U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Forsyth RL, Gunay-Aygun M. Bardet-Biedl Syndrome Overview. 2003 Jul 14 [Updated 2023 Mar 23]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Bardet-Biedl Syndrome Overview

RaeLynn Forsyth, MD[1] and Meral Gunay-Aygun, MD[2,3]

Created: July 14, 2003; Revised: March 23, 2023.

Summary

The purpose of this overview is to increase the awareness of clinicians regarding the causes of Bardet-Biedl syndrome and related genetic counseling issues.

The following are the goals of this overview:

Goal 1

Describe the clinical characteristics of Bardet-Biedl syndrome.

Goal 2

Review the genetic causes of Bardet-Biedl syndrome.

Goal 3

Provide an evaluation strategy to identify the genetic cause of Bardet-Biedl syndrome in a proband (when possible).

Goal 4

Review management of Bardet-Biedl syndrome.

Goal 5

Inform genetic counseling of family members of an individual with Bardet-Biedl syndrome.

Author Affiliations: 1 Departments of Pediatrics and Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; Email: rforsyt2@jhmi.edu. 2 Professor of Pediatrics and Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; Email: mgunaya1@jhmi.edu. 3 Section on Human Biochemical Genetics, Medical Genetics Branch, National Human Genome Research Institute, Office of Rare Diseases, National Institutes of Health, Bethesda, Maryland; Email: mgunaya1@jhmi.edu.

1. Clinical Characteristics of Bardet-Biedl Syndrome

Bardet-Biedl syndrome (BBS) is a multisystem non-motile ciliopathy primarily characterized by retinal cone-rod dystrophy, obesity and related complications, postaxial polydactyly, cognitive impairment, hypogonadotropic hypogonadism and/or genitourinary malformations, and renal malformations and/or renal parenchymal disease.

Individuals with BBS can also have other eye abnormalities (strabismus, astigmatism, cataracts), subtle craniofacial dysmorphisms, hearing loss, anosmia, oral/dental abnormalities (crowding, hypodontia, high-arched palate), gastrointestinal and liver disease, brachydactyly/syndactyly, musculoskeletal abnormalities, dermatologic abnormalities, and neurodevelopmental abnormalities including mild hypertonia, ataxia/poor coordination/imbalance, developmental delay(s), seizures, speech abnormalities, and behavioral/psychiatric abnormalities (Table 1).

The motile ciliary structure and function is essentially normal in BBS, but affected individuals have an increased prevalence of manifestations associated with motile ciliopathies, such as neonatal respiratory distress, asthma, otitis media, and thoraco-abdominal laterality defects [Shoemark et al 2015].

BBS exhibits variable expressivity and both inter- and intrafamilial variation.

Establishing the Clinical Diagnosis of Bardet-Biedl Syndrome

Forsythe & Beales [2013] suggested that a clinical diagnosis of BBS is made by the presence of either four major features or three major features and two minor features. See Table 1.

The usefulness of these clinical criteria is limited by:

- The fact that many of these clinical features emerge throughout infancy, childhood, and young adulthood; therefore, the sensitivity of the proposed clinical diagnostic criteria is likely low, especially in young children. It is important that findings as they pertain to these clinical criteria be reviewed periodically in individuals in whom the diagnosis of BBS has been considered.
- Variability in clinical features, which is increasingly realized as the underlying genetic cause is identified in a larger proportion of individuals with BBS. A recent meta-analysis [Niederlova et al 2019] found that some individuals who are homozygotes or compound heterozygotes for pathogenic variants in genes known to cause BBS do not fulfill clinical diagnostic criteria.

Table 1. Features of Bardet-Biedl Syndrome

	Feature	Incidence [1]	Comment
Major Features	Retinal cone-rod dystrophy	94%	• Retinal dystrophy symptoms often bring persons to medical attn, typically in 1st decade of life. • Other eye abnormalities (e.g., strabismus, cataracts) can also be present & are considered minor features of BBS.
	Central obesity	89%	• Birth weight typically normal • Features assoc w/obesity (incl endocrine/metabolic abnormalities & NAFLD) also common & considered minor features of BBS
	Postaxial polydactyly	79%	Brachydactyly &/or syndactyly can be present w/or w/o polydactyly & are considered minor features of BBS.

Table 1. continued from previous page.

	Feature	Incidence [1]	Comment
	Cognitive impairment	66%	Incidence may be ↓ when impairment in vision is taken into consideration (see Major Features, **Cognitive impairment**).
	Hypogonadism & genitourinary abnormalities	59%	Infertility is common, but both males & females have had biological children.
	Kidney disease	52%	Major cause of morbidity & mortality
Minor Features [2]	Neurologic abnormalities	• DD (81%) • Epilepsy (9.6%) [3] • Behavior/psychiatric abnormalities (35%) [4]	• Ataxia/poor coordination may contribute to gross motor & fine motor delays. • Speech abnormalities are common.
	Olfactory dysfunction	47%-100% [5]	Incl anosmia & hyposmia
	Oral/dental abnormalities	~50% [6]	
	Cardiovascular & other thoraco-abdominal abnormalities	1.6%-29% [7]	Incl laterality defects such as situs inversus & situs ambiguous
	Gastrointestinal abnormalities	• Hirschsprung disease (2.8%) [3] • Inflammatory bowel disease (1.1%) [3] • Celiac disease (1.5%) [3] • Liver disease (30%)	"Liver disease" is considered any abnormality on liver imaging &/or abnormal ALT level.
	Endocrine/metabolic abnormalities	Metabolic syndrome (54.3%) [8]	Presence of metabolic syndrome determined using IDF criteria [9]
		Subclinical hypothyroidism (19.4%) [8]	
		T2DM (15.8%) [8]	
		Polycystic ovary syndrome (14.7%) [8]	

ALT = alanine transaminase; DD = developmental delay; IDF = International Diabetes Federation; NAFLD = Nonalcoholic fatty liver disease; T2DM = type 2 diabetes mellitus

1. Unless otherwise noted, incidence is based on data in meta-analysis of genotype-phenotype associations of 899 individuals with BBS by Niederlova et al [2019].

2. In addition to those listed under comments of major features

3. Unpublished data from the Clinical Registry Investigating Bardet-Biedl Syndrome (CRIBBS)

4. Bennouna-Greene et al [2011]

5. Tadenev et al [2011], Braun et al [2014]

6. Forsythe & Beales [2013]

7. Olson et al [2019]

8. Mujahid et al [2018]

9. International Diabetes Federation (IDF) criteria for metabolic syndrome:

Central obesity (defined by waist circumference values that are sex and ethnicity specific) PLUS two or more of the following:

• Elevated triglyceride level (>150 mg/dL)

• Reduced high-density lipoprotein level (<40 mg/dL in males and <50 mg/dL in females)

• Hypertension (systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg)

• Elevated fasting plasma glucose OR a diagnosis of T2DM

Major Features

Cone-rod dystrophy. Early macular involvement typically presents first with night blindness, followed by progressive peripheral vision loss, diminution of color discrimination, and overall loss of visual acuity [Weihbrecht et al 2017]. These symptoms are often what brings individuals to medical attention and obtain the diagnosis of BBS, usually in the first decade of life.

Electroretinography (ERG) is more likely to show significant findings after age five years.

Individuals often become legally blind by the second to third decade of life.

Retinal disease is the most penetrant feature in BBS, affecting up to 100% of individuals in some studies [Denniston et al 2014].

Central (truncal) obesity develops in the first year of life; birth weight is usually normal. Other features commonly associated with obesity are considered minor features in BBS. Mean body mass index has been reported to be 35.7±8.0 kg/m^2 [Mujahid et al 2018].

Postaxial polydactyly are additional digits usually found on the ulnar side of the hand and/or fibular side of the foot. Mesoaxial polydactyly is also reported in individuals with pathogenic variants in *LZTFL1* (*BBS17*) [Schaefer et al 2014].

Cognitive impairment. Historical reports describing significant intellectual disability as a prominent feature did not account for visual impairments.

Kerr et al [2016] evaluated the cognitive, adaptive, and behavioral function of 24 individuals with molecularly confirmed BBS and visual acuity ≥20/400. Visual fields and visual acuity were not significantly correlated with verbal comprehension index or any of the other cognitive measures. While only 20%-25% of individuals met criteria for a diagnosis of intellectual disability, mean intellectual functioning of all participants was 1.5 SD below the mean. Individuals also had impairments in verbal fluency (22%-44%), perceptual reasoning (53%), attention capacity (69%), and functional independence (74%). Features associated with autism spectrum disorders were present in 77%.

Hypogonadism and genitourinary malformations. Hypogonadism with delay in onset of secondary sexual characteristics may not be apparent until puberty.

Males can have micropenis and/or small-volume testes. Cryptorchidism is present in 9% of males with BBS. On endocrinologic assessment in one study, 19.5% of males were hypogonadal [Mujahid et al 2018].

Females can have anatomic anomalies including hypoplastic or duplex uterus, hypoplastic fallopian tubes and/or ovaries, septate vagina, partial or complete vaginal atresia, absent vaginal and/or urethral orifice, hydrocolpos or hydrometrocolpos, persistent urogenital sinus, and vesico-vaginal fistula [Deveault et al 2011].

Infertility is common, but both sexes are known to have been able to have biological children.

Kidney disease. The renal phenotype of BBS is highly variable and can include structural anomalies, hydronephrosis and vesicoureteral reflux, and progressive renal parenchymal disease that is commonly associated with urinary concentration defects (symptoms of polyuria and polydipsia) [Putoux et al 2012].

Structural kidney disease includes developmental anomalies such as horseshoe, ectopic, duplex, or absent kidneys; or dysplastic cystic disease ranging from single unilateral to multiple bilateral cysts.

Urologic complications including neurogenic bladder and bladder outflow obstruction have been reported in 5%-10% of adults [Forsythe et al 2017].

Chronic kidney disease (CKD) is a major contributor of morbidity and mortality in individuals with BBS. In a recent study, CKD was present in 31% of children and 42% of adults; 6% of children and 8% of adults developed end-stage kidney disease requiring dialysis and/or transplantation [Forsythe et al 2017].

In the majority of children with BBS with advanced (Stage 4-5) chronic kidney disease, the initial diagnosis of renal disease was made within the first year of life and almost all were diagnosed by age five years [Forsythe et al 2017].

Comorbidities including hypertension (present in about one third of individuals with BBS) and type 2 diabetes mellitus (T2DM) may affect progression of CKD.

Favorable long-term outcomes of renal transplantation have been reported [Haws et al 2016].

Minor Features

Neurodevelopmental abnormalities. Ataxia and poor coordination with mild hypertonia of all four extremities has been described in individuals with BBS, but correlation with brain changes on MRI needs to be better characterized.

Seizures and/or epilepsy (as defined by the International League Against Epilepsy) were reported in individuals in the Clinical Registry Investigating Bardet-Biedl Syndrome (CRIBBS) database, but the majority had resolution before adulthood [Unpublished data].

Speech abnormalities including receptive and expressive speech delay, articulation defects, and nasal and/or breathy speech quality are also observed, and likely multifactorial as a result of hearing issues, oral/dental abnormalities, and primary underlying neurologic issues.

The behavioral and psychiatric abnormalities, including obsessive compulsive behavior, anxiety and mood disorder, that have been observed are also likely multifactorial.

Because of the aforementioned, developmental delay in all domains (i.e., gross motor, fine motor, speech/language) is common in children with BBS; most children do eventually attain major developmental milestones (e.g., walking, talking).

Dysmorphic craniofacial features observed in individuals with BBS include brachycephaly, macrocephaly, and narrow forehead; short, narrow, and downslanted palpebral fissures; deep and widely set eyes; large ears; long and smooth philtrum; depressed nasal bridge; malar flattening; and retrognathia. These features can be subtle and are inconsistent among the population of individuals with BBS [Forsythe & Beales 2013]. A systematic review of the incidence of dysmorphic craniofacial features has not been performed.

Anosmia/hyposmia is likely underreported. While defects in olfactory cilia are thought to be responsible, the olfactory bulb has an abnormal appearance on brain MRIs of individuals with BBS [Braun et al 2016].

Oral/dental abnormalities. Primary anomalies can include hypodontia or microdontia, dental crowding, short roots and taurodontism, posterior crossbite, enamel hypoplasia, and high-arched palate.

Potential secondary oral complications that can result from the other clinical manifestations of BBS (e.g., visual impairment, obesity, cognitive defects, renal disease, mouth breathing, incompetent lips, anosmia) include poor oral hygiene, periodontal disease, dental caries, drug-induced gingival hyperplasia, xerostomia, altered taste, and speech disturbances [Panny et al 2017].

Cardiovascular and other thoraco-abdominal abnormalities. In a retrospective study of individuals in the CRIBBS database, a small percentage (1.6%) of individuals were found to have thoraco-abdominal abnormalities, namely, laterality defects [Olson et al 2019]. This percentage reflects a 170-fold higher prevalence

compared to the general population, but is lower than that found in disorders of motile cilia, such as primary ciliary dyskinesia.

Laterality defects can range from situs inversus totalis to various features of heterotaxy (i.e., midline abdominal organs, asplenia, or polysplenia).

Congenital heart defects associated with laterality defects, including atrioventricular septal defects and vascular anomalies (i.e., bilateral persistent superior vena cava, interrupted inferior vena cava, and hemiazygos continuation) were also reported in the individuals with laterality defects in the CRIBBS database, but at a much lower rate than historically reported including in the meta-analysis by Niederlova et al [2019], which found an incidence of unspecified heart anomalies in 29% of individuals.

Dilated cardiomyopathy has been reported rarely in individuals with BBS, but exclusion of other genetic causes of these individuals' cardiomyopathy was not performed [Yadav et al 2013].

Gastrointestinal abnormalities. Hirschsprung disease and anatomic anomalies of the gastrointestinal tract (bifid epiglottis, laryngeal and esophageal webs, bowel atresia, imperforate anus) were identified in a small percentage of individuals in the CRIBBS database [Unpublished data].

Inflammatory bowel disease and celiac disease were also more prevalent in individuals with BBS compared to the general population.

Liver disease includes bile duct abnormalities with cystic dilatation, and periportal fibrosis and non-alcoholic fatty liver disease (NAFLD), thought to partially be a secondary effect of obesity [Branfield Day et al 2016].

Endocrine/metabolic abnormalities. Comorbidities of obesity, including hyperlipidemia (usually hypertriglyceridemia), insulin resistance, and elevated fasting plasma glucose with or without T2DM, are common. In addition, polycystic ovarian syndrome is common in females.

T2DM may be controlled by diet but often requires medications including insulin.

Subclinical hypothyroidism has also been reported; the clinical significance is unknown [Mujahid et al 2018].

Other Features (Not Part of the Clinical Diagnostic Criteria)

Dermatologic abnormalities. In one study, cutaneous dermatoses were present in all individuals and included seborrheic dermatitis (in 19.3%), keratosis pilaris (80.6%), and skin changes associated with obesity (e.g., striae, hidradenitis supportiva, acanthosis nigricans) [Haws et al 2019].

Subclinical sensorineural hearing loss is detected on audiometry testing in adults. Conductive hearing loss can occur in childhood as a result of recurrent otitis media. Hearing loss was reported in 17%-21% of individuals with BBS [Forsythe & Beales 2013].

Musculoskeletal abnormalities. Compared to the general population, individuals in the CRIBBS database had higher rates of: scoliosis (in 16%; usually not requiring surgery), leg length discrepancy (9.6%), club foot (1.8%; typically requiring surgery), Blount disease (0.9%), and joint laxity (27.6%) [CRIBBS database, unpublished data].

Differential Diagnosis of Bardet-Biedl Syndrome

BBS is the second most common cause of syndromic retinal degeneration, after Usher syndrome [Stone et al 2017], which is also characterized by sensorineural hearing loss.

There is significant clinical and molecular overlap between Bardet-Biedl syndrome and other ciliopathies. Pathogenic variants in several genes that cause BBS can also lead to other distinct ciliopathy syndromes (Table 2).

Table 2. Disorders to Consider in the Differential Diagnosis of Bardet-Biedl Syndrome

Gene(s) [1]	Disorder	MOI	Clinical Features of the Differential Disorder	
			Overlapping w/BBS	Distinguishing from BBS
ALMS1	Alström syndrome (AS)	AR	• Cone-rod dystrophy (presents earlier in AS) • Central obesity, insulin resistance / T2DM, & NAFLD • Chronic progressive kidney disease • Hypogonadism	In AS: • Preserved cognitive function; cardiomyopathy prevalent (in ~60%); symptomatic progressive SNHL; pulmonary fibrosis & pulmonary hypertension • Absence of polydactyly
MKKS	McKusick-Kaufman syndrome (MKS)	AR	• Postaxial polydactyly • Genitourinary malformations	In MKS: • Congenital heart disease more prevalent (in ~14%); hydrometrocolpos a cardinal feature; renal cysts/dysplasia less common (in 4%-6%) • Absence of retinal disease, obesity, & developmental disabilities
~15 genes [2]	Meckel syndrome	AR	• Postaxial polydactyly • Polycystic kidney disease • Genitourinary malformations • Hepatic fibrosis	Meckel syndrome: • Occipital encephalocele & other CNS anomalies cardinal features; orofacial clefting common • Perinatally lethal
AHI1 *CC2D2A* ***CEP290*** *CPLANE1* ***MKS1*** ***NPHP1*** *TMEM67* (>36 genes)	Joubert syndrome (JS)	AR XL [3]	• Retinal degeneration • Polydactyly • Kidney & liver disease	In JS: • Characteristic triad of molar tooth sign on brain MRI, hypotonia, & DD; breathing abnormalities that improve w/age common; eye mvmt abnormalities &/or ptosis common • Central obesity, hypogonadism, & genitourinary malformations are atypical.
CEP290 *IQCB1* ***NPHP1*** *NPHP4* ***SDCCAG8*** *TRAF3IP1* *WDR19*	Senior-Løken syndrome (SLS) (OMIM PS266900)	AR	• Retinal degeneration • Kidney disease	Absence of obesity, polydactyly, hypogonadism, & genitourinary malformations in SLS

Table 2. continued from previous page.

Gene(s) [1]	Disorder	MOI	Clinical Features of the Differential Disorder	
			Overlapping w/BBS	Distinguishing from BBS
CEP290 *CRB1* *GUCY2D* *RDH12* *RPE65* (~25 genes)	Leber congenital amaurosis / early-onset severe retinal dystrophy (LCA/EOSRD)	AR AD	Retinal degeneration & assoc symptoms (e.g., ↓ visual acuity)	Absence of other organ involvement in LCA/EOSRD

AD = autosomal dominant; AR = autosomal recessive; CNS = central nervous system; DD = developmental delay; MOI = mode of inheritance; NAFLD = nonalcoholic fatty liver disease; SNHL = sensorineural hearing loss; T2DM = type 2 diabetes mellitus; XL = X-linked

1. Pathogenic variants in **bolded** genes are also known to cause BBS.

2. See Phenotypic Series: Meckel Syndrome to view genes associated with this phenotype in OMIM.

3. Digenic inheritance has been reported.

2. Causes of Bardet-Biedl Syndrome

Bardet-Biedl syndrome (BBS) is an autosomal recessive disorder caused by biallelic loss-of-function pathogenic variants in at least 26 genes; some genotype-phenotype correlations exist (Table 3) [Niederlova et al 2019].

Table 3. Bardet-Biedl Syndrome: Genes and Distinguishing Clinical Features

Gene [1] (BBS Designation [2])	% of all BBS [3]	Distinguishing Clinical Features / Comments	Allelic Disorder(s) [4]
BBIP1 (BBS18)	<1%	Reported in 2 unrelated persons w/multiple major features of BBS but w/o polydactyly [5]	None
BBS1	23.4%	• Relatively less "syndromic" [6] w/↓ penetrance of renal anomalies & polydactyly • Founder variant in Newfoundland population [7]	
BBS2	9.6%	• Relatively more "syndromic" w/↑ penetrance of renal anomalies & polydactyly • "Leanest" of obesity phenotype	Nonsyndromic retinitis pigmentosa
BBS4	5.3%	• ↓ penetrance of renal anomalies • Early-onset morbid obesity	None
BBS5	3.7%	Relatively more "syndromic"	
BBS7	4.2%	Relatively more "syndromic" w/↑ penetrance of renal anomalies	
BBS9	3.4%	↑ penetrance of renal anomalies	
TTC8 (BBS8)	2.0%	Relatively less "syndromic" w/↓ penetrance of renal anomalies	Nonsyndromic retinitis pigmentosa
ARL6 (BBS3)	5.1%	• Least "syndromic" w/low penetrance of cognitive impairment & renal anomalies • Polydactyly often affects all 4 limbs. • Founder variant in population on La Réunion Island [8]	

Table 3. continued from previous page.

Gene [1] (BBS Designation [2])	% of all BBS [3]	Distinguishing Clinical Features / Comments	Allelic Disorder(s) [4]
BBS10	14.5%	• Most severe renal impairment • Significant adiposity • Founder variant in South African population [9]	None
BBS12	6.4%	Significant adiposity	
MKKS (BBS6)	6.3%	More likely to have CHD & genitourinary malformations	McKusick-Kaufman syndrome [10]
CFAP418 (formerly known as *C8orf37*) (BBS21)	1.6%	↑ penetrance of polydactyly	• Nonsyndromic retinitis pigmentosa • Cone-rod dystrophy w/ polydactyly (OMIM 614500)
CEP164	<1%	Reported in 1 person suspected of having PCD due to unexplained cough & bronchiectasis, but reverse phenotyping revealed features of BBS [11]	Isolated nephronophthisis
CEP290 (BBS14)	6.3%	Significant clinical overlap w/other ciliopathies	• Joubert syndrome • Leber congenital amaurosis • Meckel syndrome (OMIM 611134) • Senior-Løken syndrome (OMIM 610189) See footnote 10.
IFT27 (BBS19)	<1%	• Reported in 3 persons from 2 families, all w/major features of BBS • 1 person w/AVCD [12]	None
IFT74 (BBS20) [13]	<1%	• Reported in 2 unrelated persons; both w/retinal disease, obesity, polydactyly, & no renal involvement • 1 person w/ID [14]	
IFT172 (BBS20) [13]	1.0%	Typical BBS features	• Nonsyndromic retinitis pigmentosa • Short-rib thoracic dysplasia w/ or w/o polydactyly (OMIM 615630)
LZTFL1 (BBS17)	<1%	• Reported in 3 persons from 2 families • Mesoaxial-type polydactyly a unique feature [15]	None
MKS1 (BBS13)	1.0%	Ophthalmology exam may show bone-spicule hyperpigmentation & attenuated arteries. [16]	• Joubert syndrome • Meckel syndrome (OMIM 249000)
SCAPER	Unknown	Linkage & functional studies in 2 consanguineous families w/multiple persons w/ features of BBS support causation. [17]	ID disorder & retinitis pigmentosa (OMIM 618195)

Table 3. continued from previous page.

Gene [1] (BBS Designation [2])	% of all BBS [3]	Distinguishing Clinical Features / Comments	Allelic Disorder(s) [4]
SCLT1	<1%	Reported in 4 persons from 2 families: • In 1 family, affected persons have pituitary hypoplasia & growth hormone deficiency + obesity, retinal disease, & polydactyly. • In the other family, affected persons have major features of BBS. [18]	Possible assoc between variation in *SCLT1* & orofacial digital syndrome IX (OMIM 258865)
SDCCAG8 (BBS16)	4.3%	Intronic variants reported [11]	Senior-Løken syndrome [10] (OMIM 613615)
TRIM32 (BBS11)	<1%	Identified in a consanguineous Bedouin family [19]	Limb-girdle muscular dystrophy (OMIM 254110)
WDPCP (BBS15)	<1%	Reported in 2 unrelated persons w/BBS (clinical data unavailable) [20]	CHDs, hamartomas of tongue, & polysyndactyly (OMIM 217085)

AVCD = atrioventricular canal defect; BBS = Bardet-Biedl syndrome; CHD = congenital heart defect; ID = intellectual disability; PCD = primary ciliary dyskinesia

1. Genes are listed in alphabetic order.

2. Included when BBS designation differs from gene

3. Determined by data of 923 individuals with BBS (899 from a meta-analysis of genotype-phenotype associations by [Niederlova et al 2019], 17 from a report by [Shamseldin et al 2020] not included in the meta-analysis, and 7 from additional case reports supporting causation of rare genes).

4. Link to OMIM gene description provided if no *GeneReview* available

5. Scheidecker et al [2014], Shamseldin et al [2020]

6. Use of the word "syndromic" refers to syndromic score used by Niederlova et al [2019] calculated as number of major features present in an individual divided by five (all major features excluding reproductive system anomalies [excluded due to differences in male and female physiology]).

7. Fan et al [2004]

8. Gouronc et al [2020]

9. Fieggen et al [2016]

10. These disorders have phenotypic overlap with BBS and should be considered in the differential diagnosis of BBS (see Table 2).

11. Shamseldin et al [2020]

12. Aldahmesh et al [2014], Schaefer et al [2019]

13. In the literature, both *IFT74* and *IFT172* are associated with BBS20, so the recommendation is to discard the use of "BBS20."

14. Lindstrand et al [2016], Kleinendorst et al [2020]

15. Marion et al [2012], Schaefer et al [2014]

16. Xing et al [2014]

17. Wormser et al [2019]

18. Morisada et al [2020], Shamseldin et al [2020]

19. Chiang et al [2006]

20. Kim et al [2010], Shamseldin et al [2020]

3. Evaluation Strategies to Identify the Genetic Cause of Bardet-Biedl Syndrome in a Proband

Establishing a specific genetic cause of Bardet-Biedl syndrome (BBS) in a proband:

- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling;
- Usually involves a medical history, physical examination, laboratory testing, family history, and genomic/genetic testing.

Medical History

A diagnosis of BBS should be considered in any individual with any of the major features listed in Table 1.

BBS must be suspected in a fetus/infant with structural kidney disease, genitourinary malformations, and/or polydactyly as these may be the only features of BBS evident in this cohort.

Central obesity, which often develops in the first year of life, is another prominent early feature of BBS that should raise suspicion of this diagnosis.

Manifestations of cone-rod dystrophy (photophobia, decreased visual acuity, and loss of color discrimination) and chronic kidney disease (polyuria and polydipsia) may not be present until children are school-aged, while manifestations of hypogonadism (lack of pubertal development) are evident even later, in early adolescence.

Other features in Table 1, which are also reported in many other genetic conditions, should prompt a broad evaluation which may reveal a BBS diagnosis.

Family History

A three-generation family history should be obtained with attention to parental consanguinity and medical issues in sibs. Documentation of relevant findings in sibs can be accomplished either through direct examination of those individuals or review of their medical records.

Molecular Genetic Testing

Because BBS is genetically heterogeneous with significant clinical overlap with other ciliopathies, recommended molecular genetic testing approaches include either gene-targeted testing (**multigene panel**) or **comprehensive genomic testing** (exome sequencing). Gene-targeted testing, either with BBS-specific panels or larger ciliopathy gene panels, requires the clinician to hypothesize which gene(s) are likely involved. Genomic testing may reveal pathogenic variants in known genes not yet included in gene panels or in novel genes not previously known to be associated with BBS.

Single-gene testing (sequence analysis of a given gene, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically not recommended.

- **A multigene panel** that includes some or all of the genes listed in Table 3 is most likely to identify the genetic cause of BBS while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Of note, given the rarity of some of the genes associated with BBS some panels may not include all the genes listed in Table 3. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

Note: Unlike exome sequencing, genome sequencing can identify noncoding variants. Although most confirmed pathogenic variants identified by genome sequencing are within exons [Taylor et al 2015], a likely pathogenic variant was detected in a noncoding region of *BBS10* in an individual with inherited retinal dystrophy [Daich Varela et al 2023].

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

4. Management of Bardet-Biedl Syndrome

Evaluations Following Initial Diagnosis

To establish the extent of disease and ongoing needs in an individual diagnosed with Bardet-Biedl syndrome (BBS), the evaluations summarized in Table 4 are recommended.

Table 4. Recommended Initial Evaluations and Surveillance in Individuals with Bardet-Biedl Syndrome

System/Concern	Initial Evaluation	Frequency of Surveillance [1]
Constitutional	• Measure height, weight, head & waist circumference. • Detailed dietary history: caloric intake & dietary components • Assess daily physical activity level.	At every health care visit
Eyes/Vision	Ophthalmologic consultation in: • Infants / young children: assess for strabismus, nystagmus, & impaired visual acuity. • Older children / adults: assess for cataracts & impaired vision; perform visual field testing & electroretinography.	Annually or as directed by ophthalmologist
Oral/dental abnormalities	Routine dental care	Every 6 mos starting at age 1 yr
Cardiovascular & other thoraco-abdominal abnormalities	• Echocardiogram to assess for congenital heart defect &/or cardiomyopathy • Complete abdominal US to assess for laterality defects	• If initial eval is normal, only if cardiac symptoms/signs develop • If anatomic abnormality is present, more frequent monitoring as directed by cardiologist
Respiratory	Monitor for: • Symptoms of obstructive sleep apnea (e.g., snoring); • Recurrent infection that could indicate ciliary dysfunction.	Annually
Gastrointestinal	• Assess for anatomic abnormalities. • Monitor for symptoms/signs of IBD & celiac disease.	
Liver	• Liver US to evaluate for liver fibrosis & steatosis • Lab assessments incl hepatic enzymes & tests of synthetic function (PT, PTT)	• Annually if normal • Persons w/liver disease should be monitored as directed by hepatologist.

Table 4. continued from previous page.

System/Concern	Initial Evaluation	Frequency of Surveillance [1]
Renal	• Renal US to evaluate for congenital anomalies & assess for evidence of parenchymal disease [2] • Lab assessments incl CBC, serum electrolytes, creatine, BUN, cystatin C • Measure blood pressure w/24-hr blood pressure monitoring as needed.	• Annually if normal • Persons w/kidney disease should be monitored as directed by nephrologist.
Urologic	Ask about symptoms of neurogenic bladder & bladder outflow obstruction.	Annually
Metabolic syndrome	• Lipid panel (triglycerides, HDL, LDL, total cholesterol) • Fasting blood glucose & HgbA1c	• Annually starting at age 4 yrs if normal • Those w/metabolic syndrome will require more frequent monitoring by experienced provider.
Hypothyroidism	Check thyroid gland function.	Annually
Hypogonadism	• Pelvic US in females to assess for malformations of uterus, fallopian tubes, ovaries, & vagina • Check FSH, LH, estrogen, & testosterone levels if indicated due to delayed puberty.	Annual lab assessment starting at age 13 yrs if indicated
Musculoskeletal	Skeletal survey	As needed if signs/symptoms of scoliosis, polydactyly, or joint disease
Development	• Developmental &/or neurocognitive assessment • Consider brain MRI if neurologic abnormalities (i.e., ataxia, hypotonia, seizures). [3]	• Routine developmental assessments during early childhood • School-aged persons should have annual IEP/504 plans.
Psychiatric/ Behavioral	Neuropsychiatric eval if signs/symptoms of atypical behaviors or mood disorder	As needed
Genetic counseling	By genetics professionals [4]	To inform affected persons & their families re nature, MOI, & implications of BBS to facilitate medical & personal decision making
Family support & resources	Assess: • Use of community or online resources such as Parent to Parent; • Need for social work involvement for parental support.	

BUN = blood urea nitrogen; CBC = complete blood cell count; FSH = follicle-stimulating hormone; HDL = high-density lipoproteins; HgbA1c = hemoglobin A1c; IBD = inflammatory bowel disease; IEP = individualized education program; LDL = low-density lipoproteins; LH = luteinizing hormone; MOI = mode of inheritance; PT = prothrombin time; PTT = partial thromboplastin time; SNHL = sensorineural hearing loss; US = ultrasound

1. Recommended frequencies shown are for individuals who are stable and well-controlled. In many instances more frequent evaluations are needed. Individuals should be evaluated by a medical geneticist every one to two years, as they can help with coordination of care.

2. Prenatal ultrasonography may detect renal cysts but can be normal in 39% of individuals with renal abnormalities detected postnatally [Mary et al 2019].

3. MRI of the brain may show diffuse white matter loss predominantly in the occipital region, reduced grey matter in subcortical regions (caudate, putamen, thalamus), reduced hippocampal volume, and hippocampal dysgenesis [Baker et al 2011, Keppler-Noreuil et al 2011].

4. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Medical Issues

No therapy exists to prevent the multisystem and sometimes progressive organ involvement of BBS. Individuals with BBS require coordinated multidisciplinary care to formulate and coordinate management and therapeutic interventions.

Cone-rod dystrophy. Early educational planning should be based on the certainty of blindness. Instruction in the use of Braille, mobility training, adaptive living skills, and computing skills (including voice recognition and transcription software), as well as the use of large-print reading materials while vision is still present, are crucial.

Obesity. A healthful, reduced-calorie diet with restricted simple carbohydrate intake and regular aerobic exercise, such as walking, hiking, biking, and swimming with adaptations for the blind, are recommended to control weight gain. Employment of a helper/partner to encourage exercise and appropriate diet may be beneficial.

Metabolic syndrome and the other obesity-related complications of BBS should be treated as in the general population. All individuals will benefit from these lifestyle recommendations.

Anosmia/hyposmia. Those with absent or reduced sense of smell should have alternative ways off detecting dangerous substances (e.g., spoiled food, smoke, gas).

Renal disease, gastrointestinal and liver disease, hypothyroidism, and hypogonadism should be treated as in the general population and according to national guidelines of the various subspecialties.

Anatomic abnormalities, including **polydactyly**, **dental abnormalities**, **congenital heart disease**, **genitourinary malformations**, and **musculoskeletal abnormalities** may require surgical correction.

Neurodevelopmental Issues

The approach to **developmental delay and/or cognitive impairment** should be individualized based on age and identified needs.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, and speech therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the United States (US), early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine if any changes are needed.

    - Special education law requires that children participating in an IEP be in the least restricted environment feasible at school and included in general education as much as possible, when and where appropriate.
    - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
    - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
    - As a child enters teen years, a transition plan should be discussed and incorporated into the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and is typically performed one on one with a board-certified behavior analyst.

Concerns about depression and anxiety are common in the late teens as young persons with BBS realize the severity of its effects. These issues can be addressed by a pediatric psychiatrist.

5. Genetic Counseling of Family Members of an Individual with Bardet-Biedl Syndrome

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Bardet-Biedl syndrome (BBS) is typically inherited in an autosomal recessive manner.

Note: (1) Although oligogenic inheritance of BBS has been suggested in some families with individuals who are identified as having clinical features of BBS and variants in two or more different BBS-associated genes [Manara et al 2019], this mode of inheritance has been refuted in other studies [Abu-Safieh et al 2012]. Identification of copy number variants and intronic variants and more precise phenotypic characterization of individuals with variants of uncertain significance are likely to provide more evidence for traditional autosomal recessive inheritance in BBS [Lindstrand et al 2016, Shamseldin et al 2020]. (2) The clinical relevance of modifier gene variants in BBS is controversial at this time [Yıldız Bölükbaşı et al 2018].

Risk to Family Members (Autosomal Recessive Inheritance)

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one BBS-related pathogenic variant based on family history).
- If a molecular diagnosis has been established in the proband, molecular genetic testing of the parents is recommended to confirm that both parents are heterozygous for a BBS-related pathogenic variant and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a BBS-related pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- BBS is associated with intrafamilial variation; the clinical presentation of sibs who inherit biallelic pathogenic variants may differ from that the proband (see Clinical Characteristics).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with BBS are obligate heterozygotes (carriers) for a pathogenic variant in a BBS-related gene.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a BBS-related pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the BBS-related pathogenic variants in the family.

Prenatal Testing and Preimplantation Genetic Testing

Once the BBS-causing pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Bardet Biedl Syndrome Foundation**

  www.bardetbiedl.org

- **Bardet-Biedl Syndrome UK (BBS UK)**

  43 Balton Way

Harwich Essex CO12 4UP
United Kingdom
Phone: 01604 492916
Email: info@bbsuk.org.uk
www.bbsuk.org.uk

- **Foundation Fighting Blindness**
  7168 Columbia Gateway Drive
  Suite 100
  Columbia MD 21046
  Phone: 800-683-5555 (toll-free); 800-683-5551 (toll-free TDD); 410-423-0600
  Email: info@fightblindness.org
  www.fightingblindness.org
- **Retina International**
  Ireland
  Phone: 353 1 961 9259
  Email: info@retina-International.org
  www.retina-international.org
- **EURO-WABB Project Registry**
  EU rare diseases registry for Wolfram syndrome, Alström syndrome and Bardet-Biedl syndrome (see Farmer et al [2013])
  ww.registry.euro-wabb.org
- **The Clinical Registry Investigating Bardet-Biedl Syndrome (CRIBBS)**
  www.bbs-registry.org

Chapter Notes

Author Notes

Meral Gunay-Aygun, MD is the principal investigator of the National Institutes of Health research protocol "Clinical and Molecular Investigations into Ciliopathies" (www.ClinicalTrials.gov NCT00068224), ongoing since 2003. Under this protocol, she has prospectively evaluated patients with various ciliopathies including autosomal recessive polycystic kidney disease-congenital hepatic fibrosis, and Joubert, Bardet-Biedl, and Alström syndromes.

Dr Gunay-Aygun's website

Author History

Philip L Beales, BSc, MD, FRCP, FMedSci; University College London (2003-2020)
Elizabeth Forsythe, MBBS, BMedSci, MRCPCH; University College London (2014-2020)
RaeLynn Forsyth, MD (2020-present)
Meral Gunay-Aygun, MD (2020-present)

Alison J Ross, PhD; University College London (2003-2009)
Aoife M Waters, MB BAO, BCh, MRCPI, MSc; University College London (2009-2014)

Revision History

- 23 March 2023 (aa/gm) Revision: Daich Varela et al [2023] and information about likely pathogenic variants in noncoding regions detected by genome sequencing added to Molecular Genetic Testing
- 23 July 2020 (bp) Comprehensive update posted live; scope changed to overview
- 23 April 2015 (aa) Revision: addition of *IFT27* (BBS19); edits to Tables 1a, 1b
- 20 February 2014 (me) Comprehensive update posted live
- 29 September 2011 (cd) Revision: mutations in *WDPCP* (BBS15) and *SDCCAG8* (BBS16) possibly associated with BBS
- 18 November 2010 (cd) Revision: deletion/duplication analysis available for *BBS4, BBS5, BBS7,* and *BBS9;* deletions/duplications have been reported. Deletion/duplication analysis available for *BBS1, BBS2, ARL6, MKKS, TTC8, BBS10, TRIM32, BBS12, and MKS1*; no deletions or duplications involving any of these genes as causative of Bardet-Biedl syndrome have been reported.
- 22 July 2010 (cd) Revision: sequence analysis available clinically for all 14 BBS-related genes; targeted mutation analysis available clinically for 11/ 14 genes; prenatal testing available for most (13/14) BBS-related genes
- 13 October 2009 (me) Comprehensive update posted live
- 5 January 2007 (cd) Revision: *BBS12* identified
- 26 June 2006 (ca) Revision: *BBS10* and *TRIM32* identified as genes involved in BBS, testing for C91fsX95 mutation in *BBS10* clinically available
- 18 November 2005 (me) Comprehensive update posted live
- 17 October 2003 (pb) Revision: change in test availability
- 14 July 2003 (me) Review posted live
- 22 January 2003 (pb) Original submission

References

Literature Cited

Abu-Safieh L, Al-Anazi S, Al-Abdi L, Hashem M, Alkuraya H, Alamr M, Sirelkhatim MO, Al-Hassnan Z, Alkuraya B, Mohamed JY, Al-Salem A, Alrashed M, Faqeih E, Softah A, Al-Hashem A, Wali S, Rahbeeni Z, Alsayed M, Khan AO, Al-Gazali L, Taschner PE, Al-Hazzaa S, Alkuraya FS. In search of triallelism in Bardet-Biedl syndrome. Eur J Hum Genet. 2012;20:420–7. PubMed PMID: 22353939.

Aldahmesh MA, Li Y, Alhashem A, Anazi S, Alkuraya H, Hashem M, Awaji AA, Sogaty S, Alkharashi A, Alzahrani S, Al Hazzaa SA, Xiong Y, Kong S, Sun Z, Alkuraya FS. 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. PubMed PMID: 24488770.

Baker K, Northam GB, Chong WK, Banks T, Beales P, Baldeweg T. Neocortical and hippocampal volume loss in a human ciliopathy: a quantitative MRI study in Bardet-Biedl syndrome. Am J Med Genet A. 2011;155A:1–8. PubMed PMID: 21204204.

Bennouna-Greene V, Kremer S, Stoetzel C, Christmann D, Schuster C, Durand M, Verloes A, Sigaudy S, Holder-Espinasse M, Godet J, Brandt C, Marion V, Danion A, Dietemann J-L, Dollfus H. Hippocampal dysgenesis and variable neuropsychiatric phenotypes in patients with Bardet-Biedl syndrome underline complex CNS impact of primary cilia. Clin Genet. 2011;80:523–31. PubMed PMID: 21517826.

Branfield Day L, Quammie C, Héon E, Bhan A, Batmanabane V, Dai T, Kamath BM. Liver anomalies as a phenotype parameter of Bardet-Biedl syndrome. Clin Genet. 2016;89:507–9. PubMed PMID: 26596255.

Braun JJ, Noblet V, Durand M, Scheidecker S, Zinetti-Bertschy A, Foucher J, Marion V, Muller J, Riehm S, Dollfus H, Kremer S. Olfaction evaluation and correlation with brain atrophy in Bardet-Biedl syndrome. Clin Genet. 2014;86:521–9. PubMed PMID: 24684473.

Braun JJ, Noblet V, Kremer S, Molière S, Dollfus H, Marion V, Goetz N, Muller J, Riehm S. Value of MRI olfactory bulb evaluation in the assessment of olfactory dysfunction in Bardet-Biedl syndrome. Clin Genet. 2016;90:79–83. PubMed PMID: 26586152.

Chiang AP, Beck JS, Yen H-J, Tayeh MK, Scheetz TE, Swiderski RE, Nishimura DY, Braun TA, Kim K-YA, Huang J, Elbedour K, Carmi R, Slusarski DC, Casavant TL, Stone EM, Sheffield VC. 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. PubMed PMID: 16606853.

Daich Varela M, Bellingham J, Motta F, Jurkute N, Ellingford JM, Quinodoz M, Oprych K, Niblock M, Janeschitz-Kriegl L, Kaminska K, Cancellieri F, Scholl HPN, Lenassi E, Schiff E, Knight H, Black G, Rivolta C, Cheetham ME, Michaelides M, Mahroo OA, Moore AT, Webster AR, Arno G. Multidisciplinary team directed analysis of whole genome sequencing reveals pathogenic non-coding variants in molecularly undiagnosed inherited retinal dystrophies. Hum Mol Genet. 2023;32:595–607. PubMed PMID: 36084042.

Denniston AK, Beales PL, Tomlins PJ, Good P, Langford M, Foggensteiner L, Williams D, Tsaloumas MD. Evaluation of visual function and needs in adult patients with Bardet-Biedl syndrome. Retina. 2014;34:2282–9. PubMed PMID: 25170860.

Deveault C, Billingsley G, Duncan JL, Bin J, Theal R, Vincent A, Fieggen KJ, Gerth C, Noordeh N, Traboulsi EI, Fishman GA, Chitayat D, Knueppel T, Millán JM, Munier FL, Kennedy D, Jacobson SG, Innes AM, Mitchell GA, Boycott K, Héon E. BBS genotype-phenotype assessment of a multiethnic patient cohort calls for a revision of the disease definition. Hum Mutat. 2011;32:610–9. PubMed PMID: 21344540.

Fan Y, Esmail MA, Ansley SJ, Blacque OE, Boroevich K, Ross AJ, Moore SJ, Badano JL, May-Simera H, Compton DS, Green JS, Lewis RA, van Haelst MM, Parfrey PS, Baillie DL, Beales PL, Katsanis N, Davidson WS, Leroux MR. Mutations in a member of the Ras superfamily of small GTP-binding proteins causes Bardet-Biedl syndrome. Nat Genet. 2004;36:989–93. PubMed PMID: 15314642.

Forsythe E, Beales PL. Bardet-Biedl syndrome. Eur J Hum Genet. 2013;21:8–13. PubMed PMID: 22713813.

Forsythe E, Sparks K, Best S, Borrows S, Hoskins B, Sabir A, Barrett T, Williams D, Mohammed S, Goldsmith D, Milford DV, Bockenhauer D, Foggensteiner L, Beales PL. Risk factors for severe renal disease in Bardet-Biedl syndrome. J Am Soc Nephrol. 2017;28:963–70. PubMed PMID: 27659767.

Fieggen K, Milligan C, Henderson B, Esterhuizen AI. Bardet Biedl syndrome in South Africa: a single founder mutation. S Afr Med J. 2016;106:S72–4. PubMed PMID: 27245532.

Gouronc A, Zilliox V, Jacquemont M-L, Darcel F, Leuvrey A-S, Nourisson E, Antin M, Alessandri J-L, Doray B, Gueguen P, Payet F, Randrianaivo H, Stoetzel C, Scheidecker S, Flodrops H, Dollfus H, Muller J. High prevalence of Bardet-Biedl syndrome in La Réunion Island is due to a founder variant in ARL6/BBS3. Clin Genet. 2020;98:166–71. PubMed PMID: 32361989.

Haws RM, McIntee TJ, Green CB. Cutaneous findings in Bardet-Biedl syndrome. Int J Dermatol. 2019;58:1160–4. PubMed PMID: 30790276.

Haws RM, Joshi A, Shah SA, Alkandari O, Turman MA. Renal transplantation in Bardet-Biedl syndrome. Pediatr Nephrol. 2016;31:2153–61. PubMed PMID: 27245600.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Keppler-Noreuil KM, Blumhorst C, Sapp JC, Brinckman D, Johnston J, Nopoulos PC, Biesecker LG. Brain tissue- and region-specific abnormalities on volumetric MRI scans in 21 patients with Bardet-Biedl syndrome (BBS). BMC Med Genet. 2011;12:101. PubMed PMID: 21794117.

Kerr EN, Bhan A, Héon E. Exploration of the cognitive, adaptive, and behavioral functioning of patients affected with Bardet-Biedl syndrome. Clin Genet. 2016;89:426–33. PubMed PMID: 25988237.

Kim SK, Shindo A, Park TJ, Oh EC, Ghosh S, Gray RS, Lewis RA, Johnson CA, Attie-Bittach T, Katsanis N, Wallingford JB. Planar cell polarity acts through septins to control collective cell movement and ciliogenesis. Science. 2010;329:1337–40. PubMed PMID: 20671153.

Kleinendorst L, Alsters SIM, Abawi O, Waisfisz Q, Boon EMJ, van den Akker ELT, van Haelst MM. Second case of Bardet-Biedl syndrome caused by biallelic variants in IFT74. Eur J Hum Genet. 2020;28:943–6. PubMed PMID: 32144365.

Lindstrand A, Frangakis S, Carvalho CMB, Richardson EB, McFadden KA, Willer JR, Pehlivan D, Liu P, Pediaditakis IL, Sabo A, Lewis RA, Banin E, Lupski JR, Davis EE, Katsanis N. Copy-number variation contributes to the mutational load of Bardet-Biedl syndrome. Am J Hum Genet. 2016;99:318–36. PubMed PMID: 27486776.

Manara E, Paolacci S, D'Esposito F, Abeshi A, Ziccardi L, Falsini B, Colombo L, Iarossi G, Pilotta A, Boccone L, Guerri G, Monica M, Marta B, Maltese PE, Buzzonetti L, Rossetti L, Bertelli M. Mutation profile of BBS genes in patients with Bardet-Biedl syndrome: an Italian study. Ital J Pediatr. 2019;45:72. PubMed PMID: 31196119.

Marion V, Stutzmann F, Gérard M, De Melo C, Schaefer E, Claussmann A, Hellé S, Delague V, Souied E, Barrey C, Verloes A, Stoetzel C, Dollfus H. Exome sequencing identifies mutations in LZTFL1, a BBSome and smoothened trafficking regulator, in a family with Bardet-Biedl syndrome with situs inversus and insertional polydactyl. J Med Genet. 2012;49:317–21. PubMed PMID: 22510444.

Mary L, Chennen K, Stoetzel C, Antin M, Leuvrey A, Nourisson E, Alanio-Detton E, Antal MC, Attié-Bitach T, Bouvagnet P, Bouvier R, Buenerd A, Clémenson A, Devisme L, Gasser B, Gilbert-Dussardier B, Guimiot F, Khau Van Kien PK, Leroy B, Loget P, Martinovic J, Pelluard F, Perez M-J, Petit F, Pinson L, Rooryck-Thambo C, Poch O, Dollfus H, Schaefer E, Muller J. Bardet-Biedl syndrome: Antenatal presentation of forty-five fetuses with biallelic pathogenic variants in known Bardet-Biedl syndrome genes. Clin Genet. 2019;95:384–97. PubMed PMID: 30614526.

Morisada N, Hamada R, Miura K, Ye MJ, Nozu K, Hattori M, Iijima K. Bardet-Biedl syndrome in two unrelated patients with identical compound heterozygous SCLT1 mutations. CEN Case Rep. 2020;9:260–5. PubMed PMID: 32253632.

Mujahid S, Hunt KF, Cheah YS, Forsythe E, Hazlehurst JM, Sparks K, Mohammed S, Tomlinson JW, Amiel SA, Carroll PV, Beales PL, Huda MSB, McGowan BM. The endocrine and metabolic characteristics of a large Bardet-Biedl syndrome clinic population. J Clin Endocrinol Metab. 2018;103:1834–41. PubMed PMID: 29409041.

Niederlova V, Modrak M, Tsyklauri O, Huranova M, Stepanek O. Meta-analysis of genotype-phenotype associations in Bardet-Biedl syndrome uncovers differences among causative genes. Hum Mutat. 2019;40:2068–87. PubMed PMID: 31283077.

Olson AJ, Krentz AD, Finta KM, Okorie UC, Haws RM. Thoraco-abdominal abnormalities in Bardet-Biedl syndrome: situs inversus and hetrotaxy. J Pediatr. 2019;204:31–7. PubMed PMID: 30293640.

Panny A, Glurich I, Haws RM, Acharya A. Oral and craniofacial anomalies of Bardet-Biedl syndrome: dental management in the context of a rare disease. J Dent Res. 2017;96:1361–9. PubMed PMID: 28662344.

Putoux A, Attie-Bitach T, Martinovic J, Gubler M-C. Phenotypic variability of Bardet-Biedl syndrome: focusing on the kidney. Pediatr Nephrol. 2012;27:7–15. PubMed PMID: 21246219.

Schaefer E, Lauer J, Durand M, Pelletier V, Obringer C, Claussmann A, Braun J-J, Redin C, Mathis C, Muller J, Schmidt-Mutter C, Flori E, Marion V, Stoetzel C, Dollfus H. Mesoaxial polydactyly is a major feature in Bardet-Biedl syndrome patients with LZTFL1 (BBS17) mutations. Clin Genet. 2014;85:476–81. PubMed PMID: 23692385.

Schaefer E, Delvallée C, Mary L, Stoetzel C, Geoffroy V, Marks-Delesalle C, Holder-Espinasse M, Ghoumid J, Dollfus H, Muller J. Identification and characterization of known biallelic mutations in the IFT27 (BBS19) gene in a novel family with Bardet-Biedl syndrome. Front Genet. 2019;10:21. PubMed PMID: 30761183.

Scheidecker S, Etard C, Pierce NW, Geoffroy V, Schaefer E, Muller J, Chennen K, Flori E, Pelletier V, Poch O, Marion V, Stoetzel C, Strähle U, Nachury MV, Dollfus H. Exome sequencing of Bardet-Biedl syndrome patient identifies a null mutation in the BBSome subunit BBIP1 (BBS18). J Med Genet. 2014;51:132–6. PubMed PMID: 24026985.

Shamseldin HE, Shaheen R, Ewida N, Bubshait DK, Alkuraya H, Almardawi E, Howaidi A, Sabr Y, Abdalla EM, Alfaifi AY, Alghamdi JM, Alsagheir A, Alfares A, Morsy H, Hussein MH, Al-Muhaizea MA, Shagrani M, Al Sabban E, Salih MA, Meriki N, Khan R, Almugbel M, Qari A, Tulba M, Mahnashi M, Alhazmi K, Alsalamah AK, Nowilaty SR, Alhashem A, Hashem M, Abdulwahab F, Ibrahim N, Alshidi T, AlObeid E, Alenazi MM, Alzaidan H, Rahbeeni Z, Al-Owain M, Sogaty S, Seidahmed MZ, Alkuraya FS. The morbid genome of ciliopathies: an update. Genet Med. 2020;22:1051–60. PubMed PMID: 32055034.

Shoemark A, Dixon M, Beales PL, Hogg CL. Bardet-Biedl syndrome: motile ciliary phenotype. Chest. 2015;147:764–70. PubMed PMID: 25317630.

Stone EM, Andorf JL, Whitmore SS, DeLuca AP, Giacalone JC, Streb LM, Braun TA, Mullins RF, Scheetz TE, Sheffield VC, Tucker BA. Clinically focused molecular investigation of 1000 consecutive families with inherited retinal disease. Ophthalmology. 2017;124:1314–31. PubMed PMID: 28559085.

Tadenev ALD, Kulaga HM, May-Simera HL, Kelley MW, Katsanis N, Reed RR. Loss of Bardet-Biedl syndrome protein-8 (BBS8) perturbs olfactory functions, protein localization, and axon targeting. Proc Natl Acad Sci U S A. 2011;108:10320–5. PubMed PMID: 21646512.

Taylor JC, Martin HC, Lise S, Broxholme J, Cazier JB, Rimmer A, Kanapin A, Lunter G, Fiddy S, Allan C, Aricescu AR, Attar M, Babbs C, Becq J, Beeson D, Bento C, Bignell P, Blair E, Buckle VJ, Bull K, Cais O, Cario H, Chapel H, Copley RR, Cornall R, Craft J, Dahan K, Davenport EE, Dendrou C, Devuyst O, Fenwick AL, Flint J, Fugger L, Gilbert RD, Goriely A, Green A, Greger IH, Grocock R, Gruszczyk AV, Hastings R, Hatton E, Higgs D, Hill A, Holmes C, Howard M, Hughes L, Humburg P, Johnson D, Karpe F, Kingsbury Z, Kini U, Knight JC, Krohn J, Lamble S, Langman C, Lonie L, Luck J, McCarthy D, McGowan SJ, McMullin MF, Miller KA, Murray L, Németh AH, Nesbit MA, Nutt D, Ormondroyd E, Oturai AB, Pagnamenta A, Patel SY, Percy M, Petousi N, Piazza P, Piret SE, Polanco-Echeverry G, Popitsch N, Powrie F, Pugh C, Quek L, Robbins PA, Robson K, Russo A, Sahgal N, van Schouwenburg PA, Schuh A, Silverman E, Simmons A, Sørensen PS, Sweeney E, Taylor J, Thakker RV, Tomlinson I, Trebes A, Twigg SR, Uhlig HH, Vyas P, Vyse T, Wall SA, Watkins H, Whyte MP, Witty L, Wright B, Yau C, Buck D, Humphray S, Ratcliffe PJ, Bell JI, Wilkie AO, Bentley D, Donnelly P, McVean G. Factors influencing success of clinical genome sequencing across a broad spectrum of disorders. Nat Genet. 2015;47:717–26. PubMed PMID: 25985138.

Weihbrecht K, Goar WA, Pak T, Garrison JE, DeLuca AP, Stone EM, Scheetz TE, Sheffield VC. Keeping an eye on Bardet-Biedl syndrome: a comprehensive review of the role of Bardet-Biedl syndrome genes in the eye. Med Res Arch. 2017;5 doi: 10.18103/mra.v5i9.1526.

Wormser O, Gradstein L, Yogev Y, Perez Y, Kadir R, Goliand I, Sadka Y, El Riati S, Flusser H, Nachmias D, Birk R, Iraqi M, Kadar E, Gat R, Drabkin M, Halperin D, Horev A, Sivan S, Abdu U, Elia N, Birk OS. SCAPER localizes to primary cilia and its mutation affects cilia length, causing Bardet-Biedl syndrome. Eur J Hum Genet. 2019;27:928–40. PubMed PMID: 30723319.

Xing D-J, Zhang H-X, Huang N, Wu K-C, Huang X-F, Huang F, Tong Y, Pang C-P, Qu J, Jin Z-B. Comprehensive molecular diagnosis of Bardet-Biedl syndrome by high-throughput targeted exome sequencing. PLoS One. 2014;9:e90599. PubMed PMID: 24608809.

Yadav DK, Beniwal MK, Jain A. Bardet-Bidel syndrome a rare cause of cardiomyopathy. Indian Pediatr. 2013;50:599–601. PubMed PMID: 23942403.

Yıldız Bölükbaşı E, Mumtaz S, Afzal M, Woehlbier U, Malik S, Tolun A. Homozygous mutation in *CEP19,* a gene mutated in morbid obesity, in Bardet-Biedl syndrome with predominant postaxial polydactyly. J Med Genet. 2018;55:189–97. PubMed PMID: 29127258.

License