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CLINICAL REPORT

# Atypical phenotype of a patient with Bardet–Biedl syndrome type 4

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## Abstract

**Background:** Bardet–Biedl syndrome (BBS) is a multisystemic disorder characterized by rod–cone dystrophy, truncal obesity, postaxial polydactyly, cognitive impairment, male hypogonadotropic hypogonadism, complex female genitourinary malformations, and renal abnormalities. There is a large clinical and also genetic heterogeneity in BBS. Here, we report a patient with polydactyly, hyperechogenic kidneys increased in size with normal corticomedullary differentiation, anal imperforation, and malformation of genitals with presence of a genital tubercle with ventral urethral meatus associated with two unfused lateral genital swelling and absent urethral folds, in the context of 46, XY karyotype.

**Methods:** Karyotype and solo exome sequencing were performed to look for a genetic etiology for the features described in our patient.

**Results:** We identified a homozygous in-frame deletion of exons 4 to 6 in the *BBS4* gene (NM-033028 (BBS4-i001): c.[(157-?)_(405 +?)del] p.(Ala53-Trp135del), which is classified as pathogenic variant. This analysis allowed the molecular diagnosis of BBS type 4 in this patient.

**Conclusion:** Complex genital malformations are only reported in female BBS6 patients yet, and genital abnormalities and anal imperforation are not reported in male BBS4 patients to date. We discuss the possible hypotheses for this phenotype, including the phenotypic overlap between ciliopathies.

KEYWORDS

anal imperforation, Bardet–Biedl syndrome, genital anomalies, sex assignment

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## 1 | INTRODUCTION

Bardet–Biedl syndrome (BBS) is a rare multisystemic disorder, of the ciliopathies family, characterized by rod-cone dystrophy, truncal obesity, postaxial polydactyly, cognitive impairment, male hypogonadotropic hypogonadism, complex female genitourinary malformations, and renal abnormalities (Tobin & Beales, 2007). There is a large clinical and also genetic heterogeneity; at least 19 genes are associated with BBS, grouped into subtypes numbered 1 to 19: *BBS1* (MIM 209901), *BBS2* (MIM 615981), *ARL6* (BBS3, MIM 600151), *BBS4* (MIM 615982), *BBS5* (MIM 615983), *MKKS* (BBS6, MIM 605231), *BBS7* (MIM 615984), *TTC8* (BBS8, MIM 615985), *BBS9* (MIM 615986), *BBS10* (MIM 615987), *TRIM32* (BBS11, MIM 615988), *BBS12* (MIM 615989), *MKS1* (BBS13, MIM 615990), *CEP290* (BBS14, MIM 615991), *WDPCP* (BBS15, MIM 615992), *SDCCAG8* (BBS16, MIM 615993), *LZTFL1* (BBS17, MIM 615994), *BBIP1* (BBS18, MIM 615995), and *IFT27* (BBS19, MIM 615996) (Forsythe & Beales, 1993). More recently, other genes were reported such as *IFT74* (BBS20, MIM 617119) (Lindstrand et al., 2016) and *C8orf37* (BBS21, MIM 617406) (Héon et al., 2005; Khan et al., 2016). We report here a new case of homozygous for a pathogenic BBS4 variant, which highlights anogenital anomalies in a male that could be added to the clinical spectrum of the Bardet–Biedl syndrome.

## 2 | CLINICAL DESCRIPTION

Our patient is the first child of first-degree consanguineous parents. Several miscarriages, fetal death in utero, and perinatal death are reported in the maternal family. Natural pregnancy was complicated with gestational diabetes mellitus. Echographic examination at 22 weeks of gestation showed a polymalformative syndrome with asymmetrical enlargement of the lateral cerebral ventricles, hexadactyly of the right hand and left foot, varus malposition of both feet, suspicion of membranous ventricular septal defect (VSD), hypertrophy and hyperechogenicity of the kidneys, and oligoamnios with amnio-chorial detachment. Amniocentesis was performed at 24 SA for genetics and biochemical analyses: 7-dehydrocholesterol dosage for Smith-Lemli-Opitz syndrome was negative; karyotype was 46, XY and CGH array (Agilent kit 244A -Agilent Technologies, Santa Clara, CA-) was without unbalanced rearrangement.

Elected emergency cesarean section at the term of 33 weeks (birth weight 1275 g, 0.95 perc; birth length not specified; cranial perimeter 27.5 cm, 1.3 perc.) was decided because of fetal heart rhythm abnormalities, in the context of premature rupture of membranes.

At birth the polymalformative association was more precisely defined with spinal dysraphism localized at the lumbosacral area, excess of nuchal skin, known postaxial hexadactyly of the right hand and left foot, dysmorphism with thin-lip macrostomy and low set and posteriorly rotated ears. Perineal examination revealed anal imperforation and malformation of the genitals with presence of a genital tubercle with ventral urethral meatus associated with two unfused lateral genital swelling and absent urethral folds (Figure 1a–h), in the context of 46, XY karyotype.

Cardiac echocardiogram was reported as normal. Kidneys were globally hyperechogenic, increased in size with normal corticomedullary differentiation. Genital ultrasound examination at the level of each lateral genital swelling, detected the presence of a homogeneous rounded vascularized structure without fluid image, compatible with a testicle. There was no rectovesical interposition suggestive of uterus differentiation. Transfontanellar and spinal cord ultrasound were without particularity.

The hormonal workup performed at 2 days of life showed a testosterone secretion at 1.86 ng/ml (in the normal range for newborn males). LH, FSH, 17-hydroxyprogesterone, and androstenedione were normal. Cortisol level of 10 μg/L was low for this age.

After discussion with the parents and based on chromosomal analysis, biochemical and clinical data, male sex assignment was decided with left testicular lowering and urethral surgery of the penis with anterior cutaneous recovery by a Koyanagi flap at the age of 22 months. Additional surgeries were effected for testicular lowering, anal imperforation, hexadactyly, foot malposition, and lipoma of the filum terminale.

In light of this polymalformative syndrome, solo exome sequencing (ES) was carried out postnatally.

At last clinical evaluation, at the age of 3 years, the patient we report, born in 2015, had ophthalmological, otolaryngology, and genetics follow-up. Nutritional and endocrinological monitoring have been introduced due to significant overweight. Close nephrological management was necessary for the follow-up of a chronic renal failure of stage 2. He walked at 26 months. At 3 years of age, running and climbing stairs were still difficult. The education is done at school with an assistant of education (for speech delay).

## 3 | METHODS

Solo exome sequencing was performed on HiSeq 4000 (Illumina). Variant filtering and analysis were performed as previously described (Nambot et al., 2018).

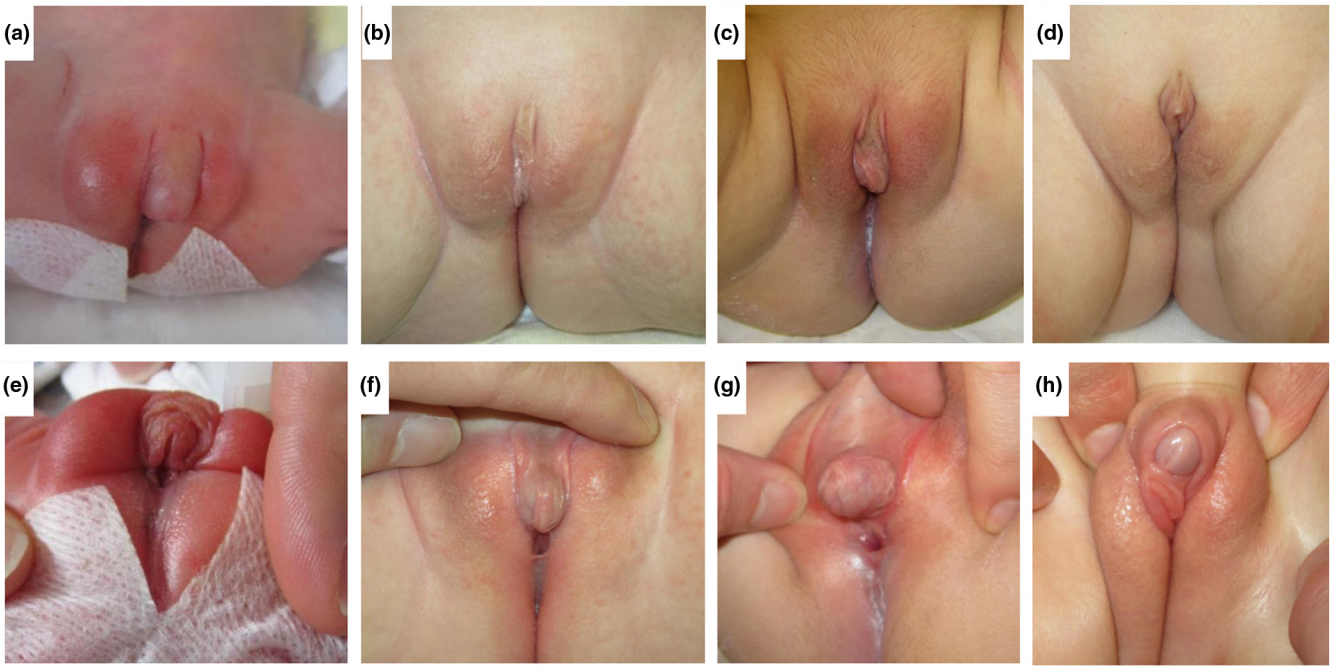


FIGURE 1 Ano-genital malformations. External genital appearance at the age of day one (a, e), 6 months (b, f), 12 months (c, g), and 19 months (d, h)

### 3.1 | Editorial policies and ethical considerations

Patients' legal representatives have accepted the use of medical data for research purposes. They signed consents from the Clinical Genetics Department of the Nancy University Hospital, with concordance with French regulations.

## 4 | RESULTS

This exome analysis identified a homozygous in-frame deletion of exons 4 to 6 of the *BBS4* gene (NM-033028 (BBS4-i001): c.[(157-?)_(405 +?)del]; [(157-?)_(405 +?)del] p.(Ala53-Trp135del)) (Figure 2), which is classified as pathogenic variant. This deletion has already been reported as pathogenic in the literature without clinical description (Redin et al., 2012). This analysis allowed the molecular diagnosis of Bardet–Biedl syndrome type 4 in this patient.

## 5 | DISCUSSION

The association of unilateral postaxial polydactyly and abnormality of the renal echodensity are in accordance with the BBS diagnosis, as the syndrome commonly includes renal cysts. However, the renal phenotype is atypical with hyperechogenic features and caliceal dilation, and the genito-anal abnormalities are not typically reported in BBS cases with a 46, XY karyotype. A clinical description of a patient with the same BBS4 pathogenic variant was reported by Karmous-Benailly et al. (2005). The patient was a girl who died at age 12 d. Since the antenatal period she presented unilateral foot polydactyly, cystic kidneys, and endocardial cushion defects. No brain anomaly was apparent, and no anal imperforation was described in this case. Among the reported cases of exons 4 to 6 deletion of BBS4 (Karmous-Benailly et al., 2005; Muller et al., 2010; Redin et al., 2012) only the work from Karmous-Benailly provided a clinical description of the patient, who did not exhibit anal imperforation.

Complex genital malformation is reported in female BBS patients, the majority in BBS6, such as hypoplastic fallopian tubes, uterus and ovaries; partial and complete vaginal atresia; septate vagina; duplex uterus; hematocolpos; persistent urogenital sinus; vesico-vaginal fistula; absent vaginal orifice; and absent urethral orifice. Some of these anomalies have also been described in McKusick–Kaufman syndrome (MIM 236700), of which some signs and symptoms overlap with BBS at birth. (Forsythe & Beales, 1993; Moore et al., 2005; Slavotinek & Biesecker, 2000) (Table 1). No clinical description of hypoplasia of the labia majora has been reported in the literature. Functional anomalies are also frequently reported in male patients with BBS with hypogonadotrophic hypogonadism during fetal life, leading to micropenis or ectopic testicles (Beales et al., 1999). In contrast, no other genital malformation other than hypovirilization due to lack of hormonal influence was described in patients with BBS,

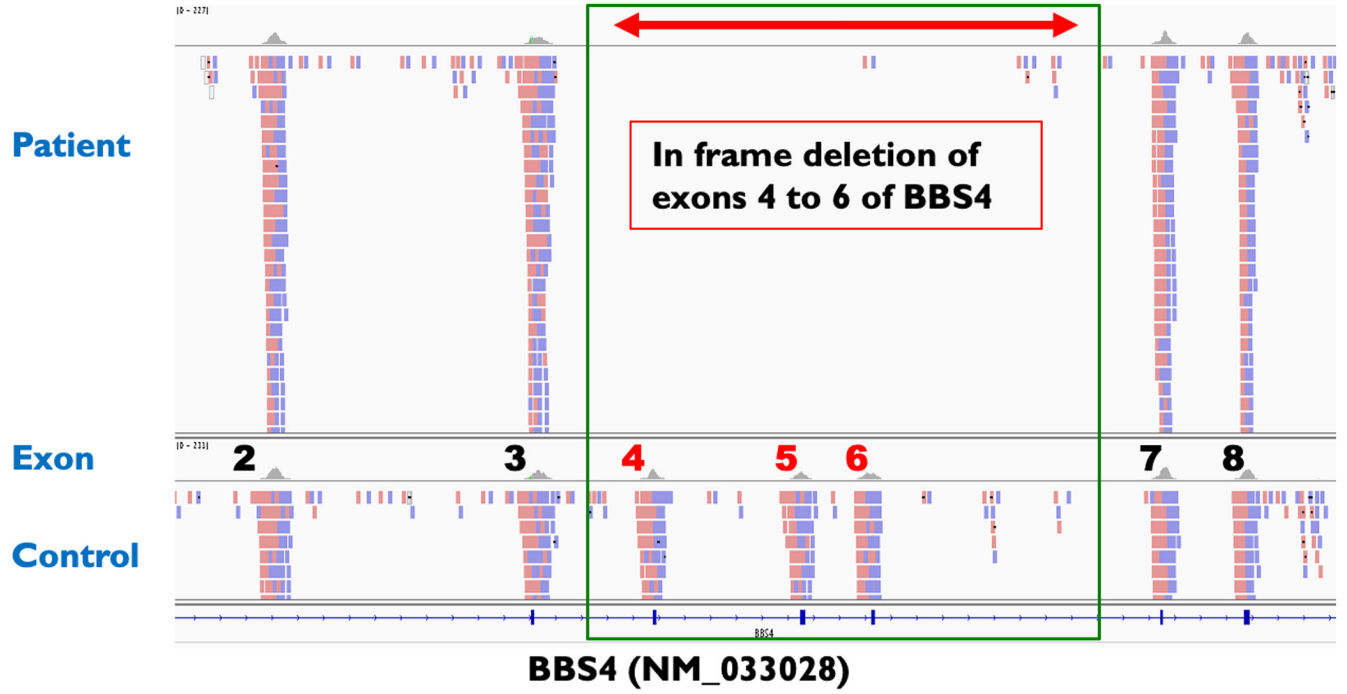


**FIGURE 2** IGV illustration. IGV illustration of the homozygous exon 4 to 6 deletion in the BBS4 gene: this in-frame deletion theoretically leads to the lack of 83 amino acids in the TPR (Tetratrico Repeat Region) motif of the protein

**TABLE 1** Description in the literature of female genital malformation in BBS (BBS6)

| Malformations | Slavotinek and Biesecker (2000) | Moore et al. (2005) |
|---|---|---|
| *Hydrometrocolpos* | 13/16 (81%) | / |
| *Vaginal agenesis* | 7/16 (44%) | 2/20 (10%) |
| *Urogenital sinus* | 4/16 (25%) | / |
| *Ectopic urethra* | 1/16 (6%) | / |
| *No urethral opening* | 1/16 (6%) | 1/20 (5%) |
| *No vaginal opening* | 2/16 (13%) | / |
| *Hypoplastic labia minora* | 3/12 (25%) | / |

regardless of the gene involved. Our patient presents a very severe phenotype with difficulties for gender assignment at birth due to the "intersexual" aspect.

While the anal imperforation presented by our patient is a sign that is not classically described in BBS, it has been reported in other ciliopathies, such as the Pallister–Hall syndrome (MIM: 146510, driven by *GLI3* variants). Recently, a fetal case of "atypical" ciliopathy was also described, in a case with a heterozygous sequence variant of *IFT27* (*BBS19*) associated with a phenotype including imperforate anus, short ribs, polydactyly, and bilateral renal agenesis (Quélin et al., 2018). This underlines the important phenotypic overlaps well known between the different ciliopathies.

We suggest several hypotheses to explain this unusual clinical presentation, including (1) an alteration of the embryological development program (2) a possible oligogenic transmission (3) a role of BBS4 as a modifier gene (4) a potential undetected variant.

1. The association of a genital malformation and an anal imperforation could evoke an early dysplasia of the embryonic caudal fold, during the pre-endocrine differentiation, in the determination of the genital area. Within the genital tubercle, the urethral epithelium is an endodermal component that expresses *Sonic hedgehog (Shh)*. Even though Shh signaling has been described as controlling the outgrowth and pattern formation of the urethral epithelium, major questions remain to be answered, including the nature of the molecular signals that initiate genital budding, sustain outgrowth, induce tissue polarity, and orchestrate urethral tubulogenesis. (Lindstrand et al., 2016) Thus, *BBS4* could be involved in the very primary polarization of the genital area, at least in the case we describe here.
2. One may question the exclusive role of homozygous sequence variant of *BBS4* in the present case. Katsanis et al. (2001) proposed that BBS may also be inherited in a more complex fashion, as an oligogenic disorder. They described a number of pedigrees in which individuals were homozygous or compound heterozygous for variants at one locus, but required the presence

of a third heterozygous variant residing at a second BBS locus to manifest the disease phenotype. In the Katsani study, a single mutation was present in *BBS6* in an affected family member, in addition to the two other *BBS2* mutations. This could suggest that three altered alleles were necessary to induce the described BBS phenotype (Katsanis et al., 2001). No additional pathogenic variant could be identified in all the genes involved to date in BBS in our patient. Thus, our data do not support the triallelism hypothesis, although triallelism with a gene not associated with BBS to date might explain the severe genital expression or the difference in the renal presentation. Similarly, the group of Slavotinek and colleagues worked on the MKKS and sequenced *BBS2* in their patients, but no pathogenic alterations could be detected (Slavotinek et al., 2002). Therefore, their data are not supporting either the triallelic hypothesis.

3. Alternatively, *BBS4* may act as a modifier gene in association with other BBS-related genes. The modifier hypothesis suggests that the BBS4 protein is a putative chaperonin, and is therefore likely to be involved in the folding and structural modification of other proteins (Slavotinek & Biesecker, 2000). Modifier alleles may account for most of the phenotypic variability (Ramsbottom, Miles, & Sayer 2015). In this work, a disparity in the viability and phenotype of different strains of mice each containing the same genetic alteration in *Cep90* suggested that there were significant genetic modifiers specific to each strain of mice, which could adversely affect the way in which this disease presented (Ramsbottom et al., 2015). The genetic diversity existing between human individuals may therefore provide some hints as to the broad range of phenotypes observed in BBS patients.
4. Lastly, in the morbid genome of ciliopathies, the presence of additional ciliopathy alleles (in BBS, MKKS, or other ciliopathy), increased the severity of disease, and in the most severe phenotypes situations, non-Mendelian inheritance patterns were necessary for the occurrence of ciliopathy disease (Ciliopathy Working Group et al., 2016). No other pathogenic, or likely pathogenic variants, were detected by exome analysis in our patient. We can also postulate that there could be another variant, usually non-pathogenic (or not described as such), in a sexual development gene, that could have played a role in the genesis of this malformation.

The description of other cases of BBS or ciliopathies presenting with the same type of genital abnormalities could be useful to define the mechanism that led to the severe anogenital malformation in our patient.

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## CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

## AUTHOR CONTRIBUTIONS

V.C and M-L.E. were in charge of the first antenatal genetic consultations. A-B.L., F.T.M-T., C.B., and C.P. performed the genetic analyses. L.L. and B.L. were in charge of the postnatal genetic consultations. V.G., J-L.L., and O.K. performed the surgeries. M-C.C-S. and M.M. were in charge of the nephrology-related care. C.L. was in charge of the endocrinology consultations. B.L. was at the origin of the case report. N.S wrote the manuscript. All the authors drafted the manuscript.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article, as no new data were created or analyzed in this study.

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