Bardet–Biedl syndrome: The pleiotropic role of the chaperonin-like BBS6, 10, and 12 proteins

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Abstract

Bardet–Biedl syndrome (BBS) is a rare pleiotropic disorder known as a ciliopathy. Despite significant genetic heterogeneity, BBS1 and BBS10 are responsible for major diagnosis in western countries. It is well established that eight BBS proteins, namely BBS1, 2, 4, 5, 7, 8, 9, and 18, form the BBSome, a multiprotein complex serving as a regulator of ciliary membrane protein composition. Less information is available for BBS6, BBS10, and BBS12, three proteins showing sequence homology with the CCT/TRiC family of group II chaperonins. Even though their chaperonin function is debated, scientific evidence demonstrated that they are required for initial BBSome assembly in vitro. Recent studies suggest that genotype may partially predict clinical outcomes. Indeed, patients carrying truncating mutations in any gene show the most severe phenotype; moreover, mutations in chaperonin-like BBS proteins correlated with severe kidney impairment. This study is a critical review of the literature on genetics, expression level, cellular localization and function of BBS proteins, focusing primarily on the chaperonin-like BBS proteins, and aiming to provide some clues to understand the pathomechanisms of disease in this setting.

KEYWORDS

Bardet–Biedl syndrome, BBS10, BBS12 and ciliopathies, BBS6/MKKS, chaperonin-like proteins, chaperonopathies

1 | INTRODUCTION

The Bardet–Biedl Syndrome (BBS; MIM#209900) is a rare pleiotropic genetic disorder whose clinical diagnosis depends on the detection of primary and secondary features. It belongs to the heterogeneous group of disorders known as ciliopathies, and it is believed to be caused by a defect in primary cilium (PC) function (Hildebrandt, Benzing, & Katsanis, 2011). The latter is a highly conserved sensorial antenna of the cell that plays a vital role in coordinating different cellular signaling pathways (Cardenas-Rodriguez & Badano, 2009; Christensen, Clement, Satir, & Pedersen, 2012). It has been shown to control cell cycle, maintenance of stem cells, developmental/differentiation processes, cell migration, and polarity (Mitchison & Valente, 2017). Its dysfunction is considered as one of the main components in BBS pathogenesis (Marion et al., 2011). Therefore, the BBS is considered a model disease to study the biology of the PC. Eight BBS proteins (BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, BBS9, and BBS18) form the multimeric complex known as BBSome (Priya, Nampoothiri, Sen, & Sripriya, 2016). This multiprotein complex has been detected at the ciliary transition zone, serving as cargo for ciliary transport. The multiprotein complex and the small guanosine...
triphosphatase Arl6 (BBSome/Arl6) have been shown to be required for the exit of signaling receptors from the PC (Nachury, 2016; Nachury et al., 2007). The BBSome complex formation is facilitated by BBS6, BBS10, and BBS12 (Marion, Stutzmann, et al., 2012). These three proteins have sequence homology with the CCT/TRiC family of group II chaperonins and are not components of the BBSome. Little information is available for the remaining BBS genes: major information on BBS genes are summarized in Table 1.

In contrast to the BBSome, chaperonin-like BBS proteins have never been detected along with the PC; as BBSome components, they have been detected at the basal body of the PC. It is of note that altogether BBS6,10, and 12 are responsible for over 30% of mutational load in patients and that some features of BBS patients recapitulate the signature of an emerging group of disorders known as chaperonopathies, including neurological defects (Abbasi, Butt, Sultan, & Munir, 2009; Bennouna-Greene et al., 2011). In the current scenario, a deeper analysis of chaperonin-like BBS proteins versus BBSome may provide a new perspective on BBS to dissect better the molecular basis of phenotypic commonalities and variabilities among patients with different genotypes. Major features of genetic loci, protein expression, subcellular localization, and functions are the main highlights of the review.

### 2 | HISTORICAL PERSPECTIVE AND EPIDEMIOLOGY OF BBS

In 1866, Laurence and Moon (ophthalmologists) reported the case of patients with familial blindness with other features that included: **TABLE 1** Characteristics of the Bardet–Biedl Syndrome (BBS genes): (HGNC, HUGO Gene Nomenclature Committee Home Page. Available online: http://www.genenames.org/, n.d.; UniProt. Accessed on April 26, 2021. Available online: https://www.uniprot.org/, n.d.)

| S. no. | Gene symbol | Gene group | Protein name | Localization |
|-------|-------------|------------|--------------|--------------|
| 1. | BBS1 | BBSome | Bardet–Biedl syndrome 1 protein | Basal body, cilium |
| 2. | BBS2 | BBSome | Bardet–Biedl syndrome 2 protein | Basal body, cilium |
| 3. | ARL6 | ARF GTPase family | ADP-ribosylation factor-like protein 6 | Basal body, cilium, cytosol, transition zone |
| 4. | BBS4 | tetratricopeptide repeat domain containingBBSome | Bardet–Biedl syndrome 4 protein | Basal body, cilium |
| 5. | BBS5 | BBSome | Bardet–Biedl syndrome 5 protein | Basal body |
| 6. | BBS6/ (MKKS) | Chaperonin-like protein | McKusick-Kaufman/Bardet–Biedl syndromes putative chaperonin | Basal body, cytosol |
| 7. | BBS7 | BBSome | Bardet–Biedl syndrome 7 protein | Basal body, cilium |
| 8. | TTC8 | Tetratricopeptide repeat domain containingBBSome | Tetratricopeptide repeat protein 8 | Basal body, cilium, IFT |
| 9. | BBS9 | BBSome | Protein PTHB1 | Cilium |
| 10. | BBS10 | Chaperonin-like protein | Bardet–Biedl syndrome 10 protein | Basal body |
| 11. | TRIM32 | Tripartite motif containing finger proteins | E3 ubiquitin-protein ligase TRIM32 | Intermediate filament |
| 12. | BBS12 | Chaperonin-like protein | Bardet–Biedl syndrome 12 protein | Basal body |
| 13. | MKS1 | B9 domain containing MKS complex | Meckel syndrome type 1 protein | Basal body |
| 14. | CEP290 | MKS complex | Centrosomal protein of 290 kDa | Basal body, centrosome |
| 15. | WDPCP | Ciliogenesis and planar polarity effector complex subunits | WD repeat-containing and planar cell polarity effector protein fritz homolog | Cytoplasm, plasma membrane, axoneme |
| 16. | SDCCAG8 | MicroRNA protein coding host genes | Serologically defined colon cancer antigen 8 | Basal body, transition zone, cilium |
| 17. | LIZTL1 | BBSome | Leucine zipper transcription factor-like protein 1 | Basal body, cilium |
| 18. | BBIP1 | IFT-B1 complex RAB, member RAS oncogene GTPases | BBSome-interacting protein 1 | Cytoplasm, cytosol |
| 19. | IFT27 | IFT-B1 complex | Intraflagellar transport protein 27 homolog | Basal body, cilium, IFT |
| 20. | IFT74 | IFT-B1 complex | Intraflagellar transport protein 74 homolog | Basal body, cilium, IFT |
| 21. | C8orf37 | Protein C8orf37 | Cilium, cilary root |
| 22. | SCLT1 | Sodium channel and clathrin linker 1 | Centriole |
| 23. | NPHP1 | NPHP complex | Nephrocystin-1 | Transition zone |
| 24. | SCAPER | Zinc fingers C2H2-type | $S$ phase cyclin A-associated protein in the endoplasmic reticulum ($S$ phase cyclin A-associated protein in the ER) | Endoplasmic reticulum |
obesity, cognitive deficit, and spastic paraparesis (Laurence & Moon, 1995). Later, Bardet and Biedl separately described similar clinical manifestations along with post-axial polydactyly and hypogonadism. In recognition of this history, the disease was named Laurence–Moon–Bardet–Biedl Syndrome. Due to the overlapping features, the cases suggested that these two syndromes reflect variable expressions of a single disorder. Then two papers, respectively, in 1969 and 1982, by Ammann, Schachat, and Maumenee, defined Laurence–Moon and Bardet–Biedl Syndrome as two different entities of the same disease spectrum (Klein & Ammann, 1969; Schachat & Maumenee, ). BBS is the standard term for current usage. The frequency of BBS varies geographically. The estimated incidence of BBS was 1 in 160,000 in Switzerland (Klein & Ammann, 1969). The incidence of BBS found in the mixed Arab population of Kuwait is 1 in 36,000 (Farag & Teebi, 1988, 1989). The incidence of BBS is quite high in small isolated populations such as Newfoundland, with an incidence of 1 in 18,000 and Kuwaiti families of Bedouins ancestry, with an incidence of 1 in 13,500 (Farag & Teebi, 1989; Moore et al., 2005). These findings reflect the higher frequency in subpopulations and relatively closed geographic areas, as expected in autosomal recessive disorders (Katsanis et al., 2000). To date, there is no gender bias. Multiple shreds of evidence indicated that renal functional loss is one of the root causes of BBS patients’ highest mortality rate.

3 | CLINICAL MANIFESTATION OF BARDET–BIEDEL SYNDROME

Beales and colleagues compiled primary and secondary features associated with BBS. These signs and symptoms are used to make the clinical diagnosis of BBS. According to the Forsythe and Beales diagnostic criteria, a patient should be diagnosed with BBS in the presence of four primary features or three primary and two secondary characteristics. The primary cardinal features include rod-cone dystrophy, polydactyly, truncal obesity, learning disabilities, hypogonadism, renal malformations, or renal parenchymal defects (Beales, Elcioglu, Woolf, Parker, & Flinter, 1999). Clinical variability is relatively high among BBS patients (Forsythe et al., 2017; Zacchia et al., 2016, 2021). Among primary features, retinal dystrophy and obesity/overweight, especially in infancy, are among the most constant signs (Forsyth & Gunay-Aygun, 2020; Mujahid et al., 2018). These features are also highly shared with other syndromic ciliopathies, suggesting a crucial role of ciliary proteins in retinal and energy homeostasis. Secondary features include diabetes mellitus, poor coordination, hepatic fibrosis, behavior anomalies, subtle craniofacial dysmorphism, hypertension, Hirschsprung disease, and orodental defects (Forsyth & Gunay-Aygun, 2020). Signs and symptoms develop gradually over time, with a complete clinical picture varying among individuals; according to Beales et al., the average age for the diagnosis is 9 years (Beales et al., 1999). Table 2 shows the main clinical features of BBS patients and their frequency according to the literature.

| TABLE 2 | Criteria for clinical diagnosis of BBS, indicating primary and secondary characteristics |
|-----------------|-------------------------------|-------------------------------|
| **Diagnostic criteria** | **Characteristics** | **Incidences** |
| Primary diagnostic features | Retinal degeneration | 94% (Forsyth & Gunay-Aygun, 2020) |
| | Obesity | 89% (Forsyth & Gunay-Aygun, 2020) |
| | Postaxial polydactyly (toe and finger variations: Short (brachydactyly); curved (clindactyly), mild webbing (syndactyly) are considered as secondary features of BBS) | 79% (Forsyth & Gunay-Aygun, 2020) |
| | Cognitive impairment/learning disabilities | 66% (Forsyth & Gunay-Aygun, 2020) |
| | Renal anomalies | 52% (Forsyth & Gunay-Aygun, 2020) |
| Secondary diagnostic features | Developmental delays | 81% (Forsyth & Gunay-Aygun, 2020) |
| | Behavioral abnormalities | 35% (Bennouna-Greene et al., 2011; Forsyth & Gunay-Aygun, 2020) |
| | Hypertension/type-II diabetes mellitus | 15.8% (Forsyth & Gunay-Aygun, 2020; Mujahid et al., 2018) |
| | Dental anomalies (small teeth, small lower jaw, short teeth) | 50% (Forsyth & Gunay-Aygun, 2020) |
| | Olfactory dysfunction/anosmia | 47–100% (Forsyth & Gunay-Aygun, 2020) |
| | Thyroid dysfunction | 19.4% (Forsyth & Gunay-Aygun, 2020; Mujahid et al., 2018) |

4 | STRUCTURE AND INTERACTION OF CHAPERONIN-LIKE BBS PROTEINS

BBS6 (MIM#604896), BBS10 (MIM# 610148), and BBS12 (MIM# 610683) account for over ~30% of the mutational load in BBS (Billingsley et al., 2010). This finding is even more relevant considering the high genetic heterogeneity of BBS with at least 24 genes currently identified and considering the fact that several BBS patients have only clinical diagnosis in developing countries (Mitchison & Valente, 2017). The genetic products of these loci consist of proteins with a sequence homology of type II chaperonin proteins.

Chaperone proteins represent a ubiquitous and essential family of proteins. They serve as facilitators and regulators of protein conformational change within the cells (Hartl & Hayer-Hartl, 2002). Interestingly, chaperone-like proteins share with chaperonins the structures.
but are not necessarily responsible for the final structure of proteins. The chaperons encompass many fundamental biological processes, including assisting the correct folding of newly synthesized, non-native polypeptides, migration to the cellular site in which they will function, protein transportation, signal transduction, protein quality control and refolding. A class of molecular chaperones includes the “Heat Shock Proteins” (for Hsp) or stress proteins (Stone et al., 2000).

These proteins are tremendously expressed under high cellular stress conditions. The name “Hsp” was coined because heat shocks induce their parent genes expression, and in other cases, different stressors such as pH, osmolarity or pressure, chemicals/heavy metals and hormones. These heat shock proteins are classified according to their molecular mass and denoted as Hsp90, Hsp70, Hsp60, Hsp40, and Hsp27 (Schiller et al., 1988). They have also been classified as Group I and Group II chaperones. Group I chaperone proteins are conserved in bacteria and mitochondria, while Group II have been detected in eukaryotes and cytoplasm of archaea (e.g., eukaryotic CCT or TRiC). Most notably, Group II are characterized by a CCT or TRiC domain, consisting of two stacked rings composed of 8-CCT monomers arranged radially, forming functional hetero-oligomeric complexes.

TRiC plays an essential role in folding many critical and newly translated proteins (primarily soluble), including cytoskeletal proteins like tubulin and actin (primary substrate), in an ATP-dependent manner. Genetic and acquired defects in chaperonins or chaperonin-like proteins cause human diseases, known as chaperonopathies. Examples of chaperonopathies include neurological disorders such as distal hereditary motor neuropathies, McKusick-Kaufman Syndrome (MKKS), X-linked retinitis pigmentosa, and according to some studies, also a subclass of Bardet-Biedl Syndrome (Álvarez-Satta, Castro-Sánchez, & Valverde, 2017; Katsanis et al., 2000; Macario, Grippo, & De Macario, 2005; Slavotinek et al., 2000; Stone et al., 2000).

The chaperonin-like BBS genes are characterized by a relatively simple gene structure, with very few exons, making them suitable for mutational screening. Besides, these genes have a broad distribution of pathogenic variants throughout the coding sequence (Billingsley et al., 2010; Muller et al., 2010). Chaperonin-like BBS proteins emerged as highly divergent members of the CCT chaperonin family, according to phylogenetic analysis. The high divergence rate observed for BBS6/MKKS, BBS10, and BBS12 compared with canonical CCT chaperonins is not reflected through their primary structure, which is primarily conserved. BBS12 emerges as the most divergent member of the BBS chaperonin-protein family, due to the difference in the various secondary-structure motifs, including the ATP-hydrolysis motif.

Consequently, the typical chaperonin structure, consisting of three domains (apical, intermediate, and equatorial), is primarily conserved in chaperonin-like BBS proteins. However, they have an additional insertion in the intermediate and equatorial domain as two in MKKS/BBS6, three in BBS10, and five in the BBS12 sequence (Kim et al., 2005; Stoetzel et al., 2006, 2007). Despite the structural similarities, several lines of evidence point out that chaperonin-like BBS proteins may not function as bona fide chaperonins. It is debated whether BBS-like chaperonins perform the folding activity. Oligomerization and protein folding, an important distinction, is widely believed to be requisite for chaperonin activity. Furthermore, according to Kim et al. and Stoetzel et al., the ATP-hydrolysis motif, essential in protein-folding and highly conserved in CCT proteins, is either not conserved in MKKS/BBS6 and BBS12 or partially conserved in BBS10 (Kim et al., 2005; Stoetzel et al., 2007). These findings suggest that BBS6, BBS10, and BBS12 are not likely to have an ATPase activity.

Although these proteins’ role has not been well characterized or may differ from natural protein folding, recent studies highlighted that BBS6, BBS10, and BBS12 proteins mediate the association of BBS7 with six canonical CCT proteins (CCT1-5 and CCT8) thus, acting as a substrate-binding unit of the chaperone complex (Seo et al., 2010). Interestingly, BBS10 regulates the interaction of BBS6, BBS12, and BBS7 intermediate with CCT proteins to form the TriC/CCT/BBS complex without being structurally involved (Zhang, Yu, Seo, Stone, & Sheffield, 2012). Moreover, after the initial assembling of the BBSome complex, the interaction between BBS2 and BBS7 is coupled while BBS6 and BBS12 are released from the complex; also, CCT proteins are released after the BBSome core complex formation (BBS2–BBS7–BBS9). Thus, chaperonin-like BBS proteins might have evolved to mediate the association of CCT/Tric chaperonins with β-propeller domain-containing BBSome subunits such as BBS2 and BBS7. The formation of mature BBSome complexes is finally accomplished by intrinsic protein–protein interaction among the BBSome components that contain β-propeller, tetratricopeptide repeats, and pleckstrin homology domains (Zhang et al., 2012). The putative interactors of BBS6, 10, and 12 are listed and depicted in Figure 1a,b, respectively.

Interestingly, BBS6, BBS10, and BBS12 are vertebrate-specific, and none of their homologs is found in invertebrates. Despite decoding the mechanistic insight and distinct roles of chaperonin-like BBS proteins, the details on the complex formation (BBS/Tric/CCT) and how the transition of BBS7 to BBSome completes requires attention. Also, it is still unknown whether, in invertebrates, CCT chaperonins do not need BBS6, BBS10, and BBS12 to interact with BBSome subunits or the BBSome assembles without molecular chaperone functions (Seo et al., 2010).

### 5 | GENETICS, EXPRESSION, AND PROTEIN LOCALIZATION OF CHAPERONIN-LIKE BBS PROTEINS

Over 24 loci have been associated with BBS (Forsyth & Gunay-Aygun, 2020; Slavotinek, 2020). However, information regarding all genes/proteins is still elusive. BBS2 (MIM# 60615) was recognized as the first chromosomal disease locus by traditional linkage analysis on the tribal Bedouin population (Kwitek-Black et al., 1993). Subsequent studies identified a second locus, BBS1 (MIM# 209901). Later studies also described the third locus, BBS3 (MIM# 608845; Carmi et al., 1995) and fourth disease locus, BBS4 (MIM# 600374; Chiang et al., 2004). Out of all ciliopathies, BBS represents a remarkable condition caused by genetic defects in chaperone genes. Besides BBS, McKusick-Kaufman Syndrome (MKKS; MIM# 604896) shares the same feature. However, it is essential to highlight that MKKS is
caused by mutations in the MKKS/BBS6 gene, which determines Meckel syndrome and BBS (Billingsley et al., 2010; Deveault et al., 2011; Muller et al., 2010). BBS6, BBS10, and BBS12 account for ~30% of BBS diagnosis in western countries (Seo et al., 2010). The localization of these chaperonin-like BBS proteins on centrosomes and basal ciliary bodies has been demonstrated in different mammalian cell lines, including human HeLa, murine inner medullary collecting duct and murine embryonic fibroblasts, with a cell cycle-dependent localization (Marchese, Ruoppolo, Perna, Capasso, & Zacchia, 2020; Marion et al., 2009). MKKS/BBS6 was the first gene coding a putative chaperonin associated with the human inherited disorder, MKKS and later with BBS (Katsanis et al., 2000; Slavotinek et al., 2000; Stone et al., 2000). BBS6 mapped on chromosome 20p12.2 and encodes a 570 amino acid protein. BBS6 evolved from a CCT subunit and resided within the pericentriolar material, a proteinaceous tube surrounding centrioles for specialized functions (Marion et al., 2009). Over 50 deleterious variants, predominantly missense and nonsense mutations, have been reported yet (Stenson et al., 2017). Only 3–5% of families harboring two disease-causing variants in the multi-ethnic cohorts are defined globally; thus, BBS6 is a minor contributor of the syndrome (Deveault et al., 2011; Muller et al., 2010). In vivo studies on BBS6 have revealed expression changes during different developmental stages; BBS6 showed a prominent expression during embryogenesis in mice, especially in the heart, brain, limb buds, neural tube, and retina. Furthermore, BBS6 protein has been demonstrated in ciliated epithelial cells of renal tubules, olfactory epithelia and retina (Kim et al., 2005; Marchese et al., 2020). Interestingly, most causal variants described in MKKS have also been identified in BBS patients; conclusively, it has been suggested that the two syndromes are different clinical entities sharing the genetic landscape (Álvarez-Satta et al., 2017; Katsanis et al., 2000; Schaefer et al., 2011).

BBS10 is one of the major contributors of BBS, accounting for ~20% of all cases with few exceptions in the ethnically homogenous group as Danish and Spanish BBS cohort (Álvarez-Satta et al., 2017; Hjortshøj et al., 2010). BBS10, located on chromosome 12q21.2 and first identified by Stoetzel et al., encodes a 723 amino acid protein. BBS10 is composed of two exons and seems to be a bona fide chaperonin, unlike BBS6, which has lost its ATP binding site and provides a new angle on the function aspect of BBS (Stoetzel et al., 2006). BBS10 protein has three functional domains: the apical domain, the intermediate domain, and the equatorial domain. Two mutations (NM_024685.3:c.1677C>A and c.1974T>G) cause termination of the BBS10 protein in the intermediate and equatorial domain, respectively, that is, responsible for hydrolysis and ATP binding, to act on non-native polypeptides and facilitate their unfolding and folding (Billingsley et al., 2010; Imhoff et al., 2011; Stoetzel et al., 2006). At protein levels, BBS10 has been detected at the basal body of the PC in ciliated inner medulla collecting duct (IMCD) cells (Cognard et al., 2015); however, its low endogenous protein levels have made it difficult to address whether it has additional sub-cellular localization. It is unknown, to date, if stressing conditions may increase protein abundance, as demonstrated for other chaperonins.

The cytogenetic location of the BBS12 gene identified at chromosome 4q27c was first demonstrated in two consanguineous Gypsy families with BBS. The contribution of BBS12 has grown in

| Protein description | Gene name and synonyms | UniProt ID |
|---------------------|------------------------|------------|
| Bardet-Biedl syndrome 10 protein | BBS10 (C12orf158) | Q8TAM1 |
| Bardet-Biedl syndrome 12 protein | BBS12 (C4orf24) | Q6ZW61 |
| Bardet-Biedl syndrome 7 protein | BBS7 (BBS2L1) | Q8WZ26 |
| MKKS/BBS6 | MKKS/ BBS6 | Q1NF31 |
| T-complex protein 1 subunit alpha | TCP1 (CCT1 CCA) | P17987 |
| T-complex protein 1 subunit beta | CCT2 (9DFR1 CCTB) | P78371 |
| T-complex protein 1 subunit delta | CCT4 (CCTD SRB) | P50991 |
| T-complex protein 1 subunit epsilon | CCT5 (CCTE KIAA0098) | P46643 |
| T-complex protein 1 subunit gamma | CCT8/CCTG TRIC5 | P46648 |
| T-complex protein 1 subunit theta | CCT8 (C21orf112 CCTQ KIAA0002) | P50990 |

FIGURE 1 (a) Table with interaction network of BBS6, BBS10 and BBS12 proteins according to CORUM-Helmholtz Zentrum München, UniProt, Gene Ontology Resource, STRING Search tool in Homo sapiens (Humans); in the panel, (b) Graphical interaction between BBS-Chaperonin complex (image source: CORUM. Circles (nodes) represent proteins, whereas the lines (edges) connecting two circles signify an interaction between two proteins.
importance over recent years, accounting for 8–11% of the total cases in most of the cohorts reported. About 60 pathogenic variants of BBS12 have been currently identified in human BBS (Stoetzel et al., 2007). Nonsense and frameshift mutations have been reported in BBS12 which account for up to 5% of families with BBS (Stoetzel et al., 2007). Its product localizes to the basal body of the PC, whereas other BBS proteins have also been detected all along the cilium (Marion et al., 2009). BBS12, together with BBS6 and BBS10, defines a new vertebrate-specific and divergent branch of chaperonin-like proteins with particular sequence insertions, with respect to the typical group II chaperonins (Stoetzel et al., 2007).

6 | THE EXTRA-CILIARY FUNCTION OF THE CHAPERONIN-LIKE BBS PROTEINS

The functional outline of the BBS proteins has provided critical information to understand interactions between different BBS gene products and to elucidate their biological role. BBS proteins share biological functions, forming multiprotein complexes. Mutations in several BBS genes affect the same biological processes, including the formation/function of the PC. This feature is shared with other ciliopathy proteins localized to the PC, the basal body and the centrioles. However, the exact function of many ciliopathy proteins not rarely remains unknown (Novas, Cardenas-Rodriguez, Irigoin, & Badano, 2015).

BBS6, BBS10, and BBS12, unlike any other BBS genes, are specific to vertebrates (Imhoff et al., 2011; Marion et al., 2009). They are not included in the BBSome complex but may aid the folding of other BBS proteins. Their functionality in non-ciliated organisms has not been fully explored. Multiple shreds of evidence suggest that the chaperonin-like BBS6, 10, and 12 may play cilia-unrelated functions. BBS6 has been identified to not only functions as chaperonin-complex but is also actively transported between the nucleus and cytoplasm (Hurd, Fan, & Margolis, 2011; Kee & Verhey, 2013; Kee et al., 2012; Knockenhauer & Schwartz, 2016; Reiter, Blacque, & Leroux, 2012). Interestingly, additional studies have shown a high degree of resemblance between the nuclear-pore complex and cilia transition zone, both the gatekeepers of their respective cellular compartments, suggesting the possibility that BBS proteins also participate in nuclear transport (Starks et al., 2015). Of note, other ciliary proteins have been shown to play a role into the nucleus. It is the case of CEP164 and CEP290. CEP164, as an example, has been shown to have a role in DNA damage signaling, proliferation and induction of apoptosis (Sluats et al., 2014).

As stated above, mutations in BBS6 are associated with two similar but different clinical conditions, the BBS and McKusick–Kaufman syndrome (MKKS). According to Scott et al., MKKS-associated allele, BBS6H4Y; A242S, can still function in cilia-related processes but is malfunctioning in its ability to enter the nucleus, providing an explanation of why the same gene, when mutated, can cause different clinical conditions. By performing in vivo and in vitro experiments on zebrafish and mammalian cell culture, a novel BBS6 interacting protein, SMARCC1, a SWI/SNF chromatin remodeling protein, was found. BBS6 modulates the subcellular localization of SMARCC1, with reduced or increased cytoplasmic SMARCC1 in BBS6 knockout and over-expressing cell lines, respectively. This finding suggests that BBS6 participates in cellular transport pathways not restricted to the PC and may provide a clue into understanding the pathophysiology of congenital heart defects in MKKS syndrome (Scott et al., 2017; Seo et al., 2010). This study indicates that BBS6 evolved from a CCT subunit and diverged to acquire specialized functions with centrosomes and the basal body’s pericentriolar material (PCM). BBS6 association with the centrosome is independent of the dynein molecular motor and is conferred by its apical domain. This putative substrate-binding domain probably plays an essential role in its function, as numerous patient-derived mutations cause BBS6 mislocalization. Notably, BBS6 disruption impacted cytokinesis and produced multi-centrosomal and multinucleate cells (Seo et al., 2010).

Additional studies signify BBS chaperonin-like proteins engage in several cellular processes, such as trafficking multiple cellular receptors. According to Stark et al., BBS proteins control the routing to the cell membrane of the insulin receptor (IR), and the loss of BBS proteins leads to a defect in transport and localization of IR to the surface, using mice lacking various BBS genes (Starks et al., 2015). Resembling the phenotype of BBS patients, BBS6−/− mice showed hyperglycemia, hyperinsulinemia, glucose intolerance, and insulin resistance. Through this observation, the authors elucidated the regulatory role of BBS proteins in glucose metabolism and insulin sensitivity through BBS6 influence in the trafficking of IR to the plasma membrane (Marion, Mockel, et al., 2012). Fewer data are available on the biological functions of BBS10 and BBS12, besides their role in forming the chaperonin complex aiding BBSome formation.

BBS10 has been shown to participate in insulin signaling by direct interaction with the IR. Wang et al. showed that insulin signaling was impaired in BBS1 and BBS10 human mutant fibroblasts, more severely in BBS10 mutated cells (Wang et al., 2021). These findings are consistent with the greater severity of insulin resistance in BBS10 patients than in BBS1 patients (Feuillan et al., 2011). Interestingly, BBS1 and BBS10 co-immunoprecipitated with the IR and BBS10 mutations decreased IR autophosphorylation upon interaction with insulin, in human fibroblasts. Similarly, leptin signaling was deregulated in both BBS1 and BBS10 mutated hypothalamic derived neurons; whether BBS10 defects impaired leptin receptor (LR) trafficking via BBSome abnormalities, or it may contribute to the control of LR stability by itself has not been investigated (Wang et al., 2021).

Interestingly, Haq et al. showed that the loss of BBS proteins resulted in a significant reduction of dendritic spines in principal neurons of Bbs mouse models. Hence, the presence of BBS proteins, including BBS10, in the postsynaptic density (PSD) of spines suggests a direct synaptic function of BBS proteins, in addition to ciliary function. The authors concluded that the role of BBS proteins in dendritic spine homeostasis might be linked to the cognitive phenotype observed in BBS (Haq et al., 2019).

Cytoskeleton regulation and cell division defects have been described in several cellular models of BBS. Kidney medullary cells
taken from Bbs6−/− mice showed abnormal motility and cytokinesis, along with disorganization of the actin cytoskeleton; these defects have also been demonstrated in other BBS models, as Bbs4−/− cells, suggesting that some extraciliary dysfunction are shared among BBS proteins (Hernandez-Hernandez et al., 2013). Similarly, we showed that inner medulla collecting duct (IMCD3) cells lacking Bbs10 displayed impaired trafficking of the water channels Aquaporin 2 (AQP2) to the apical membrane; this finding was paralleled by a dramatic reduction of acetylated tubulin staining in subapical confocal sections, suggesting a role of Bbs10 in protein trafficking to the plasma membrane, probably via abnormal cytoskeleton organization (Zacchia, 2014).

Of note, several Bbs proteins, including BBS6 and BBS10, showed a direct interaction with a chromatin remodeler of the polycomb group, NF2, further suggesting a nuclear role of these proteins (Gascue et al., 2012). Deeper studies on BBS12 extraciliary processes are lacking. The absence of BBS12 in adipocytes has been shown to impair adipogenesis. Inactivation of BBS12 in human bone marrow mesenchymal stem cells (MSC) favored programming of MSC toward adipocyte differentiation, with increased glucose uptake and triglyceride synthesis (Scott et al., 2017). Simultaneous inhibition of anti-adipogenesis and activation of pro-adipogenesis pathways lead to these metabolic aberrations. The increased leptin secretion by BBS-depleted adipocytes in vitro provides an additional explanation for hyperleptinemia, a documented finding in BBS patients.

It is unclear if extraciliary functions of the chaperonin-like BBS proteins may underlie some clinical features of BBS patients. Conclusive studies addressing whether mutations of BBS6, 10, and 12 may affect biological functions in a BBSome-independent manner are still lacking. In this case, significant clinical differences should be expected among patients with chaperonin-like and BBSome components gene mutations.

A recent metaanalysis showed that patients with mutations in BBS6, 10 and 12 show renal defects with a higher frequency than patients with mutations in BBS3 and a trend toward an increased frequency compared with patients with BBSome mutations (Niederlova, Modrak, Tsyklauri, Huranova, & Stepanek, 2019). Several independent reports support the hypothesis of a difference in the severity of renal phenotype between chaperonin-like and BBSome mutations (Esposito et al., 2017; Marion et al., 2011; Zacchia, Di Iorio, Trepiccione, Caterino, & Capasso, 2017). Additional studies are required to confirm further and better address the reasons underlying this evidence. The biological roles of BBS proteins are depicted in Figure 2 and listed in Table 3.

7 | CONCLUDING REMARKS/FUTURE PERSPECTIVE

BBS is a pleiotropic disorder known as ciliopathy. Since cloning the first BBS gene, ample work has followed regarding genetics or deciphering the molecular functions of BBS proteins. The identification of BBSome was a milestone to elucidate their role in cilia biology and to dissect the syndrome’s molecular basis. BBS6, 10 and 12 are
### TABLE 3  Biological roles of chaperonin-like BBS proteins

| Gene/MIM no.          | Phenotype no. | Cytogenetic location | Exons | Amino acids | Pathogenic Variants & Mutation Load (%) | Molecular/biological function | References |
|-----------------------|---------------|----------------------|-------|-------------|-----------------------------------------|------------------------------|------------|
| BBS6/MKKS *604896     | 605,231 (BBS6) | 20p12.2              | 6     | 570         | 57 and 6.3%                            | Translational function:      | (Katsanis et al., 2000) |
| autosomal             | 236,700 (MKKS)|                      |       |             |                                         | Chaperone-mediated protein complex assembly | (Álvarez-Satta et al., 2017) |
| recessive             |               |                      |       |             |                                         | Regulation of protein containing-complex assembly | (Seo et al., 2010) |
|                       |               |                      |       |             |                                         | Unfolded protein binding/protein folding | (Forsyth & Gunay-Aygun, 2020) |
|                       |               |                      |       |             |                                         | Protein trafficking to the plasma membrane | (Marion, Mockel, et al., 2012) |
|                       |               |                      |       |             |                                         | Cytokinesis | (Seo et al., 2010) |
|                       |               |                      |       |             |                                         | Ciliary function:            | (Forsyth & Gunay-Aygun, 2020) |
|                       |               |                      |       |             |                                         | Cilium assembly | (Marion et al., 2011; Zacchia et al., 2017) |
|                       |               |                      |       |             |                                         | Non-motile cilium assembly/cilium assembly | (Gascue et al., 2012) |
|                       |               |                      |       |             |                                         | Regulation of cilium beat frequency involved in ciliary motility | (Stone et al., 2000) |
|                       |               |                      |       |             |                                         | Release of extracellular vesicles | (Forsyth & Gunay-Aygun, 2020) |
|                       |               |                      |       |             |                                         | Transcriptional level function: | (Marion, Mockel, et al., 2012) |
|                       |               |                      |       |             |                                         | ATP binding | (Seo et al., 2010) |
|                       |               |                      |       |             |                                         | RNA polymerase II repressing transcription factor binding | (Seo et al., 2010) |
|                       |               |                      |       |             |                                         | Negative regulation of Actin filament polymerization | (Gascue et al., 2012) |
|                       |               |                      |       |             |                                         | (Forsyth & Gunay-Aygun, 2020) |

| BBS10 *610148         | 615,987       | 12q21.2              | 2     | 723         | 99 and 14.5%                           | ATP ligand binding | (Álvarez-Satta et al., 2017) |
| autosomal             |               |                      |       |             |                                         | RNA polymerase II repressing transcription factor binding | (Seo et al., 2010) |
| recessive             |               |                      |       |             |                                         | Chaperone-mediated protein complex assembly | (Stone et al., 2000) |
|                       |               |                      |       |             |                                         | Non-motile cilium assembly | (Forsyth & Gunay-Aygun, 2020) |
|                       |               |                      |       |             |                                         | Photoreceptor cell maintenance | (Marion et al., 2011; Zacchia et al., 2017) |
|                       |               |                      |       |             |                                         | Regulation of protein-containing complex assembly | (Forsyth & Gunay-Aygun, 2020) |
|                       |               |                      |       |             |                                         | Unfolded protein binding | (Marion et al., 2011; Zacchia et al., 2017) |
|                       |               |                      |       |             |                                         | Protein trafficking to the plasma membrane (AQP2) | (Marion et al., 2011; Zacchia et al., 2017) |

| BBS12 *610683         | 615,989       | 4q27                 | 2     | 710         | 59 and 6.4%                            | Chaperone-mediated-protein complex assembly | (Forsyth & Gunay-Aygun, 2020); Marion, Mockel, et al., 2012) |
| autosomal             |               |                      |       |             |                                         | Protein folding | (Forsyth & Gunay-Aygun, 2020); Marion, Mockel, et al., 2012) |
| recessive             |               |                      |       |             |                                         | Regulation of fat cell differentiation | (Forsyth & Gunay-Aygun, 2020); Marion, Mockel, et al., 2012) |
|                       |               |                      |       |             |                                         | Intraciliary transport | (Forsyth & Gunay-Aygun, 2020); Marion, Mockel, et al., 2012) |
|                       |               |                      |       |             |                                         | Leptin signaling | (Forsyth & Gunay-Aygun, 2020); Marion, Mockel, et al., 2012) |
|                       |               |                      |       |             |                                         | Visual transduction | (Forsyth & Gunay-Aygun, 2020); Marion, Mockel, et al., 2012) |
chaperonin-like proteins; their genetic defect accounts for over 30% of BBS diagnosis in western countries, with BBS10 as significant component.

An increasing body of data demonstrates that BBS proteins are involved in multiple signaling pathways, serving several cellular processes that are likely not functionally restricted to the primary cilium. This peculiarity could explain why BBS is one of the most pleiotropic, multisystemic ciliopathy and could be relevant to understanding the disorder’s etiology fully (Novas et al., 2015). Dissecting cilia versus non-ciliary functions of the BBS proteins could provide critical insight to understand the pathophysiology of several clinical features of BBS. Identifying target proteins and establishing their roles are vital aspects offering new elements to study. Elucidating the role of BBS proteins might be challenging and may provide novel entry-points for improving clinical management.

In this respect, chaperonin-like proteins act as a model for investigating the impact of the deleterious variant in protein structure and function and could represent a promising mechanism not explored till now to characterize their role further (E. C. de Macario, Robb, & Macario, 2017). Besides this, identifying the specific chaperones and partners involved in folding BBSome components and deciphering putative BBSome-independent functions, if any, could provide novel research ideas for improving patient diagnosis, management, and coherent design of therapeutic interventions.

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CONFLICT OF INTEREST

Authors have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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