Journal of Pediatric Genetics 2 (2013) 77–83
DOI 10.3233/PGE-13051
IOS Press

Review Article

Bardet-Biedl syndrome: A rare genetic disease

Diana Valverde*, Sheila Castro-Sánchez and María Álvarez-Satta
Department of Biochemistry, Genetics and Immunology, Faculty of Biology, University of Vigo, Vigo, Spain

Received 8 October 2012
Revised 12 April 2013
Accepted 12 April 2013

Abstract. Bardet-Biedl syndrome (BBS) is a rare multisystem genetic disease, with high phenotypic and genetic heterogeneity. Rod-cone dystrophy, obesity, polydactyly, hypogonadism, cognitive impairment and renal abnormalities have been established as primary features. There are 17 BBS genes (BBS1-BBS17) described to date, which explain 70–80% of the patients clinically diagnosed, therefore more BBS genes remain to be identified. BBS belongs to a group of diseases known as ciliopathies. In general, ciliopathies and BBS in particular share a partial overlapping phenotype that makes them complicated to diagnose. We present an up-to-date review including clinical, epidemiologic and genetic aspects of the syndrome.

Keywords: Bardet-Biedl syndrome, ciliopathy, BBS genes, BBS proteins

1. Historical background

Bardet-Biedl syndrome (BBS) is a rare genetic disease, described independently between 1920 and 1922 by two European researchers, George Bardet and Arthur Biedl [1]. Patients in their 1st study showed, among other clinical features, polydactyly, retinitis pigmentosa and cognitive impairment. Solis-Cohen and Weiss (1925) grouped BBS together with Laurence-Moon syndrome into a single entity, the Laurence-Moon-Biedl syndrome, due to their similar characteristics [1]. However, in 1970 Ammann, studying and comparing the phenotype of both syndromes, decided to separate them into two distinct clinical entities, as is still current nowadays [1]. Today it is considered that individuals affected by Laurence-Moon syndrome characteristically show retinitis pigmentosa, intellectual disability, hypogonadism, and spastic paraparesis. Individuals affected with BBS suffer of obesity and hypogonadism in addition to retinitis pigmentosa, postaxial polydactyly and learning disabilities [1].

*Corresponding author: Diana Valverde, Department of Biochemistry, Genetics and Immunology, University of Vigo, Campus As Lagoas-Marcosende, 36310, Vigo, Spain. Tel.: +34 986 811 953; Fax: +34 986 812 556; E-mail: dianaval@uvigo.es.

2. Prevalence and epidemiology

The prevalence of BBS is low in the general population, ranging from 1:125,000–1:160,000 in Europe [2] and 1:100,000–1:140,000 in North America [3,4]. In Europe, the prevalence varies from 1:125,000 in the United Kingdom, 1:160,000 in Switzerland [5,6] to 1:59,000 in Denmark [7]. There are some isolated populations with a higher prevalence, such as the Faroe Islands (Denmark), with the highest prevalence of BBS found to date, 1:3,700 [8], and Newfoundland (Canada), with 1:17,500 [3]. This increase is due to consanguinity because of the small population size, and a possible founder effect given the geographic isolation. Moreover, the tradition of intra-family marriages also

raises the prevalence in the Bedouins of Kuwait and Arab populations, reaching 1:13,500 [3] and 1:65,000 [2] respectively. Finally, the BBS prevalence also differs according to sex, being higher in men, with a ratio of 1.3:1 [9].

3. Phenotype

Clinical manifestations of BBS are diverse, and there is a pronounced inter- and intra-familial variability in both clinical features and their frequency [3,10]. This is due to the genetic heterogeneity of the syndrome and the variable degree of expressivity. Given this variability, some authors have tried to classify symptoms according to their relative prevalence, establishing a series of primary and secondary features [3] (Table 1). Nowadays, there are six cardinal diagnostic criteria, which define the syndrome [9].

3.1. Retinitis pigmentosa

Typical retinitis pigmentosa is the most frequent (100%) ocular manifestation of BBS, and consists of a degeneration of photoreceptors in the retina, usually early-onset and severe. Retinitis pigmentosa is characterized by a progressive loss of central and peripheral vision from the second decade of life, although sometimes it may appear during the first decade [3,11]. The first symptom is night blindness, generally associated with impaired color vision and macular degeneration, and additional pigment deposits visible on fundus examination, leading to total blindness [11].

Table 1
Clinical diagnostic criteria for Bardet-Biedl syndrome [9]

Primary clinical features
Retinitis pigmentosa (rod-cone dystrophy)
Obesity
Polydactyly
Hypogonadism
Intellectual disability/cognitive impairment
Renal abnormalities
Secondary clinical features
Diabetes mellitus type II
Cardiovascular problems
Hearing loss
Speech deficiency
Behavioral problems
Craniofacial dysmorphism
Short stature
Hepatic involvement
Eye abnormalities
Ataxia
Dental and palatal abnormalities
Anosmia
Hirschsprung disease

3.2. Obesity

The second most frequent feature, appearing in 72–96% of the patients, is obesity. Usually, it is acentral-type obesity, with a distribution of adipose tissue mainly in the abdominal area [3]. The penetrance of obesity in the syndrome suggests that BBS proteins play a critical role in the regulation of energy metabolism [12]. A study by Marion et al. [13] found that preadipocytes show primary cilia with receptors for signalling pathways involved in adipogenesis during differentiation, so that inhibition of BBS protein expression leads to the accumulation of triglycerides.

3.3. Polydactyly and other limb abnormalities

Postaxial polydactyly is the most common anomaly of the upper and lower limbs (50–80%), although its presence is more frequent in feet [9]. Other malformations like brachydactyly (shorter fingers) and/or partial syndactyly (joining or skin webbing between two fingers) may be present [9]. This feature is very important for the clinical diagnosis of BBS.

3.4. Hypogonadism and other anomalies of the reproductive system

Hypogonadism is much more common in males than in women. Most female patients are fertile, while only two cases of affected men who have had children are known. Furthermore, affected women might present with anomalies in the fallopian tubes, ovaries and uterus, or have absence of the vaginal or urethral orifice [3]. In a few cases, the presence of polydactyly when accompanied with hydrometrocolpos (accumulation of secretions in the vagina and uterus secondary to a congenital vaginal obstruction or atresia) can complicate prenatal or early childhood diagnosis of BBS since it may be confused with McKusick-Kaufman syndrome [14]. In fact, some authors suggest that hydrometrocolpos should be considered a diagnostic feature of BBS in women to improve the diagnostic sensitivity [15].

3.5. Intellectual disability/cognitive impairment

This clinical feature is perhaps one of the most controversial, because the evaluation criteria of the intelligence quotient or the degree of cognitive development are partly subjective and vary among specialists. Several studies have shown the presence of mental disability in a high proportion of patients with BBS [3]. However, if the degree of intellectual disability is classified as mild, moderate and severe, most patients have a mild-to-moderate level. BBS patients also show speech or walking difficulties and about one third of them present with hearing deficiencies during childhood that can be overcome with therapy in adulthood. Speech deficiencies can also be corrected with appropriate therapy. Special education in different levels is often needed to help patients. Severe learning disabilities such as inability to read or write have been found in BBS patients, making them completely dependent on parental care [5].

3.6. Renal abnormalities

Patients with BBS may present different renal abnormalities, such as the formation of renal cysts (most frequently) or glomerulonephritis [9]. However, early renal dysfunction is usually hard to detect if not accompanied by clinical features [3]. Renal dysfunction combined with complications due to obesity can lead to terminal renal failure and is the most common cause of premature death in patients.

3.7. Other features

Other less common signs can be detected in BBS patients, such as hepatic involvement, dental and palatal abnormalities, hearing loss (deafness), behavioral problems, characteristic facial features (deep-set eyes, a prominent forehead and jaw), short stature, cardiovascular problems, neurological, metabolic and endocrine abnormalities (such as diabetes mellitus type II, hypertension and hypercholesterolemia), total or partial anosmia and Hirschsprung disease [3,9,16]. It is important to note that while some of the features of the syndrome can be detected prenatally or at birth (structural renal anomalies, polydactyly), most of them (retinitis pigmentosa, obesity, cognitive delay) begin to appear during childhood or early adolescence leading to a misdiagnosis or even to confusion with other syndromes that share symptomatology [17]. Beales et al. [9] revised the clinical diagnosis criteria of the syndrome and established the requirement of four primary features, or three primary and two secondary features to confirm the clinical diagnosis of BBS.

4. Inheritance

BBS was considered to be inherited in an autosomal recessive manner. However, the high phenotypic variability observed and the genetic heterogeneity associated with the syndrome suggested the possibility of oligogenic inheritance [17–21]. Although currently authors maintain that autosomal recessive inheritance is the most common, there is an alternative mode of inheritance called triallelic inheritance [21] or, according to other authors, autosomal recessive inheritance with a modifier of penetrance [22]. According to this new model, phenotype development requires three mutant alleles in two distinct genes: two mutated copies of 1 BBS gene (one allele mutated in homozygosity or two alleles mutated in compound heterozygosity) and a 3rd mutation in another BBS gene [21]. Other studies have also found cases of tetra-allelic inheritance in addition to those of triallelic inheritance [17]. Two mutations in a single gene may be responsible for altering the protein structure and consequently triggering the disease and the 3rd mutation could act as a modulator of penetrance and expressivity of the syndrome, having an epistatic effect on the other 2 mutations [23]. Surprisingly, BBS genes are known to adopt either the modulator or the causal role in different families [23]. Another consideration to take into account is that some BBS genes appear to contribute more than others to triallelic inheritance. Recent studies consider that the genes *BBS1-8* and *BBS10* are the most frequently implicated in riallelic inheritance [4].

5. Genetics of BBS

To date, 17 genes are associated with BBS: *BBS1-12*, *BBS13/MKS1*, *BBS14/CEP290*, *BBS15/WDCPC*, *BBS16/SDCCAG8/C2ORF86* and *BBS17* [2,4,24–26], which cause the high genetic and phenotypic heterogeneity of the syndrome. Four of the previous genes (*BBS11*, *BBS13*, *BBS14* and *BBS15*) have been found mutated only once in a single family [4,27]. The total number of mutations found in all of these genes explains 70–80% of the patients, which indicates that there must be at least another gene that has not been identified [27]. Both the contribution of each gene to the overall

Table 2
Contribution of each *BBS* gene to the total mutational load (% of Bardet-Biedl syndrome attributed to mutations in each gene) [12]

Gene	Implication
BBS1	23.30%
BBS10	20.0%
BBS2	8.10%
BBS9	6.00%
BBS6	5.80%
BBS12	5.00%
BBS13	4.50%
BBS4	2.30%
BBS7	1.50%
BBS8	1.20%
BBS14	0.60%
BBS5	0.40%
BBS3	0.40%
BBS11	0.10%
Unknown	20.80%

mutational load and the frequency of mutant alleles are highly variable among populations [12] (Table 2). The *BBS1* and *BBS10* genes are the major contributors in the European population, each accounting for 20–25% of the cases, while the remaining BBS genes account for less than 10% [2,4]. Two widespread single mutations are responsible for a large part of the aforementioned 20–25% of the cases: p.M390R in *BBS1* and p.C91fsX95 in *BBS10* [2,27]. The number of genes implicated in BBS and their different contribution to the total mutational load has important implications in the establishment of the molecular diagnosis algorithm for the syndrome. In this way, *BBS1* and *BBS10* have priority as 1st genes to analyze.

6. BBS as a ciliopathy

BBS belongs to a group of diseases known as ciliopathies, which share a common etiology: defects in the structure and/or function of cilia [12]. These diseases are characterized by multisystemic involvement due to the wide variety of ciliated cell types, producing overlapping phenotypes among the different syndromes, as Alström syndrome, McKusick-Kaufman syndrome, Joubert syndrome, Meckel-Gruber syndrome or polycystic kidney disease. There is also genetic overlap, since common genes involved in the pathogenesis of several of ciliopathies have been identified [12].

Cilia are specialized organelles found in most vertebrate cells [18] that project from the surface of the cell. They consist of a basal body located beneath the cell surface and a projected structure called axoneme [19]. A basal body comprises a pair of centrioles embedded in pericentriolar material, while the axoneme contains nine peripheral microtubule doublets, which may or may not be organized around a central pair of microtubules, and has an essential role in the formation and functionality of the cilia (Fig. 1). An axoneme allows both movement of the cilia and bidirectional transport of proteins via intraflagellar transport (IFT) (Fig. 1) [19]. It is considered that ciliary dysfunction and IFT failures are the major pathophysiological mechanisms leading to the BBS phenotype [20]. Cilia were 1st classified into two main groups: those with sensory capacity (primary cilia, 9 +0 structure) and those with motility (motile cilia, 9 +2 structure), characterized by the absence or presence of the central pair of microtubules. Given the complexity of the various types of cilia, recent studies have proposed a new classification into four types: motile (9 +2), motile (9 +0), non-motile (9 +2) and non-motile (9 +0) [19].

The study of BBS, among others diseases, has contributed to the understanding of the many ciliary functions essential for tissue development and homeostasis [12]. In recent years, cilia have acquired an important role in the field of extracellular signal transduction; in fact, it is known that the morphogen Sonic Hedgehog requires IFT for its signaling pathway [18].

7. BBS proteins: BBSome and BBS/CCT complex

The proteins encoded by BBS genes only appear in ciliated organisms, as demonstrated in *Caenorhabditis elegans* and *Chlamydomonas reinhardtii*, and are highly conserved in all of them [28]. BBS proteins are found in many different tissues and cells such as kidney, retina or olfactory and nervous tissue, localized in the basal bodies, centrosome and axoneme of primary cilia, with typically non-motile 9+0 structure [17].

BBS proteins have important functions in maintaining the ciliary structure and function [28], so they are essential for the development and homeostasis of ciliated cells [20]. For example, BBS proteins are required for ciliary localization of various proteins, such as rhodopsin [17]. At a molecular level, BBS proteins are involved in the transport of vesicles and proteins across ciliary microtubules [28], as demonstrated by studies in zebrafish (*Danio rerio*) where the lack of expression of the BBS genes affects retrograde transport of melanosomes [29]. Furthermore, it has been shown that

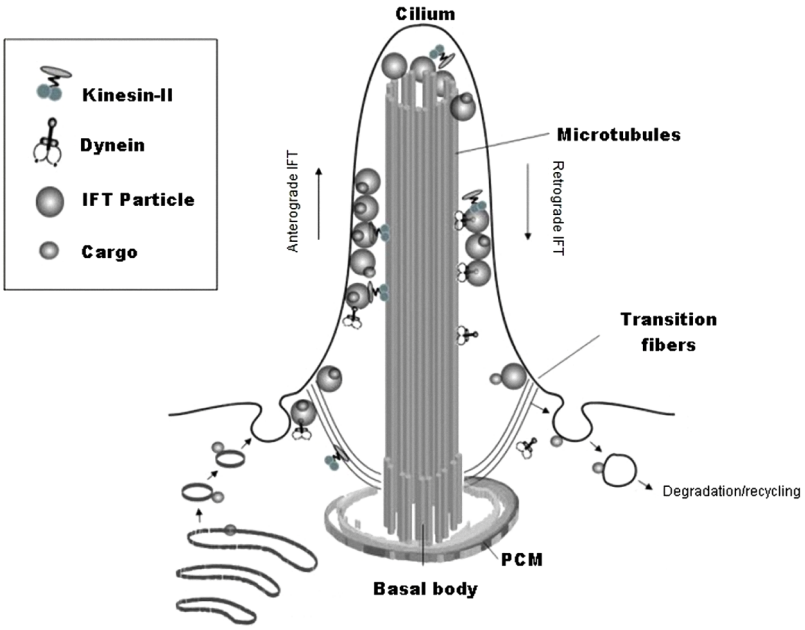

Fig. 1. Representation of the cilium structure and the process of intraflagellar transport. (modified from Waters AM, Beales PL. Bardet-Biedl Syndrome. 2003 Jul 14 [Updated 2011 Sep 29]. In: Pagon RA, Bird TD, Dolan CR, et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1363/).

the BBS proteins interact with IFT particles, stabilizing them and playing a key role in the IFT [12].

Seven BBS proteins (BBS1, 2, 4, 5, 7, 8 and 9) form a stoichiometric multiprotein complex of 438 kDa named the BBSome that is located both in cytoplasmic non-membranous centriolar satellites, and in ciliary and pre-ciliary membrane [18]. The BBSome is formed by a sequential mechanism based on protein-protein interactions between BBS2, BBS9 and BBS7, which form a core with the rest of proteins [25]. The loss of any protein from the BBSome complex makes it lose its functionality [28], and thus the functionality of the cilium, causing degeneration and cell death [29]. This complex is required for ciliary membrane biogenesis through the small guanosine-triphosphatase Rab8 and its respective interacting protein, Rabin8 [12]. Part of Rabin8 is located in the basal body and centrosome and interacts physically with BBS1 via its c-terminal region. Rabin8 is essential for the entry of Rab8 in the cilium, and its removal causes loss BBS4 from the BBSome, [18]. Thus, the function of Rabin8 is to contribute to BBSome recruitment through BBS1, and activate Rab8, promoting ciliogenesis.

The BBSome complex is also involved in IFT, regulating certain transduction signals. Its subunits contain domains that mediate protein-protein interactions, for example, the BBS1 protein, which contains beta-propeller domains. Another example is the BBS3 protein, a member of the small guanosine-triphosphate-binding proteins of the Ras superfamily, required for the ciliary localization of the BBSome [12].

Furthermore, BBS6, BBS10 and BBS12 constitute a new group of proteins specific to vertebrates that belongs to the group II chaperonin family. These proteins have the typical architecture of chaperonins (equatorial, apical and intermediate domains, which are highly conserved), but show no conserved specific insertion regions. Additionally, the functional motif responsible for the hydrolysis of adenosine-triphosphate is not conserved in BBS12 and BBS6, unlike the classical chaperonins, in which this motif is essential for its function [30]. BBS6, BBS10 and BBS12 proteins are localized in the pericentriolar material of centrosomes and basal bodies [28].

BBS6, BBS10 and BBS12 form a protein complex with six other group II chaperonins of the CCT/TRiC family, whose function is to assemble the BBSome. Specifically, the BBS/CCT complex participates in the binding between the BBS7 subunit of the BBSome and CCT chaperonins, responsible for producing the proper folding and assemblage of the protein complex [28]. Mutations in any of these 3 genes produce a non-functional BBSome, triggering the BBS phenotype [28].

8. Future perspectives

The large number of BBS genes and the phenotypic variability in the syndrome make an early-specific diagnosis complicated. Furthermore, the overlapping clinical characteristics with other ciliopathies and the progressive appearance of some clinical features can delay diagnosis and treatment. There is no clear genotype-phenotype correlation which helps us to determine optimal molecular studies. Currently, many efforts are being made to develop simple and rapid methods of molecular diagnosis to identify or discard causal mutations in BBS patients.

The 1st approach could be the screening of the most frequent mutations in *BBS1* and *BBS10*, by direct sequencing. Subsequently, others methods, for example, a microarray-based test that includes the most common mutations associated with BBS, allow molecular screening of the patients, simplifying the diagnosis in many cases. This chip is constantly being improved with new mutations described in patients. Moreover, other technological advances like Next-Generation Sequencing have been used to improve molecular diagnosis. Undoubtedly, the establishment of a simple diagnostic algorithm would facilitate the molecular and clinical study of BBS, avoiding delayed diagnosis or misdiagnosis that could impair the quality of life in BBS patients.

References

[1] Online Mendelian Inheritance in Man (NCBI) [homepage on the internet]. c2012 [updated: 2012 May 24; cited: 2012 July 15]. Available from: http://omim.org/entry/209900.

[2] Janssen S, Ramaswami G, Davis EE, Hurd T, Airik R, Kasanuki JM, et al. Mutation analysis in Bardet-Biedl syndrome by DNA pooling and massively parallel resequencing in 105 individuals. Hum Genet 2011;129(1):79–90.

[3] Katsanis N, Lupski JR, Beales PL. Exploring the molecular basis of Bardet-Biedl syndrome. Hum Mol Genet 2001;10(20): 2293–9.

[4] 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(8):5317–24.

[5] Beales PL, Warner AM, Hitman GA, Thakker R, Flinter FA. Bardet-Biedl syndrome: a molecular and phenotypic study of 18 families. J Med Genet 1997;34(2):92–8.

[6] 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(15):1002–9.

[7] Hjortshøj TD, Grønskov K, Philp AR, Nishimura DY, Riise R, Sheffield VC, et al. Bardet-Biedl syndrome in Denmark-report of 13 novel sequence variations in six genes. Hum Mutat 2010;31(4):429–36.

[8] Hjortshøj TD, Grønskov K, Brøndum-Nielsen K, Rosenberg T. A novel founder BBS1 mutation explains a unique high prevalence of Bardet-Biedl syndrome in the Faroe Islands. Br J Ophthalmol 2009;93(3):409–13.

[9] 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(6): 437–46.

[10] Pereiro 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.

[11] Héon E, Westall C, Carmi R, Elbedour K, Panton C, Mackeen L, et al. Ocular phenotypes of three genetic variants of Bardet-Biedl syndrome. Am J Med Genet A 2005;132A(3):283–7.

[12] Zaghloul NA, Katsanis N. Mechanistic insights into Bardet-Biedl syndrome, a model ciliopathy. J Clin Invest 2009;119(3): 428–37.

[13] Marion V, Stoetzel C, Schlicht D, Messaddeq N, Koch M, Flori E, et al. Transient ciliogenesis involving Bardet-Biedl syndrome proteins is a fundamental characteristic of adipogenic differentiation. Proc Natl Acad Sci U S A 2009;106(6): 1820–5.

[14] Schaefer E, Durand M, Stoetzel C, Doray B, Viville B, Hellé S, et al. Molecular diagnosis reveals genetic heterogeneity for the overlapping MKKS and BBS phenotypes. Eur J Med Genet 2011;54(2):157–60.

[15] Dulfer E, Hoefsloot LH, Timmer A, Mom C, van Essen AJ. Two sibs with Bardet-Biedl syndrome due to mutations in BBS12: no clues for modulation by a third mutation in BBS10. Am J Med Genet A 2010;152A(10):2666–9.

[16] Kulaga HM, Leitch CC, Eichers ER, Badano JL, Lesemann A, Hoskins BE, et al. Loss of BBS proteins causes anosmia in humans and defects in olfactory cilia structure and function in the mouse. Nat Genet 2004;36(9):994–8.

[17] Blacque OE, Leroux MR. Bardet-Biedl syndrome: an emerging pathomechanism of intracellular transport. Cell Mol Life Sci 2006;63(18):2145–61.

[18] Nachury MV, Loktev AV, Zhang Q, Westlake CJ, Peränen J, Merdes A, et al. A core complex of BBS proteins cooperates with the GTPase Rab8 to promote ciliary membrane biogenesis. Cell 2007;129(6):1201–13.

[19] D'Angelo A, Franco B. The dynamic cilium in human diseases. Pathogenetics 2009;2(1):3.

[20] Pawlik B, Mir A, Iqbal H, Li Y, Nürnberg G, Becker C, et al. A novel familial BBS12 mutation associated with a mild phenotype: implications for clinical and molecular diagnostic strategies. Mol Syndromol 2010;1(1):27–34.

[21] Katsanis N, Ansley SJ, Badano JL, Eichers ER, Lewis RA, Hoskins BE, et al. Triallelic inheritance in Bardet-Biedl syndrome, a Mendelian recessive disorder. Science 2001;293 (5538):2256–9.

[22] Burghes AH, Vaessin HE, de La Chapelle A. Genetics. The land between Mendelian and multifactorial inheritance. Science 2001;293(5538):2213–4.

[23] Katsanis N. The oligogenic properties of Bardet-Biedl syndrome. Hum Mol Genet 2004;13(1):65–71.

[24] Kim J, Krishnaswami SR, Gleeson JG. CEP290 interacts with the centriolar satellite component PCM-1 and is required for Rab8 localization to the primary cilium. Hum Mol Genet 2008;17(23):3796–805.

[25] 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(24):20625–35.

[26] Cox KF, Kerr NC, Kedrov M, Nishimura D, Jennings BJ, Stone EM, et al. Phenotypic expression of Bardet-Biedl syndrome in patients homozygous for the common M390R mutation in the BBS1 gene. Vision Res 2012;75:77–87.
[27] Muller J, Stoetzel C, Vincent MC, Leitch CC, Laurier V, Danse JM, et al. Identification f 28 novel mutations in the Bardet-Biedl syndrome genes: the burden of private mutations in an extensively heterogeneous disease. Hum Genet 2010; 127(5):583–93.
[28] Seo S, Baye LM, Schulz NP, Beck JS, Zhang Q, Slusarski DC, et al. BBS6, BBS10, and BBS12 form a complex with CCT/TRiC family chaperonins and mediate BBSome assembly. Proc Natl Acad Sci U S A 2010;107(4):1488–93.
[29] Yen HJ, Tayeh MK, Mullins RF, Stone EM, Sheffield VC, Slusarski DC. Bardet-Biedl syndrome genes are important in retrograde intracellular trafficking and Kupffer's vesicle cilia function. Hum Mol Genet 2006;15(5):667–77.
[30] Stoetzel C, Muller J, Laurier V, Davis EE, Zaghloul NA, Vicaire S, et al. Identification of a novel BBS gene (BBS12) highlights the major role of a vertebrate-specific branch of chaperonin-related proteins in Bardet-Biedl syndrome. Am J Hum Genet 2007;80(1):1–11.