A case of Bardet-Biedl syndrome caused by a recurrent variant in *BBS12*: A case report

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Abstract. Bardet-Biedl syndrome (BBS) is a clinically and genetically heterogenous disorder that manifests as a result of primary cilia impairment. Cilia are present on most cell types, thus BBS is a multisystemic condition involving the majority of organ systems. The core features of the syndrome include retinal degeneration, obesity, polydactyly, cognitive impairment, renal anomalies and urogenital malformations. To date, pathogenic variants in 26 genes have been shown to be involved in the molecular basis of this rare ciliopathy. Of these causal loci, *BBS12* accounts for ~8% of all cases. In this case report, an individual with BBS caused by a rare recurrent variant in *BBS12* (NM_152618.3: c.1063C>T; p.Arg355*) is described and compared with others with the same DNA variant, placing this finding in the context of the current literature.

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Key words: Bardet-Biedl syndrome, cilia, ciliopathies, chaperonin, oligogenic, pleiotropy

Introduction

Bardet-Biedl syndrome (BBS) [Mendelian Inheritance in Man (MIM), 209900] is a heterogenous disorder that is caused by the impairment of primary cilia. It belongs to a broad group of disorders known as ciliopathies, and represents a hallmark exemplar with a highly variable clinical presentation, likely due to second-site modification of primary causal loci (1-3). The predominant clinical features associated with BBS are retinal degeneration, obesity, polydactyly, cognitive impairment, renal disease and hypogonadism or urogenital malformations. Minor symptoms that may complicate a clinical diagnosis of BBS include developmental delay, behavioral and psychiatric abnormalities, metabolic and endocrine impairment, cardiovascular involvement, liver disease, Hirschsprung disease and olfactory deficits (4). Given the wide phenotypic variability that exists within and amongst BBS families, a clinical diagnosis of BBS may prove to be challenging. However, a diagnostic algorithm has been proposed by the presence of either four major features, or three major features and two minor symptoms (5). Moreover, it is difficult to make an accurate early diagnosis since the majority of the symptoms may only occur over time. Therefore, the median age of diagnosis is 9 years of age, and typically the diagnosis is associated with the occurrence of retinal degeneration (5,6). Although certain symptoms can be detected at an antenatal stage, such as polydactyly or genitourinary abnormalities, in the absence of a positive family history and established molecular underpinnings, such a diagnosis is rarely established in early childhood (7). Obesity, which is

Table I. Causal Bardet-Biedl syndrome genes.

Gene no.	Gene name	Alias	MIM number	Chromosomal location	Subcellular location of related proteins
1	*BBS1*		209901	11q13.2	BBSome
2	*BBS2*	RP74	606151	16q13	BBSome
3	*ARL6*	BBS3, RP55	608845	3q11.2	BBSome associated
4	*BBS4*		600374	15q24.1	BBSome
5	*BBS5*		603650	2q31.1	BBSome
6	*MKKS*	HMCS, KMS, MKS, BBS6	604896	20p12.2	Chaperonin complex
7	*BBS7*		607590	4q27	BBSome
8	*TTC8*	BBS8, RP51	608132	14q31.3	BBSome
9	*PTHB1*	BBS9	607968	7p14.3	BBSome
10	*BBS10*	C12orf58, FLJ23560	610148	12q21.2	Chaperonin complex
11	*TRIM32*	HT2A, LGMDR8, BBS11	602290	9q33.1	Cilium base
12	*BBS12*	FLJ35630, C4orf24	610683	4q27	Chaperonin complex
13	*MKS1*	MKS, BBS13, JBTS28	609883	17q22	Basal body
14	*CEP290*	KIAA03733H11AG, JBTS5, SLSN6, LCA10, BBS14	610142	12q21.32	Basal body
15	*WDPCP*	C2orf86, BBS15, CHDTHP	613580	2p15	Basal body
16	*SDCCAG8*	CCCAP, SLSN7, BBS16	613524	1q43-q44	Basal body
17	*LZTFL1*	BBS17	606568	3p21.31	BBSome associated
18	*BBIP1*	NCRNA00081, BBIP10, BBS18	613605	10q25.2	BBSome
19	*IFT27*	RABL4, BBS19	615870	22q12.3	IFT
20	*IFT74*	CCDC2, CMG1	608040	9p21.2	IFT
21	*CFAP418*	C8orf37, CORD16, RP64, BBS21	614477	8q22.1	Cilium base
22	*NPHP1*		607100	2q13	Transition zone
23	*IFT172*		607386	2p23.3	IFT
24	*SCAPER*		618195	15q24.3	Cilium tip
25	*SCLT1*		611399	4q28.2	Distal appendage
26	*CEP164*		614848	11q23.3	Distal appendage

BBS, Bardet-Biedl syndrome; IFT, intraflagellar transport; MIM, Mendelian Inheritance in Man.

noted in 72-92% of patients with BBS, becomes evident during the first 3 years of life. Typically, the birth weight is normal, and the weight gain commences during the first year (5,7). Obesity is associated with a higher risk of developing diabetes, metabolic syndrome or hypertension (8,9). Cognitive difficulties are common (>60% of individuals with BBS), although only 25% of those observed fulfill the intellectual disability consensus criteria (10). Some specific deficits, such as perceptual reasoning, attention capacity and functional independence, appear to be the most severely affected (10). Other neuropsychiatric abnormalities have been observed in BBS, including developmental delay, either motor or language impairment, and a broad spectrum of behavioral disturbances, such as emotional instability, disinhibition, aggressiveness, self-injury or obsessive-compulsive behavior (10). Kidney disease affects 53-82% of patients with BBS, and this represents the common cause of morbidity and mortality (11). The renal phenotype is highly variable, with renal dysfunction leading to end-stage renal failure in 42% of adult patients, as revealed by a large BBS cohort study (12). Individuals with BBS also display structural anomalies ranging from cysts, fetal lobulation, renal dysplasia, calyceal distortion and hydronephrosis to ectopic, atrophic, horseshoe kidney or renal agenesis (13,14). Hypogonadism and genital anomalies are observed in 59-98% of patients. Small penile length has also been identified in nearly all males with BBS, whereas hypoplastic labia minora is common in females. Less frequently, hydrometrocolpos may complicate many of the malformations, including vaginal atresia and septate or imperforate vagina, which may be identified antenatally or shortly after birth (5,11,15). In a minority of individuals, valvular stenosis, atrial/ventricular septal defects or cardiomyopathy are observed, which may be diagnosed at the prenatal or neonatal stage (5,16), whereas anosmia, hearing loss, liver disease, Hirschsprung disease and laterality defects have been reported at different ages of onset (4,17,18).

At the time of this report, 26 genes have been associated with the pathogenesis of BBS (Table I). The majority of the encoded BBS proteins localize to the base of the cilium, and all have been shown to be involved in ciliary biogenesis or function (Fig. 1) (11). The BBS1, BBS2, BBS4, BBS5, BBS7, TTC8/BBS8, BBS9 and BBIP1/BBS18 proteins are components of the BBSome, a macromolecular complex

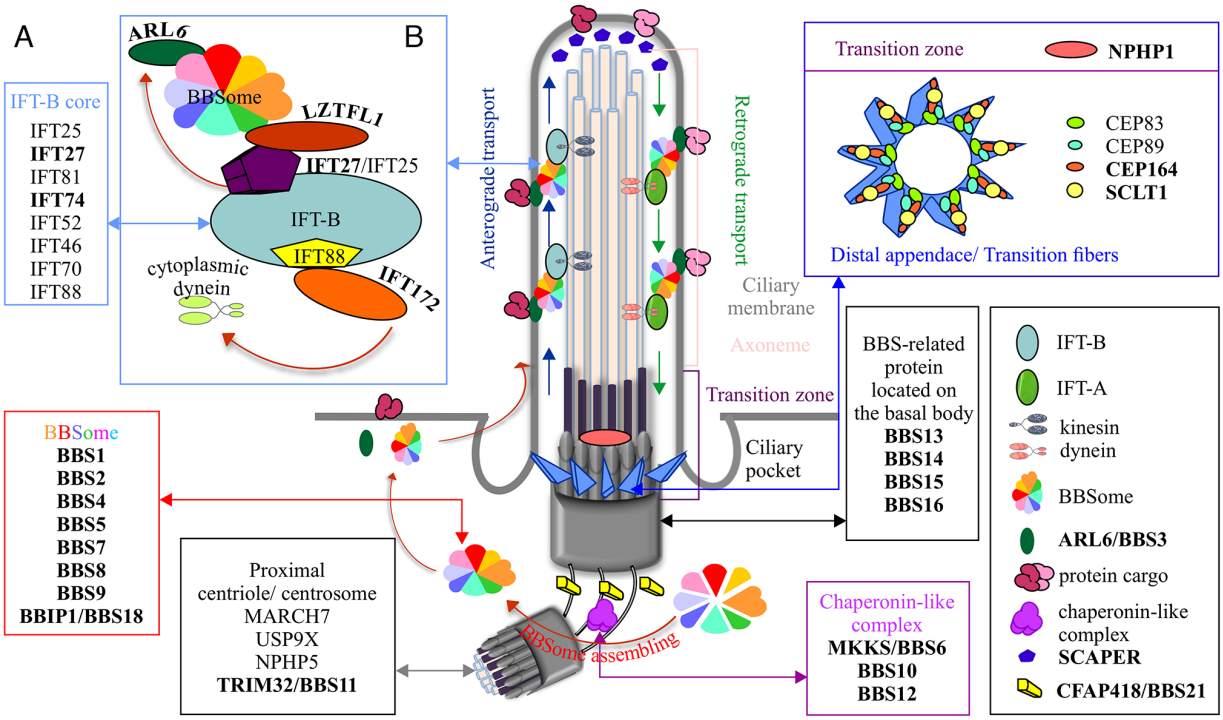

Figure 1. Location and interaction of BBS proteins within cilium. (A) Overview of BBS protein complexes at the cilium. (B) Details of anterograde transport molecule assembly. The BBS proteins are shown in bold. BBS, Bardet-Biedl syndrome.

that functions as an adaptor for intraflagellar transport (IFT) molecules (19,20). IFT molecules undergo bidirectional movement along the microtubule backbone (IFT-A and IFT-B protein complexes), acting as a carrier for proteins involved either in signaling pathways or in ciliary homeostasis (21). IFT27/BBS19, IFT74/BBS20 and IFT172 are components of the IFT-B complex, which confers anterograde IFT (22). IFT27/BBS19 has been suggested to interact with ADP ribosylation factor like GTPase 6 (ARL6)/BBS3, hence modulating the ciliary export of hedgehog signaling molecules. It has also been proposed that IFT27/BBS19 may interface with the BBSome complex through an interaction with leucine zipper transcription factor like 1 (LZTFL1)/BBS17 (23,24). IFT74/BBS20 has been shown to interact with IFT27/BBS19, whereas the remaining IFT-B molecules, including IFT172, play an important role in cilium stability (25,26). The position of the BBSome within the cilium is stabilized by ARL6/BBS3, a small GTPase that recruits the BBSome to ciliary membranes (19). The MKKS centrosomal shuttling protein (MKKS)/BBS6, along with the BBS10 and BBS12 proteins form part of the chaperonin-like complex that has an important role in BBSome assembly (27,28). Several proteins function at the basal body (MKS1/BBS13, CEP290/BBS14, WDPCP/BBS15 and SDCCAG8/BBS16) and are involved in ciliogenesis and the modulation of BBSome trafficking within the ciliary compartment (29-31). Tripartite motif containing 32/BBS11 is an E3 ubiquitin ligase that regulates components of the cytoskeleton, whereas LZTFL1/BBS17 is hypothesized to regulate BBSome activity through transient interaction with BBS9 (32-34). Cilia and flagella associated protein (CFAP)418/BBS21 is located at the base of the cilium, and appears to have a role in facilitating protein transport, although its complete function and mode of interaction within the BBS protein network have yet to be fully elucidated (35). Nephrocystin 1 (NPHP1), localized in the ciliary transition zone, has been shown to regulate the early stage of cilia formation (31,36) Recently associated with BBS, sodium channel and clathrin linker 1 (SCLT1) and centrosomal protein (CEP)164 are components of the distal appendages that are responsible for docking the cilium to the plasma membrane (37-39). Both of these are required for ciliary initiation. Another gene that has recently been shown to be associated with BBS is S-phase cyclin A associated protein in the ER (SCAPER), which was found to localize at the ciliary tip, suggesting that it may be involved in ciliary dynamics during the cell cycle (40). Pathogenic variants in these genes have been identified in >80% of patients with BBS, and this percentage has increased rapidly during the past decade due to the extensive use of next-generation sequencing approaches (7). The most common pathogenic variants occur in *BBS1* and *BBS10*, accounting for ~45% of clinically assessed cases. Considered together, the genes that code for components of the BBSome are most frequently (up to 57%) found mutated in patients with BBS, and these are followed by the group of genes that encode chaperonin-like proteins (~30%). Pathogenic variants identified in ARL6/BBS3 account for ~8% of the clinically diagnosed individuals. The remainder of the BBS genes are rarely found to be causal, and these account for ~5% of cases; moreover, certain variants found in these genes have been reported in only a few families (41,42). However, the frequency of a specific pathogenic variant appears to be correlated with the ethnic background of the affected individuals. Whereas *BBS1* and *BBS10* are most frequently impaired amongst individuals of European descent, pathogenic variants in *BBS4*, *BBS5* and *BBS8* appear to be enriched in Middle Eastern and North African populations (43-45). Notably, there is a higher

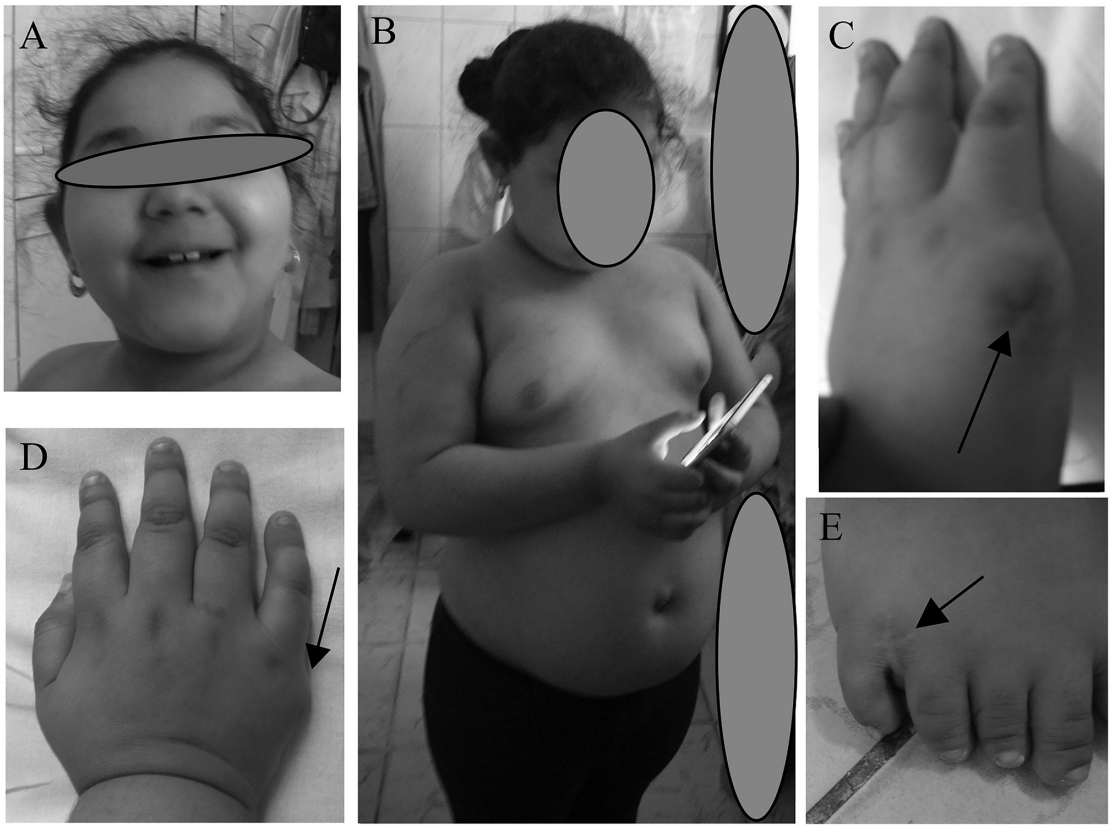

Figure 2. Images of the presented case. Images of the patient at (A-E) 5 and (B) 6 years-old, showing: (A) Tooth anomalies and dysmorphic craniofacial features, such as narrow forehead, decreased bitemporal diameter, sparse eyebrows, long and smooth philtrum and full cheeks; (B) Obesity; (C-E) scars and (C and D) reminiscent bone deformity after removal of polydactyly (black arrows); (D) brachydactyly, conic fingers, hypoplasia of distal phalanges and hypoplastic nails; and (E) partial cutaneous syndactyly of the second and third toes, and hypoplastic nails.

prevalence of *ARL6*/*BBS3* pathogenic variants in consanguineous Saudi and Indian families (46,47).

BBS has been shown to be predominantly inherited in an autosomal recessive fashion, although it may also be inherited as an oligogenic trait (48,49). The underlying molecular mechanism is often complicated through the intervention of a third mutant locus, giving rise to 'triallelic inheritance', which may explain the extensive clinical variability of patients with BBS (50). Similarly, it has been hypothesized that the presence of second-site modifier or epistatic interactions are responsible both for intrafamilial or interfamilial clinical heterogeneity and for the severity of the phenotype (2,51,52). Copy number variants and retrotransposon insertions have been proposed to contribute to the pathogenesis of BBS (53,54). Furthermore, it has been suggested that even environmental events may be involved in defining the complexity of the BBS phenotype (55).

Here, a hitherto unreported case of BBS, clinically diagnosed in accordance with consensus criteria established by Beales *et al* (5), that was caused by a rare recurrent c.1063C>T; p.Arg355* variant in *BBS12* is described. The molecular finding was identified by whole exome sequencing (WES) and confirmed by Sanger sequencing.

Case report

Written informed consent was obtained from the legal guardian of this patient and her family members, and they were all enrolled in the research study approved by Institutional Review Board of University of Medicine and Pharmacy 'Carol Davila' Bucharest (approval no. 29700, T.42; Oct 01, 2015). Additionally, the present study conformed to the guidelines of the Declaration of Helsinki (56). EDTA-treated peripheral blood samples from willing family members were collected (the patient, the patient's sibling and their parents) subsequent to informed consent. Genomic DNA was extracted from the blood using the PureLink® Genomic DNA Extraction kit (Invitrogen; Thermo Fisher Scientific, Inc.) according to the manufacturer's instructions. WES was performed by the Advanced Center for Translational and Genetic Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, IL, USA, according to a research study approved by the Lurie Children's Hospital IRB (approval no. IRB 2019-3057; Aug 5, 2019). WES was performed on proband genomic DNA samples according to an established protocol (LC Sciences, LLC). Fragmented DNA samples generated via sonication were subjected to library construction. Exome capture was performed using an Agilent SureSelect Human All Exon V6 kit (Agilent Technologies, Inc.) according to the manufacturer's instructions, and next generation sequencing was subsequently performed using an Illumina Novaseq6000 system at Lianchuan Bio for a 150 bp paired-end run, to a mean target depth of 147X, generating a total of 74,060,974 paired-end reads.

For bioinformatics analysis, and prior to alignment, low-quality reads (first, reads containing sequencing adaptors, and secondly, nucleotides with a quality score <20) were removed to yield a total of 73,150,226 cleaned paired-end reads. The Burrows-Wheeler Aligner (57) was utilized to

perform reference genome alignment (hg19) with reads contained in paired FASTQ files. As the first post-alignment processing step, Picard (a collection of command-line tools for handling high-throughput sequencing data; broadinstitute.github.io/picard/) was utilized to identify and mark duplicate reads from BAM files. In the second post-alignment processing step, local read realignment was performed to correct for potential alignment errors around indels. Variant calls were generated using GATK HaplotypeCaller (gatk.broadinstitute.org/hc/en-us) (58) [which calls single-nucleotide polymorphisms (SNPs) and indels simultaneously via local *de novo* assembly of haplotypes in an active region] or UnifiedGenotyper (59) (which calls SNPs and indels on a per-locus basis) (60). A Gaussian mixture model was used to assign accurate confidence scores to each putative variant call, and SnpEff (pcingola.github.io/SnpEff/) (an open-source tool that annotates variants and predicts their effects on genes by using an interval forest approach) was utilized to add biological information for the variants (61). Rare variants with gnomAD minor allele frequency <0.01 were retained, and functional DNA changes impacting amino acid sequence and intron-exon junctions in the 26 known BBS genes (Table I) were prioritized for further analysis using the Integrated Genomics Viewer (software.broadinstitute.org/software/igv/home) (62). *BBS12* c.1063C>T; p.Arg355* was confirmed in the proband and available family members by PCR amplification with the following thermocycling conditions: Initial denaturation, 95˚C for 5 min; followed by 10 cycles of denaturation at 95˚C for 30 sec, annealing at 66˚C for 30 sec, and extension at 72˚C for 30 sec (-1˚C/cycle); 40 cycles of denaturation at 95˚C for 30 sec, annealing at 56˚C for 30 sec, and extension at 72˚C for 30 sec; and a final extension step at 72˚C for 10 min. The sequences of the primers used were: BBS12_PCR1 forward, 5'-TTGTGTGCAACAAGGCAAC-3' and reverse, 5'-TTCACTGAGCCGATTACCAAC-3'. This was followed by capillary sequencing using BigDye terminator 3.1 chemistry using an ABI 3730xl DNA Analyzer according to the manufacturer's protocols (Applied Biosystems; Thermo Fisher Scientific, Inc.).

The proband was the first daughter of a young (mother 17 years-old, father 20 years-old) and apparently healthy Romani couple. The family self-reported as non-consanguineous. The second daughter was reported to be healthy. The family history included Down's syndrome in a paternal cousin, as well as several (>3 cases) familial cases of intellectual disability on the father's side of the family. The patient was born at 42 weeks by vaginal delivery after an uneventful pregnancy. The physical parameters at birth were within the expected normal range [weight, 3,070 g (70th percentile); length, 50 cm (30th percentile); the occipitofrontal circumference (OFC) was not provided]. The patient was admitted to the intensive care unit for 12 h, needing incubator support due to the poor adaptation. Subsequently, the post-natal development progressed normally. Postaxial polydactyly was noted in all four limbs, and supernumerary digits were removed surgically at 8 months (Fig. 2). Psychomotor development was normal (the patient was able to sit at 6 months; walk without support at 14 months; said the first syllables at 6 months; and the first words at 12 months). The patient was evaluated at 6 years of age by a multidisciplinary team, including a pediatrician, child psychiatrist, child neurologist, psychologist, clinical geneticist and ophthalmologist.

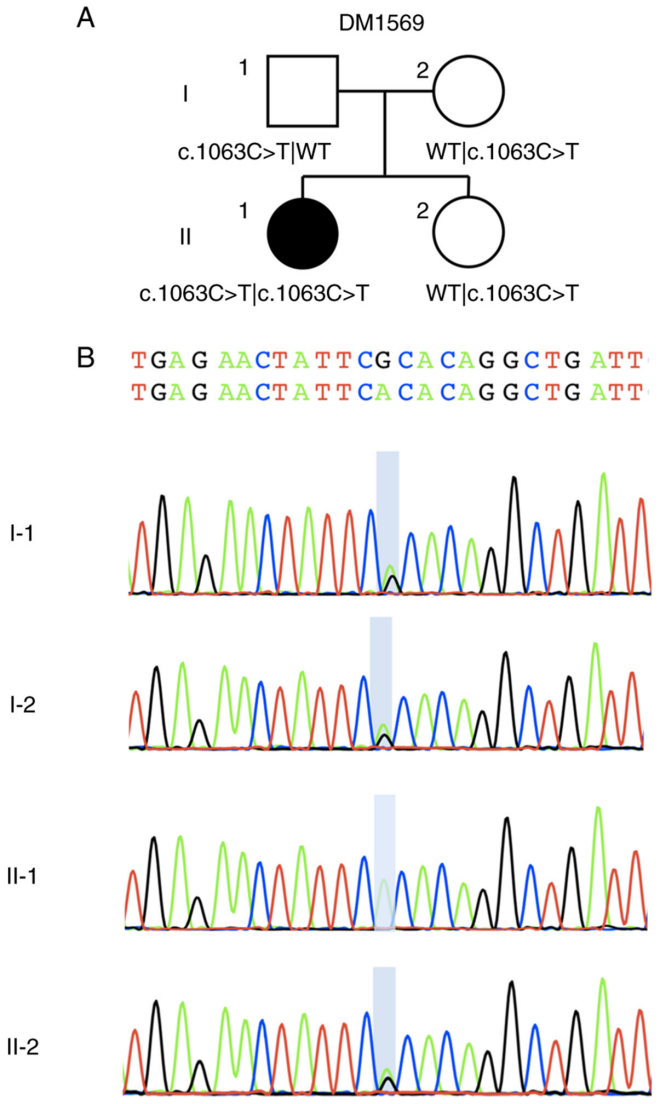

Figure 3. Pedigree and segregation analysis of *BBS12* NM_152618.3: c.1063C>T, p.Arg355*. (A) Pedigree of the family. White shapes, unaffected; black shapes, affected; squares, males; circles, females. The genotype of the BBS variant are shown. (B) Chromatograms showing sequence traces flanking the c.1063C>T variant. Both parents are heterozygous and the proband is homozygous for the pathogenic change. WT, wild type; BBS, Bardet-Biedl syndrome.

Clinical workup revealed that she was obese [her weight was 52 kg (>7.5 standard deviations (SD) above the mean)]; she was of tall stature [her height was 128 cm (>2.5 SD above the mean)]; and relative macrocephaly was identified [her OFC was 56 cm (>3.6 SD above the mean)]. Several dysmorphic traits were also observed, namely a narrow forehead, a decreased bitemporal diameter, sparse eyebrow hypertelorism, long and smooth philtrum, large ears and full cheeks. Furthermore, oral/dental abnormalities were identified, including dysplastic teeth, a high-arched palate and digit anomalies, such as brachydactyly, conic fingers, partial cutaneous syndactyly of the second and third toes, and hypoplasia of the nails were also noted. An ophthalmological examination revealed retinal dystrophy; the patient's night vision was also very poor, and her daylight vision was weak (she frequently collides with objects while walking) as reported by her. However, specific measurements of visual acuity could not be obtained due to non-cooperation

Table II. Clinical findings of the patients with BBS harboring the BBS12:c.1063C>T homozygous variant.

Patient characteristics	Present case	Case #1 and #2	Case #3	Case #4
Reference	-	(57)	(62)	(63)
Additional genomic variants	-	-	-	BBS1:c.1016A>T
Age at time of report	7 years	NP	5 months	NP
Sex	Female	NP	Male	Female
Ethnic background	Romani	Romani	NP	NP
Phenotype				
Retinitis pigmentosa	Yes	NP	No	Yes
Obesity	Yes (>6 standard deviations)	NP	Yes (>97th percentile)	No
Intellectual disability	Severe (IQ 36) (cognitive and language impairment)	NP	No	Yes (cognitive, language and motor impairment)
Polydactyly	All limbs	NP	Feet	Feet
Genital anomalies/ hypogonadism	Yes (hypoplastic genitalia)	NP	Yes (small penis, small testicles)	Yes (NS)
Kidney disfunction/ anomaly	Yes (elevated levels of creatinine and urea)	NP	No	Yes (NS)
Miscellaneous	Severe behavioral abnormalities, hypercholesterolemia, hypertension, brachydactyly, syndactyly of 2-3 toes	NP	Heart anomaly, brachydactyly, syndactyly of 5-6 left toes	Hypercholesterolemia

and severe intellectual disability. The neurological evaluation revealed language impairment (echolalia, bradylalia, a limited vocabulary and the use of expressions that the patient had heard on television) and no sphincter control. Psychiatric and psychological workup revealed severe intellectual disability (IQ score 36), behavioral disturbances, including emotional instability, self-aggressiveness, addictive behavior towards the phone and television (the patient liked to listen to music, sing and dance), severe hyperkinesia and abnormal food behavior (the patient asked repeatedly for food). The patient knew her name and age, and could count up to 10; however, she could not recognize colors or play with a puzzle. Abdominal ultrasound revealed the presence of hypoplastic genitalia, although her liver and kidneys appeared normal. Likewise, electroencephalography and brain MRI investigations were unremarkable. Over the course of the last year (at 7 years of age) slightly elevated levels of cholesterol [5.4 mmol/l (normal range <5.2 mmol/l)], creatinine [68 μmol/l (normal range 35-65 μmol/l)] and urea [8.4 mmol/l (normal range 1.4-8.3 mmol/l)] were recorded for the patient, and she displayed several episodes of high blood pressure that responded well to treatment.

Discussion

In this case report, a homozygous *BBS12* NM_152618.3: c.1063C>T, p.Arg355* variant was identified using WES. This change was confirmed by Sanger sequencing and was shown to segregate with disease in the pedigree; both parents and the unaffected sibling were heterozygous carriers (Fig. 3). This variant has been reported previously in dbSNP (rs121918327; ncbi.nlm.nih.gov/snp/), and in ClinVar (VCV000001147.9; ncbi.nlm.nih.gov/clinvar/) as being pathogenic according to the American College of Medial Genetics and Genomics guidelines (63) (PVS1, PP3, PM2). The variant is a nonsense mutation that is predicted to result in a premature stop codon within the apical domain of the protein (64). Experimental validation remains necessary to determine whether p.Arg355* produces an unstable protein that is targeted for degradation, or whether it generates a stable polypeptide with compromised function.

BBS12 (MIM 610683) is located on chromosome 4q27 and contains two exons, which code for a protein of 710 amino acids that belongs to a chaperonin-like complex, in addition to MKKS/BBS6 and BBS10 (41). The chaperonin-like complex, MKKS/BBS6-BBS10-BBS12, was initially considered to be vertebrate specific, and the proteins have similarity to the canonical type II chaperonins that are present in eukaryotic organisms (64-66). Subsequently, new evidence revealed that the proteins evolved earlier, due to the presence of several orthologs in ancient eukaryotes (67). Whereas canonical eukaryotic chaperonins utilize an ATP-specific hydrolytic site for protein folding, the rapidly evolved chaperonin-like proteins lost the ATPase hydrolytic site, but acquired novel functions, including the transduction of different morphogenetic signals from cilia (64,67).

The three chaperonin-like proteins have been shown to be localized at the base of the cilium, in the pericentriolar region of the basal body and centrosome. They are required for initial assembly of the BBSome, and operate through stabilizing

the BBS7 protein and subsequently recruiting BBS2 protein as an intermediary protein for the binding of a six prototypic chaperonin-containing tailless complex, which is responsible for completion of the folding process (27). Disruption of one of the chaperonin-like BBS genes leads to degradation of at least two subunits of the BBSome. The remaining BBSome proteins either stand as monomers or form aggregates with unspecified proteins (27).

As a consequence associated with this phenotype, it has been suggested that the deleterious variants in the MKKS/BBS6-BBS10-BBS12 complex may lead to a more severe phenotype and earlier onset of the disease compared with variants in the BBSome subunits (68,69). This may be accounted for by the existence of an intermediary complex that manages to retain some residual function in spite of a BBSome component being impaired, whereas alteration of the chaperonin-like complex components serve to restrain the aggregation of any functional complex (28). There is also some evidence to suggest that visual impairment is most severe in cases associated with alterations in the chaperonin-like BBS genes, with similar effects observed for all three genes (68). Furthermore, cognitive impairment is highly prevalent in individuals with *BBS12* variants, whereas urogenital abnormalities are more common in those carrying *BBS10* pathogenic variants (69).

Four cases with *BBS12* c.1063C>T, p.Arg355*, have been reported previously (Table II) (64,70,71). In total, 3 of the 5 patients (including the presented case) reported are Romani; however, the ethnic backgrounds of the other 2 patients have not been provided, so it is not possible to conclude whether they share the same ethnicity. Interestingly, one of the patients reported previously is also Romanian, and although he is not located in the same geographic area as the current patient, the presence of a putative founder mutation cannot be excluded. Furthermore, the phenotypes of patients #1 and #2 were not reported. For the remaining 3 patients, some similarities have been observed: Genital anomalies were present in all cases. The other findings are variable, and may be explained either by the young age of patient #3 at the time of study, given that certain symptoms occur later in life, or by an additional genomic variant in patient #4 that may have influenced the phenotype. Even though they harbored the same variants, polydactyly was noted in all four limbs in the current patient, whereas in patient #3 polydactyly was observed only in the feet. The heart anomaly described in patient #3 was not present in the patient reported here. Therefore, further studies are required to elucidate the complex pathological mechanisms underpinning this highly heterogenous ciliopathy.

In conclusion, the present case report has provided novel evidence in terms of defining the phenotype associated with this rare variant in *BBS12*.

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Availability of data and materials

Due to constraints of participant consent, whole exome sequencing data are not posted to public databases, but we will make portions of the dataset available to researchers upon reasonable request.

Authors' contributions

IOF collected the data, wrote the manuscript, and prepared the figures and the tables. MBu and CB provided the clinical care of the patient. SK performed Sanger confirmation and segregation analysis. AS assisted with organization of clinical samples and data. LCB facilitated the initial preparation of samples. EED conducted the genetic testing and edited the manuscript. MBa designed the study, and revised the manuscript. All authors have read and approved the final manuscript. SK and EED confirm the authenticity of all the raw sequencing data.

Ethics approval and consent to participate

Willing family members were enrolled in the PhD research study approved by Institutional Board of University of Medicine and Pharmacy 'Carol Davila' Bucharest, (approval no. 29700, T.42; Oct 01, 2015), and all experiments conformed with the guidelines of the Declaration of Helsinki. The use of whole exome sequencing was approved by the Institutional Review Board of the Ann & Robert H. Lurie Children's Hospital, Chicago (approval no. IRB 2019-3057, August 5, 2019).

Patient consent for publication

Written informed consent was obtained from legal guardians of the patient included in the study for genetic testing and publication of data and images, as well from all the other participants from whom samples were obtained.

Competing interests

The authors declare that they have no competing interests.

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