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Review

First reports of fetal *SMARCC1* related hydrocephalus

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ABSTRACT

The *SMARCC1* gene has been involved in congenital ventriculomegaly with aqueduct stenosis but only a few patients have been reported so far, with no antenatal cases, and it is currently not annotated as a morbid gene in OMIM nor in the Human Phenotype Ontology. Most of the reported variants are loss of function (LoF) and are often inherited from unaffected parents. *SMARCC1* encodes a subunit of the mSWI/SNF complex and affects the chromatin structure and expression of several genes. Here, we report the two first antenatal cases of *SMARCC1* LoF variants detected by Whole Genome Sequencing (WGS). Ventriculomegaly is the common feature in those fetuses. Both identified variants are inherited from a healthy parent, which supports the reported incomplete penetrance of this gene. This makes the identification of this condition in WGS as well as the genetic counseling challenging.

1. Introduction

Congenital hydrocephalus is characterized by abnormal accumulation of cerebrospinal fluid in children's brain. The main sign is dilatation of cerebral ventricles (ventriculomegaly), often associated with an increase of intracranial pressure (KT et al., 2016). It is caused by overproduction of cerebrospinal fluid, insufficient reabsorption to the systemic circulation, abnormal cilium flow, partial or complete obstruction of the ventricular system. This obstruction may be secondary (infections, cerebral hemorrhage, tumor …) or primary. Aqueduct stenosis can cause primary congenital hydrocephalus (KT et al., 2016). Endoscopic third ventriculostomy is the first-line treatment for hydrocephalus caused by aqueduct stenosis (Cinalli et al., 2011) but complications (recurrence, hernia) can occur and lead to death (PARK, 2022). The other common treatment for hydrocephalus, the ventriculoperitoneal shunt surgery has severe complications too (shunt dysfunction or infection) and the risk is more important if the surgery is performed during childhood (Riva-Cambrin et al., 2016). Moreover, neurocognitive disorders still persist in some patients despite successful surgeries (Riva-Cambrin et al., 2022). Congenital hydrocephalus remains a serious disease with high mortality (Tully et al., 2022) and usually has a poor outcome due to irreversible cell damage during pregnancy (McAllister, 2012). Several genes are currently known to be responsible for primary congenital hydrocephalus, including *L1CAM, MPDZ, CRB2* (Al-Dosari et al., 2013; H et al., 2013; Lamont et al., 2016).

SMARCC1 encodes a subunit of the Brg1 Associated Factors complex

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(BAFs), the catalytic subunits of mSWI/SNF (ML et al., 1999) and affects chromatin structure and expression of several genes (Y et al., 2019). Eight post-natal cases of patients with congenital hydrocephalus have been reported with causative variants in *SMARCC1* (CG et al., 2018; SC et al., 2020). Most of these variants are loss of function (LoF) and inherited from unaffected parents. For now, *SMARCC1* is still not annotated as a morbid gene in the OMIM catalog of genetic disorders and is absent from the Human Phenotype Ontology (HPO) gene database.

Here, we report on the first two antenatal cases and neuropathological description of ventriculomegaly with novel *SMARCC1* pathogenic variants and we review the previously reported patients (Table 1).

2. Clinical report

Family A (Fig. 1)

During the first pregnancy of healthy couple, ultrasound examination performed at 23 gestation weeks (GW) showed severe ventriculomegaly (around 25 mm) with abnormal gyration, macrocephaly, and ventricular septal rupture (Fig. 1). At 25 GW, fetal MRI confirmed the triventricular dilatation with severe gyration delay (fasciculation defect) without sign of hemorrhage or primary aqueductal stenosis. The vermis was normal, and the cerebellum was noted as small.

Due to the uncertain prognosis of the unborn child, pregnancy was terminated at 25 GW, in accordance with the French law. Fetopathological and neuropathological examination performed with parental consent confirmed the male fetus presented macrocephaly with a triventricular dilatation with atresia-forking of the aqueduct (Fig. 1) and a gyration delay. Other findings were clinodactyly of the 5th fingers, abnormal bone maturation on the calcaneum, lung lobulation defect (3 on left and 5 on right), small pancreas, mild aortic hypoplasia, right pelvic testicle, and left inguinal testicle.

At the second pregnancy, the 18 GW ultrasound examination revealed ventriculomegaly (around 15 mm) with septal rupture, macrocephaly and right pyelectasis. At 19 GW, reference ultrasound examination confirmed the previous findings and revealed an abnormal aspect of frontal horns and short nasal bones. In accordance with the French law, pregnancy was terminated at 19 GW. During both pregnancies, genetic investigations on amniotic fluid (karyotype, chromosomal micro-array analysis (CMA), FISH (Fluorescence in Situ Hybridization) 13, 18, 21) were normal.

Trio (case 2 and parents) whole genome sequencing (WGS) in the fetus revealed a maternally inherited frameshift variant in *SMARCC1*: NM_003074.3:c.1436dup p.(Asn479LysfsTer18). This variant was not present in GnomAD v2.1.1 exomes and GnomAD v3.1.2 genomes and was predicted to result in nonsense-mediated mRNA decay (NMD). The mother shows no sign of skeletal malformations. A subsequent Sanger sequencing found the same *SMARCC1* variant in the first fetus.

Family B (Fig. 1)

During first pregnancy of healthy parents, an ultrasound examination at 15 GW showed isolated ventriculomegaly (around 12 mm). At 19 GW, an ultrasound reference examination confirmed ventriculomegaly (around 19 mm) with a septal rupture (Fig. 1). The vermis and the corpus callosum seemed normal. The aqueduct of Sylvius was not seen, suggestive of stenosis. In accordance with the French law, pregnancy was terminated at 20 GW. Fetopathological and neuropathological examination found out an eutrophic male fetus, with no skeletal abnormalities nor visceral malformations. Brain examination confirmed macrocephaly and severe dilatation of the ventricles and atresia-forking of the aqueduct (Fig. 1). No defect of the pyramidal fascicles was found but a corpus callosum agenesis was present. Karyotype and CMA were normal.

Trio WGS revealed a paternally inherited frameshift variant in *SMARCC1:* NM_003074.3: c.1668dup p.(Asn557Ter). This variant was not present in GnomAD v2.1.1 exomes and GnomAD v3.1.2 genomes and was predicted to result in nonsense-mediated mRNA decay (NMD).

Subsequent Sanger sequencing identified the variant in the grandmother too. The grandmother and the father showed no sign of skeletal malformations and no neurological symptoms. However, a brain MRI was not performed.

3. Discussion

Here we report three fetal cases from two families with hydrocephaly, a phenotype previously reported in children and adults with *SMARCC1* pathogenic variants.

To date, 9 pathogenic *SMARCC1* variants were reported in 10 patients from 9 families. All variants and phenotypic features are summarized in Table 1. WES was performed in 177 probands with congenital hydrocephalus (CG et al., 2018) and identified 5 variants in *SMARCC1* gene (Table 1; Fig. 2), 4 of which were LoF and 3 of which were inherited. All these cases had aqueductal stenosis and from the prevalence of this sub-phenotype, the probability of these variants occurring randomly in *SMARCC1* was extremely low. So, they suggested a causative effect on the phenotype with incomplete penetrance. Subsequently, WES performed on 381 patients with congenital hydrocephalus found 3 new LoF variants in *SMARCC1*, 2 of which were inherited (SC et al., 2020).

In accordance with previous findings, the two cases we report here confirm the incomplete penetrance and variable expressivity of *SMARCC1* but with even more severe spectrum.

There are several pitfalls that make the identification of causative variants in *SMARCC1* challenging. First, most pathogenic variants are inherited from healthy parents. This can cause the variants to be missed if the filtering is based solely on segregation analysis. Secondly, *SMARCC1* is currently not reported as a disease-causing gene in both OMIM and HPO databases which can also cause the variant to be missed if only variants in OMIM and/or HPO morbid genes are analysed. Moreover, it is also not present in the current Genomics England PanelApp list of hydrocephalus genes (v2.1123). This underscores the importance of a correct phenotypic annotation of genes.

This article is the third independent one on hydrocephalus with variants in *SMARCC1*, and the first antenatal reports, now counting 10 cases with this specific sign. Moreover, both our variants are LoF as well as most previously reported variants, in a gene which is very intolerant to LoF (PLi = 1 and LOEUF = 0.116 in GnomAD v2.1.1). Hence, we strongly believe that there is now enough evidence to consider *SMARCC1* with certainty as a disease-causing gene responsible for autosomal dominant hydrocephalus. Moreover, we used the ClinGen methodological approach (https://www.clinicalgenome.org/docs/gene-disease-validity-standard-operating-procedure-version-9/) to provide gene-disease assertion. We applied it for *SMARCC1* and the assertion is strong (Supplemental Material). Therefore, it should be annotated as such in OMIM and HPO and added in hydrocephalus gene panel lists such as Genomics England Panel App.

Aqueductal forking observed in the fetuses was first described by (Russel, 1949) and consists of a narrowed lumen of the aqueduct forming multiple indentations. This aspect of the aqueduct stenosis has been described in fetuses with hydrocephalus linked to *MPDZ* pathogenic variants (Saugier-Veber et al., 2017) and *CCDC88C* pathogenic variants (Marguet et al., 2021). Interestingly, a rare cerebellar malformation called rhombencephalosynapsis is associated in 39% of cases with an atresia-forking malformation (Pasquier et al., 2009). It would be interesting to explore *SMARCC1* in this malformation.A first hypothesis is a defect in the ependymal barrier, in particular in cell membrane junction components (gap junctions, adhesion molecules)(Jiménez et al., 2014). A defect in the ependymal cell planar polarity resulting in a of a dysfunction of ependymal cell cilia and related proteins is also suggested (Rodríguez et al., 2012). Rather to the establishment of apicobasal polarity and cell–cell junction formation and maintenance, a role in apical cell constriction was recently shown for *CCDC88C* and *MPDZ* that work cooperatively to drive apical constriction of the neural plate cells during neurulation (Marivin et al., 2019; Marivin and

Table 1
SMARCC1 related phenotypes reported in the literature.

Case	Age	Sex	*SMARCC1* NM_003074.3	NP_003065.3	Inheritance	Ventriculo-megaly	Aqueductal stenosis	Septal agenesis rupture	Corpus callosum defects	Developmental delay	Epilepsy	Macro-cephaly	Dysmorphism	Skeletal defects	Reference
1	N/A	M	c.2672del	p.(Lys891ArgfsTer6)	Paternal	+	+	+	+ (not specified)	+	+	–	–	–	Furey et al., 2018
2	N/A	F	c.1577A>C	p.(His526Pro)	De novo	+	+	+	+ (not specified)	+	–	+	–	+ (not specified)	Furey et al., 2018
3	N/A	F	c.535A>T	p.(Lys179Ter)	Paternal	+	+	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Furey et al., 2018
4	N/A	M	c.1242_1243dup	p.(Thr415LysfsTer29)	N/A	+	+	+	+ (not specified)	–	+	–	–	+ (not specified)	Furey et al., 2018
5	N/A	M	c.1602_1603ins ACTGGGGACTC	p.(Val535ThrfsTer29)	Maternal	+	+	+	+ (not specified)	+	–	+	+	–	Furey et al., 2018
6[a]	10 months	F	c.836G>A	p.(Trp279Ter)	De novo	N/A	N/A	N/A	N/A	+	–	N/A	+	+[b]	Al Mutairi et al. 2018
7[a]	10 months	F	c.836G>A	p.(Trp279Ter)	De novo	–	–	–	–	–	–	N/A	–	–	Al Mutairi et al. 2018
8	N/A	F	c.1571+1G>A	p.?	De novo	+	+	+	+ (not specified)	+	+	+	–	–	Jin et al., 2020
9	N/A	M	c.1723C>T	p.(Gln575Ter)	Maternal	+	+	+	+ (not specified)	–	–	–	–	–	Jin et al., 2020
10	N/A	F	c.1954C>T	p.(Arg652Cys)	Maternal	+	+	N/A	N/A	+	–	+	+	–	Jin et al., 2020
11	Fetus (25 GW)	M	c.1436dup	p.(Asn479LysfsTer18)	Maternal	+	+	+	–	N/A	N/A	+	+	+	Our study
12	Fetus (19 GW)	M	c.1436dup	p.(Asn479LysfsTer18)	Maternal	+	N/A	+	N/A	N/A	N/A	+	+	–	Our study
13	Fetus (20 GW)	M	c.1668dup	p.(Asn557Ter)	Paternal	+	+	–	+ (agenesis)	N/A	N/A	+	–	–	Our study
Total		F/M 0,46	4 frameshit 4 nonsense 2 missense 1 splice site	Fig. 2	Inherited Ratio 0,6	11/13	10/13	8/13	7/13	6/13	3/13	7/13	5/13	4/13	

N/A: not available
F: female
M: male.
[a] Case 6 and 7 are twins.
[b] Meningomyelocele, scoliosis, solitary kidney, imperforated anus with rectovaginal fistula, vertebral segmentation anomalie, right iliac bone hypoplasia.

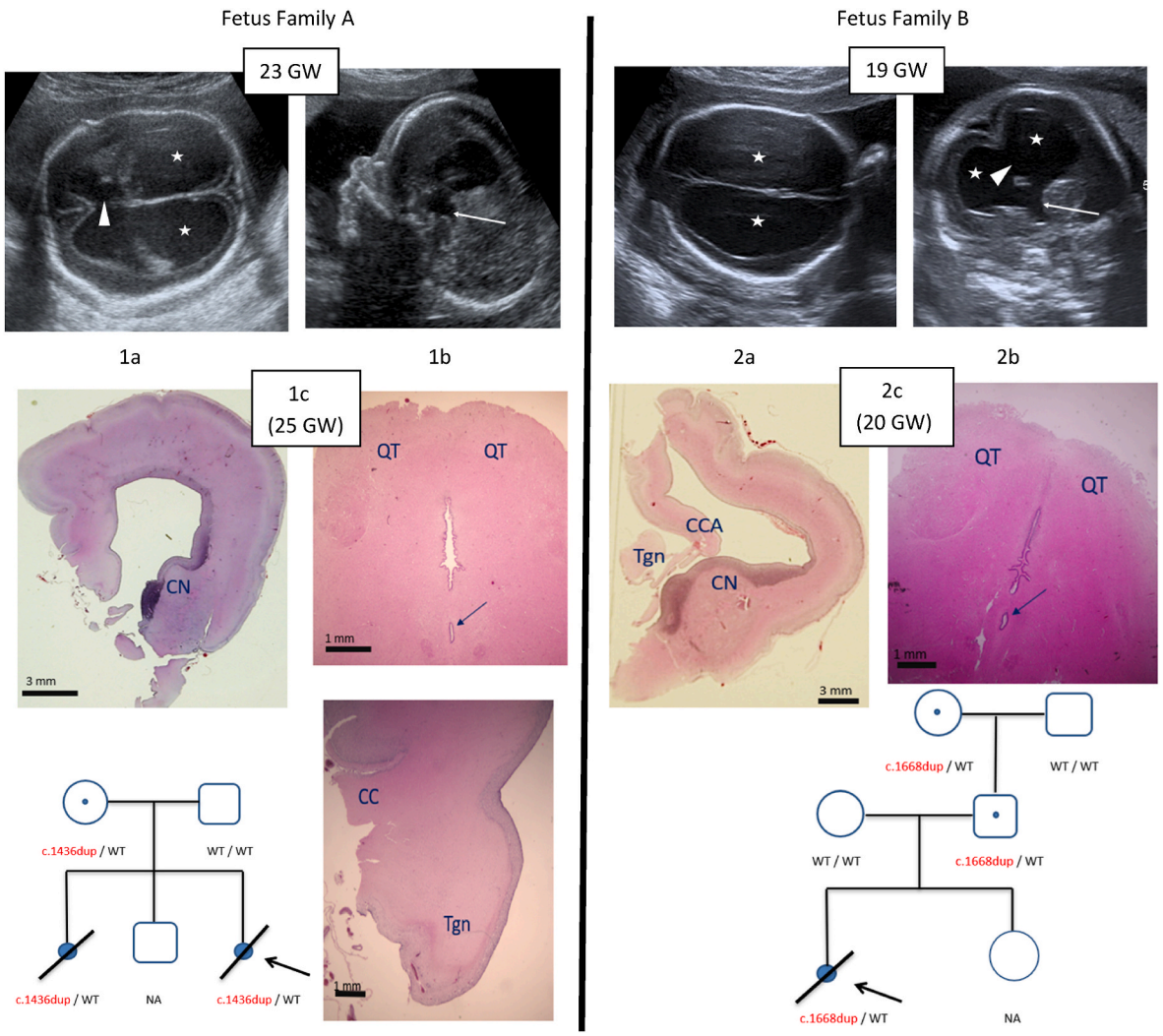

Fig. 1. Family pedigree, ultrasound, and neuropathological examination.
Ultrasound examination: US axial (1a) and midsagittal (1b) images at 23 + 2 weeks of gestation. Both lateral ventricles (stars) are markedly enlarged with subsequent septal disruption (arrowhead). The third ventricle (arrow) shows enlargement of the suprapineal and supraoptic recesses. These findings are in keeping with aqueductal stenosis. US axial (2a) and coronal (2b) images at 19 + 3 weeks of gestation. Both lateral ventricles (stars) are markedly enlarged. The septal disruption (arrowhead) is well visualized on the coronal view. The third ventricle (arrow) et slightly enlarged. All these findings were suggestive of aqueductal stenosis. Neuropathological examination (1c, 2c) : CCA: corpus callosum agenesis; CN: caudate nucleus; Tgn: fornix ; O: olivary nucleux; Py: pyramidal tract ; QT: quadrigeminal tubercules Arrow : atresia-forking of Sylvius aqueduct.

Garcia-Marcos, 2019). These different hypotheses could explain hydrocephalus (Jiménez et al., 2014; Rodríguez et al., 2012) but also neural tube defects as observed in patients reported by (F et al., 2018).

Indeed, a LoF variant in *SMARCC1* was reported in twins with neural tube defects (F et al., 2018). Since it is the only report with this phenotype and taking into account that *SMARCC1* variants have an incomplete penetrance in hydrocephalus, one cannot exclude the possibility that in this latter report, the variant is not causative of the twins' disease. On the other hand, it could also reflect an even greater variable expressivity of *SMARCC1-related phenotype*. More hindsight is necessary to decide between these two hypotheses.

SMARCC1 encodes a subunit of SWI/SNF complexes, also known as protein BAF155 (W et al., 1996), with two distinct known domains SWIRM and SANT (https://www.uniprot.org/). SWIRM domain is implicated in chromatin remodeling, gene expression and can bind both nucleosomal and double-stranded DNA (L and LM, 2002). SANT domain has a similar function and interacts with histone, even if the interaction remains unclear (LA et al., 2004). Most variants seem to occur between these 2 domains (Fig. 2).

No homozygous pathogenic variants have been described in patients. In homozygous mice, embryonic lethality has been described (JK et al., 2001). In heterozygous mice for *Srg3* (mouse ortholog of human *SMARCC1*) malformations are present in 20% of cases: exencephaly, abnormal embryonic neuroepithelial differentiation, ventricle defects, stenosis of the lateral ventricles (JK et al., 2001). *SMARCC1* seems to have an important role in the neurodevelopment of the embryo even if the mechanism by which *SMARCC1* acts remains unknown. Recently, the deletion of two subunits of BAF complexes in mice (including the mouse ortholog of *SMARCC1* and *SMARCC2*) have shown severe craniofacial defects and embryonic lethality (Bi-Lin et al., 2021).

SWI/SNF complexes are multimeric molecular assemblies that regulate chromatin architecture using ATP (C and GR, 2015; Wu et al., 2009). Three classes of SWI/SNF complexes are described: BRGI/BRM-associated factor complexes (BAFs), polybromo-associated BAF complexes (PBAFs), and non-canonical BAFs (ncBAFs) (N et al., 2018). *SMARCC1* is present in the three classes. Interestingly, *SMARCC1* often forms a homodimer, but sometimes *SMARCC1* forms a heterodimer with *SMARCC2* (N et al., 2018). We made the assumption that this fact could explain the incomplete penetrance. Using whole genome sequencing, we searched for a possibly pathogenic variant in *SMARCC2*

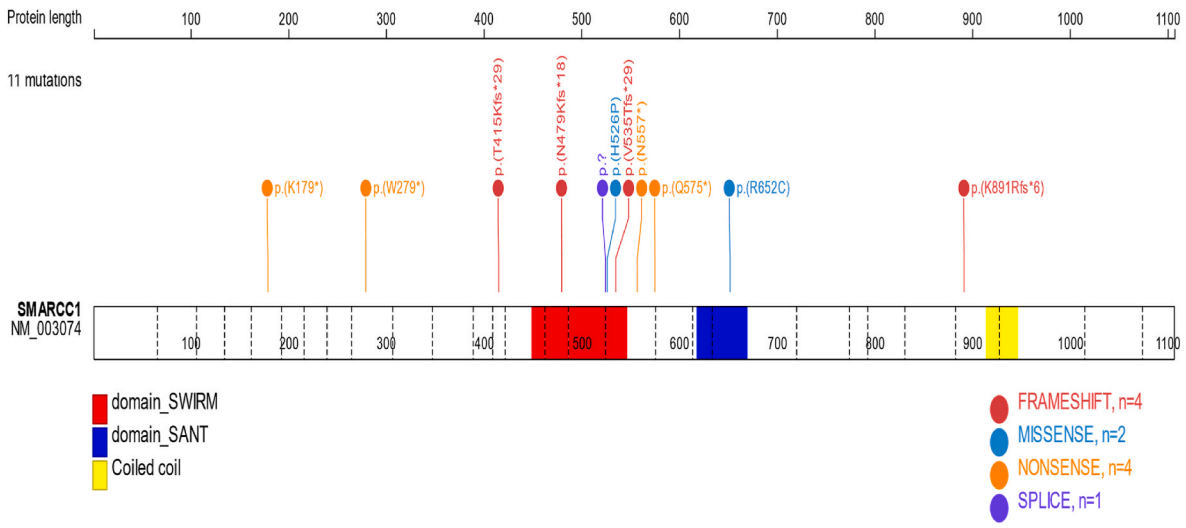

Fig. 2. Variants and domains in *SMARCC1*.
Footnotes: Protein modeling by ProteinPain St Jude Cloud (https://pecan.stjude.cloud/proteinpaint).

(including intronic variations), in our fetuses, whether de novo or transmitted by the parent who does not carry the variant in *SMARCC1*. Unfortunately, we did not find any variant of interest. We also explored other genes implicated in the SWI/SNF complex (*SMARCD1, SMARCD2, SMARCD3, SMARCB1, SMARCE1, ARID1A, ARID1B, DPF1, DPF2, DPF3, PHF10, BRD7, BICRA, BICRAL, BRD9, BCL7A, BCL7B, BCL7C, SS18, SS18L1, ACTL6A, ACTB, SMARCA2, SMARCA4, PBRM1, ARID2*) and found no variants of interest in both fetuses.

In conclusion, we report the first antenatal cases of *SMARCC1* variants responsible for hydrocephalus, confirming the implication of this gene in this condition despite a yet unexplained pathophysiology. Incomplete penetrance is an important feature of these condition which makes their identification challenging.

CRediT authorship contribution statement

Nicolas Rive Le Gouard: Writing – original draft, preparation, Data Collection. **Romain Nicolle:** Genomic, Investigation, Writing – review & editing, Reviewing. **Mathilde Lefebvre:** foetopathological and neuropathological examination. **Antoinette Gelot:** foetopathological and neuropathological examination. **Solveig Heide:** clinical data, Investigation, (geneticist). **Anna Gerasimenko:** clinical data, Investigation, (geneticist). **Romulus Grigorescu:** foetopathological and neuropathological examination. **Nicolas Derive:** Genomic platform, Data curation. **Jean-Marie Jouannic:** clinical data (pregnancy terminated). **Catherine Garel:** radiologist data/investigation (ultrasound photos). **Stéphanie Valence:** clinical data (pregnancy prognosis. **Geneviève Quenum-Miraillet:** Cytogenetic data/investigation. **Sandra Chantot-Bastaraud:** Cytogenetic data/investigation. **Boris Keren:** Genomic, Investigation, Writing – review & editing, Writing and Reviewing. **Delphine Heron:** Clinical, data, Investigation, Writing – review & editing, Writing and Reviewing. **Tania Attie-Bitach:** Supervision, Genomic, Investigation, Neuropathological and Foetopathological examination, Writing and Reviewing.

Declaration of competing interest

The authors declare no potential conflict of interest.

Data availability

Data will be made available on request.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2023.104797.

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