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Clinical variability of *BBS1* across siblings

Vanna Giang [1], Sarah R Weber [1,2], Jeffrey M Sundstrom [1,2]

[1]Ophthalmology, Penn State College of Medicine, Hershey, Pennsylvania, USA
[2]Kellogg Eye Center, Michigan Medicine, Ann Arbor, Michigan, USA

Correspondence to
Vanna Giang;
vgiang@pennstatehealth.psu.edu

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SUMMARY

Bardet–Biedl syndrome (BBS), an autosomal recessive ciliopathy with pleiotropic effects, manifests as a spectrum of anomalies involving multiple genes and affects fewer than 3,000 individuals in the USA. Due to its rarity and phenotypic variability, early diagnosis of BBS poses a significant challenge. Therefore, we aim to shed light on the intrafamilial phenotypic variation of BBS resulting from a *BBS1* variant by delineating the clinical presentation in two siblings.

BACKGROUND

Bardet–Biedl syndrome (BBS), an autosomal recessive ciliopathy with pleiotropic effects, manifests as a spectrum of anomalies that can be caused by variations in multiple genes. Although the frequency of this syndrome varies geographically, it is rare, affecting 1 in 120,000 to 160,000 individuals in North America and Europe.[1] To date, 26 genes have been identified as causative for BBS, the most common of which is the *BBS1* variant, with more continuing to be discovered with advancements in genetic testing.[2] BBS exhibits significant phenotypic variability, with clinical manifestations ranging from postaxial polydactyly to obesity, retinal dystrophy, renal dysfunction, developmental delay, cognitive impairment, learning disability and hypogonadism.[2 3] In particular, patients with the *BBS1* variant typically present with night blindness, hyperopic astigmatism, ptosis or mild blepharospasm, foot polydactyly, fifth finger clinodactyly, history of headaches and variable, diet-responsive obesity.[4] The syndrome progresses slowly during the first decade of life but significantly worsens by the second and third decades. This, coupled with its variable phenotypic presentation, poses substantial challenges for diagnosis, often resulting in patients receiving a diagnosis in late childhood or early adulthood.[3] Therefore, improving our understanding of both interfamilial and intrafamilial phenotypic variation in BBS is crucial as early diagnosis can enable patients to access necessary support services and healthcare more promptly, leading to improved health outcomes. Thus, we aim to highlight the intrafamilial phenotypic variation of BBS caused by the *BBS1* variant, as seen in two siblings.

CASE PRESENTATION

Case 1: An early adolescent male with polydactyly, autism spectrum disorder (ASD), attention-deficit hyperactivity disorder (ADHD) and esotropia was referred to ophthalmology for evaluation of suspected retinal dystrophy. Pregnancy was uncomplicated with normal fetal development, and he was born full term via vaginal cephalic birth without complications. At birth, he was noted to have an extra finger and toe on his left side along with initial concerns regarding his left ear hearing test, which later resolved on retesting. Surgical removal of the appendage on his left hand via a tight suture was performed at 1 month of age; subsequently, x-rays of his left hand and foot were obtained. X-ray of his foot showed a well-formed toe with nail and bony components, and removal of the appendage was planned for the beginning of the following year. Due to the unilateral postaxial polydactyly in the absence of family history, genetic testing was recommended by his primary care physician (PCP). However, after genetic counseling determined that his general phenotypic features and development were normal, further genetic evaluation was not pursued. As part of the genetic workup, he was referred for ophthalmic evaluation 3 months later, which revealed no evidence of ocular anomalies.

Approximately a year and a half later, he was once again referred for ophthalmic evaluation for esotropia and a conjunctival lesion on the nasal aspect of his left eye with waxing and waning redness. Glasses were prescribed for his esotropia, and he was started on topical steroids for his conjunctival lesion to help determine its etiology. Follow-up a month later revealed that correction with glasses resolved his esotropia; however, his conjunctival lesion persisted despite treatment. Further evaluation by a cornea specialist identified the lesion as an amelanotic conjunctival nevus. Over the next 3 years, regular follow-ups showed stability in both his esotropia and the size of his conjunctival nevus.

After this 3-year period, he presented for follow-up with ophthalmology with concerns for possible vision defects. Examination revealed residual esotropia, leading to the prescription of bifocal lenses, which were removed several years later due to patient discomfort. Several years later, psychiatric evaluation confirmed ASD and ADHD. As a preschooler, his mother reported inattention, moody/irritable temperament, and frequent temper tantrums. At school, he struggled with language pragmatics including dysgraphia, idiosyncratic and literal thinking, and abilities involving rote memory, such as memorizing the alphabet or acquiring advanced vocabulary. He received additional support resources and accommodations at school (504 plan) for motor and sensory processing concerns. Sleep difficulties were also reported by his mother, which may have been impacting his attention, mood and behaviour. As he grew and reached puberty, his body mass index (BMI) consistently remained at 28 kg/m^2.

The patient followed-up regularly with ophthalmology for the next 3 years later until retinal

evaluation during a follow-up visit suggested retinal pigment epithelium (RPE) hypopigmentation in the central retina, prompting referral to a retina specialist for evaluation of inherited retinal disease. Optical coherence tomography (OCT) showed evidence of RPE disturbance bilaterally and fundus imaging showed central RPE mottling with positive autofluorescence. Further evaluation by a retina specialist along with additional testing was suggestive of Best disease, a type of retinal dystrophy, but with scotopic and photopic changes on electroretinography (ERG). The patient was then referred for genetic counseling, which identified two copies of the c.1169T>G; p.Met390Arg mutation in the *BBS1* gene, a well-known pathogenic variant consistent with BBS.[5 6]

Case 2: The patient's sister, in middle childhood with a history of polydactyly, dyslexia and hydronephrosis, also presented for ophthalmic evaluation of possible retinal dystrophy. Born 4 years after her brother at full term via vaginal cephalic birth with no complications, she was found to have an extra toe on her right foot, which was removed 7 months later. Polydactyly was not appreciated on prenatal ultrasound; however, unlike her brother, prenatal evaluation revealed hydronephrosis and ultrasound showed bilateral enlargement of her kidneys with abnormal echogenicity. Repeat ultrasounds over the next 4 years showed improvement and eventual resolution of her hydronephrosis. The review of this pregnancy revealed no differences compared with the previous pregnancy in terms of medications, infections or other complications.

7 years after her brother was diagnosed with BBS, she sought ophthalmic care, where bilateral RPE mottling with disruption of the central RPE at the fovea was observed. OCT showed evidence of bilateral parafoveal photoreceptor thinning with disruption of the inner segment/outer segment junction at the central fovea, and fundus imaging displayed bilateral central foveal hypopigmentation. Her clinical presentation was consistent with BBS, although genetic testing was deferred at her mother's request. 2 months later, she underwent psychological evaluation for concerns regarding low self-confidence, dyslexia and slow processing speed. Her mother noted struggles in school, especially with spelling, including mispronouncing words and difficulty with chunking words to read and spell, lack of confidence in all areas, and frustration with multiple-step math problems. She usually scored low/average on assessments, despite diligent efforts. Unlike her brother, she exhibited cooperative and easygoing behavior during early childhood.

OUTCOME AND FOLLOW-UP

Both siblings are followed by ophthalmology on an annual basis with dilated fundus exam as well as a range of imaging studies including OCT, Optos Ultra-widefield imaging, color fundus photography and fundus autofluorescence. Additionally, they receive regular checkups from their PCP to evaluate other organ systems that can be impacted by BBS. The patient in case 1 also has regular visits with his optometrist to monitor his left esotropia and conjunctival nevus.

Aside from this, both siblings attend school full-time, with the brother benefitting from school services including occupational therapy (OT) and small-group study hall. While there are currently no effective treatments for BBS-associated retinal degeneration, long-term disease management involves annual assessments of clinical parameters, including, but not limited to, weight, blood pressure, lipid profile and blood glucose levels, in addition to prompt and aggressive treatment of metabolic syndrome, diabetes, and hypertension.[7 8] Recent introduction of medications such as setmelanotide, a melanocortin-4 receptor agonist, have been shown to help reduce BMI as well as improve overall physical and mental health in patients with obesity-related genetic disorders.[9]

DISCUSSION

The pathology underlying BBS involves a number of variations that disrupt the function of the primary cilium, a microtubule-based organelle found on the apical surface of cells. This cilium plays a pivotal role in cell signaling, which is crucial for developmental processes and the maintenance of homeostasis.[10] For instance, dysfunction of the primary cilium and BBS genes are implicated in adipocyte differentiation, leading to the development of obesity in BBS patients. Polydactyly can be explained by dysregulation of the sonic hedgehog signaling pathway, culminating in abnormal limb development and left/right asymmetry. Cognitive impairment stems from defective neurogenesis signaling and hippocampal development.[11] The manifestation of BBS varies depending on the specific BBS proteins affected. Variations in genes such as *BBS6*, *BBS10* and *BBS12* tend to yield more severe renal phenotypes, while variations in *BBS2*, *BBS3* and *BBS4* typically result in distinct ocular phenotypes.[10] In the case with *BBS1*, it is also important to note that this gene is by itself subjected to clinical variability, with cases previously reporting isolated retinal degeneration.[12]

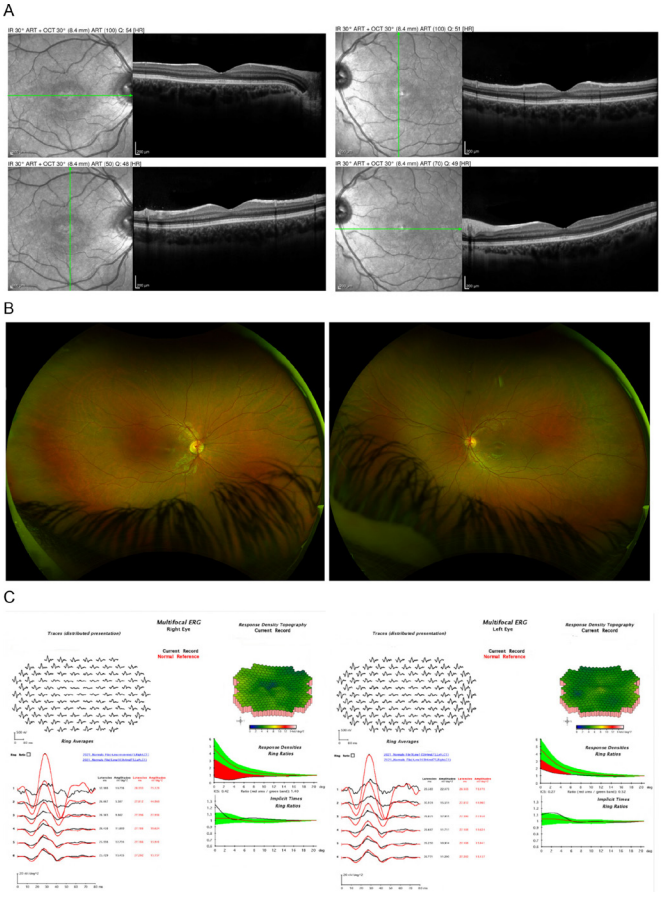

Figure 1 Initial imaging in case 1. (A) Optical coherence tomography imaging shows evidence of retinal pigment epithelium (RPE) disturbance in both eyes. (B) Wide-field fundus imaging shows central RPE mottling with positive autofluorescence in both eyes. (C) Multifocal electroretinography shows central depression in both eyes.

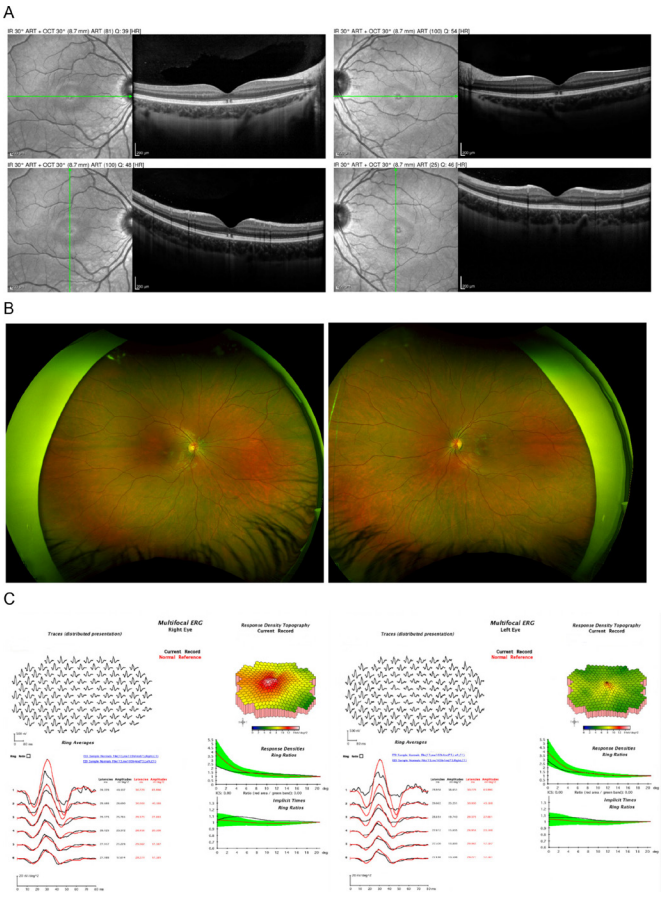

Figure 2 Initial imaging in case 2. (A) Optical coherence tomography shows parafoveal photoreceptor thinning with disruption of the inner segment/outer segment junction at the central fovea in both eyes. (B) Wide-field fundus imaging showing central foveal hypopigmentation in both eyes. (C) Multifocal electroretinography showing central b-wave depression to approximately 60% of normal in both eyes.

Diagnosis of BBS originally relied on the presence of at least four primary features (rod-cone dystrophy, polydactyly, obesity, learning disabilities, hypogonadism in males, and renal abnormalities) or the presence of three primary and two secondary features (speech disorder/delay, strabismus/cataracts/astigmatism, developmental delay, polyuria/polydipsia, ataxia/poor coordination/imbalance, mild spasticity, diabetes mellitus, dental crowding/hypodontia/small roots/high arched palate, left ventricular hypertrophy/congenital heart disease and hepatic fibrosis). Recommendations for initial assessment of a patient with suspected BBS include obtaining baseline ERG/visually evoked responses, renal ultrasound, intravenous pyelogram or dimercaptosuccinic acid/diethylenetriamine pentaacetic acid (DMSA/DPTA) scan, ECG and echocardiogram, and molecular testing to rule out Prader–Willi syndrome. Further testing such as CT/MRI brain scan/renal and electroencephalogram (EEG) as well as speech assessment and therapy, documentation of educational needs, and registration of blindness may also be warranted. Following the initial assessment, it is recommended to follow-up with biannual urine dipstick analysis and annual measurement of blood pressure and urea and creatinine levels to screen for renal abnormalities. Family members of patients diagnosed with BBS should also undergo screening for renal malformations and carcinoma.[13] With advancements in genetic testing, new BBS diagnostic criteria are organized by age group and incorporate results of genetic testing along with primary and secondary clinical features, allowing for the stratification of patients into different levels of diagnostic confidence. For instance, if a patient were to have positive genetic testing results and at least one primary clinical feature (eg, polydactyly and hyperechogenic kidneys) in utero, their diagnostic confidence is high; if an affected sibling has positive genetic testing and the patient has at least one primary clinical feature in utero, their diagnostic confidence is classified as moderate.[3]

Table 1 Presentation of major BBS clinical features in cases 1 and 2

Major clinical features	Case 1	Case 2
Rod–cone dystrophy	x	x
Polydactyly	x	x
Obesity		
Learning disability		
Hypogonadism (males)		
Renal abnormalities		x

Both siblings had polydactyly and rod–cone dystrophy and experienced learning difficulties without diagnosis of a specific learning disability. Patient in case 1 meets clinical criteria for classification as overweight, and patient in case 2 has a history of renal abnormalities in utero.
BBS, Bardet–Biedl syndrome.

In case 1, the patient was born with unilateral postaxial polydactyly and subsequently developed strabismus. However, symptomatic rod–cone dystrophy was not clinically evident until adolescence. His initial OCT, fundus imaging and ERG results can be seen in figure 1. There was no indication of obesity, hypogonadism or renal abnormalities. Psychiatric evaluation revealed a diagnosis of ASD and ADHD. Although academic challenges were noted, he was not diagnosed with a specific learning disability. Sleep difficulties, while not a criterion for diagnosis, have been found to be common in patients with BBS.[14]

In case 2, the patient was also born with unilateral postaxial polydactyly. However, in addition to this, she was prenatally diagnosed with renal abnormalities. Along with polydactyly, renal abnormalities in utero are classic presentations of BBS; however, they are non-specific. One study looking at prenatal ultrasound and/or autopsy data from 74 fetuses with suspected BBS found that of those 74 cases, 45 were positive for BBS variants.[15] Given the varied clinical presentation of BBS and high prevalence in patients with certain clinical findings, another recent study examining genotype–phenotype correlations of children recommended that those with polydactyly, kidney disorders, or early-onset obesity be evaluated for BBS as early diagnosis, monitoring and treatment are important for managing BBS-associated comorbidities.[16] Rod–cone dystrophy was identified earlier in her case, prompted by ophthalmic evaluation following her brother's presentation of ocular symptoms and eventual diagnosis of BBS. Her initial OCT, fundus imaging, and ERG results are shown in figure 2. Similar to her brother, she experienced learning difficulties, although she was not diagnosed with a specific learning disability. Major clinical features of BBS and their presence or absence in each of these cases are demonstrated in table 1.

Learning points

- Bardet–Biedl syndrome (BBS) presents with substantial intrafamilial and interfamilial phenotypic variation.
- Recognition of the variable presentation of BBS within families can help prompt identification of affected individuals.
- Earlier detection allows for expedited workup and referral for genetic testing to determine causative genes, ultimately optimizing patient care.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

ORCID iDs
Vanna Giang http://orcid.org/0009-0006-6900-6058
Sarah R Weber http://orcid.org/0000-0001-6313-5947

REFERENCES

1 Beales PL, Warner AM, Hitman GA, *et al*. Bardet-Biedl syndrome: a molecular and phenotypic study of 18 families. *J Med Genet* 1997;34:92–8.
2 Melluso A, Secondulfo F, Capolongo G, *et al*. Bardet-Biedl Syndrome: Current Perspectives and Clinical Outlook. *Ther Clin Risk Manag* 2023;19:115–32.
3 Dollfus H, Lilien MR, Maffei P, *et al*. Bardet-Biedl syndrome improved diagnosis criteria and management: Inter European Reference Networks consensus statement and recommendations. *Eur J Hum Genet* 2024;32:1347–60.
4 Cox KF, Kerr NC, Kedrov M, *et al*. Phenotypic expression of Bardet-Biedl syndrome in patients homozygous for the common M390R mutation in the BBS1 gene. *Vis Res* 2012;75:77–87.
5 Fadaie Z, Whelan L, Dockery A, *et al*. *BBS1* branchpoint variant is associated with non-syndromic retinitis pigmentosa. *J Med Genet* 2022;59:438–44.
6 Guardiola GA, Ramos F, Izquierdo NJ, *et al*. A Genotype–Phenotype Analysis of the Bardet–Biedl Syndrome in Puerto Rico. *OPTH* 2021;Volume 15:3757–64.
7 Forsythe E, Kenny J, Bacchelli C, *et al*. Managing Bardet-Biedl Syndrome-Now and in the Future. *Front Pediatr* 2018;6:23.
8 Priya S, Nampoothiri S, Sen P, *et al*. Bardet-Biedl syndrome: Genetics, molecular pathophysiology, and disease management. *Indian J Ophthalmol* 2016;64:620–7.
9 Forsythe E, Haws RM, Argente J, *et al*. Quality of life improvements following one year of setmelanotide in children and adult patients with Bardet-Biedl syndrome: phase 3 trial results. *Orphanet J Rare Dis* 2023;18:12.
10 Novas R, Cardenas-Rodriguez M, Irigoín F, *et al*. Bardet-Biedl syndrome: Is it only cilia dysfunction? *FEBS Lett* 2015;589:3479–91.
11 M'hamdi O, Ouertani I, Chaabouni-Bouhamed H. Update on the genetics of bardet-biedl syndrome. *Mol Syndromol* 2014;5:51–6.
12 Estrada-Cuzcano A, Koenekoop RK, Senechal A, *et al*. BBS1 Mutations in a Wide Spectrum of Phenotypes Ranging From Nonsyndromic Retinitis Pigmentosa to Bardet-Biedl Syndrome. *Arch Ophthalmol* 2012;130:1425.
13 Beales PL, Elcioglu N, Woolf AS, *et al*. New criteria for improved diagnosis of Bardet-Biedl syndrome: results of a population survey. *J Med Genet* 1999;36:437–46.
14 Pomeroy J, VanWormer JJ, Meilahn JR, *et al*. Sleep and physical activity patterns in adults and children with Bardet-Biedl syndrome. *Orphanet J Rare Dis* 2021;16:276.
15 Mary L, Chennen K, Stoetzel C, *et al*. Bardet-Biedl syndrome: Antenatal presentation of forty-five fetuses with biallelic pathogenic variants in known Bardet-Biedl syndrome genes. *Clin Genet* 2019;95:384–97.
16 Nowak-Ciołek M, Ciołek M, Tomaszewska A, *et al*. Collaborative effort: managing Bardet-Biedl syndrome in pediatric patients. Case series and a literature review. *Front Endocrinol (Lausanne)* 2024;15:1424819.