

Bardet–Biedl syndrome: Genetics, molecular pathophysiology, and disease management

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Primary cilia play a key role in sensory perception and various signaling pathways. Any defect in them leads to group of disorders called ciliopathies, and Bardet–Biedl syndrome (BBS, OMIM 209900) is one among them. The disorder is clinically and genetically heterogeneous, with various primary and secondary clinical manifestations, and shows autosomal recessive inheritance and highly prevalent in inbred/consanguineous populations. The disease mapped to at least twenty different genes (*BBS1*–*BBS20*), follow oligogenic inheritance pattern. BBS proteins localizes to the centrosome and regulates the biogenesis and functions of the cilia. In BBS, the functioning of various systemic organs (with ciliated cells) gets deranged and results in systemic manifestations. Certain components of the disease (such as obesity, diabetes, and renal problems) when noticed earlier offer a disease management benefit to the patients. However, the awareness of the disease is comparatively low and most often noticed only after severe vision loss in patients, which is usually in the first decade of the patient's age. In the current review, we have provided the recent updates retrieved from various types of scientific literature through journals, on the genetics, its molecular relevance, and the clinical outcome in BBS. The review in nutshell would provide the basic awareness of the disease that will have an impact in disease management and counseling benefits to the patients and their families.

Key words: Bardet–Biedl syndrome, Bardet–Biedl syndrome genes, ciliopathy, Indian population

Bardet–Biedl syndrome (BBS; OMIM 209900), a clinically and genetically heterogeneous, autosomal recessive, ciliopathy disorder, was first described in 1866 by ophthalmologists Laurence and Moon. The condition is often being considered as two entities, namely, Laurence–Moon syndrome (LMS) and BBS with overlapping phenotypes.^[1] The differentiating features between LMS and BBS include progressive spastic paraparesis and distal muscle weakness in the former and polydactyly in the later.^[2] These disorders, classified as ciliopathy, arise due to functional relevance of BBS genes in ciliary biogenesis and trafficking.^[3] The prevalence of the disease varies between isolated, inbred (Bedouin and Newfoundland - 1:13,500 and 1:16,000),^[4,5] consanguineous (Arab - 1:65,000),^[6] and other populations (North America and Europe - 1:140,000 and 1:160,000).^[7,8] We have performed PubMed search with search terms “BBS, genetics of BBS, ciliopathy” and retrieved the current update from various original/review articles, case reports and brief communications on the above-mentioned aspect of BBS.

Definition of Bardet–Biedl Syndrome

The primary clinical features of BBS include rod–cone dystrophy, polydactyly or dystrophic extremities (brachydactyly and syndactyly), obesity, reduced intelligence, renal dysfunction,

and male hypogonadism that manifests in the first decade of life with polydactyly as a congenital feature [Fig.1].^[9] The other commonly associated secondary features include hepatic fibrosis, endocrinological disturbances such as diabetes mellitus, hypercholesterolemia, and reproductive abnormalities, short stature, speech defects, and developmental delay. In view of such diverse clinical manifestations, a criterion for the precise diagnosis of BBS requires either combination of (i) three primary and two secondary features or (ii) only four primary features.^[10]

Genetic Etiology of Bardet–Biedl Syndrome

Twenty different genes (*BBS1*–*BBS20*) have been mapped [Table 1] till date for the disease that shows variable expressivity with incomplete penetrance.^[11,12,20,21] Autosomal recessive mode of inheritance usually observed for the diseases and occasionally oligogenic inheritance has also been reported.^[10]

Mutation Spectrum of Bardet–Biedl Syndrome Genes

Mutations in *BBS1* to *BBS18* gene accounts for about 70%–80%^[22] with frequent recurrent mutations in *BBS1* and *BBS10* gene reported in certain populations like European and

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Caucasian descents. In patients of Northern European descent, *BBS1* and *BBS10* contribute approximately to 40%–50%.^[23] The role of founder effect has also been implicated in certain populations like the M390R in *BBS1* and C91fsX95 in *BBS10* genes.^[24] To the contrast, in Asian descents (Saudi Arabia, India), a novel, different spectrum of mutations in BBS genes and high prevalence for *BBS3*, *BBS9* genes when compared to the other populations have been observed.^[25,26] *BBS1* and *BBS10* mutations accounted for only 7% and 10% in Indian population, respectively, with a very low prevalence of known mutations.^[26] The frequency of mutation was observed in other genes being *BBS3* (14%), *BBS9* (10%), and *BBS6* (10%).^[26] A varied spectrum

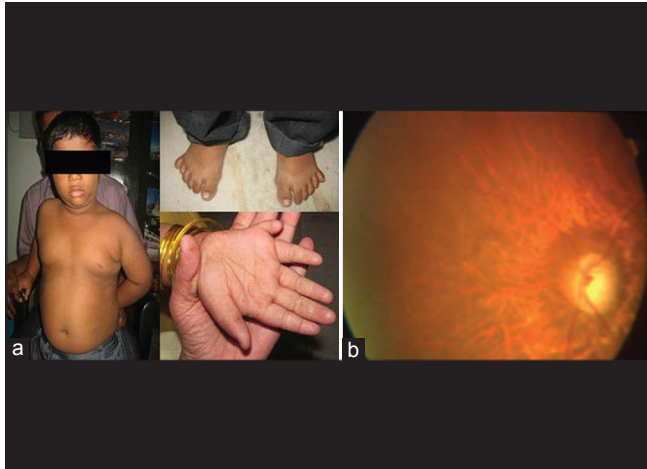


Figure 1: Three primary clinical features in Bardet-Biedl syndrome patients (a) truncal obesity, polydactyly in hand and feet (b) fundus photograph

of BBS mutations observed worldwide demonstrates genetic heterogeneity.

Triallelism, Epistasis, and Genetic Modifiers in Bardet-Biedl Syndrome Pathology

The discovery of triallelic inheritance, in which affected individuals harbor three mutations at two loci, raised an alternative possibility for explaining the difference in the clinical outcome observed within certain families.^[27] Oligogenic inheritance of BBS places it in between Mendelian and complex disease adding a layer of complexity to the genetic characterization in these patients.^[27,28] It has been observed that a third mutation was required to develop BBS.^[29] However, lack of substantive differences implicated between individuals or families with either two or three mutations has also been reported.^[30,31] These reports suggest that BBS mutations *per se* might exert an epistatic effect on the BBS phenotype by modifying the onset and/or severity of various aspects of the disorder.^[31]

Epistasis refers to the interactions between genes and has been recognized as a fundamentally important phenomenon in understanding both structure and function of genetic pathways and the evolutionary dynamics of complex genetic systems.^[32] Such interactions between candidate genes are implicated in many complex diseases such as coronary artery disease, diabetes, bipolar disorder, and autism.^[33] Second-site phenotypic modification, whereby mutation at a second gene modulates the penetrance and/or expressivity of recessive mutations at a primary locus,^[28] has also been observed in BBS. Some of these interactions include *MGC1203/CCDC28B*^[34] with *BBS1*, 2, 4, 5, 6, 7, and 8;^[35] hypomorphic mutations in *MKS1* and

Table 1: Chromosomal localization, proteins, and the respective functions for the Bardet-Biedl syndrome genes (*BBS1*-*BBS20*) in cilia

S. No	Gene name	Chromosomal loci	Protein name	Functions ^[11-19]
1	<i>BBS1 (BBS2L2)</i>	11q13	-	Forms BBSome complex
2	<i>BBS2</i>	16q21	-	Forms BBSome complex
3	<i>BBS3</i>	3p13-p12	ARL6	GTPase; facilitates vesicular and intercilary trafficking
4	<i>BBS4</i>	15q22.3-q23	-	Forms BBSome complex
5	<i>BBS5</i>	2q31.1	-	Forms BBSome complex
6	<i>BBS6</i>	20p12	MKKS	Forms chaperonin complex
7	<i>BBS7 (BBS2L1)</i>	4q27	-	Forms BBSome complex
8	<i>BBS8 (RP51)</i>	14q31.3	TTC8	Forms BBSome complex
9	<i>BBS9</i>	7p14	PTHB1	Forms BBSome complex
10	<i>BBS10 (C12orf58)</i>	12q21.2	-	Forms chaperonin complex
11	<i>BBS11</i>	9q33.1	TRIM32	E3 ubiquitin complex
12	<i>BBS12 (C4orf24)</i>	4q27	-	Chaperonin complex
13	<i>BBS13</i>	17q22	MKS1	Ciliary formation and epithelial morphogenesis
14	<i>BBS14</i>	12q21.32	CEP290/NPHP6/LCA10	Microtubule-associated protein transport
15	<i>BBS15</i>	2p15	WDPCP/FRITZ	Regulate cell polarity and directional cell migration
16	<i>BBS16</i>	1q43	SDCCAG8	Regulate cell polarity
17	<i>BBS17</i>	3p21.3	LZTFL1	Negatively regulates the BBSome trafficking
18	<i>BBS18</i>	10q25.2	BBIP1/10	Forms BBSome complex
19	<i>BBS19</i>	22q13.1	IFT27	In intraflagellar transport
20	<i>BBS20</i>	17q25.3	AZI1/CEP131	In ciliogenesis and length control

CEP290 genes;^[21] *RPGRIPL* variants.^[36] It has been predicted *in silico* that neutral variants can also act as modifiers to exacerbate phenotypes across the ciliopathy spectrum.^[37] Whole exome sequencing in a proband with severe form of BBS (with kidney impairment) has shown mutations in both *MKKS* (compound heterozygous) and *NPHP4* genes when compared to the other affected siblings (without kidney impairment), thus suggesting the role of epistatic interaction between *BBS* and *NPHP* genes contributing to the interfamilial phenotypic differences.^[38]

Implications of Other Ciliopathy Genes in Bardet–Biedl Syndrome

Recent genetic studies have demonstrated that mutations in other ciliopathy genes can also cause BBS. A clinical overlap exists between BBS and Alström syndrome although the two entities are genetically distinct. *ALMS1* gene mutations are implicated in 4.2% BBS patients.^[26,39] Apart from *ALMS1* gene, *NPHP* genes are also implicated in BBS as reported by^[40] a homozygous and heterozygous deletion (copy number variant) in *NPHP1* gene in addition to the primary BBS mutations. Functional analysis of this variant along with the primary BBS loci increases the phenotype severity in zebrafish models.^[40]

Bardet–Biedl Syndrome: A Model Ciliopathy

BBS occurs as a result of defect in BBS genes that codes for many ciliary-related proteins, and hence grouped as a ciliopathy disorder that arises due to ciliary dysgenesis and dysfunction.^[3] Ciliated mammalian cell types are extensively distributed in the vertebrate body as motile and nonmotile cilia [Fig. 2]. Primary cilia (nonmotile) are defined by their unique 9 + 0 structure with 9 microtubule triplets arranged in a circle with an outer membrane. Unlike motile cilia, primary cilia lacks the central microtubule pair necessary for ciliary mobility can vary greatly in length and are involved in cell signaling, left-right asymmetry, tissue formation, and homeostasis.^[41] Intraflagellar transport (IFT) and an active transport of proteins along the microtubules in cilia are necessary for the formation

and maintenance of cilia and play an important role in cell mobility, in transport of fluids over epithelial cells and in sensory perception. The BBS proteins are also involved in ciliogenesis and ciliary trafficking of certain proteins (e.g., G-protein coupled receptor, somatostatin receptor, etc.) across the cilia.^[42,43]

The BBS (1, 2, 4, 5, 7, 8, 9, and 18) proteins form a complex called BBSome complex and functions at the ciliary transition zone as a cargo for the antero- and retro-grade transport. This complex formation is facilitated by BBS-chaperonin complex formed by BBS-6, 10, and 12 with BBS7.^[15] The other BBS proteins function independently at the base of the cilium or in the centrosome for recruiting the BBSome.^[15] ARL6/BBS3 facilitates/modulates the transition between vesicular and intraciliary trafficking by forming a ring-shaped structure at the distal end of the transition fibers. It interacts with other BBS proteins to restrict the entry of ciliary vesicle into the cilium and also modulates Wnt signaling.^[16] BBS11/TRIM32 encodes an E3 ubiquitin ligase probably for BBS2.^[19] BBS14, BBS15, and BBS16 functions at the centriolar satellite and probably facilitate the recruitment of BBSome.^[18,44] BBS17 exerts a negative regulation on BBSome trafficking.^[17] IFT27/BBS19 encodes a component of the IFT-B complex required for anterograde transport of ciliary proteins with a speculated role in linking the BBS cargo to IFT machinery.^[12] AZI1/BBS20, a centriolar satellite protein, is a novel BBSome interacting protein, through BBS4. The protein when depleted localizes more BBSomes to the cilia, thus negatively regulating the ciliary trafficking of BBSome complex [Fig. 3].^[13]

Clinical Manifestations and Molecular Relevance

Ocular manifestations

The presence of rod-cone dystrophy (90%–100% prevalence) remains as the most important evidence for a clear diagnosis of BBS.^[45,46] An early onset, severe, and progressive retinal dystrophy due to both rods and cones dysfunction has been reported. The patients present with a history of night blindness since early childhood. Decreased vision in the first decades of life has been reported in BBS patients^[47] with the majority

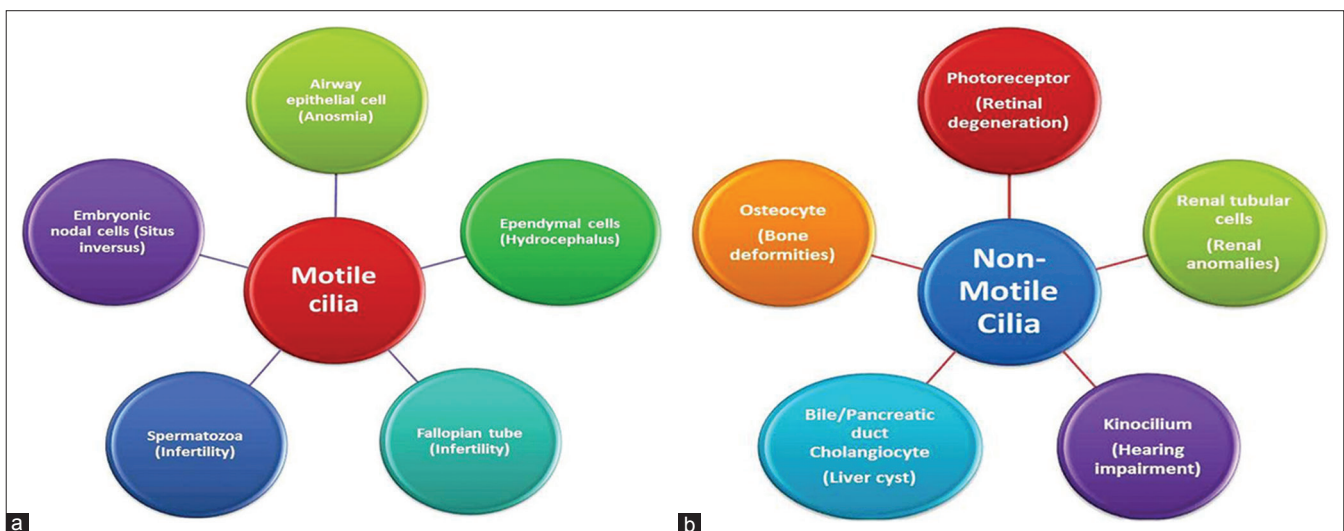


Figure 2: Different types of cells with (a) motile (b) nonmotile cilia and the respective clinical manifestations due to defective ciliary biogenesis/functions as observed in ciliopathy disorders

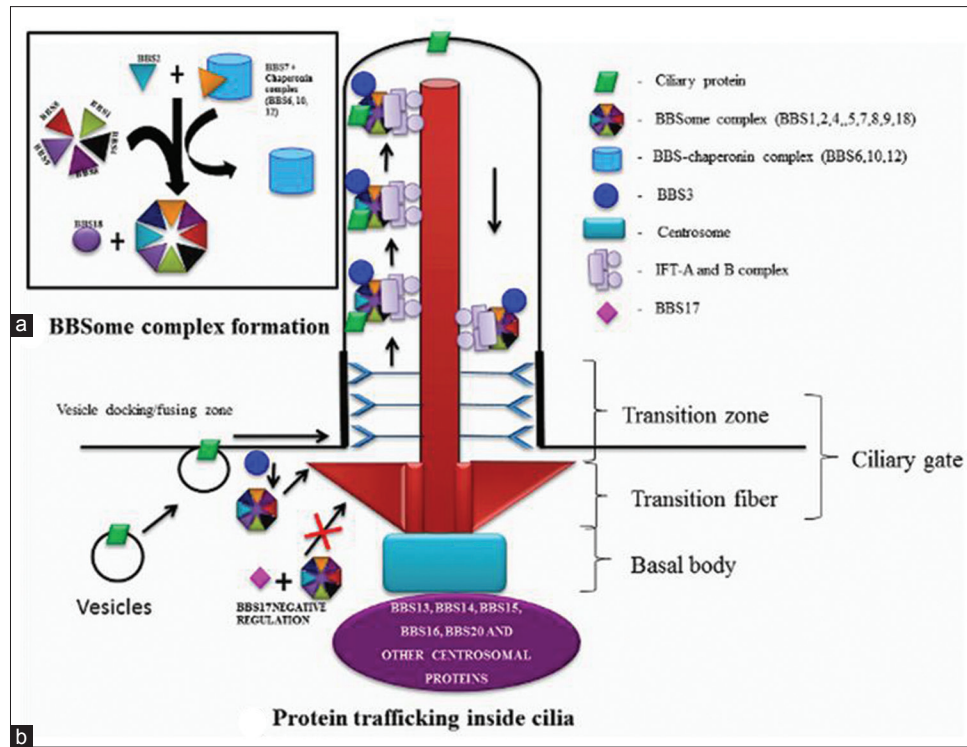


Figure 3: Diagrammatic representation of (a) BBSome complex formation and (b) protein trafficking inside the cilia

being legally blind (best-corrected visual acuity $<6/60$) by the second or the third decade of life. The visual impairment in BBS has been consistently early in onset; between 8 and 9 years and 98% of patients suffered complete loss of vision by the third decade.^[8] Electroretinogram (ERG) and visual evoked potentials (VEP) are often normal up to 5 years of age, but attenuated ERGs are typically seen in 10 years of age. The other ocular features include retinal dystrophy, myopia, astigmatism, strabismus, cataract, and color defects.

Rod and cone photoreceptor cells, responsible for the night and day vision, are modified ciliated cells. The outer segments (OSs) of photoreceptor cells function as specialized sensory cilia that elaborate into unique OS discs to provide extensive surface area for maximal photon capture and efficient visual transduction. The daily renewal of approximately 10% of OSs, therefore, demands a precise control of ciliary transport. It has been hypothesized that ciliary trafficking of the rhodopsin molecule is mediated by BBSome complex along with Rab8 and they interact during IFT.^[48] Knock-out mice models of *Bbs2*, *Bbs3L*, *Bbs4*, *Bbs6*, and *Bbs14* genes showed that rhodopsin mislocalization and accumulation in the inner segment (IS) of rod cells have been observed. This accumulation disturbs the cellular homeostasis and induces a slow process of degeneration eventually causing the total loss of the photoreceptors.^[48]

Obesity

Obesity, one of the cardinal features in BBS manifest by 2–3 years of age, is due to (i) deregulation of appetite, (ii) altered leptin resistance, (iii) altered neuroendocrine signaling from ciliated neurons to fat storage tissues, (iv) impaired leptin receptor signaling, (v) reduced number of cilia due to BBS gene mutations and alteration in the sonic hedgehog (Shh) and Wnt

signaling pathway in the differentiating preadipocytes.^[49] In 12-week-old knockout mice for *Bbs2*, *Bbs4*, and *Bbs6* genes, a progressive weight gain is observed when compared to birth weight, mainly due to excessive food intake which was otherwise runty by birth.^[50] Specific single nucleotide polymorphisms (SNPs) in BBS genes correlated with differences in the age of onset and morbidity for obesity. Nucleotide polymorphism in *BBS2* (rs4784675) was associated with common adult obesity; *BBS4* (rs7178130) and 6 (rs6108572 and rs221667) were associated with early-onset childhood obesity and common adult morbid obesity.^[51]

Limb anomalies

Postaxial polydactyly, one of the frequently reported systemic manifestations in BBS, provides a useful diagnostic clue for BBS as 63%–81% of patients manifest the same. Polydactyly of toes is seen more common than fingers^[8] with other radiological features including short metacarpals, metatarsals, and phalanges. High frequency of short ulna, broad hamate, clinodactyly of fifth finger, and increased sandal gap are also reported.^[52]

The molecular link between the ciliary proteins and limb formation, especially in BBS, is the Shh pathway^[53] which is activated through the Patched 1 (Ptch1), Smoothed (Smo), and transduces the signal via Gli transcription factors. Ptch1 and Smo strongly interact with BBS1. Thus, Smo and Ptch1 are endogenous cargos of the BBSome. The loss of *Bbs* genes in mice results in accumulation of Smo and Ptch1 in cilia and lead to a quantitative decrease in Shh response which might result in polydactyly.^[54]

One of the BBS genes, *LZTFL1* gene (*BBS17*) coding the human leucine zipper transcription factor-like 1, acts as a negative regulator for the ciliary trafficking mediated by

BBSome and the Shh signaling.^[17] Mis-sense mutations detected in this gene (by exome sequencing) is often correlated with mesoaxial polydactyly in BBS patients, thus making this gene as a prompting diagnostic tool in patients with such similar clinical feature.^[55]

Hypogonadism

Hypogonadism manifests as genital anomalies in females and small penis buried in the adipose tissue, with undescended testes in males. There is no delay in the onset of menarche in females, but with irregular cycles and polycystic ovaries are reported in the majority of cases, explaining the low rates of fertility observed in BBS female patients while male patients are invariably infertile.^[53]

Bbs2/Bbs4 knockout mice did not reproduce due to lack of flagella in sperm, demonstrating the requisite of these proteins in flagella formation during spermatogenesis.^[56] *In vitro* studies show that BBS4 localizes to the centriolar satellites of centrosomes and basal bodies, necessary to recruit PCM1 to centrosomal satellites, probably by acting as an adaptor between PCM1 and the dynein-dynactin motor complex. *BBS4* null/truncating mutations resulted in PCM1 and their associated protein mislocalization resulting in severe microtubule disorganization. This disrupts the normal function of centrosomes and basal bodies and in-turn the ciliary function.^[57]

Developmental delay

Developmental delay remains as one of the least-understood ciliopathy phenotypes. The behavioral changes observed in these patients include emotional immaturity, poor reasoning, and attention span. A similar phenotype of behavioral abnormalities has also been observed in *Bbs* knockout mice. Despite the presence of *Bbs3/Arl6* in neural tissues, the function of BBS proteins in cognitive impairment remains unknown.^[58] The involvement of BBS proteins in Shh and planar cell polarity (PCP) signaling suggests that they might be involved in proliferation of developing neuronal populations and migration of neurons during brain development.^[59]

Renal anomalies

Renal failure is another common cause of morbidity and mortality in these patients due to cystic tubular disease, lower urinary tract malformation, chronic glomerulonephritis, and defective tubular concentrating ability.^[8]

Bbs mutant mice models have shown initial structural abnormalities of the renal tubule cilia followed by defective cilia assembly or maintenance/regulation of ciliary length, thus explaining the renal pathology seen in these patients. The role of pathways upstream to mammalian target of rapamycin (mTOR) (Wnt PCP) pathway has been implicated in the kidney phenotypes. Rescue of the kidney cysts upon treating the *BBS* mutant embryos with mTOR signaling inhibitor rapamycin is being observed in zebrafish models.^[60] BBS proteins (BBS1, -2, -4, and -7) interact with proteins present in the kidney. In BBS patients with near normal kidney function without renal cysts and urinary concentration defect, the renal cells lacked cilia and showed normal cell cycle and inactive intracellular machinery for water absorption.^[61]

Another molecule implicated in the renal failure of BBS patients is the vasopressin receptor which is located in renal

epithelial cells and plays chemosensory role.^[62] The BBS1 protein found abundant in the kidney has shown to be involved in the transport of GLIS2, essential for maintaining the renal functions by regulating genes which are involved in epithelial-to-mesenchymal transition, fibrosis, and apoptosis.^[63]

Other features

The dysmorphic features of BBS include deep-set eyes, hypertelorism, downslanting palpebral fissure, broad forehead, flat nasal bridge, anteverted nares, long philtrum, thin upper lip, early balding, and speech defect with high pitched, and nasal voice has also been observed. Noninsulin-dependent diabetes mellitus has been described in around 45% patients with BBS.

Histopathology

Very few studies are available on the histopathology of retinal layers in BBS. Bek and Rosenberg studied the histological sections of the eye of a 60-year-old patient with BBS that showed a total lack of photoreceptor cells in all retinal areas with discontinuous retinal pigment epithelial layer, thickened Bruch's membrane, disrupted choroid, and complete absence of choroidal vessels. Inner retina also revealed a decrease in the number of inner nuclear layer cells as well as the ganglion cells. Glial tissue was seen to be increased across all layers.^[64]

Clinical Diagnostics

The divergent clinical/syndromic features of BBS and varying age of onset often complicates the diagnosis of BBS. Congenital manifestation of polydactyly (seen in 69%) often underestimated to be a clinical symptom. The obese feature that develops by 2–3 year of age and retinal degeneration observed by 8–9 years, ignites the query of BBS diagnosis. A combination of renal ultrasound study and intravenous pyelography (IVP) is advised on early identification of renal anomalies.

It is more often observed that first entry for the disease diagnosis in most of the cases remains to be the ocular clinic when the patient reports the ophthalmologists for his ocular distress. The details of the various tests recommended for BBS diagnosis are given as follows.

Fundus examination

It reveals typical presence of retinitis punctata albescence or retinitis pigmentosa "sine pigmento." Disc pallor, arteriolar attenuation, yellowish spots in the background with minimal to no pigment are some of the salient features. Macular degeneration is seen early on which is responsible for the poor visual acuity in many of these patients in the early years of life. Azari *et al.* in their study of ten patients with BBS showed maculopathy to be an early feature of the disease with advanced forms showing peripheral retinal degeneration and peripheral pigments as well.^[65]

Full field electrophysiology

It may show decrease in the rod and cone amplitudes as early as 2 years of life. Scotopic ERGs are known to get affected before the photopic responses. Typically, these patients are characterized by unrecordable responses eventually with elevated dark-adapted thresholds.^[47] However, negative ERGs indicating greater inner than outer retinal dysfunction have also been described by Azari *et al.* They however hypothesize

it to be a disease stage rather than primary disease feature with the disease process primarily affecting the photoreceptors, followed by a subsequent effect on the inner retinal function as well of the rod pathway.^[65]

Optical coherence tomography

The most common feature on time domain-optical coherence tomography (OCT) in patients with BBS is definable lamination with thinning in and around the fovea with varying severity of paracentral thinning and normal nerve fiber layer around the optic nerve with no genotype-phenotype correlation.^[65] Gerth *et al.* described preserved inner layer with disruption of the outer layer and absence of the connecting cilium at the IS-OS junction using Fourier domain OCT (Fd-OCT). Other features observed in BBS patients on OCT include internal limiting membrane wrinkling and deposits adjacent to and anterior to Bruch's membrane.^[66]

Recommendations of Other Investigations in Bardet–Biedl Syndrome Patients

Baseline:

- ERG/VEP
- Renal ultrasound
- IVP
- Echocardiography
- Speech assessment and therapy.

Semi-annually:

- Urine analysis.

Annually:

- Blood pressure
- Serum urea and creatinine levels
- Blood sugar
- Lipid profile
- Liver function tests.

Genetics Diagnostics

Genetic heterogeneity complicates clinical testing and critical for early diagnosis, carrier testing and if requested, prenatal testing. Genetic testing in BBS supports their clinical confirmation, carrier risk identification in families, and help in predicting severity of disease to certain extent. The various strategies of genetic screening in BBS include (i) homozygosity mapping using SNPs arrays,^[19,23,25,26,31,67] (ii) mutation screening of all BBS genes by direct sequencing,^[30] and (iii) next generation sequencing (NGS) platforms.^[11,17,68,69] Such high-throughput sequencing technologies offer the advantage of screening of even the other ciliopathy genes such as nephronophthisis (1–12) genes, the *ALMS1* gene, and the *CCDC28B* gene and overcome the limitation of genetic heterogeneity in a cost-effective manner. In addition to this, the technique also has the advantage of identifying the modifiers/epistatic effect of other genes that possibly could explain the phenotypic variability observed in families.

Disease Management and Genetic Counseling

The risk of recurrence remains 25% for a family with an affected child, especially for consanguineous couples. The prenatal appearance of enlarged hyperechoic kidneys without

corticomedullary differentiation often prompts a diagnosis of recurrence in the family especially when polydactyly is present.^[70] In nonaffected families, BBS has been suggested as a differential diagnosis when *in utero* shows such abnormalities and recommended for follow-up with postnatal evaluation. Due to the relatively high incidence of renal developmental anomalies and renal cell carcinoma in relatives of BBS patients,^[71] a detailed clinical history of other systemic features has also been recommended. An annual assessment of weight, blood pressure, lipid profile, liver function tests, and blood glucose level are required for effective health management, especially for controlling the complications of obesity and diabetes.

Conclusion/Future Direction

BBS, a ciliopathic disorder, with an autosomal recessive/oligogenic mode of inheritance exhibits high clinical and genetical heterogeneity. The syndromic features of this disorder could be effectively managed by prompt diagnosis, and disease awareness in the patients. A detailed genetic analysis becomes mandatory in these patients and the degree of heterogeneity could be made simple by sequencing of the coding regions of the known BBS genes/other ciliary genes preferably like targeted resequencing using NGS platforms. At present, it is expected that NGS in combination with network analysis and other advanced bioinformatics tools allows prioritizing candidate genes and has an increasingly important role in the diagnosis of these disorders.^[38] Moreover, NGS provides a unique possibility for investigating the presence of additional mutations that may modify the expressivity of BBS phenotype. To date, there is no effective treatment for BBS-associated retinal degeneration and progressive decrease in vision. Simons *et al.* described that gene therapy by adeno-associated virus-mediated *Bbs4* delivery into the rods of *Bbs4*-null mice can rescue rhodopsin mislocalization in this *Bbs* mouse model.^[72] This is a first encouraging step toward preserving vision in BBS patients. However, an important prerequisite for gene therapy is timely genetic diagnosis before extensive photoreceptor death could occur. Hence, appropriate genetic counseling for families and adequate medical follow-up for affected children is required for effective disease management.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

References

- Abdulla AB, Niloy AA, Shah TA, Biswas SK, Imran AK, Murshed KM, *et al.* Laurence moon Bardet Biedl syndrome. *Mymensingh Med J* 2009;18 1 Suppl: S124-8.
- Blacque OE, Leroux MR. Bardet-Biedl syndrome: An emerging pathomechanism of intracellular transport. *Cell Mol Life Sci* 2006;63:2145-61.
- Tobin JL, Beales PL. The nonmotile ciliopathies. *Genet Med* 2009;11:386-402.
- Farag TI, Teebi AS. High incidence of Bardet Biedl syndrome among the Bedouin. *Clin Genet* 1989;36:463-4.
- Fan Y, Rahman P, Peddle L, Hefferton D, Gladney N, Moore SJ, *et al.* Bardet-Biedl syndrome 1 genotype and obesity in the Newfoundland population. *Int J Obes Relat Metab Disord* 2004;28:680-4.
- Cherian MP, Al-Sanna'a NA. Clinical spectrum of Bardet-Biedl syndrome among four Saudi Arabian families. *Clin Dysmorphol* 2009;18:188-94.
- Pearce WG, Gillan JG, Brosseau L. Bardet-Biedl syndrome and retinitis punctata albescens in an isolated northern Canadian community. *Can J Ophthalmol* 1984;19:115-8.
- Beales PL, Elcioglu N, Woolf AS, Parker D, Flinter FA. New criteria for improved diagnosis of Bardet-Biedl syndrome: Results of a population survey. *J Med Genet* 1999;36:437-46.
- Schachat AP, Maumenee IH. Bardet-Biedl syndrome and related disorders. *Arch Ophthalmol* 1982;100:285-8.
- Badano JL, Leitch CC, Ansley SJ, May-Simera H, Lawson S, Lewis RA, *et al.* Dissection of epistasis in oligogenic Bardet-Biedl syndrome. *Nature* 2006;439:326-30.
- Aldahmesh MA, Li Y, Alhashem A, Anazi S, Alkuraya H, Hashem M, *et al.* IFT27, encoding a small GTPase component of IFT particles, is mutated in a consanguineous family with Bardet-Biedl syndrome. *Hum Mol Genet* 2014;23:3307-15.
- Chamling X, Seo S, Searby CC, Kim G, Slusarski DC, Sheffield VC. The centriolar satellite protein AZI1 interacts with BBS4 and regulates ciliary trafficking of the BBSome. *PLoS Genet* 2014;10:e1004083.
- Zhang Q, Yu D, Seo S, Stone EM, Sheffield VC. Intrinsic protein-protein interaction-mediated and chaperonin-assisted sequential assembly of stable bardet-biedl syndrome protein complex, the BBSome. *J Biol Chem* 2012;287:20625-35.
- Wiens CJ, Tong Y, Esmail MA, Oh E, Gerdes JM, Wang J, *et al.* Bardet-Biedl syndrome-associated small GTPase ARL6 (BBS3) functions at or near the ciliary gate and modulates Wnt signaling. *J Biol Chem* 2010;285:16218-30.
- Marion V, Stutzmann F, Gérard M, De Melo C, Schaefer E, Claussmann A, *et al.* Exome sequencing identifies mutations in LZTFL1, a BBSome and smoothed trafficking regulator, in a family with Bardet – Biedl syndrome with situs inversus and insertional polydactyly. *J Med Genet* 2012;49:317-21.
- Schaefer E, Zalozyc A, Lauer J, Durand M, Stutzmann F, Perdomo-Trujillo Y, *et al.* Mutations in SDCCAG8/NPHP10 cause Bardet-Biedl syndrome and are associated with penetrant renal disease and absent polydactyly. *Mol Syndromol* 2011;1:273-81.
- Chiang AP, Beck JS, Yen HJ, Tayeh MK, Scheetz TE, Swiderski RE, *et al.* Homozygosity mapping with SNP arrays identifies TRIM32, an E3 ubiquitin ligase, as a Bardet-Biedl syndrome gene (BBS11). *Proc Natl Acad Sci U S A* 2006;103:6287-92.
- Billingsley G, Bin J, Fieggen KJ, Duncan JL, Gerth C, Ogata K, *et al.* Mutations in chaperonin-like BBS genes are a major contributor to disease development in a multiethnic Bardet-Biedl syndrome patient population. *J Med Genet* 2010;47:453-63.
- Leitch CC, Zaghoul NA, Davis EE, Stoetzel C, Diaz-Font A, Rix S, *et al.* Hypomorphic mutations in syndromic encephalocele genes are associated with Bardet-Biedl syndrome. *Nat Genet* 2008;40:443-8.
- Scheidecker S, Etard C, Pierce NW, Geoffroy V, Schaefer E, Muller J, *et al.* Exome sequencing of Bardet-Biedl syndrome patient identifies a null mutation in the BBSome subunit BBIP1 (BBS18). *J Med Genet* 2014;51:132-6.
- Zaghoul NA, Liu Y, Gerdes JM, Gascue C, Oh EC, Leitch CC, *et al.* Functional analyses of variants reveal a significant role for dominant negative and common alleles in oligogenic Bardet-Biedl syndrome. *Proc Natl Acad Sci U S A* 2010;107:10602-7.
- M'hamdi O, Ouertani I, Chaabouni-Bouhamed H. Update on the genetics of bardet-biedl syndrome. *Mol Syndromol* 2014;5:51-6.
- Harville HM, Held S, Diaz-Font A, Davis EE, Diplas BH, Lewis RA, *et al.* Identification of 11 novel mutations in eight BBS genes by high-resolution homozygosity mapping. *J Med Genet* 2010;47:262-7.
- Estrada-Cuzcano A, Koenekoop RK, Senechal A, De Baere EB, de Ravel T, Banfi S, *et al.* BBS1 mutations in a wide spectrum of phenotypes ranging from nonsyndromic retinitis pigmentosa to Bardet-Biedl syndrome. *Arch Ophthalmol* 2012;130:1425-32.
- Abu Safieh L, Aldahmesh MA, Shamseldin H, Hashem M, Shaheen R, Alkuraya H, *et al.* Clinical and molecular characterisation of Bardet-Biedl syndrome in consanguineous populations: The power of homozygosity mapping. *J Med Genet* 2010;47:236-41.
- Sathya Priya C, Sen P, Umashankar V, Gupta N, Kabra M, Kumaramanickavel G, *et al.* Mutation spectrum in BBS genes guided by homozygosity mapping in an Indian cohort. *Clin Genet* 2015;87:161-6.
- Beales PL, Badano JL, Ross AJ, Ansley SJ, Hoskins BE, Kirsten B, *et al.* Genetic interaction of BBS1 mutations with alleles at other BBS loci can result in non-Mendelian Bardet-Biedl syndrome. *Am J Hum Genet* 2003;72:1187-99.
- Katsanis N. The oligogenic properties of Bardet-Biedl syndrome. *Hum Mol Genet* 2004;13:R65-71.
- Kaushik AP, Martin JA, Zhang Q, Sheffield VC, Morcuende JA. Cartilage abnormalities associated with defects of chondrocytic primary cilia in Bardet-Biedl syndrome mutant mice. *J Orthop Res* 2009;27:1093-9.
- Abu-Safieh L, Al-Anazi S, Al-Abdi L, Hashem M, Alkuraya H, Alalm M, *et al.* In search of triallelism in Bardet-Biedl syndrome. *Eur J Hum Genet* 2012;20:420-7.
- Laurier V, Stoetzel C, Muller J, Thibault C, Corbani S, Jalkh N, *et al.* Pitfalls of homozygosity mapping: An extended consanguineous Bardet-Biedl syndrome family with two mutant genes (BBS2, BBS10), three mutations, but no triallelism. *Eur J Hum Genet* 2006;14:1195-203.
- Xu L, Jiang H, Chen H, Gu Z. Genetic architecture of growth traits revealed by global epistatic interactions. *Genome Biol Evol* 2011;3:909-14.
- Phillips PC. Epistasis – The essential role of gene interactions in the structure and evolution of genetic systems. *Nat Rev Genet* 2008;9:855-67.
- Redin C, Le Gras S, Mhamdi O, Geoffroy V, Stoetzel C, Vincent MC, *et al.* Targeted high-throughput sequencing for diagnosis of genetically heterogeneous diseases: Efficient mutation detection in Bardet-Biedl and Alström syndromes. *J Med Genet* 2012;49:502-12.
- Cardenas-Rodriguez M, Osborn DP, Irigoín F, Graña M, Romero H, Beales PL, *et al.* Characterization of CCDC28B reveals its role in ciliogenesis and provides insight to understand its modifier effect on Bardet-Biedl syndrome. *Hum Genet* 2013;132:91-105.
- Chen J, Smaoui N, Hammer MB, Jiao X, Riazuddin SA, Harper S, *et al.* Molecular analysis of Bardet-Biedl syndrome families: Report of 21 novel mutations in 10 genes. *Invest Ophthalmol Vis Sci* 2011;52:5317-24.

37. Badano JL, Ansley SJ, Leitch CC, Lewis RA, Lupski JR, Katsanis N. Identification of a novel Bardet-Biedl syndrome protein, BBS7, that shares structural features with BBS1 and BBS2. *Am J Hum Genet* 2003;72:650-8.
38. González-Del Pozo M, Méndez-Vidal C, Santoyo-Lopez J, Vela-Boza A, Bravo-Gil N, Rueda A, *et al.* Deciphering intrafamilial phenotypic variability by exome sequencing in a Bardet-Biedl family. *Mol Genet Genomic Med* 2014;2:124-33.
39. Aliferis K, Hellé S, Gyapay G, Duchatelet S, Stoetzel C, Mandel JL, *et al.* Differentiating Alström from Bardet-Biedl syndrome (BBS) using systematic ciliopathy genes sequencing. *Ophthalmic Genet* 2012;33:18-22.
40. Lindstrand A, Davis EE, Carvalho CM, Pehlivan D, Willer JR, Tsai IC, *et al.* Recurrent CNVs and SNVs at the NPHP1 locus contribute pathogenic alleles to Bardet-Biedl syndrome. *Am J Hum Genet* 2014;94:745-54.
41. Satir P, Pedersen LB, Christensen ST. The primary cilium at a glance. *J Cell Sci* 2010;123(Pt 4):499-503.
42. Berbari NF, Lewis JS, Bishop GA, Askwith CC, Mykytyn K. Bardet-Biedl syndrome proteins are required for the localization of G protein-coupled receptors to primary cilia. *Proc Natl Acad Sci U S A* 2008;105:4242-6.
43. Jin H, White SR, Shida T, Schulz S, Aguiar M, Gygi SP, *et al.* The conserved Bardet-Biedl syndrome proteins assemble a coat that traffics membrane proteins to cilia. *Cell* 2010;141:1208-19.
44. Sung CH, Leroux MR. The roles of evolutionarily conserved functional modules in cilia-related trafficking. *Nat Cell Biol* 2013;15:1387-97.
45. Klein D, Ammann F. The syndrome of Laurence-Moon-Bardet-Biedl and allied diseases in Switzerland. Clinical, genetic and epidemiological studies. *J Neurol Sci* 1969;9:479-513.
46. Green JS, Parfrey PS, Harnett JD, Farid NR, Cramer BC, Johnson G, *et al.* The cardinal manifestations of Bardet-Biedl syndrome, a form of Laurence-Moon-Biedl syndrome. *N Engl J Med* 1989;321:1002-9.
47. Berezovsky A, Rocha DM, Sacai PY, Watanabe SS, Cavascan NN, Salomão SR. Visual acuity and retinal function in patients with Bardet-Biedl syndrome. *Clinics (Sao Paulo)* 2012;67:145-9.
48. Mockel A, Perdomo Y, Stutzmann F, Letsch J, Marion V, Dollfus H. Retinal dystrophy in Bardet-Biedl syndrome and related syndromic ciliopathies. *Prog Retin Eye Res* 2011;30:258-74.
49. Guo DF, Rahmouni K. Molecular basis of the obesity associated with Bardet-Biedl syndrome. *Trends Endocrinol Metab* 2011;22:286-93.
50. Seo S, Guo DF, Bugge K, Morgan DA, Rahmouni K, Sheffield VC. Requirement of Bardet-Biedl syndrome proteins for leptin receptor signaling. *Hum Mol Genet* 2009;18:1323-31.
51. Benzinou M, Walley A, Lobbens S, Charles MA, Jouret B, Fumeron F, *et al.* Bardet-Biedl syndrome gene variants are associated with both childhood and adult common obesity in French Caucasians. *Diabetes* 2006;55:2876-82.
52. Rudling O, Riise R, Tornqvist K, Jonsson K. Skeletal abnormalities of hands and feet in Laurence-Moon-Bardet-Biedl (LMBB) syndrome: A radiographic study. *Skeletal Radiol* 1996;25:655-60.
53. Forsythe E, Beales PL. Bardet-Biedl syndrome. *Eur J Hum Genet* 2013;21:8-13.
54. Zhang Q, Seo S, Bugge K, Stone EM, Sheffield VC. BBS proteins interact genetically with the IFT pathway to influence SHH-related phenotypes. *Hum Mol Genet* 2012;21:1945-53.
55. Schaefer E, Lauer J, Durand M, Pelletier V, Obringer C, Claussmann A, *et al.* Mesoaxial polydactyly is a major feature in Bardet-Biedl syndrome patients with LZTFL1 (BBS17) mutations. *Clin Genet* 2014;85:476-81.
56. Mykytyn K, Mullins RF, Andrews M, Chiang AP, Swiderski RE, Yang B, *et al.* Bardet-Biedl syndrome type 4 (BBS4)-null mice implicate Bbs4 in flagella formation but not global cilia assembly. *Proc Natl Acad Sci U S A* 2004;101:8664-9.
57. Kim JC, Badano JL, Sibold S, Esmail MA, Hill J, Hoskins BE, *et al.* The Bardet-Biedl protein BBS4 targets cargo to the pericentriolar region and is required for microtubule anchoring and cell cycle progression. *Nat Genet* 2004;36:462-70.
58. Zaghoul NA, Katsanis N. Mechanistic insights into Bardet-Biedl syndrome, a model ciliopathy. *J Clin Invest* 2009;119:428-37.
59. Louvi A, Grove EA. Cilia in the CNS: The quiet organelle claims center stage. *Neuron* 2011;69:1046-60.
60. Cardenas-Rodriguez M, Irigoín F, Osborn DP, Gascue C, Katsanis N, Beales PL, *et al.* The Bardet-Biedl syndrome-related protein CCDC28B modulates mTORC2 function and interacts with SIN1 to control cilia length independently of the mTOR complex. *Hum Mol Genet* 2013;22:4031-42.
61. Marion V, Schlicht D, Mockel A, Caillard S, Imhoff O, Stoetzel C, *et al.* Bardet-Biedl syndrome highlights the major role of the primary cilium in efficient water reabsorption. *Kidney Int* 2011;79:1013-25.
62. Raychowdhury MK, Ramos AJ, Zhang P, McLaughlin M, Dai XQ, Chen XZ, *et al.* Vasopressin receptor-mediated functional signaling pathway in primary cilia of renal epithelial cells. *Am J Physiol Renal Physiol* 2009;296:F87-97.
63. Kim YH, Epting D, Slanchev K, Engel C, Walz G, Kramer-Zucker A. A complex of BBS1 and NPHP7 is required for cilia motility in zebrafish. *PLoS One* 2013;8:e72549.
64. Bek T, Rosenberg T. Clinical pathology and retinal vascular structure in the Bardet-Biedl syndrome. *Br J Ophthalmol* 1995;79:76-80.
65. Azari AA, Aleman TS, Cideciyan AV, Schwartz SB, Windsor EA, Sumaroka A, *et al.* Retinal disease expression in Bardet-Biedl syndrome-1 (BBS1) is a spectrum from maculopathy to retina-wide degeneration. *Invest Ophthalmol Vis Sci* 2006;47:5004-10.
66. Gerth C, Zawadzki RJ, Werner JS, Héon E. Retinal morphology in patients with BBS1 and BBS10 related Bardet-Biedl Syndrome evaluated by Fourier-domain optical coherence tomography. *Vision Res* 2008;48:392-9.
67. Pereira I, Valverde D, Piñeiro-Gallego T, Baiget M, Borrego S, Ayuso C, *et al.* New mutations in BBS genes in small consanguineous families with Bardet-Biedl syndrome: Detection of candidate regions by homozygosity mapping. *Mol Vis* 2010;16:137-43.
68. Ajmal M, Khan MI, Neveling K, Tayyab A, Jaffar S, Sadeque A, *et al.* Exome sequencing identifies a novel and a recurrent BBS1 mutation in Pakistani families with Bardet-Biedl syndrome. *Mol Vis* 2013;19:644-53.
69. Wang H, Chen X, Dudinsky L, Patenia C, Chen Y, Li Y, *et al.* Exome capture sequencing identifies a novel mutation in BBS4. *Mol Vis* 2011;17:3529-40.
70. Cassart M, Eurin D, Didier F, Guibaud L, Avni EF. Antenatal renal sonographic anomalies and postnatal follow-up of renal involvement in Bardet-Biedl syndrome. *Ultrasound Obstet Gynecol* 2004;24:51-4.
71. Beales PL, Reid HA, Griffiths MH, Maher ER, Flinter FA, Woolf AS. Renal cancer and malformations in relatives of patients with Bardet-Biedl syndrome. *Nephrol Dial Transplant* 2000;15:1977-85.
72. Simons DL, Boye SL, Hauswirth WW, Wu SM. Gene therapy prevents photoreceptor death and preserves retinal function in a Bardet-Biedl syndrome mouse model. *Proc Natl Acad Sci U S A* 2011;108:6276-81.