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REVIEW

Bardet-Biedl Syndrome: Current Perspectives and Clinical Outlook

Andrea Melluso[1], Floriana Secondulfo[1], Giovanna Capolongo[1], Giovambattista Capasso[1,2], Miriam Zacchia[1]

[1]Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy; [2]Biogem Scarl, Ariano Irpino, AV, 83031, Italy

Correspondence: Miriam Zacchia, Via Pansini 5, Naples, 80131, Italy, Tel +39 081 566 6650, Fax +39 081 566 6671, Email miriam.zacchia@unicampania.it

Abstract: The Bardet Biedl syndrome (BBS) is a rare inherited disorder considered a model of non-motile ciliopathy. It is in fact caused by mutations of genes encoding for proteins mainly localized to the base of the cilium. Clinical features of BBS patients are widely shared with patients suffering from other ciliopathies, especially autosomal recessive syndromic disorders; moreover, mutations in cilia-related genes can cause different clinical ciliopathy entities. Besides the best-known clinical features, as retinal degeneration, learning disabilities, polydactyly, obesity and renal defects, several additional clinical signs have been reported in BBS, expanding our understanding of the complexity of its clinical spectrum. The present review aims to describe the current knowledge of BBS i) pathophysiology, ii) clinical manifestations, highlighting both the most common and the less described features, iii) current and future perspective for treatment.

Keywords: Bardet-Biedl syndrome, ciliopathies, chronic kidney disease, genetics, metabolic disorders

Introduction

The Bardet-Biedl syndrome (BBS) is an inherited disorder affecting multiple organs and systems.

It is a rare condition, and its frequency varies among different geographic areas. The distribution of the syndrome is in fact not homogeneous, as it was noted by Klein and Ammann in Switzerland, in 1969.[1] In North America and Europe, it ranges between 1:120.000 and 1:160.000 individuals.[2] In some isolated communities, due to increased marriages among consanguineous, it is far higher: 1:36,000 among the mixed Arab population in Kuwait, 1:13,500 among Bedouins, 1:6900 in Jahra district, 1 in 18,000 in Newfoundland and 1:3700 in Faroe Islands.[3–5]

The BBS is considered a model of non-motile ciliopathy. The latter includes a heterogenous spectrum of conditions characterized by the dysfunction of the primary cilium (PC). At least 35 different ciliopathies have been described; their clinical complexity ranges from multiorgan disorders, even with embryonic lethality, to non-syndromic and late onset forms.[6–8]

For decades, the PC has been considered only a vestigial organelle; however, in the recent years, it has been shown to play a pivotal role in several signalling pathways regulating important cellular functions, including cellular division, polarity and metabolism. Accordingly, emerging evidence demonstrated a crucial role in several human diseases.[9]

The PC is a dynamic organelle that appears as a subcellular component extruding from the cell surface and acting as an antenna sensing external stimuli. Its structure consists of a microtubule-based axonema emerging from a basal body and surrounded by a ciliary membrane (Figure 1). The basal body derives from the mother centriole, the major organizing center for mitotic spindles during cell division: in quiescent cells, it serves as the anchoring structure of the PC. Proteomic studies have demonstrated that the PC contains at least 600 different proteins;[10,11] there is no evidence of protein synthesis within cilia, thus ciliary proteins reach and leave the PC through sophisticated mechanisms of transport that have been a hot topic in the field.[12]

Clinical Diagnosis and Natural History of BBS

The diagnosis of BBS is based on clinical criteria published by Beales et al and requires the presence of at least four primary features or three primary features and two secondary features (Table 1) (Figure 2).[13] Negative family history for

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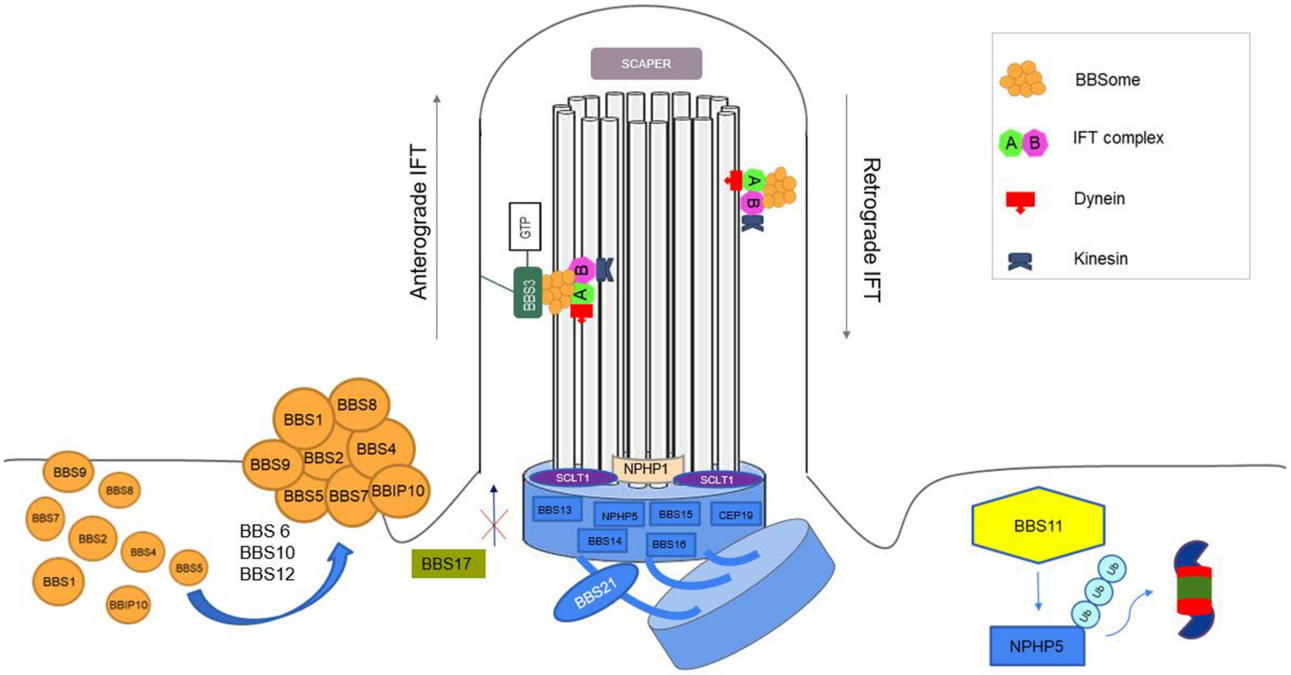

Figure 1 Diagram of Bardet Biedl syndrome (BBS) proteins and their relationship with the primary cilium. The BBSome complex, constituted by BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, BBS9 and BBIP1 (represented on the left), is assembled with the assistance of chaperonin-like proteins (BBS6, BBS10 and BBS12). The link between BBSome and BBS3 GTPase protein allows the intraflagellar transport. On the other hand, the link to BBS17 keeps the BBSome at basal body level. IFT-A complex mediates retrograde trafficking from the tip of cilia to the base, powered by dynein. IFT-B complex (which includes BBS19 and BBS20, not shown in figure) mediates anterograde trafficking, powered by kinesin. BBS11, as shown on the right, favors protein ubiquitination.

BBS is common, as shown in other autosomal recessive disorders. Moreover, early diagnosis is further difficult, due to the progressive onset of all clinical signs over time.

One of the earliest signs is polydactyly; its association with genito-urinary anomalies on prenatal ultrasound, when present, should induce the clinical suspicious.[14] Hyperechoic kidneys, cysts, pelvic dilation have been described in

Table 1 Clinical Signs of BBS Patients

Primary Diagnostic Features	Secondary Diagnostic Features	Described BBS Features Non Included in the Diagnostic Criteria
Retinal Degeneration	Strabismus, cataracts, and astigmatism	Cutaneous Dermatoses
Obesity	Metabolic/endocrine abnormalities (metabolic syndrome, subclinical hypothyroidism, polycystic ovary s.)	Hearing loss
Postaxial polydactyly	Brachydactyly/syndactyly	Asthma
Renal Anomalies	Anosmia/olfactory dysfunction	Dysregulated immune and hematopoietic systems
Learning Disabilities	Neurodevelopmental abnormalities (developmental delay, speech delay, epilepsy, behavioral disturbances, ataxia/poor coordination, mild spasticity)	Musculoskeletal abnormalities
Hypogonadism and Genitourinary Abnormalities	Liver and other gastrointestinal diseases (Hirschsprung disease, inflammatory bowel disease, celiac disease)	
	Cardiovascular and thoraco-abdominal abnormalities	

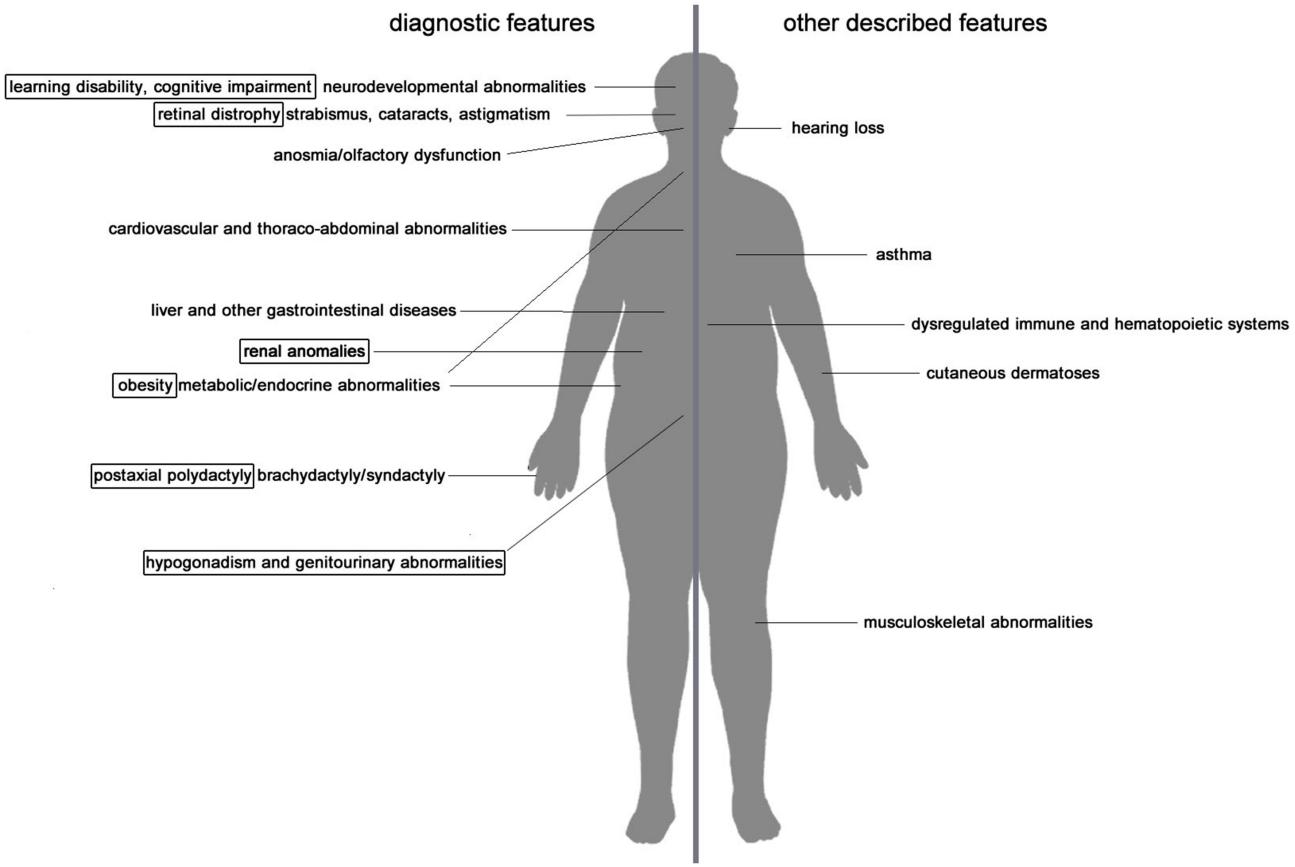

Figure 2 Major clinical features of BBS patients. On the left side diagnostic clinical features are listed (primary features outlined with rectangles). On the right side, less described clinical traits.

infants. These findings are clearly non-specific. Pre/peri-natal hyperechoic kidneys can also be found in other conditions as autosomal recessive polycystic kidney disease (ARPKD) and sometimes in autosomal dominant polycystic kidney disease (ADPKD), besides other syndromic ciliopathies, as Meckel-Gruber syndrome.[15]

Obesity is another quite early sign; while patients have normal body weight at the birth, they often develop obesity during the first year of life.[16]

Other major symptoms and signs emerge later, generally during the first decade of life; thus, the phenotype very commonly does not meet the criteria for diagnosis early in life. The average age at diagnosis is 9 years, according to Beales et al.[13] In the Clinical Registry Investigation of BBS (CRIBBS), the median age at diagnosis is 5.8 years.[17] Of note, phenotypic variability of BBS patients is quite high, even in the same family, making difficult the clinical diagnosis. Paucisymptomatic forms have been also described.[18]

Another difficulty in making the clinical diagnosis is the phenotypic overlap with other syndromic ciliopathies. Adult BBS patients often show clinical overlapping with Senior-Løken and Alström Syndromes.

The Senior-Løken syndrome (SLS) is an autosomal recessive disease characterized by development of retinal degeneration and a progressive tubulointerstitial kidney disease, leading to the end-stage kidney disease. In SLS obesity, polydactyly, hypogonadism and genitourinary malformations are uncommon.[19]

Alström syndrome is an autosomal recessive disorder characterized by cone-rod dystrophy, hearing loss, childhood truncal obesity, type 2 diabetes, hypertriglyceridemia, short stature, dilated cardiomyopathy and progressive pulmonary, hepatic and renal dysfunction.[20] In AS, liver fibrosis and dilated cardiomyopathy are prevalent but show late onset (in ~ 60%); polydactyly is not reported.[19]

Retinal Dystrophy

Retinal dystrophy is the most penetrant feature, affecting up to 100% of individuals.[13,21] The most common reported pattern is a rod–cone dystrophy with early macular involvement.[21] Visual impairment has a quite early onset. The most frequent clinical presentation is nyctalopia, around the age of 4 to 8 years, followed by progressive peripheral vision loss and, lastly, decline of color vision and visual acuity. Sometimes, instead, patients lose first cones and then rods. Most patients reach legal blindness between the second and third decade of life.[16,22] Fundus examination shows atypical pigmentary retinal dystrophy with macular involvement.[23] Electroretinography could detect signs of retinopathy before clinical presentation, more likely after the age of five years, but early changes could be recognized within two years of life.[16] Physicians should consider that some patients develop refractive errors or strabismus (minor features) before retinal dystrophy becomes evident.[13] Denniston et al proposed a retinopathy grading system which reflected the stage of disease and the photoreceptors affected for standardization purposes.[21] Understanding the pathogenesis of retinal degeneration (RD) in ciliopathies is a prerequisite to develop targeted therapy. The retina is affected in almost all ciliopathies. In fact, photoreceptors light-sensing outer segments are specialized cilia, thus highly vulnerable in this setting.[24] Defective Rhodopsin trafficking is considered a common feature of RD in multiple ciliopathy models; moreover, in BBS animal models, endoplasmic reticulum stress response has been described.[25]

Obesity

BBS patients commonly manifest with obesity, in 72–92% of cases. Patients typically show normal body weight at birth, but in 90% of cases they gain weight in the first year of life and obesity becomes evident during the first 3 years of life. In adulthood, obesity is mainly truncal but in childhood it is usually described as diffuse.[16,26,27]

Its pathogenesis is multifactorial and includes both central and peripheral control of energy expenditure. The mechanisms are mainly based on the role of BBS proteins into the trafficking of proteins to the 1) PC or 2) to the plasma membrane. Proopiomelanocortin (POMC)-neurons of mice lacking *Bbs1* showed reduced plasma membrane abundance of serotonin (5-HT2C) receptor, with abnormal cytoplasmic accumulation.[28] Some studies suggest that cilia are necessary for leptin signaling in the hypothalamus.[27] Mice models of BBS, namely Bbs2-/-, Bbs4-/- and Bbs6-/- mice, showed leptin resistance and hyperleptinemia and BBS1 has been shown to physically interact with leptin receptor, suggesting a central role of BBS proteins in the controls of body weight.[29] Moreover, a peripheral dysfunction of adipogenesis has been described, since a PC is present in differentiating preadipocytes and contains receptors for Wnt and hedgehog pathways.[30]

Abnormal leptin signaling has been confirmed in patients. Plasma leptin levels were higher in BBS individuals than in controls, suggesting leptin resistance. Targeting leptin signalling for treating obesity in BBS is an emerging therapeutical approach under study. Finally, BB1 and BBS2 are required for insulin receptor trafficking to the membrane and Bbs2, Bbs4 and Bbs6 null mice show insulin resistance, indicating further extra ciliary functions of BBS proteins and their role in metabolism.[31]

Postaxial Polydactyly

Postaxial polydactyly is common (63–81%). BBS1 interacts with components of the Hedgehog Pathway as the smoothened, frizzled family receptor (Smo) and the human patched 1 (Ptch1), involved in limb formation. The loss of *Bbs* in mice result in a reduced Shh response that might cause polydactyly.[32] The majority of the patients have fully formed additional digit on the lateral border of the foot (more frequently) or hand; polydactyly can be present in all four limbs (21%), only on the hands (8%) or only on the feet (21%).[13]

Interestingly, the uncommon mesoaxial polydactyly is associated to mutations in BSS17 (LZTFL1) gene.[33] Secondary features are: brachydactyly (46%), syndactyly (8%; usually between second and third toes), fifth finger clinodactyly, thumb placed proximally, "sandal gap" between I and II toes.[13]

Renal Impairment

Kidney abnormalities in BBS are indeed both anatomical and functional and include fetal lobulation, cystic dysplasia, small kidneys, horseshoe, ectopic/duplex/absent kidneys, calyceal clubbing or blunting, tubular and interstitial nephritis, glomerulosclerosis, polyuria and urine concentrating defects.[34] Low urinary tract defects, as neurogenic bladder, bladder outflow obstruction or vesicoureteral reflux have been reported in 5–10% of adults.[19]

The prevalence of kidney disease among patients varies among studies of the literature; one of the reason is the definition of kidney disease, as some studies consider structural kidney abnormalities and some others loss of renal function.[35–37]

The study conducted by Forsythe et al in 350 BBS patients showed that 31% of children and 42% of adults had chronic kidney disease (CKD), stage 2–5; the prevalence of latest CKD stages was 6% and 8% in pediatric and adult patients, respectively. However, the comparison between adult and children is made difficult for the low number of subjects older than 30 year-old.[38] Meyer et al have recently analyzed the presence of kidney failure (KF) in a cohort of 607 BBS patients of the Clinical Registry Investigation of BBS (CRIBBS); 364 individuals had genetic confirmation of BBS. KF was present in 44 (7.2%) of individuals; when considering the three most common genotypes, namely *BBS1,2* and *10*, the authors found a significantly increased risk of KF in patients carrying *BBS2* and *BBS10* mutations. *BBS10*, the second most common gene in the CRIBBS cohort, was present in 32.4% of the KF population with genetic confirmation, accounting for 26.6% of genotyped patients.

The pathogenesis of kidney disease is largely unknown. Lower urinary tract dysfunction, when present, can cause upper renal tract sequelae.[38] Hypertension, obesity and diabetes, frequently observed in these patients, are known risk factors for kidney disease progression; however, their contribution into the progression of kidney disease in this setting requires deeper analysis; based on Forsythe et al, CKD stage 2–5 correlated with hypertension and urinary tract abnormalities.[38–40]

We have recently shown that renal hyposthenuria is associated with a faster decline of the estimated glomerular filtration rate (eGFR) in a population of 54 Italian BBS patients; urine concentrating defect could represent a marker of tubulointerstitial defect.[36,41] Consistent with this hypothesis, we have recently show that BBS patients with still preserved eGFR show abnormal functional Magnetic Resonance parameters, especially in the medulla, supporting the fact that kidney disease is mainly a primitive tubulointerstitial disorder.[42]

The expression of BBS proteins in the kidney suggests that at least in part local factors may contribute to kidney disease;[43] in consistency with this hypothesis, we have recently shown that the absence of one of major BBS gene, namely *BBS10*, caused several metabolic aberrations, in a renal-epithelial-derived cell line (IMCD3-Bbs10-/-); these abnormalities included increased aerobic glycolysis, abnormal cytoplasmic lipids accumulation and mitochondrial dysfunction, possible factors contributing to kidney disease progression.[44,45] These biological aberrations are known to correlate with the onset of chronic kidney dysfunction in the general population and might contribute to the high incidence of kidney dysfunction in this setting.

Learning Disabilities

Cognitive impairment is present in 60–66% of subjects. Magnetic resonance imaging shows a reduction in volume of hippocampus grey matter, white matter volume loss in the right inferior longitudinal fasciculus, volume loss in the anterior temporal lobes and in the medial orbitofrontal cortex.[32,46,47]

In 2011, Mockel et al observed that intellectual performance of 4% of patients was in the higher range of abilities for the normal population. Developmental delay is often global but sometimes is specific for some areas, like motor and/or language. Speech is nasal, slow, with misarticulations, substitutions and omissions, the voice high pitched and/or of breathy quality. Speech delay is often responsive to speech therapy.[13,19,48] Kerr et al reported that the mean intellectual functioning of patients was 1.5 standard deviations below normal expectations, but only 20–25% of patients met diagnostic criteria (*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, DSM-5) for intellectual disability. 22–40% of patients had severe impairment in verbal fluency and auditory rote learning, 53% in perceptual reasoning, 69% in attention capacity, 74% in functional independence.[41]

Hypogonadism and Genitourinary Abnormalities

Hypogonadism or genitourinary abnormalities are present in 59% of BBS subjects.[19] Patients can manifest delayed onset of secondary sexual characteristics, cryptorchidism (9%), micropenis buried in adipose tissue, small volume testes, malformed uterus, hydrometrocolpos, vaginal atresia and other genital anomalies. Female have often irregular menstrual cycle and polycystic ovaries (14.7%; a minor feature).[18,19] Mujahid reported that 19.5% of male BBS patients were hypogonadal, but pituitary anomalies were uncommon.[49]

Recently, using CRIBBS registry, Meyer et al identified Eagle Barrett syndrome in four children.[50] Reproduction is difficult but some patients gave birth to children.

These patients are generally female, but rare cases of male patient with descendants are reported.[13]

Secondary Features

Several secondary clinical features have been described: they include speech delay, behavioral anomalies, developmental delay, metabolic syndrome, diabetes mellitus, hypothyroidism, polycystic ovary syndrome, dental anomalies, facial dysmorphism, congenital heart disease, laterality defects, brachy- and syndactyly, strabismus, cataract, astigmatism, mild spasticity, ataxia/poor coordination, anosmia/hyposmia, hepatic fibrosis/disease and other gastrointestinal disease (Hirschsprung disease, inflammatory bowel disease, celiac disease).

Insulin resistance is a common feature in BBS patients; however, the progression to type 2 diabetes mellitus is not strikingly high, based on the literature. Diabetes prevalence is: 15.8% in patients with a mean age of 33 years; 6% and 48% in patients aged 26.3 and 43 years, respectively.

Hypothyroidism is present in 19.4% of patients (vs 4.6% of the control subjects). In Mujahid's study, the prevalence of metabolic syndrome (using International Diabetes Federation criteria) is 54.3%: all metabolic syndrome parameters were higher in BBS group compared with control group, except for HDL-C. Polycystic ovary syndrome is present in 14.7% of female with BBS.[49]

Facial dysmorphism is often subtle; some individuals show hypertelorism, downward slanting palpebral fissures, large ears, enophthalmos, retrognathia, flat nasal bridge, anteverted nares long philtrum, thin upper lip, early frontal balding in adult male.[13,16]

Orodental anomalies are common, with a prevalence >50%; the most frequently reported anomalies are: hypodontia, high-arched palate (35%), malocclusion, microdontia, crowding of the teeth (46%), short dental roots.[51]

Anosmia/hyposmia has been reported in 50% of BBS patients, but the percentage could be higher because of the difficulties in its evaluation in clinical practice.[52] MRI evaluation of olfactory bulb can help physicians to assess olfactory dysfunction.[53]

Olfaction impairment is related to defects in olfactory cilia or in the olfactory bulb.[54]

Cardiovascular disease is another secondary feature sometimes observed in BBS. The frequency of heart anomalies reported by Niederlova et al was 29.8% and included congenital heart disease as atrial septal defect and other anomalies. Previously, Beales reported that congenital heart defects, including aortic stenosis, patent ductus arteriosus and unspecified cardiomyopathy, were present in 7% of patients.[13,18] Several types of heart and vascular (eg, bilateral persistent superior vena cava, interrupted inferior vena cava, hemiazygos continuation, right sided aorta or left sided vena cava) anomalies have been described and males seem to be more affected than female.[40,55] Olson et al used the CRIBBS registry to determine the prevalence of thoraco-abdominal abnormalities and midlines defects that was 1.6%. Prevalence in BBS patients may be underestimated, since comprehensive imaging was available only for some patients. Cilia are fundamental for the correct development of laterality and several types of anomalies for various organs have been reported. In some cases, physicians should consider and investigate the presence of two ciliopathies: Olson et al reported the presence of clinical criteria for both BBS and primary cilium dyskinesia in the same patient.[56] It has been suggested that atrioventricular canal defects (AVCD) and laterality defects can be an important signal for a possible early diagnosis of BBS and ciliopathies with atypical features. Digilio et al reported that 7.7% of patients with AVCD and ciliopathy had BBS.[57]

Liver disease, defined as abnormalities on liver imaging and/or high plasma transaminase enzymes level, occurs in 30% of patients; additional gastrointestinal abnormalities are more common than expected in the general population and include Hirschsprung disease (2.8%), celiac disease (1.5%), inflammatory bowel disease (1.1%), anal stenosis and other

anatomic anomalies.[19] Obesity and metabolic impairment may contribute to liver disease, especially for non-alcoholic fatty liver disease.[58]

Neuropsychiatric disorders are not uncommon. Autism-related signs were present in 77% of participants.[59] Behavioral anomalies have an incidence of 33% and include obsessive compulsive and ritualistic behavior, anxiety, emotional immaturity, labile behavior, disinhibition, hyperactivity.[13] Depression can present when the subject realizes the impact of the syndrome. BBS proteins are normally expressed in human hippocampus and brain; primary cilia seem to be important for hippocampal neurogenesis.[60] Other neurological aspects include epilepsy (9.6%); ataxia has been documented in BBS and seems to affect lower limbs to a greater degree than upper limbs.[13] Seizures/epilepsy has been reported in some patients in the CRIBBS registry but, in most of the cases, it is resolved before adulthood.[19] Mild spasticity has also been reported.

Additional Clinical Manifestations

Other clinical features have been described in BBS subjects that are not listed among clinical diagnostic criteria. Hawks et al found cutaneous dermatoses, such as keratosis pilaris, seborrheic dermatitis and obesity-related dermatologic disorders, in all subjects with BBS. This study suggests the presence of defect of keratinization and keratinocyte function, highlighting the importance of dermatological care as part of clinical management.[61]

Hearing loss was detected in 21% of patients and in most of them was conductive and associated with chronic otitis media in childhood (and no more present in adulthood). A smaller percentage of patients, instead, show sensorineural hearing loss.[13] Forsyth and Gunay-Aygun reported a high rate of musculoskeletal abnormalities registered in CRIBBS, including joint laxity (27.6%), scoliosis (16%), leg length discrepancy (9.6%), club foot (1.8%), Blount disease (0.9%).[19]

It has been reported that BBS patients have a high prevalence of neonatal respiratory distress at birth (12% vs 3% UK population) asthma (21% vs 8–10% UK population) and rhinitis (36% vs 18.25 UK population).[62]

Interestingly, autoimmune diseases have a higher prevalence in BBS. A recent study of Tsyklauri et al revealed the possible connection between BBS and dysregulated immune and hematopoietic systems; in this study, BBS patients showed decreased platelet and red blood counts, increased total white blood cells, neutrophils, and eosinophils.[63]

The incidence of cancer has never been systematically assessed in BBS patients. Three independent reports have described four cases of endometrial carcinoma in BBS patients.[64–66] The association between the BBS and this cancer may be correlated with the presence of risk factors as hyper-estrogenism due to truncal obesity, hyperinsulinemia and ovulatory dysfunction.

The study by Beales et al analyzed the incidence of cancer in unaffected relatives of 109 BBS patients, thus, in the setting of heterozygote BBS mutation.[67] The authors found that three out of 180 relatives had renal cell carcinoma, estimating an increased risk of RCC in BBS gene carriers compared with the general population. A subsequent study does not confirm this finding. Hjortshøj et al performed a population-based study to examine the incidence of cancer in 116 BBS patients and 428 relatives.[68] The study excluded the presence of an increased risk of renal cancer among family members of BBS patients, confuting previous data. Additional studies are needed to better understand the possibility of this relationship. Perhaps further understanding of the role of the PC in renal pathophysiology will clarify this issue.

Genetics of BBS and Genotype-to-Phenotype Correlation

The BBS has an autosomal recessive inheritance, although some authors suggested a oligogenic inheritance.[69–72] Currently, thanks to the progress in genetics, twenty-six genes have been associated with the syndrome, an increasing number over years (Table 2).[50] However, mutations in *BBS1* to *BBS18* account for about 70–80% of cases worldwide[73] and about 50% of diagnosis in the western countries are due to mutations in three genes: *BBS1, BBS2* and *BBS10*.[19,74] In Caucasian populations, indeed, mutations in *BBS1* and *BBS10* are detected in 21–30% of patients,[75] a percentage rising to 40–50% in Northern European patients.[76] A founder effect is responsible for the two most common mutations in Northern Europe: p.M390R (*BBS1*, accounting for 50% of *BBS*1 cases) and p.C91Lfs*5 (*BBS10*).[77]

In Indian population, instead, *BBS1* and *BBS10* mutations represent only 7% and 10% of diagnosis, respectively, while *BBS3* (14%), *BBS9* (10%), and *BBS6* (10%) mutations are more frequent.[78]

Table 2 Known Causative Genes of Human Bardet–Biedl Syndrome[88,144,145]

Gene	Name	Chromosomal Coordinate	Localization of the Protein in the Cell	Tissue Specificity	Protein Function
BBS1	**Bardet-Biedl syndrome 1**	11q13.2	Cilium and basal body	Low	Component of BBSome complex
BBS2	**Bardet-Biedl syndrome 2**	16q13	Cilium and basal body	Low	Component of BBSome complex
BBS3/ARL6	**Bardet-Biedl syndrome 3/ ADP ribosylation factor like GTPase 6**	3q11.2	Cilium, basal body, transition zone and cytosol	Low	GTP-binding protein involved in ciliary trafficking[146]
BBS4	**Bardet-Biedl syndrome 4**	15q24.1	Cilium and basal body	Low	Component of BBSome complex
BBS5	**Bardet-Biedl syndrome 5**	2q31.1	Basal body	Low	Component of BBSome complex
BBS6/MKKS	**Bardet-Biedl syndrome 6/ MKKS centrosomal shuttling protein**	20p12.2	Cilium and basal body	Low	Chaperonin like protein assisting BBSome formation
BBS7	**Bardet-Biedl syndrome 7**	4q27	Cilium and basal body	Low	Component of BBSome complex
BBS8/TTC8	**Bardet-Biedl syndrome 8/ tetratricopeptide repeat domain 8**	14q31.3	Cilium, IFT and basal body	Low	Component of BBSome complex
BBS9	**Bardet-Biedl syndrome 9**	7p14.3	Cilium	Low	Component of BBSome complex
BBS10	**Bardet-Biedl syndrome 10**	12q21.2	Basal body	Low	Chaperonin like protein assisting BBSome formation
BBS11/TRIM32	**Bardet- Biedl syndrome 11- tripartite motif containing 32**	9q33.1	Intermediate filaments	Low	E3 ubiquitin ligase; it promotes degradation of several targets[147]
BBS12	**Bardet-Biedl syndrome 12**	4q27	Basal body	Low	Chaperonin like protein assisting BBSome formation
BBS13/MKS1	**Bardet-Biedl syndrome 13/MKS transition zone complex subunit 1**	17q22	Basal body	Low	Component of the tectonic-like complex localized at the transition zone of primary cilium[148]
BBS14/CEP290	**Bardet-Biedl syndrome 14/centrosomal protein 290**	12q21.32	Basal body and centrosome	Low	Centrosomal protein involved in primary cilium formation[149]
BBS15/WDPCP	**Bardet-Biedl syndrome 15/WD repeat containing planar cell polarity effector**	2p15	Cytosol, axoneme and plasma membrane,	Low	Controls ciliogenesis[150]

(*Continued*)

Table 2 (Continued).

Gene	Name	Chromosomal Coordinate	Localization of the Protein in the Cell	Tissue Specificity	Protein Function
BBS16/SDCCAG8	**Bardet-Biedl syndrome 16/SHH signaling and ciliogenesis regulator SDCCAG8**	1q43-q44	Basal body, transition zone and centriole	Low	Involved in ciliogenesis and Sonic Hedgehog signaling pathway
BBS17/LZTFL1	**Bardet-Biedl syndrome 17/leucine zipper transcription factor like 1**	3p21.31	Cilium and basal body	Mainly in lymphoid tissue	Regulator of BBSome trafficking and Sonic Hedgehog signalling[151]
BBS18/BBIP1	**Bardet-Biedl syndrome 18/BBSome interacting protein 1**	10q25.2	Cytosol	Mainly in testis	Component of BBSome complex
BBS19/IFT27	**Bardet-Biedl syndrome 19/intraflagellar transport 27**	22q12.3	Cilium, IFT and basal body	Low	Intraflagellar trafficking (IFT-B) component[151]
BBS20/IFT172	**Bardet-Biedl syndrome 20/ intraflagellar transport 172**	2p23.3	Vesicles	Low	Intraflagellar trafficking (IFT-B) component[152]
BBS21/ CFAP418/ C8orf37	**Bardet-Biedl syndrome 21/ cilia and flagella associated protein 418**	8q22.1	Basal body and ciliary root	Low	Unknown[153]
BBS22/IFT74	**Bardet-Biedl syndrome 22/ intraflagellar transport 74**	9p21.2	Cilium, IFT and basal body	Low	Intraflagellar trafficking (IFT-B) component[152]
CEP19	**Centrosomal protein 19**	3q29	Centrosome	Low	Recruits the RABL2B GTPase to the ciliary base and intraflagellar transport (IFT) complex B[154]
NPHP1	**Nephrocystin 1**	2q13	Transition zone	Mainly in skeletal muscle	Cell-matrix signaling at focal adhesions[155]
SCAPER	**S-phase cyclin A associated protein in the ER**	15q24.3	Endoplasmic reticulum and ciliary tip	Low	Ciliary dynamics and disassembly[156]
SCLT1	**Sodium channel and clathrin linker 1**	4q28.2	Centriole	Low	Component of distal appendages which anchor the cilium to the plasma membrane, involved in ciliogenesis[157]

BBS1, BBS3, and *BBS4* mutations are commonly reported in Saudi Arabia,[72,79] while pathogenic variants in *BBS1, BBS2* and *BBS8* are common in Tunisia;[80] Middle Eastern and North African individuals have a high frequency of *BBS4, BBS5*, and *TTC8* variants.[81] A possible bias is the underdiagnosis and scarcity of large studies from some areas of the world;[74,82–84]in isolated populations characterized by a high frequency of marriages among consanguineous, the frequency of the disease is higher and founder effects are common; the Faroe Islands (c.1091 + 3G>C in BBS1),[5] Tunisia (p.R189* in *BBS2* and c.459 + 1G>A in *BBS8*)[80,85,86] and the Hutterite population (c.472–2A>G in *BBS2*) are

some examples.[32,73,87] Similarly, we have recently found a possible *BBS4* (c.332+1G>GTT) founder mutation in a restricted geographic area of the province of Naples.[74]

Most BBS genes have a low tissue specificity. Few exceptions are *BBIP1*, which is mainly expressed in the testis, *LZTFL1*, expressed in lymphoid tissue and *NPHP1*, in the skeletal muscle.[88]

Almost all BBS genes are related to the function of the PC and many of them have been described also in other ciliopathies; *BBS15, BBS13* and *SDCCAG8* mutations have been reported in Meckel syndrome[89–91] and *CEP290/NPHP6* mutations in Joubert, Senior–Løcken, Meckel–Gruber, nephronophthisis and Leber congenital amaurosis.[45]

Major BBS gene products have been detected on the base of the PC. Some of them have been detected along the cilium[92]; extracilia localization include the nucleus[93] and the endoplasmic reticulum.[34,94]

Functional studies demonstrated that they form two multimeric complexes: the BBSome and chaperonin complex. The BBSome is a cargo adaptor involved into intra-ciliary trafficking; it mediates vesicular trafficking of membrane proteins to the primary cilium (Figure 1).[34,95] BBSome is an octamer composed of BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, BBS9, and BBIP10, encoded by the respective genes.[96]

Chaperonin complex mediates BBSome assembly with a multistep process.[17,97–99]

The chaperonins-like proteins include MKKS/BBS6, BBS10 and BBS12.[98]

Genotype–phenotype correlation is made difficult by the unavailability of large cohort studies.[100] Genetic heterogeneity further complicates the analysis.[34]

Nevertheless, several studies have discussed this topic, many of them describing a milder phenotype in the presence of *BBS1* variants.[101–106] This can be partially explained by the high prevalence of the hypomorphic *BBS1*M390R variant,[105] but also by the minimal effect of loss of BBS1 function on BBSome formation and stability, according to in vitro studies.[107] Some reports also suggested that mutations in *BBS1, BBS2, BBS3*, and *BBS4* could be associated to specific ocular phenotypes and digital malformations.[34,73,108]

The meta-analysis recently published by Niederlova et al analyzed the largest cohort of BBS patients, with a total of 899 individuals, by assembling data from 85 articles focused on gene-phenotype correlation.[14]

The authors used a parameter, the syndromic score, to quantify disease severity. Patients with assumed loss of function mutations (as frameshifts or splicing mutations) turned out to have higher syndromic score than those with missense mutations and a higher frequency of the most severe form of the disease.[18]

The study also showed that patients with mutations *in BBS3/ARL6* had a significantly lower syndromic score than patients with mutations in the BBSome or chaperonin BBS genes. In particular, BBS3/ARL6 deficiency was characterized by a lower penetrance of cognitive impairment, renal anomalies and heart anomalies. Conversely, mutations in the BBSome-encoding and chaperonin-encoding genes had similar effects.[18]

Among patients with mutations in BBSome components, those with mutations in *BBS1* and *BBS8/TTC8* showed the lowest mean syndromic score, while patients with mutations in *BBS2* and B*BS7* the highest. Renal anomalies showed a low frequency in patients with mutations in *BBS1, BBS4*, or *BBS8/TTC8* and a high frequency in those with mutations in *BBS2, BBS7*, or *BBS9*.

The similar effect on phenotype in patients with *BBS1* and *BBS8/TTC8* could be explained by the direct interaction of the two subunits.[109] On the other hand, *BBS2, BBS7* and *BBS9* were previously proposed to form the core of the BBSome.[110] It is plausible that the BBSome core is specifically involved in the kidney disease. In contrast, BBS1, BBS4, and BBS8/TTC8 genes encode peripheral BBSome subunits probably less important in the overall BBSome function.[111–113]

Some studies suggested a milder obesity phenotype in BBS1 compared to other BBS genotypes, a difference that seems to shrink in adolescence. An independent study demonstrated that children with loss of function variants showed the highest risk for severe obesity, consistent with other BBS clinical traits.[17]

The meta-analysis did not take in account all secondary BBS clinical signs; additional studies are required to elucidate some still open questions.[101,102]

Current Knowledge on Patients' Survival and Clinical Management

Nowadays, there is no targeted treatment available for the syndrome. Interestingly, the 22-year prospective cohort study of Moore et al[4] on Newfoundland's population described a median patients survival of 63 years. O'Dea reported that about

Table 3 Causes of Death of BBS Patients

Age at Death (Years)	Primary Cause of Death	Source
40, 48, 50, 53, 54	Myocardial infarction	Moore et. Al (2005)[4]; Riise (1996)[114]
67	Valvulopathy	Riise (1996)[114]
63, 37	Cerebrovascular disease	Moore et. Al (2005)[4]; Riise (1996)[114]
19, 27, 53, 35, 60, 24, 37	Renal disease	Moore et. Al (2005)[4]; Riise (1996)[114]
63	Renal carcinoma	Moore et. Al (2005)[4]
62	Septicemia secondary to urinary tract infection	Moore et. Al (2005)[4]
1.5	Hirschsprung disease	Moore et. Al (2005)[4]
45	Gastro-intestinal hemorrhage after colonic resection	Moore et. Al (2005)[4]
32, 34	Embolism/thrombosis	Moore et. Al (2005)[4]; Riise (1996)[114]
52	Aspiration pneumonia (seizure due to a meningioma)	Moore et. Al (2005)[114]

25% of patients died before reaching the age of 44, compared to the 2% of the unaffected siblings; 72% of dead patients had renal impairment, with chronic uremia as cause of death for 38% of them.[35] In 1996, Riise highlighted the prominent role of kidney failure (50% of cases) and cardiovascular diseases as causes or contributing cause of death in BBS.[114] Also, other previous studies confirmed the major role of kidney disease as cause of mortality[115,116] (Table 3).

Given its pleiotropic nature, a multidisciplinary management is required[14].

Based on our experience and data from the literature, even if scarce, at baseline, medical assessment should include:[16,19,117]

- Family history
- Anthropometric assessment, vital signs and accurate clinical examination
- Neuropsychological testing adapted to age and low vision
- Ophthalmological evaluation: complete eye examination, visual acuity, visual field testing, fundus examination, electroretinogram (generally from 4–5 years of age) and, if necessary, visually evoked responses and optical coherence tomography (OCT)
- Orodental assessment
- Audiometry
- Echocardiogram, electrocardiogram (ECG)
- Abdominal ultrasound
- Analysis of renal function, including the estimation of the glomerular filtration rate (GFR), albuminuria, electrolytes and acid base balance; urine osmolality
- If neurological abnormalities are present, consider brain magnetic resonance (MRI)
- Laboratory tests: liver function tests, complete blood count, electrolytes, creatine, urea, lipid panel, blood glucose (HbA1c, oral glucose tolerance test for older children/adults and plasma insulin concentration), gonadotropins and sex hormones (if in age of puberty), thyroid hormones
- Genetic analysis and counseling.

Major clinical signs are treated by specific-disease specialists, including nephrologist, dental specialist, endocrinologist, psychologist/psychiatrist, dietitian, ophthalmologist, gastroenterologist, neurologist, urologist, gynecologist, dermatologist and others.[19]

There is no treatment to prevent deterioration of vision and early educational planning (eg: Braille, mobility training, dedicated software for electronic devices) is fundamental to reduce the impact of vision loss, developing independent

living skills. Low vision aids are also important when vision begins to decrease, and tinted glasses can be used if photophobia is present. Sometimes correction of refractive errors is also needed. In case of cataracts, surgery should be considered.[19]

In the presence of cognitive impairment and/or developmental delay, it is pivotal an early, age-based and personalized treatment with special education, speech therapy and physiotherapy. A clinical psychologist or a psychiatrist could be necessary if the patient shows behavioral disorders.[16,117]

The screening at renal function at basal is mandatory, given the common presence of kidney dysfunction. Periodic follow-up, based on kidney disease stage, should be suggested.[36,38,42] Specific intervention to slow the progression of CKD are unknown. Dervisoglu et al reported a mild improvement of creatinine clearance in two obese siblings affected by BBS, after two years of hypocaloric and low protein diet.[118] For patients in end stage renal disease, organ transplantation can be considered, although obesity should be a limit, especially for adult subjects. In fact, outcomes are comparable to those of the general population. It is reported an increase of the median BMI of the renal transplant cohort compared to the non-transplant cohort.[119]

A low-calorie diet and practice aerobic exercises to try to control obesity; for high-risk obese patients, bariatric surgery has to be considered.[120,121] There are few data on long-term safety and efficacy but a recent review reported that benefits may be less durable in hyperphagic disorders.[122,123]

Patients with autism-related symptoms can receive treatment of autism spectrum disorder, like ABA (applied behavior analysis).[19] New studies suggest that more attention should be given to bone metabolism disorders.[124] The risk of developing type 2 diabetes mellitus increases with age and it is desirable to try to prevent it with lifestyle modifications.[49] In fact, it is fundamental that metabolic syndrome, diabetes and hypertension are well-controlled to avoid serious secondary damages on organs already affected by BBS.[14] Thyroid function has to be controlled annually and, if laboratory values are abnormal, exams for thyroid autoimmunity should be requested.[49]

Surgery has a role in treatment of polydactyly (removal of accessory digits), genitourinary, orodental (eg, dental extraction for dental crowding), heart anomalies and other anatomical abnormalities. Imaging, such as CT angiography to detect possible vascular anomalies, is very important for preoperative planning.[56] When anesthesia is required, it is necessary to have a multidisciplinary preoperative evaluation for the risk of airway obstruction and the risks related to cardiovascular, kidney and/or endocrine diseases.[125] Appropriate planning (also for dental operations) is important to avoid perioperative and postoperative complications, considering concomitant medications and all the features of the syndrome, such as obesity, anxiety, structural cardiopathy (eg, risk of endocarditis), autistic-like behavior.[51] In 2011, an interesting case report described the resolution/improvement of clinical abnormalities that was maintained at least for three years (when case report was published) after that a child was treated with dietary supplementation (based on detailed biochemical testing that showed multiple nutrient deficiencies). This report suggested that a nutritional status assessment could be useful; we did not find any similar new case reports in literature.[126]

Future Perspectives

Research on gene therapy is one of the main prospective in BBS.[14,127]

Gene therapy using a viral vector is generally used to target a single organ like the eye and has been attempted in animal models of BBS for treating retinal degeneration.[128,129]

The recent approval of voretigene neparvovec as gene therapy for another form of retinal dystrophy increases expectations on gene therapy also in this setting.[127,130]

Whether other organs, as the kidney, could be targeted using this approach is debated; clearly, gene delivery from the blood is affected by glomerular filtration and only few studies have been reported about gene therapy in other kidney diseases.[131,132]

The eye is easy to access, there is a control eye and patients typically develop symptoms only in mid-late childhood.[14] Gene editing therapies and CRISPR/Cas9 tools could be of interest.[127]

Read-through therapy could be used for nonsense mutations (premature termination codons), responsible of approximately the 12% of Bardet Biedl cases[127] and its efficacy has already been assessed at a preclinical stage on other ciliopathies.[133–135]

Recently, Eintracht and others demonstrated that PTC124 (ataluren) or amlexanox cause the recovery of full-length BBS2 expression and correction of ciliary defects in BBS2 mutated fibroblasts.[136]

Some BBS mutations influences splicing and could be targeted by splicing-correcting approaches like antisense oligonucleotides, snRNAs and RNA interference. It has also been demonstrated in vivo the potential therapeutic effects in fibroblasts with a BBS1 mutation.[14,127,137]

New therapies are emerging for BBS-related obesity. Pomeroy et al observed that strategies to increase sleep duration could be useful to mitigate obesity.[138] In 2009, Seo et al demonstrated that intravenous melanocortin receptor agonist administration reduced body weight and food intake in *Bbs* knockout mice;[29] interestingly, in November 2020 and July 2021, in USA and EU, respectively, a new drug named setmelanotide has been approved for the treatment of obesity due to mutations in POMC, PCSK1 and LEPR. Setmelanotide is a melanocortin-4 receptor (MC4R) agonist and according to a phase-two study, it mitigates hyperphagia in BBS, reducing weight and hunger.[139] A phase-3 study is ongoing.[140] Ganawa et al reported a successful use of GLP-1 agonists for reducing the body mass index (BMI) in a young woman with BBS that showed childhood-onset obesity and hyperphagia. It was necessary to maintain the drug in therapy, because it was observed a weight regain after dose reduction.[141]

Pre-clinical studies demonstrated that the use of roscovitine and rapamycin was able to rescue renal cysts in zebrafish models of BBS.[142]

A novel target for therapy in BBS is glycosphingolipid metabolism, in experimental models of disease. It has been shown that it is impaired in this syndrome, with consequent accumulation of monosialodihexosylganglioside in *Bbs2*-/- mice. Indeed, it has been demonstrated that the glucosylceramide synthase inhibitor Genz-667161 decreased obesity, liver disease, retinal degeneration and olfaction defect in *Bbs*2-/- mice and preserved ciliary structure and signaling.[143]

In addition, to reduce adverse effects of current symptomatic treatment predicting how patients will respond to drugs, pharmacogenomics profile of BBS patients could be studied. In some countries, private companies offer pharmacogenomics gene panels, even if evidence base is still unclear for many of them.[14,127]

Technological advances like data sharing in the Cloud or telemedicine, may be useful, especially for who lives far from reference centers and/or have a more severe phenotype.[14]

Conclusions

The BBS is a rare pleiotropic disorder considered a model of ciliopathy. Given its rarity, its genetic and clinical heterogeneity, our understanding of the pathophysiology of major clinical signs is limited and data on genotype to phenotype correlation are scanty. To date, there is no specific therapy and supportive treatment is the milestone of patients' care. A multidisciplinary approach is mandatory in BBS, considering the presence of multiple organ dysfunction, and personalized follow-up is required. Recent investigations have provided insight into the understanding the function of BBS proteins, highlighting their ciliary and extraciliary functions. Dissecting their role in cellular biology is a prerequisite to develop specific therapy.

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Disclosure

The authors declare no competing interests.

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