, severe global developmental delay and facial dysmorphic features. *Smg9* knock-out mice showed embryonic lethality in a context of major brain, eye, and cardiovascular malformations hence recapitulating the human phenotype. No additional patient or family has been described since this report to our knowledge, indicating a high rarity for this disease. In an effort to further delineate this rare developmental disorder, we herein report the detailed clinical and molecular presentation of an unrelated fourth patient, and review the overall phenotype associated with *SMG9* deficiency.

2 | PATIENT AND RESULTS

2.1 | Clinical description

We report the case of a 5-year-old female born to healthy consanguineous parents (Figure 1; Table 1). Pregnancy follow up revealed polyhydramnios requiring amnioreduction at 29 weeks of gestation, lateral cleft lip and palate, and intrauterine growth restriction related to a single umbilical artery with abnormalities on Doppler ultrasound. Standard karyotyping performed on amniotic cells was normal, as well as fetal brain MRI performed at 29 weeks of gestation. She was born premature at 30 weeks of gestation by caesarian section performed in the context of fetal cardiac rhythm abnormality. Birth weight was 970 g (8th percentile), height was 34.5 cm (4th percentile) and occipitofrontal circumference was 25.5 cm (7th percentile). Clinical examination at birth confirmed the left cleft lip and palate, and revealed facial dysmorphic features (Figure 1a) including bi-temporal retraction with frontal bossing, upslanting palpebral fissures with hypertelorism, a wide nasal bridge, midface hypoplasia, low-set square ears with attached earlobes and a transient frontal white hair lock; she also had brittle and dysplastic toenail. Screening for malformations identified a congenital heart defect with a ventricular septal defect, a bicuspid aortic valve and aortic dilatation. In addition, cerebral MRI performed at the age of 12 months revealed enlarged four ventricles with a dysmorphic appearance, a thin corpus callosum, a cavum septum pellucidum, and a Blake's pouch cyst (Figure 1d).

Premature birth was complicated by respiratory distress syndrome and chronic lung disease. She presented early and severe feeding difficulties, which required gastrostomy and prolonged enteral feeding. Despite an active nutrition follow-up and normal growth hormone (GH) secretion, she underwent a severe postnatal growth restriction in height, weight and head circumference (all three metrics <−3 *SD* at

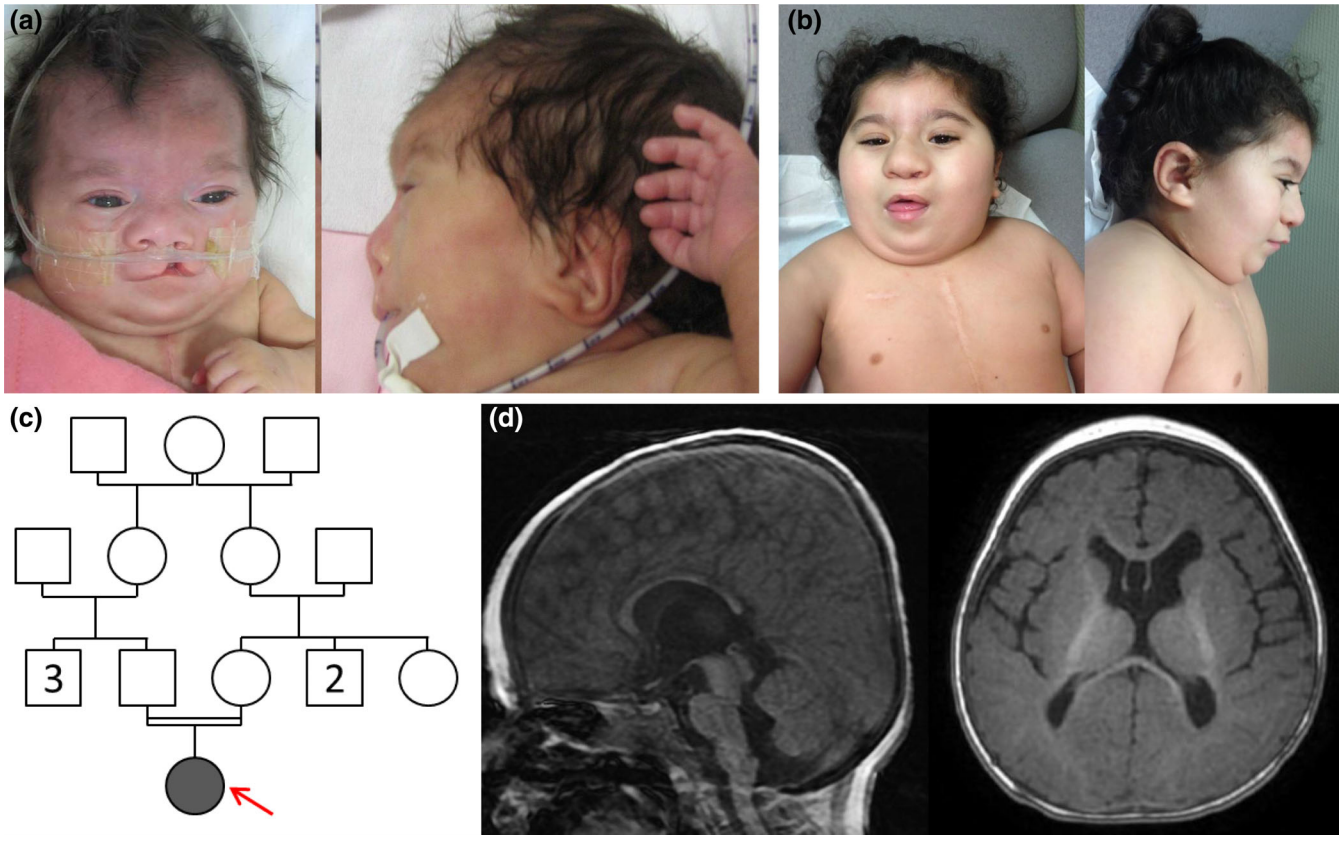

FIGURE 1 Clinical description. (a) Facial clinical features at the age of 3 months (front view) and 1 month (side view). Note the presence of prominent metopic suture with bitemporal retraction and frontal bossing, ptosis, hypertelorism, upslanding palpebral fissures, cleft lip, and dysplastic ears. (b) Facial clinical features at 3 years of age. (c) Pedigree of the family. (d) T1-weighted brain MRI at the age of 12 months. Sagittal view: short and thin corpus callosum, large fourth ventricle communicating with cisterna magna (Blake's pouch cyst). Axial view: persistence of cavum septum pellucidum and delayed myelination [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Clinical features of our proband (referred to as patient 4) and previously described patients

		Patient 1	Patient 2	Patient 3	Patient 4
		Family 1, IV:5 (Shaheen et al., 2016)	Family 2, V:1 (Shaheen et al., 2016)	Family 2, IV:3 (Shaheen et al., 2016)	This report
SMG9 homozygous variant		NM_019108.3: c.520_521delCC	NM_019108.3:c.701+4A>G	NM_019108.3:c.701+4A>G	NM_019108.3:c.1177C>T
Gender		Female	Female	Female	Female
Family history		Consanguinity, one similarly affected sibling	Consanguinity, one similarly affected cousin	Consanguinity, one similarly affected cousin	Consanguinity, no other affected relatives
Prenatal history	2/4	Polyhydramnios, Abnormal umbilical artery Doppler, Splaying of the cerebellum, VSD	NA	Uneventful pregnancy and delivery	Single umbilical artery with Doppler abnormality, IUGR, Polyhydramnios requiring amnioreduction, Lateral cleft lip and palate, Prematurity induced for fetal heart rate abnormality
Weight, length, head circumference at birth		2,13 kg (−1,65SD) 44 cm (−2,4SD) 31,5 cm (−2,2SD)	2,26 kg (−2,2SD) 47 cm (−1SD) 32 cm (−1,8SD)	NA	0.95 kg (−1,5SD) 34,5 cm (−1,5SD) 25,5 cm (−1,5SD)
Facial dysmorphic features	4/4	Prominent forehead and occiput, Low set malformed ears, Wide anterior Fontanelle, Depressed nasal bridge and anteverted nares, High arched palate	Narrow forehead, Prominent metopic suture, Posteriorly rotated ears with attached lobules, Hypertelorism, Small eyes, Broad nasal bridge, Full and everted lower lip, Right-sided cleft lip	Dysmorphic features	Left cleft lip and palate, Transient frontal white hair lock, Bi-temporal retraction with frontal bossing, Upslanting palpebral fissures with hypertelorism, Broad nasal bridge, Midface hypoplasia, Low-set posteriorly rotated ears with attached lobules, Widow's peak
Extremities	3/4	Clenched hands with camptodactyly	Syndactyly between 2nd and 3rd toes	NA	Brittle toenail
Neurologic	4/4	Seizures	Global developmental delay, Truncal hypotonia, Exaggerated deep tendon reflexes with clonus	Global developmental delay, Truncal hypotonia, Peripheral hypertonia, Exaggerated deep tendon reflexes	Global developmental delay, No language
Ophthalmologic	3/4	Microphthalmia	Poor vision	NA	Bilateral cataracts
Cardiovascular	4/4	Interrupted aortic arch, Hypoplastic tricuspid and aortic valves, Large muscular VSD	Large VSD	VSD	VSD, Aortic valve bicuspidy and aortic dilatation

(Continues)

TABLE 1 (Continued)

		Patient 1	Patient 2	Patient 3	Patient 4
Infections	2/4	Sepsis, deceased at 7 weeks	NA	NA	Several sepsis, one life-threatening
Feeding/digestive	2/4	NA	NA	Major gastroesophageal reflux, Dependent to NG feeding	Gastroesophageal reflux, Severe feeding difficulties, Dependent of NG feeding
Growth restriction	3/3	NA	Failure to thrive, Microcephaly	Failure to thrive, Microcephaly	Failure to thrive, Microcephaly
Other				Bronchial stenosis, Laryngeal cleft type 1	Respiratory distress syndrome, Grade II and III vesico-ureteral reflux
Brain radiologic features	4/4	Dandy–Walker malformation, Cerebellar vermis hypoplasia, Hypoplastic corpus callosum	Dandy–Walker malformation, Decreased myelination, Brain atrophy	Brain atrophy, Prominent ventricular system, Thin corpus callosum	Brain atrophy, Thin corpus callosum, Blake pouch cyst
Abdominal ultrasound	1/4	Normal	Normal	Normal	Bilateral kidney hypoplasia

Abbreviations: NA, not available; IUGR, intrauterine growth restriction; NG, nasogastric; VSD, ventricular septal defect.

the age of 2.5 years). Nutritional monitoring allowed weight improvement around −2 *SD*, whereas height remained near −3 *SD* requiring GH supplementation. The ventricular septum defect was treated sequentially, with an initial symptomatic treatment of pulmonary artery cerclage, followed at the age of 18 months old by proper surgical closure. She also underwent surgeries for cleft lip and palate, as well as for bilateral cataracts at the age of 5 years. She presented grade II and III vesico-ureteral reflux with bilateral kidney hypoplasia, and a dorsal-lumbar kyphosis.

She was subject to several acute infections requiring hospitalizations. The most significant episode consisted in a pyelonephritis caused by *Klebsiella pneumoniae*, associated with a severe dehydration caused by rotavirus gastroenteritis at 7 months of age. This event was complicated by an acute respiratory distress syndrome, as well as neurological symptoms which were later attributed to a parieto-occipital junctional stroke identified on cerebral MRI performed at 12 months of age.

Psychomotor development was severely delayed. She sat unaided at the age of 3 years. At last follow up at the age of 5, she did not stand alone and only used sounds and vocalizations but no words. She needed multidisciplinary care including physical therapy, psychomotor sessions, and speech therapy. She will not be able to go to elementary school and will require special schooling.

2.2 | Genetic testing

Genetic testing was carried out after obtaining the informed written consent of both parents. The testing strategy included an array comparative genomic hybridization, the targeted analysis of the *TFAP2A* gene involved in the branchio-oculo-facial syndrome (OMIM: #113620), the sequencing of 42 genes involved in intellectual disability associated with cleft lip and palate and *CHD7*, *EFTUD2* and *HOXA1* screening with the hypothesis of a CHARGE syndrome. As these tests did not identify the cause of the disease, we performed whole exome sequencing of the patient and unaffected parents.

Exonic sequences of the trio were enriched by capture (Agilent SureSelect All Exon V6) and sequenced with standard paired-end sequencing method (Illumina) at the Centre National de Recherche en Génomique Humaine (CNRGH, Evry, France). Standard bioinformatics pipeline was used in order to detect sequence variants and copy number variants, as described elsewhere (Grangeon et al., 2019). Rare coding variants fitting a de novo, autosomal recessive or X-linked model were considered for further interpretation, with a focus on genes involved in human Mendelian disorders in the OMIM catalog. Variant interpretation relied on the American College of Medical Genetics and Genomics—Association for Molecular Pathology (ACMG-AMP) guidelines (Richards et al., 2015). This approach identified a homozygous nonsense variant in *SMG9*, inherited from heterozygous parents: NM_019108.3:c.1177C>T, p.(Gln393*). This variant was absent from gnomAD v2.1 (Karczewski et al., 2019). It was predicted to result in a premature stop codon leading to nonsense-mediated decay within this single transcript gene. Therefore, and because bi-allelic loss of function was the known mechanism in the associated disease (Heart

and brain malformation syndrome, OMIM #616920), we considered this variant as pathogenic (ACMG-AMP class 5). Targeted Sanger sequencing confirmed this variant as homozygous in the patient and heterozygous in both parents.

3 | DISCUSSION

Exome sequencing led to the diagnosis of SMG9 deficiency in our proband. Phenotypical presentation was highly consistent with the three patients already described (Table 1). Features observed in all patients were facial dysmorphism (4/4), severe global developmental delay (3/3), ventricular septal defects (4/4), growth restriction (3/3), microcephaly (3/3) and brain abnormalities (4/4). Prenatal abnormalities were observed in two patients, including our proband, and consisted in polyhydramnios (2/4), abnormalities of the umbilical arteries (2/4), and prenatal identification of various malformations. Recurrent dysmorphic features included prominent forehead or metopic suture (3/3), broad nasal bridge (2/3), abnormalities of the ears (3/3), and cleft lip and/or palate (2/4). All patients with a clinical follow-up presented with severe developmental delay, both in growth motor skills (sitting position was acquired in patient 2 and in our proband at the age of 3 years and so far no ability to unaided walk is reported) and in language acquisitions (our proband had no spoken language). Pyramidal signs were reported in two patients and epilepsy in one patient (patient 1), who deceased in her first weeks of life. Brain imaging showed abnormalities in all patients, with Dandy-Walker abnormalities (2/4), thin or hypoplastic corpus callosum (3/4), vermis hypoplasia (1/4), decreased myelination (1/4) and dysmorphic appearance of the ventricular system (1/4). All three patients with a follow-up evolved to some degree of generalized brain atrophy. Ophthalmological features appeared diverse and included microphthalmia in one patient, poor vision in another and bilateral cataracts in our proband. Congenital heart defects affected all patients, with large ventricular septal defects diagnosed in all patients, requiring a surgical procedure. Our proband presented with severe infections with sepsis, which is reminiscent of the patient 1 who died in a context of sepsis at the age of 7 weeks. Based on this observation, one could make the hypothesis of an immunological susceptibility to bacterial infections in patients with *SMG9* deficiency, but routine biological check-up in our proband did not confirm this assumption. Feeding difficulties were a major concern in two patients, including our proband who is still dependent of gastrostomy feeding at the age of 5 years. All patients presented growth delay with microcephaly, which could appear in utero or within the first months of life.

The *SMG9* gene encodes a major protein from the nonsense-mediated decay (NMD) machinery (Fernández et al., 2011). The absence of *Smg9* in mice resulted in the dysregulation of many transcripts (Shaheen et al., 2016). In contrast, there was no evidence of widespread perturbation of the degradation by the NMD of premature termination codon (PTC)-containing transcripts. The observation of a globally homogeneous phenotype between all affected individuals indeed supports the hypothesis that this disease results from a consistent dysregulation mechanism rather than from the effect of the specific family-dependent background of PTC-containing genes that would be incorrectly silenced by the NMD pathway.

In summary, *SMG9* deficiency leads to a quite specific form of syndromic encephalopathy. However, despite being a potentially recognizable association, the great rarity of this disease means that it will probably only be diagnosed by a pangenomic sequencing approach. Therefore, in this context of retro-phenotyping, further clinical characterization of this entity will be useful for the process of variant interpretation. All variants reported so far are truncating variants predicted to trigger NMD, which are straightforward to interpret as pathogenic in this context, but we can anticipate the existence of pathogenic missense variants in *SMG9*, as in most autosomal recessive disorders, or even other types of variants. In these more challenging interpretation contexts, a precise clinical description will be helpful to implicate or reject new candidate variants.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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