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Bardet-Biedl Syndrome

[*Biedl-Bardet Syndrome*]

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Summary

Disease characteristics. Bardet-Biedl syndrome (BBS) is characterized by cone-rod dystrophy, truncal obesity, postaxial polydactyly, cognitive impairment, male hypogonadotrophic hypogonadism, complex female genitourinary malformations, and renal dysfunction. The visual prognosis for children with Bardet-Biedl syndrome is poor: night blindness is usually evident by seven to eight years of age; the mean age at which affected individuals become legally blind is 15.5 years. Birth weight is usually normal, but significant weight gain begins within the first year and becomes a lifelong issue for most individuals. A majority of individuals have significant learning difficulties, but only a minority have severe impairment on IQ testing. Renal disease is a major cause of morbidity and mortality.

Diagnosis/testing. The diagnosis of Bardet-Biedl syndrome is established by clinical findings. Twelve genes are known to be associated with Bardet-Biedl syndrome: *BBS1*, *BBS2*, *ARL6/BBS3*, *BBS4*, *BBS5*, *MKKS/BBS6*, *BBS7*, *TTC8/BBS8*, *B1/BBS9*, *BBS10*, and *TRIM32/BBS11* and *BBS12*. Molecular genetic testing is available on a clinical basis for M390R, the common mutation in *BBS1* that is present in approximately 18%-32% of individuals with BBS and p.C91LfsX4 (also known as C91fsX95), a common mutation in *BBS10*, that is present in 10% of individuals with BBS.

Management. Individuals with Bardet-Biedl syndrome need visual aids and educational programs for the visually impaired. Diet, exercise, and behavioral therapies are used to manage obesity; hypercholesterolemia and diabetes mellitus are treated as in the general population. Surgery to remove accessory digits prevents functional interference and poor fitting of footwear. Early intervention and special education address cognitive disability; speech delay/impairment is addressed with speech therapy. Hydrocolpos, vaginal atresia, or hypospadias may be surgically corrected. Hormone replacement therapy is used to correct hypogonadism. Renal anomalies and hypertension are treated as in the general population; renal transplantation has been successful. Surveillance includes regular ophthalmologic evaluation, annual blood pressure measurement, monitoring of renal function, and regular testing for diabetes mellitus and lipid profiling.

Genetic counseling. Bardet-Biedl syndrome is inherited in an autosomal recessive manner. In some families, the presence of at least three mutations seems to be required for the phenotype

to be clinically expressed (triallelic inheritance). However, such families are difficult to identify and by previous estimations may account for fewer than 10% of all BBS. It is thus prudent to use the following autosomal recessive risk figures when providing genetic counseling: At conception, each sib of an affected individual has 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. Carrier testing is clinically available for at-risk family members of individuals with documented p.M390R mutations in *BBS1*. Prenatal diagnosis using second trimester ultrasound examination to detect anomalies such as postaxial polydactyly and renal cysts found in individuals with Bardet-Biedl syndrome has been reported. Prenatal testing may be available through laboratories offering custom prenatal testing.

Diagnosis

Clinical Diagnosis

The diagnosis of Bardet-Biedl syndrome is established by clinical findings. Beales et al (1999, 2001) have suggested that the presence of four primary features or three primary features plus two secondary features is diagnostic.

Primary features

- **Cone-rod dystrophy.** The fundus abnormality in Bardet-Biedl syndrome is an atypical pigmentary retinal dystrophy with early macular involvement [Amman 1970, Bergsma & Brown 1975, Campo & Aaberg 1982]. Full-field rod and cone electroretinograms are the investigations of choice and may be abnormal as early as 14 months of age [Runge et al 1986]. Visual acuity (central retinal function mediated by cones), dark adaptation, and peripheral visual fields (peripheral retina function mediated by rods) are affected. Optic disks and retinal vessels are normal in infancy; disk pallor and attenuated retinal vessels develop with age. Pigmentary changes are observed in the peripheral fundus [Riise et al 1996]. Significant cone-rod dystrophy is not apparent in most children under five years of age and cooperation with ERG testing at that age is often poor. Unless strongly indicated, ERG testing may be deferred until at least four years of age.
- **Postaxial polydactyly.** Additional digits on the ulnar side of the hand and the fibular side of the foot
- **Truncal obesity.** Obesity can be defined as a body mass index (BMI) greater than 30 or greater than 97th centile. BMI equals weight in kilograms divided by the square of the height in meters (kg/m^2).
- **Learning disabilities.** Cognitive impairment
- **Hypogonadism in males or genital abnormalities in females:**
  - **Males.** Small penile shaft and/or reduced volume of testes
  - **Females.** Hypoplastic fallopian tubes, uterus, and ovaries; partial and complete vaginal atresia; septate vagina; duplex uterus; hydrometrocolpos; persistent urogenital sinus; vesico-vaginal fistula; absent vaginal orifice; and absent urethral orifice [McLoughlin & Shanklin 1967, Klein & Ammann 1969, Nadjmi et al 1969, Campo & Aaberg 1982, Srinivas et al 1983, Cramer et al 1988, Green et al 1989, Stoler et al 1995, Mehrotra et al 1997, Uguralp et al 2003]
- **Renal anomalies.** The combination of calyceal clubbing, tubular cystic diverticula, and persistent fetal lobulation is characteristic and may be pathognomonic of Bardet-Biedl syndrome.

Note: Intravenous pyelography (IVP) is better than ultrasound examination in identifying communicating cysts and diverticula, but ultrasound examination and IVP are comparable in documenting cortical changes [Cramer et al 1988].

Secondary features

- **Speech disorder/delay.** Disordered speech refers to delay in onset (individuals often not establishing intelligible speech until four years of age) and phonation difficulties such as breathy, high-pitched qualities. Disordered speech has been reported infrequently in Bardet-Biedl syndrome [Garstecki et al 1972, Beales et al 1999]. It has been suggested that substitutions of consonants at the beginning of words and the omission of the final consonant may be distinctive of Bardet-Biedl syndrome [Beales et al 1999]. Videofluoroscopy and palatal articulation studies point to incoordination of the pharyngeal and/or laryngeal muscles as the possible basis of the problem.
- **Strabismus/cataracts/astigmatism**
- **Brachydactyly/syndactyly.** Brachydactyly of both the hands and feet is common [Rudling et al 1996] as is partial syndactyly (most usually between the second and third toes). Formal measures of digit length and width and comparison with normalized charts may be helpful in determining brachydactyly.
- **Developmental delay.** Many children with Bardet-Biedl syndrome are delayed in reaching major developmental milestones including gross motor skills, fine motor skills, and psychosocial skills (interactive play/ability to recognize social cues).
- **Polyuria/polydipsia (nephrogenic diabetes insipidus).** Polyuria and polydipsia may be present in the absence of any renal structural abnormality.
- **Ataxia/poor coordination/imbalance.** A large proportion of individuals describe a degree of clumsiness and often demonstrate a wide-based gait. Tandem walking (in a straight line with one toe abutting the other heel) is usually impossible. Repetitive supination and pronation of the hands at the wrist is slow (dysdiadochokinesia). Despite occasional reports of cerebellar involvement, there is no indication that cerebellar function is abnormal. More likely, a yet-to-be-delineated defect in coordination and processing movements exists. It is not known when these features become evident.
- **Mild hypertonia (especially lower limbs).** It is not known when this becomes evident.
- **Diabetes mellitus.** Diabetes mellitus tends to become evident in adolescence or adulthood. It is usually non-insulin dependent diabetes mellitus (NIDDM)/Type 2 diabetes mellitus, although occasionally insulin is required for acute control of hyperglycemia. Diabetes mellitus may relate to level of obesity. Impaired glucose tolerance has been described in younger individuals prior to the onset of NIDDM [Green et al 1989].
- **Dental crowding/hypodontia/small dental roots/high-arched palate** [Borgström et al 1996]
- **Cardiovascular anomalies.** Echocardiographic studies of 22 individuals with Bardet-Biedl syndrome revealed cardiac abnormalities in 50% [Elbedour et al 1994]. The study of Beales et al (1999) identified congenital heart disease in approximately 7% of individuals, equally divided between aortic stenosis, patent ductus arteriosis, and unspecified cardiomyopathy. Valvular stenoses and atrial/ventricular septal defects are the most commonly reported lesions [Blumel & Kniker

1959, McLoughlin & Shanklin 1967, Farag & Teebi 1988, Elbedour et al 1994, Beales et al 1999, Slavotinek & Biesecker 2000].

- **Hepatic involvement.** Perilobular fibrosis, periportal fibrosis with small bile ducts, bile duct proliferation with cystic dilatation, biliary cirrhosis, portal hypertension, and congenital cystic dilations of both the intrahepatic and extrahepatic biliary tract have been described in individuals with Bardet-Biedl syndrome [Meeker & Nighbert 1971, Tsuchiya et al 1977, Pagon et al 1982, Roussel et al 1985, Croft & Swift 1990, Nakamura et al 1990].

Note: (1) Brachycephaly, macrocephaly, bitemporal narrowing, male frontal balding, large ears, short and narrow palpebral fissures, a long shallow philtrum, thin upper lip, and small downturned mouth are characteristic [Beales et al 1999, Lorda-Sanchez et al 2001, Moore et al 2005]. Increased awareness of the facial dysmorphology may facilitate the early diagnosis of BBS. (2) Partial or complete anosmia has been described following initial observations in mouse models of the condition [Kulaga et al 2004, Nishimura et al 2004, Fath et al 2005, Iannacone et al 2005]. It remains to be seen whether a relatively simple smell identification test is of diagnostic value.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Genes. Twelve genes are known to be associated with Bardet-Biedl syndrome (see Table 1).

Table 1. BBS Known Genes

GeneName	Percent of Causative Mutations
BBS1	~23.2% [1]
BBS2	~8.1% [1]
ARL6/BBS3	~0.4% [1]
BBS4	
BBS5	~0.4% [1]
MKKS/BBS6	~5.8% [1]
BBS7	~1.5% [1]
TTC8/BBS8	~1.2% [1]
B1/BBS9	Not yet known [1]
BBS10	~20% [2]
TRIM32 [3]	<0.4%
BBS12	~5% [4]

1. Katsanis 2004
2. Stoetzel et al 2006
3. Chiang et al 2006
4. Stoetzel et al 2007

Other loci. Approximately 20% to 30% of persons with BBS do not have identifiable mutations in any of the twelve known BBS genes; therefore, it is possible that more BBS genes are yet to be identified.

Clinical uses

- Confirmatory diagnostic testing
- Carrier detection
- Prenatal diagnosis

Clinical testing

- **Targeted mutation analysis**
  - The most common mutation, the *BBS1* p.M390R mutation, is present in 18%-32% of individuals with BBS.
  - The p.C91LfsX4 (c.271_272insT) mutation in *BBS10* accounts for 46% of mutant *BBS10* alleles [Stoetzel et al 2006] and is identified in approximately 10% of all individuals with BBS.

Research testing

- **Direct DNA.** *BBS1*, *BBS2*, *ARL6/BBS3*, *BBS4*, *MKKS/BBS6*, *BBS7*, *TTC8/BBS8*, *B1/BBS9, BBS10, BBS11/TRIM32* and *BBS12* are of moderate size and together comprise approximately 137 exons; therefore, mutation screening for any given individual is a large undertaking. Mutations range from missense and nonsense to insertions, deletions, and splice site disruptors for most of these genes. Such testing is available on a research basis only.

Table 2 summarizes molecular genetic testing for this disorder.

Table 2. Molecular Genetic Testing Used in Bardet-Biedl Syndrome

Test Methods	Mutation Detected	Mutation Detection Frequency [1]	Test Availability
Targeted mutation analysis	*BBS1* p.M390R	18%-32%	Clinical Testing
	BBS10 p.C91LfsX4 (also known as C91fsX95)	~10%	Clinical Testing
Direct DNA	All types of mutations in *BBS1*, *BBS2*, *ARL6/BBS3*, *BBS4*, *MKKS/BBS6*, *BBS7*, *TTC8/BBS8*, *B1/BBS9*, *BBS10*, *TRIM32* and *BBS12*	Unknown	Research

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, and/or test method

Genetically Related (Allelic) Disorders

McKusick-Kaufman syndrome. Mutations in *BBS6/MKKS* are also associated with McKusick-Kaufman syndrome (MKS) (see Differential Diagnosis). Given the clinical and molecular overlap between MKS and Bardet-Biedl syndrome [David et al 1999, Slavotinek & Biesecker 2000], it must be seriously considered whether MKS is part of the spectrum of Bardet-Biedl syndrome.

Meckel-Gruber syndrome. Mutations in three BBS genes *(BBS2*, *BBS4*, and *BBS6*) were identified in several cases of Meckel-Gruber syndrome [Karmous-Benailly et al 2005]. Meckel-Gruber syndrome is usually lethal and typically comprises the triad of occipital encephalocele, large polycystic kidneys, and postaxial polydactyly. Associated abnormalities include orofacial clefting, genital anomalies, CNS malformations, and fibrosis of the liver. Pulmonary hypoplasia is the leading cause of death.

Clinical Description

Natural History

A wide range of clinical variability is observed within and among families with Bardet-Biedl syndrome [Riise et al 1997]. The main clinical features are cone-rod dystrophy, with childhood-onset vision loss preceded by night blindness; postaxial polydactyly; truncal obesity that manifests during infancy and remains problematic throughout adulthood; specific learning difficulties, which appear to be the norm in the majority of individuals (although mental retardation is often cited); male hypogenitalism and complex female genitourinary malformations; and renal dysfunction, which is a major cause of morbidity and mortality.

Diagnosis is often delayed in Bardet-Biedl syndrome as a result of the slow emergence and variable expression of the clinical features [Beales et al 1999]. Difficulties in diagnosis arise, for example, in an obese child with learning difficulties and developmental delay but without polydactyly. Until he or she develops visual disturbance, the differential diagnosis is broad.

Cone-rod dystrophy. The earliest signs of retinal dysfunction are often not apparent until seven to eight years of age, when night blindness insidiously ensues [Beales et al 1999]. Even this feature may be missed, only becoming apparent to parents in retrospect.

The visual prognosis for children with Bardet-Biedl syndrome is poor. The visual fields are usually abnormal by age ten years. As early as 17 years, rarely more than a central island of vision remains [Jacobson et al 1990, Riise et al 1996]. The mean age at which affected individuals are registered as legally blind in the UK is 15.5 years [Beales et al 1999]. Thus, the mean time for progression from diagnosis to blindness is approximately seven years.

The appearance of the fundus does not predict visual function. The macula is occasionally involved in the first decade [Fulton et al 1993], and in all individuals in the second decade, accompanied by visual acuity of 20/200 or worse [Fulton et al 1993]. Several extraretinal clinical signs including nystagmus, strabismus, high myopia, cataract, and glaucoma may also occur.

Polydactyly. Postaxial polydactyly is common but not invariably present. Presence ranges from 58% [Green et al 1989] to 69% [Ammann 1970, Beales et al 1999, Ramirez et al 2004]. Brachydactyly of the fingers and toes is common, as are partial syndactyly (most usually between the 2nd and 3rd toes), fifth finger clinodactyly (inwardly curved little finger), and a prominent "sandal gap" between the first and second toes. In a recent orthopedic study of 27 affected individuals, 17 had polydactyly, four had scoliosis, two had tibia valga, two had tibia vara, and one had Legg-Calve-Perthes [Ramirez et al 2004].

Obesity. Birth weight is usually normal in Bardet-Biedl syndrome. Significant weight gain begins within the first year and becomes a lifelong issue for most individuals. The distribution of adipose tissue is widespread in childhood but becomes most prominent in the trunk and proximal limbs in adulthood. The cause is unknown; abnormalities of both the pituitary and hypothalamus have been implicated [Burn 1950, Bell 1958]. Although studies are few, no abnormality of basal metabolic rate has been identified as a cause of the weight gain. Caloric intake exceeding daily requirements and, possibly, low activity levels may be responsible for weight gain in individuals with Bardet-Biedl syndrome. The basal metabolic rate (BMR) and body composition were shown to be normal in 20 adult volunteers with Bardet-Biedl syndrome (11 male and nine female) compared with 20 matched controls, but energy intake may be higher in affected individuals than in controls [Grace et al 2003].

Cognitive impairment. Although mental retardation has been described as a major feature of Bardet-Biedl syndrome, often the effects of visual impairment have not been considered. Several studies have now concluded that a majority of individuals have significant learning difficulties and only a minority have severe impairment on IQ testing [Klein 1968, Green et al 1989, Beales et al 1999, Barnett et al 2002, Moore et al 2005].

Hypogonadism/genital abnormalities. Hypogonadism, which is probably hypogonadotrophic in origin, appears to be more frequent in males with Bardet-Biedl syndrome than in females [Bell 1958, Klein & Ammann 1969]. The finding may be artifactual in that the external genitalia are more easily examined in males. Nonetheless, several recent reports indicate that affected females may have complex genitourinary malformations such as hypoplastic fallopian tubes, uterus and ovaries; partial and complete vaginal atresia; septate vagina; duplex uterus; hematocolpos; persistent urogenital sinus; vesico-vaginal fistula; absent vaginal orifice; and absent urethral orifice. Some of these anomalies have been described in McKusick-Kaufman syndrome; however, not all females with Bardet-Biedl syndrome who have these anomalies have mutations in *MKKS*, suggesting that this component of the syndrome is common to more than one type of Bardet-Biedl syndrome. Most males have micropenis at birth with small volume testes, and atrophic seminiferous tubules have been reported. Several affected women have successfully given birth; in contrast, only two affected males have fathered children [Bell 1958, Klein & Ammann 1969, Green et al 1989, O'Dea et al 1996, Beales et al 1999].

Renal abnormalities. A high frequency of structural urinary tract abnormalities was observed postmortem [McLoughlin & Shanklin 1967, Nadjmi et al 1969]. In a review of 330 individuals with Bardet-Biedl syndrome reported in the literature, Nadjmi et al (1969) found that ten of 14 individuals undergoing autopsy had urinary tract malformations (71%), ranging from renal hypoplasia and hydronephrosis to chronic pyelonephritis and glomerulonephritis. In the study of Klein & Ammann (1969), three of 57 individuals had cystic kidneys, one had proteinuria and hypertension, two had glomerulonephritis, and one had nephrosclerosis with unilateral hydronephrosis.

Cassart et al (2004) studied 11 fetuses by ultrasound scan and concluded that in families in which BBS had occurred previously, the prenatal appearance of enlarged hyperechoic kidneys without corticomedullary differentiation should be considered recurrence of Bardet-Biedl syndrome, and that in a family with no previous history of BBS, such prenatal findings should suggest the possibility of Bardet-Biedl syndrome.

Alton & McDonald (1973) reported that over 30% of individuals with Bardet-Biedl syndrome die of uremia [Alton & McDonald 1973]. O'Dea et al (1996) followed 36 individuals with Bardet-Biedl syndrome and reported that by age 48 years, 25% had developed chronic renal failure (CRF). Beales et al (1999) reported that, of 57 individuals imaged, 26 (46%) had renal structural abnormalities. However, only 5% had renal impairment at the time of assessment. Other reports have described CRF in up to 100% of individuals [Hurley et al 1975, Linne et al 1986, Harnett et al 1988, Garber & de Bruyn 1991].

Hypertension. Hypertension is common in Bardet-Biedl syndrome [Price et al 1981, Tieder et al 1982, Fralick et al 1990, Riise 1996], occurring in 50% [Harnett et al 1988] to 66% of affected individuals [O'Dea et al 1996].

Speech impairment. Acquisition of intelligible speech and proper sentence formation is commonly delayed until four years of age, but individuals tend to respond to early therapy. Even after language acquisition impediments such as prolonged syllable repetition times or a tendency to substitute consonants or drop suffixes may remain [Beales et al 1999, Moore et al 2005].

Neurologic abnormalities. Ataxia and impaired coordination is commonly encountered (up to 86%), as is mild hypertonia affecting all four limbs [Beales et al 1999, Moore et al 2005]. In the Moore et al (2005) study, 75% of individuals had a paucity of facial movement sometimes associated with facial asymmetry and difficulty in smiling. As no weakness was present, they concluded that the defects were the result of impaired coordination.

Psychiatric problems. A relatively high proportion of individuals develop a psychiatric illness in their lifetime [Beales et al 1999, Moore et al 2005], including anxiety, mood disorders, depression, bipolar disorder, obsessive compulsive behavior, and psychosomatic manifestations. Several children fall within the spectrum of autistic disorders [Barnett et al 2002, Moore et al 2005].

Hearing loss. Almost half of adults with BBS develop a subclinical hearing loss (nonconductive) that is only detectable by audiologic evaluation [Ross et al 2005]. The implications of this finding are as yet unknown. Glue ear (acute and chronic otitis media) resulting in conductive loss early in childhood appears to be common [Beales et al 1999].

Genotype-Phenotype Correlations

Some genotype/phenotype correlations have been reported, such as the pattern of distribution of extra digits in BBS4 [Carmi et al 1995] and characteristic ocular phenotypes in BBS2, BBS3, and BBS4 [Riise et al 2002, Heon et al 2005]. By and large, however, correlations between phenotype and genotype have not been confirmed in larger studies.

Penetrance

Penetrance was originally thought to be complete; however, several examples of unaffected individuals with two mutations have recently been reported.

Nomenclature

Historically, several terms have been used to describe the condition currently known as Bardet-Biedl syndrome. These include: Laurence-Moon-Biedl syndrome, Laurence-Moon-Bardet-Biedl syndrome (LMBBS), and Laurence-Moon syndrome (LMS).

JZ Laurence and RC Moon described a family with obesity, retinitis pigmentosa, and intellectual impairment in London in 1866. However, no further cases were published until the 1920s, when George Bardet reported two French girls with the triad of obesity, polydactyly, and retinitis pigmentosa; in 1922, the Austrian endocrinologist, Arthur Biedl, published a short case report of two siblings with retinitis pigmentosa, polydactyly, obesity, hypogenitalism, and intellectual impairment.

In 1925, Solis-Cohen and Weiss coined the term "Laurence-Moon-Bardet-Biedl syndrome" (LMBBS).

Ammann (1970) and more recently, following a review of the literature, Schachat and Maumenee (1982), highlighted essential differences between the Laurence-Moon and Bardet-Biedl syndromes. The medical and scientific communities have now adopted this split nomenclature. Because the family described by Laurence and Moon subsequently developed a progressive spastic paraparesis and because no mention was made of polydactyly, the Laurence-Moon syndrome is considered to comprise retinal dystrophy, obesity, hypogenitalism, and spastic paraparesis without polydactyly. In the authors' opinion and experience, little evidence exists to maintain this division and in fact, mutations have now been detected in Bardet-Biedl syndrome genes in families conforming to an LMS diagnosis [Moore et al 2005].

Prevalence

Among the nonconsanguineous populations of Northern Europe and America, the prevalence ranges from one in 100,000 (North America) [Croft & Swift 1990] to one in 160,000 (Switzerland) [Klein & Ammann 1969]. Among the Bedouin peoples of Kuwait, where consanguinity is frequent, the prevalence is estimated at one in 13,500 [Farag & Teebi 1989]. In the population isolate of the island of Newfoundland, Green et al (1989) reported a prevalence of one in 17,500, from a founder effect.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

McKusick-Kaufman syndrome (MKS) is characterized by the triad of hydrometrocolpos (HMC), postaxial polydactyly (PAP), and congenital heart disease (CHD). Hydrometrocolpos (HMC) in infants is dilatation of the vagina and uterus as a result of the accumulation of cervical secretions from maternal estrogen stimulation. HMC can be caused by failure of the distal third of the vagina to develop (vaginal agenesis), a transverse vaginal membrane, or an imperforate hymen. Many cases of Bardet-Biedl syndrome have been misdiagnosed as McKusick-Kaufman syndrome in infancy or early childhood prior to the development of other manifestations of Bardet-Biedl syndrome [David et al 1999]. MKS is caused by mutations of the *MKKS* gene, which can also cause BBS. MKS is inherited in an autosomal recessive manner.

Alström syndrome is characterized by cone-rod dystrophy, obesity, progressive sensorineural hearing impairment, dilated cardiomyopathy, the insulin resistance syndrome, and developmental delay. Cone-rod dystrophy presents as progressive visual impairment, photophobia, and nystagmus starting between birth and 15 months of age. Affected individuals have no light perception by age 20 years. Children usually have normal birth weight but become obese during their first year, resulting in childhood truncal obesity. Progressive sensorineural hearing loss presents in the first decade in as many as 70% of individuals. Hearing loss may progress to the moderately severe range (40-70 db) by the end of the first to second decade. Insulin resistance/type 2 diabetes mellitus often presents in childhood and is typically accompanied by the skin changes of acanthosis nigricans. Up to 60% of individuals with Alström syndrome develop cardiac failure as a result of dilated cardiomyopathy at some stage of their lives. About 50% of individuals have delays in early developmental milestones. Males may have hypogonadotrophic hypogonadism. Renal disease may present as polyuria and polydipsia resulting from a concentrating defect secondary to interstitial fibrosis. End-stage renal disease (ESRD) can occur as early as the late teens. In contrast to Bardet-Biedl syndrome, Alström syndrome is characterized by relative preservation of cognitive function and the absence of polydactyly. Alström syndrome is caused by mutations in the gene *ALMS1* and is inherited in an autosomal recessive manner.

Biemond 2 syndrome is characterized by mental retardation, coloboma, obesity, polydactyly, hypogonadism, hydrocephalus, and facial dysostosis. No responsible genes have been mapped or identified.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Bardet-Biedl syndrome (BBS):

- Ophthalmologic assessment should be sought as soon as possible to determine visual acuity, field deficits, or refractive errors. Fundoscopic photographs should be filed for later comparison.
- Examination of the genitalia in both sexes. It is important to adequately image the ovaries, fallopian tubes, uterus, and vagina in all affected females. Pelvic ultrasound examination is preferred.
- Calculation of body mass index (BMI) (weight in kg divided by the height in meters squared) can aid in identifying medically significant obesity.
- Dietary evaluation is appropriate if obesity is present (BMI>30).
- Renal function studies and renal ultrasound for assessment of possible structural renal anomalies. If significant abnormalities are identified, referral to a nephrologist is desirable.
- Baseline blood pressure assessment should be made.
- As nephrogenic diabetes insipidus is a commonly overlooked feature of BBS, questioning the individual or parents of the individual with regard to their fluid intake and output can be a simple but helpful diagnostic aid. In some instances, tests of renal concentrating ability may be helpful.
- Cardiac evaluation should include auscultation, ECG, and echocardiography.
- Developmental assessment and/or educational evaluation are important for intervention and planning.
- Endocrinologic testing may be necessary and includes glucose tolerance testing (GTT) for diabetes mellitus, lipid levels, and assessment of thyroid and liver functions. More formal tests of the pituitary gland may be warranted particularly in assessing fertility and virility. Infertility should not be assumed in all males or females.
- Hearing evaluation: otoacoustic emissions (OAE) and audiometry may reveal subclinical hearing loss in adults. Conductive loss is common in children as a result of otitis media.
- Dental evaluation should assess for hygiene, dental crowding, and hypodontia.
- Neurologic examination should assess forataxic gait, poor coordination, dysdiadochokinesia, inability to perform tandem gait walking, poor two-point discrimination, and diminished fine motor skills.

Treatment of Manifestations

To treat manifestations of BBS:

- No therapy for the progressive visual loss exists, but early evaluation of visual acuity facilitates the provision of visual aids and helps prepare the child for a future with little or no sight. Educational planning should take future blindness into consideration.
- To manage obesity, multiple strategies are advocated, including diet, exercise and behavioral therapies. Education and dietary measures to control weight gain education must be initiated at an early age. No formal trials of drug therapy (appetite suppressants or lipase inhibitors) have been reported; however, such therapy may be attempted providing the individual does not have contraindications to specific drug use (i.e., renal or hepatic dysfunction).
- Complications of obesity, such as hypercholesterolemia and diabetes mellitus, should be treated as in the general population.

- Cognitive disability should be addressed through early intervention and special education, as indicated by evaluation. It is advisable to make careful assessment of individual needs with respect to education, as many adults are capable of attaining independent living skills.
- Speech therapy should be offered at the first sign of speech delay and/or impairment.
- Treatment of renal functional or structural anomalies and hypertension is similar to that of the general population.
- Renal transplantation has been successful, although the immunosuppressants used following transplantation can compound the weight problem.
- Surgical correction of hydrocolpos, vaginal atresia, or hypospadias may be warranted. As children approach puberty, gonatrophin and sex hormone levels should be monitored to determine if hormone replacement therapy is indicated.
- Treatment of cardiac abnormalities is the same as for the general population.
- It is important to offer contraceptive advice to all females with Bardet-Biedl syndrome rather than assume likely infertility.
- The earliest and most common intervention for polydactyly is removal of the accessory digit. Indicators are functional interference and poorly fitting footwear. Most children have their accessory digits removed within the first two years.
- Dental extractions as required for dental crowding is appropriate.
- Prompt treatment for acute and chronic otitis media should be considered. Insertion of grommets is commonplace.

Prevention of Secondary Complications

Antibiotic prophylaxis for surgical and dental procedures is indicated for individuals with structural cardiac anomalies.

Surveillance

Appropriate surveillance includes the following:

- Regular ophthalmologic evaluations
- Routine (at least annual) measurement of blood pressure
- Judicious monitoring of renal function (via blood chemistry initially) is warranted in all individuals. If serum concentrations of urea, creatinine, and electrolytes are abnormal, renal function scans may be warranted. Early serial renal imaging is important in children [Cramer et al 1988], although only a relatively small proportion of individuals develop end-stage renal disease (ESRD).
- Regular testing for diabetes mellitus by fasting glucose or glucose tolerance testing
- Regular lipid profiling
- Occasional liver function testing to assess for hepatic failure
- Thyroid function testing particularly if there is weight gain, changes in temperament and/or diminished activity

Agents/Circumstances to Avoid

Any substances contraindicated in persons with renal impairment should be avoided.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Bardet-Biedl syndrome is usually inherited in an autosomal recessive manner (see multiallelic inheritance below).

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has 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.
- Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with Bardet-Biedl syndrome are obligate carriers for the disease-causing mutation involved.

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

Carrier Detection

Carrier testing using molecular genetic techniques is available for at-risk family members of individuals with BBS mutations identified in a clinical laboratory.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk is before pregnancy.

Multiallelic inheritance. The risks outlined above are those for straightforward autosomal recessive patterns of disease inheritance. However, some cases of Bardet-Biedl syndrome seem to require the presence of at least three mutations for the phenotype to manifest (triallelic inheritance).

Katsanis et al (2001) proposed that Bardet-Biedl syndrome may also be inherited in a more complex fashion, as an oligogenic disorder. They described a number of pedigrees in which individuals were homozygous or compound heterozygous for mutations at one locus, but required the presence of a third heterozygous mutation residing at a second BBS locus to manifest the disease phenotype — a pattern termed triallelism.

Following the identification of *BBS1*, Mykytyn et al (2002) and Mykytyn et al (2003) failed to find any examples of multialleleic inheritance in their cohort to support the theory of Katsanis et al (2001). Beales et al (2003) found evidence for more than two mutations at two BBS gene loci including *BBS1*. Badano et al (2003) reported a family with multiallelism involving *BBS7*.

Fauser et al (2003) reported examples of complex inheritance in 21 persons with BBS. In testing six BBS genes in 27 families, Hichri et al (2005) did not identify any individuals with mutations in more than one BBS gene; however, the excess of heterozygous mutations observed was consistent with complex inheritance.

At present, the extent to which possible multiallelism accounts for the phenotype is unknown. In practical terms, however, identification of such families is difficult and by previous estimations may account for less than 10% of all BBS. Therefore, until testing improves and further multiallelic cases are reported, it is prudent to use autosomal recessive risk figures when providing genetic counseling and to note that in some cases BBS may not conform to Mendelian laws of inheritance.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells). Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which molecular genetic testing is available on a research basis only. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Molecular genetic testing. No laboratories offering molecular genetic testing for prenatal diagnosis of Bardet-Biedl syndrome are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for certain families in which the disease-causing mutations have been identified in an affected family member in a research or clinical laboratory. For laboratories offering custom prenatal testing, see Testing.

Ultrasound examination. Prenatal diagnosis using second trimester ultrasound examination to detect anomalies such as postaxial polydactyly and renal cysts found in individuals with Bardet-Biedl syndrome has been reported [Dar et al 2001].

Preimplantation genetic diagnosis (PGD). Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have been identified in an affected

family member in a research or clinical laboratory. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Bardet-Biedl Syndrome

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name
BBS1	*BBS1*	11q13	Bardet-Biedl syndrome 1 protein
BBS10	*BBS10*	12q	Bardet-Biedl syndrome 10 protein
BBS11	*TRIM32*	9q31-q34.1	Tripartite motif protein 32
BBS2	*BBS2*	16q21	Bardet-Biedl syndrome 2 protein
BBS3	*ARL6*	3p12-q13	ADP-ribosylation factor-like protein 6
BBS4	*BBS4*	15q22.3-q23	Bardet-Biedl syndrome 4 protein
BBS5	*BBS5*	2q31	Bardet-Biedl syndrome protein 5 isoform 2
BBS6	*MKKS*	20p12	McKusick-Kaufman/Bardet-Biedl syndromes putative chaperonin
BBS7	*BBS7*	4q27	Bardet-Biedl syndrome 7 protein
BBS8	*TTC8*	14q32.1	Tetratricopeptide repeat protein 8
BBS9	*B1*	7p14	Parathyroid hormone- responsive B1 gene

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Bardet-Biedl Syndrome

209900	BARDET-BIEDL SYNDROME; BBS
209901	BBS1 GENE; BBS1
600374	BBS4 GENE; BBS4
602290	TRIPARTITE MOTIF-CONTAINING PROTEIN 32; TRIM32
603650	BBS5 GENE; BBS5
604896	MKKS GENE; MKKS
606151	BBS2 GENE; BBS2
607590	BBS7 GENE; BBS7
607968	PARATHYROID HORMONE-RESPONSIVE B1 GENE
608132	TETRATRICOPEPTIDE REPEAT DOMAIN 8; TTC8
608845	ADP-RIBOSYLATION FACTOR-LIKE 6; ARL6

Table C. Genomic Databases for Bardet-Biedl Syndrome

Gene Symbol	Locus Specific	Entrez Gene	HGMD
BBS1		582 (MIM No. 209901)	BBS1
BBS10			
TRIM32	TRIM32	22954 (MIM No. 602290)	TRIM32
BBS2		583 (MIM No. 606151)	BBS2
ARL6		84100 (MIM No. 608845)	ARL6
BBS4		585 (MIM No. 600374)	BBS4
BBS5		129880 (MIM No. 603650)	
MKKS		8195 (MIM No. 604896)	MKKS
BBS7		55212 (MIM No. 607590)	BBS7
TTC8		123016 (MIM No. 608132)	
B1		27241 (MIM No. 607968)	

For a description of the genomic databases listed, click here.

Molecular Genetic Pathogenesis

Defects in cilia or intraflagellar transport (IFT) have been associated with several human disorders including Bardet-Biedl syndrome, Kartagener syndrome, autosomal dominant polycystic kidney disease, and nephronophthisis.

Cilia protrude from almost all vertebrate cells and extend from basal bodies within the cell. Cilia are classified as primary cilia or motile cilia. Primary cilia have a 9+0 axonemal microtubule formation, are usually immotile, lack dynein arms, and are hypothesized to function as sensory organelles [Pazour & Witman 2003]. Motile cilia have a 9+2 axonemal microtubule formation and are usually involved in generating flow or movement. The assembly and maintenance of cilia depend on intraflagellar transport that moves particles from the basal body along the microtubular structure of the ciliary axoneme to the tip.

A significant leap in understanding the molecular pathogenesis of BBS emerged from the discovery of the *BBS8* gene, which led to the proposal of ciliary involvement in BBS [Ansley et al 2003]. Compelling evidence was subsequently provided from comparative genomic studies that identified all known *BBS* orthologues among genes present exclusively in ciliated organisms [Avidor-Reiss et al 2004, Li et al 2004]. All known *C.elegans bbs* orthologues are exclusively expressed in a subset of ciliated sensory neurons [Ansley et al 2003, Fan et al 2004, Li et al 2004], and *bbs-7* and *bbs-8* mutants have structural and functional ciliary defects [Blacque et al 2004]. Furthermore, several BBS proteins localize to the centrosome (the "microtubule organizing center" of the cell) and basal body (a product of the centrosome that is positioned at the base of the cilium and required for cilia formation) [Ansley et al 2003, Kim et al 2004, Li et al 2004, Kim et al 2005]. A study of the BBS4 protein suggested that it may act as an adaptor protein facilitating the microtubule-dependent intracellular transport within the cilium or in the cytosol [Kim et al 2004].

Studies of mouse knockouts of *Bbs1* [Kulaga et al 2004], *Bbs2* [Nishimura et al 2004], *Bbs4* [Kulaga et al 2004, Mykytyn et al 2004] and *Bbs6* [Fath et al 2005, Ross et al 2005] have provided further support for ciliary involvement in BBS. Mice display sperm flagellation defects, retinal degeneration likely secondary to defective IFT, as well as olfactory dysfunction presenting as partial or complete anosmia with diminution of the ciliated olfactory epithelium.

Humans with BBS were subsequently identified with partial or complete anosmia [Kulaga et al 2004, Iannaccone et al 2005]. All of the known BBS genes are down-regulated in the retina of *Bbs4*-null mice [Nishimura et al 2005].

A summary of the localization and putative role of the BBS proteins is illustrated in Figure 1. For a recent review of the current state of genetics of BBS, see Beales (2005).

BBS1

Normal allelic variants: *BBS1* is composed of 17 exons and encodes a 593-amino acid protein, with the ATG start codon lying within exon 1 [Mykytyn et al 2002, Beales et al 2003, Mykytyn et al 2003].

Pathologic allelic variants: A common p.M390R mutation within exon 12 of the *BBS1* gene was shown to be involved in 30% of individuals in a cohort of 129 probands with Bardet-Biedl syndrome [Mykytyn et al 2003]. In a further study of 259 individuals with Bardet-Biedl syndrome, a total of 74 p.M390R mutant alleles were identified, with M390R contributing to 18% of the cohort and involved in 79% of all families with *BBS1* mutations [Beales et al 2003]. In addition, frameshift and nonsense mutations have been identified within the *BBS1* coding sequence. See Table 3. (For more information, see Genomic Databases table above.)

Normal gene product: The sequence of the protein encoded by *BBS1* displays no significant homology to any other known proteins, with the exception of a region near the N terminal shared with BBS2 and BBS7 containing a predicted beta-propeller domain. In *C.elegans* it is expressed exclusively in ciliated cells and predominantly localizes to the transition zones (akin to basal bodies) as well as moving bidirectionally along the ciliary axoneme [Blacque et al 2004].

Abnormal gene product: *Bbs1*-null mice display olfactory deficiencies and defects in olfactory structure and function [Kulaga et al 2004].

BBS2

Normal allelic variants: The *BBS2* gene is composed of 17 exons and encodes a 721-amino acid protein; the start codon lies within exon 1 [Nishimura et al 2001] (See Table 4).

Pathologic allelic variants: A variety of nucleotide changes resulting in frameshift, nonsense, and missense mutations have been identified throughout the *BBS2* gene; there is no known mutation hot spot (See Table 5) [Nishimura et al 2001,Katsanis et al 2000,Katsanis et al 2001,Katsanis et al 2002]. (For more information, see Genomic Databases table above.)

Normal gene product: The sequence of the protein encoded by *BBS2* displays no significant homology to any other known proteins, with the exception of a region near the N terminal shared with BBS1 and BBS7 containing a predicted beta-propeller domain. In *C.elegans* it is expressed exclusively in ciliated cells and predominantly localizes to the transition zones (akin to basal bodies) as well as moving bidirectionally along the ciliary axoneme [Blacque et al 2004].

Abnormal gene product: *Bbs2*-null mice display obesity, retinal degeneration, renal cysts, male infertility, and olfactory deficiencies [Nishimura et al 2004].

ARL6/BBS3

Normal allelic variants: The *ARL6* gene is composed of nine exons and encodes a 186-amino acid protein; the start codon lies within exon 3 [Fan et al 2004, Chiang et al 2004].

Pathologic allelic variants: Mutations in *ARL6* account for only a small percentage of BBS (~0.4%). To date, only four homozygous missense mutations and one nonsense mutation have been identified within the coding sequence. (For more information, see Genomic Databases table above.)

Normal gene product: The *ARL6* gene encodes an ADP-ribosylation-like factor (ARL) protein that belongs to the Ras superfamily of small GTP-binding proteins essential for various membrane-associated intracellular trafficking events [Fan et al 2004, Chiang et al 2004]. The *C.elegans ARL6* orthologue is specifically expressed in ciliated cells and undergoes IFT within the ciliary axoneme [Fan et al 2004].

Abnormal gene product: Protein modeling suggests that the four missense mutations identified so far (p.G169A, p.T31M, p.L170W, and p.T31R) alter residues near to or within the GTP-binding site and are therefore likely to abrogate GTP binding [Fan et al 2004].

BBS4

Normal allelic variants: *BBS4* is composed of 16 exons and has an open reading frame of 519 codons with the start codon positioned within the first exon [Mykytyn et al 2001] (See Table 6).

Pathologic allelic variants: A variety of nucleotide changes resulting in frameshift, nonsense, and missense mutations have been identified throughout the *BBS4* gene, as well as one large intragenic deletion. There is no known mutation hot spot (See Table 7) [Katsanis et al 2001,Katsanis et al 2002,Mykytyn et al 2001,Nishimura et al 2005]. (For more information, see Genomic Databases table above.)

Normal gene product: The protein encoded by *BBS4* contains at least ten TPR domains, which are thought to be involved in protein-protein interactions. It localizes to the basal body and centrosome in cultured cells and may function as an adaptor protein facilitating the loading of cargo onto the dynein-dynactin molecular motor in preparation for microtubule-dependent intracellular transport within the cilium or in the cytosol [Kim et al 2004].

Abnormal gene product: Mice null for *Bbs4* are obese and have retinal degeneration, sperm flagellation defects, olfactory deficiencies, and defects in olfactory structure and function [Kulaga et al 2004, Mykytyn & Sheffield 2004]. Silencing of *BBS4* in cultured cells leads to de-anchoring of microtubules, arrest of cell division, and apoptopic cell death [Kim et al 2004].

BBS5

Normal allelic variants: *BBS5* is composed of 12 exons and has an open reading frame of 342 codons [Li et al 2004].

Pathologic allelic variants: Mutations in *BBS5* account for only a small percentage of BBS (~0.4%). To date, one splice donor mutation that leads to a frameshift and a premature termination codon in exon 7, two nonsense mutations [Li et al 2004], and one large intragenic deletion [Nishimura et al 2005] have been identified. (For more information, see Genomic Databases table above.)

Normal gene product: The protein encoded by *BBS5* localizes to the basal bodies and faintly within the ciliary axomene in the ependymal cells lining the ventricles of the brain in mouse [Li et al 2004]. In *C.elegans bbs-5* is expressed exclusively in ciliated cells and predominantly localizes to the base of the cilia in ciliated head and tail neurons [Li et al 2004].

Abnormal gene product: Silencing of *BBS5* in *Chlamydomonas* results in an aflagellated phenotype [Li et al 2004].

MKKS

Normal allelic variants: The *MKKS* gene is composed of six exons and encodes a 570-amino acid protein [Stone et al 2000]. The start codon lies within exon 3 and two alternatively spliced 5' exons are not translated (See Table 8) [Stone et al 2000, Slavotinek et al 2002].

Pathologic allelic variants: Nucleotide changes have been identified in all of the coding exons of the *MKKS* gene that result in frameshift, nonsense, and missense mutations; there is no known mutation hot spot. For a number of individuals, only one heterozygous mutation has been identified; one possible explanation includes triallelic inheritance, as these individuals may harbor mutations at one of the other BBS loci [Katsanis et al 2001]. See Table 9. (For more information, see Genomic Databases table above.)

Normal gene product: The 570-amino acid protein encoded by *MKKS* [Stone et al 2000], shows strong homology to archeobacterial chaperonins and the eukaryotic T-complex-related-proteins (TCPs), which belong to the type II class of chaperonins [Kim et al 2005]. These proteins are implicated in facilitation of nascent protein folding in an ATP-dependent manner [reviewed by Wickner et al 1999]. MKKS localizes to the pericentriolar material (PCM), a proteinaceous tube surrounding centrioles but during mitosis it is also found at intracellular bridges [Kim et al 2005].

Abnormal gene product: The predicted substrate binding apical domain of the protein encoded by *MKKS* is sufficient for centrosomal localization, but several patient-derived missense mutations in this domain (p.G52D, p.D285A, p.T325P, and p.G345E) result in the protein mislocalization in cells [Kim et al 2005]. Silencing of MKKS in cultured cells leads to multinucleate and multicentrosomal cells with cytokinesis defects [Kim et al 2005]. Mice null for *Mkks/Bbs6* are obese and have retinal degeneration, sperm flagellation defects, olfactory deficiencies, and defects in olfactory structure and function [Fath et al 2005, Ross et al 2005].

BBS7

Normal allelic variants: The *BBS7* gene is composed of 19 exons and encodes a 672-amino acid protein [Badano et al 2003]. An alternative isoform results from differential splicing of an alternative exon 18 resulting in an additional 44 residues and a discrete 3' UTR [Badano et al 2003].

Pathologic allelic variants: Only four different pathogenic mutations have been identified in the *BBS7* gene thus far: one that results in a frameshift and the introduction of a premature termination codon, two missense mutations, and one large intragenic deletion [Badano et al 2003, Nishimura et al 2005]. See Table 10. (For more information, see Genomic Databases table above.)

Normal gene product: The sequence of the protein encoded by *BBS7* displays no significant homology to any other known proteins, with the exception of a region near the N terminal shared with BBS1 and BBS2 containing a predicted beta-propeller domain. In *C.elegans*, it is expressed exclusively in ciliated cells and predominantly localizes to the transition zones (akin to basal bodies) as well as moving bidirectionally along the ciliary axoneme [Blacque et al 2004].

Abnormal gene product: *C.elegans* with mutations with the *bbs-7* orthologue have structural and functional ciliary defects and compromised intraflagellar transport [Blacque et al 2004].

TTC8/BBS8

Normal allelic variants: The *TTC8* gene is composed of 16 exons and encodes a 531-amino acid protein.

Pathologic allelic variants: Mutations in *TTC8* account for only a small percentage of BBS. Two families with identical six base-pair deletions resulting in the deletion of two amino acids and another with a three base-pair deletion abolishing the splice donor site of exon 10 have been identified [Ansley et al 2003]. (For more information, see Genomic Databases table above.)

Normal gene product: BBS8 was identified because of its similarity to the BBS4 protein, containing eight TPR domains possibly involved in protein-protein interactions [Ansley et al 2003]. It also exhibits similarity to a prokaryotic domain *pilF* involved in twitching mobility and type-IV pilus assembly. The BBS8 protein localizes to the centrosome and basal body of cultured ciliated cells [Ansley et al 2003]. In *C.elegans* it is expressed exclusively in ciliated cells and predominantly localizes to the transition zones (akin to basal bodies) as well as moving bidirectionally along the ciliary axoneme [Ansley et al 2003, Blacque et al 2004].

Abnormal gene product: *C.elegans* with mutations with the *bbs-8* orthologue have structural and functional ciliary defects and compromised intraflagellar transport [Blacque et al 2004].

B1/BBS9

Normal allelic variants: The parathyroid hormone-responsive gene B1 *(B1)* was recently identified as *BBS9* [Nishimura et al 2005]. It is composed of 25 exons, with all except the first contributing to its various protein isoforms that range between 879-916 amino acids in length.

Pathologic allelic variants: A total of seven *B1* mutations, including nonsense, splice site, missense, and frameshift, have been identified [Nishimura et al 2005] (For more information, see Genomic Databases table above.)

Normal gene product: The *B1* gene is widely expressed. It has no similarity to other BBS proteins and its specific function is unknown.

Abnormal gene product: The *B1* gene is down-regulated in the retina of BBS4-null mice [Nishimura et al 2005].

BBS10

Normal allelic variants: A vertebrate-specific chaperonin-like gene was recently identified as *BBS10* [Stoetzel et al 2006]. It is composed of two exons encoding a 723-amino acid protein, with the start codon contained within exon 1.

Pathologic allelic variants: *BBS10* is a major locus for BBS, contributing mutant alleles in ~20% of all individuals with BBS. There are numerous missense, frameshifting, and nonsense mutations spread throughout the coding region, with no mutational hot spot [Stoetzel et al 2006].

Normal gene product: BBS10 has a chaperonin domain organization conserved with all three major functional domains — equatorial, intermediate, and apical — and the flexible protrusion region specific to group II chaperonins. The ATP hydrolytic domain is conserved in BBS10, suggesting that it may be an active enzyme, in contrast to BBS6, where this catalytic site is absent.

Abnormal gene product: Suppression of bbs10 expression in zebrafish embryos causes shortening of the body axis and dorsal thinning, broadening and kinking of the notochord, and elongation of the somites [Stoetzel et al 2006].

TRIM32

Normal allelic variants: TRIM32 (BBS11), a ubiquitin ligase, was recently identified [Chiang et al 2006]. It is composed of two exons encoding a 652-amino acid protein, with the ATG start codon in exon 2.

Pathologic allelic variants: The only mutation identified to date in *BBS11* associated with BBS is a homozygous missense mutation p.P130S, which lies in the N-terminal B-box domain, in affected individuals in an inbred Bedouin Arab family [Chiang et al 2006]. However, a missense variant, p.D487N in the C-terminal NHL domain of TRIM32, was previously associated with autosomal recessive limb-girdle muscular dystrophy (LGMD) [Frosk et al 2002].

Normal gene product: TRIM32 is a member of the TRIM family that is characterized by a common domain structure composed of a RING finger, B-box, and a coiled-coiled motif. It also contains five C-terminal NHL repeats. TRIM32 is thought to have E3 ubiquitin ligase activity, binds to myosin, and ubiquitinates actin, implicating TRIM32 in regulating components of the cytoskeleton.

Abnormal gene product: Zebrafish embryos with knockdown of *BBS11* expression display an abnormal Kuppfer's vesicle, a transient ciliated organ involved in left-right patterning and a delay in melanosome transport. The p.P130S mutant allele associated with BBS fails to rescue these abnormal phenotypes, in contrast to the p.D487N allele associated with LGMD, suggesting that each mutation disrupts different functions of TRIM32/BBS11 [Chiang et al 2006].

BBS12

Normal allelic variants: *BBS12* is a vertebrate-specific predicted chaperonin-like protein [Stoetzel et al 2007]. It is composed of two exons, of which only the second is coding, for a predicted protein of 710 amino acids.

Pathologic allelic variants: *BBS12* is mutated in approximately 5% of families affected with [Stoetzel et al 2007]. Mutations identified include frameshifts [one of which, F372X (also known as F372fsX373), is recurrent and present in several families], nonsense, small in-frame deletions, a mutation that is predicted to extend the C-terminus of the protein, and missense alleles.

Normal gene product: BBS12 is related to the group II chaperonins and to a family of vertebrate-specific chaperonin-like sequences encompassing BBS10 and BBS6 [Stoetzel et al 2007]. The classical chaperonin domain architecture (equatorial, intermediate and apical domains) is conserved, but BBS12 has an additional five specific inserted sequences within the intermediate and equatorial domains. However, the functional ATP hydrolysis motif is not conserved in BBS12, as is the case for BBS6.

Abnormal gene product: Injection of bbs12-specific morpholino into zebrafish embryos results in phenotypes consistent with convergence and extension (CE) defects, including shortened body axis, broadened somites, kinked notochord and dorsal thinning [Stoetzel et al 2007]. Simultaneous suppression of *bbs12*, *bbs10*, and *bbs6* gene expression yielded similar

but more severe phenotypes, suggesting a possible partial functional redundancy within this protein family.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

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References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Alton DJ, McDonald P. Urographic findings in the Bardet-Biedl syndrome, formerly the Laurence-Moon-Biedl syndrome. Radiology. 1973;109:659–63. [PubMed: 4772182]

Ammann F. Investigations clinique et genetique sur le syndrome de Bardet-Biedl en Suisse. J Genet Hum. 1970;118:1–310.

Ansley SJ, Badano JL, Blacque OE, Hill J, Hoskins BE, Leitch CC, Kim JC, Ross AJ, Eichers ER, Teslovich TM, Mah AK, Johnsen RC, Cavender JC, Lewis RA, Leroux MR, Beales PL, Katsanis N. Basal body dysfunction is a likely cause of pleiotropic Bardet-Biedl syndrome. Nature. 2003;425:628–33. [PubMed: 14520415]

Avidor-Reiss T, Maer AM, Koundakjian E, Polyanovsky A, Keil T, Subramaniam S, Zuker CS. Decoding cilia function: defining specialized genes required for compartmentalized cilia biogenesis. Cell. 2004;117:527–39. [PubMed: 15137945]

Badano JL, Ansley SJ, Leitch CC, Lewis RA, Lupski JR, Katsanis N. Identification of a novel Bardet-Biedl syndrome protein, BBS7, that shares structural features with BBS1 and BBS2. Am J Hum Genet. 2003;72:650–8. [PubMed: 12567324]

Badano JL, Kim JC, Hoskins BE, Lewis RA, Ansley SJ, Cutler DJ, Castellan C, Beales PL, Leroux MR, Katsanis N. Heterozygous mutations in BBS1, BBS2 and BBS6 have a potential epistatic effect on Bardet-Biedl patients with two mutations at a second BBS locus. Hum Mol Genet. 2003;12:1651–9. [PubMed: 12837689]

Barnett S, Reilly S, Carr L, Ojo I, Beales PL, Charman T. Behavioural phenotype of Bardet-Biedl syndrome. J Med Genet. 2002;39:e76. [PubMed: 12471214]

Beales PL, Badano JL, Ross AJ, Ansley SJ, Hoskins BE, Kirsten B, Mein CA, Froguel P, Scambler PJ, Lewis RA, Lupski JR, Katsanis N. Genetic interaction of BBS1 mutations with alleles at other BBS loci can result in non-Mendelian Bardet-Biedl syndrome. Am J Hum Genet. 2003;72:1187–99. [PubMed: 12677556]

Beales PL. Lifting the lid on Pandora's box: the Bardet-Biedl syndrome. Curr Opin Genet Dev. 2005;15:315–23. [PubMed: 15917208]

Beales PL, Elcioglu N, Woolf AS, Parker D, Flinter FA. New criteria for improved diagnosis of Bardet-Biedl syndrome: results of a population survey. J Med Genet. 1999;36:437–46. [PubMed: 10874630]

Beales PL, Katsanis N, Lewis RA, Ansley SJ, Elcioglu N, Raza J, Woods MO, Green JS, Parfrey PS, Davidson WS, Lupski JR. Genetic and mutational analyses of a large multiethnic Bardet-Biedl cohort reveal a minor involvement of BBS6 and delineate the critical intervals of other loci. Am J Hum Genet. 2001;68:606–16. [PubMed: 11179009]

Bell J. The Laurence-Moon syndrome. In: Penrose LS (ed) The Treasury of Human Inheritance. Cambridge University Press, UK, pp 51-96. 1958

Bergsma DR, Brown KS. Assessment of ophthalmologic, endocrinologic and genetic findings in the Bardet-Biedl syndrome. Birth Defects Orig Artic Ser. 1975;11:132–6. [PubMed: 776244]

Blacque OE, Reardon MJ, Li C, McCarthy J, Mahjoub MR, Ansley SJ, Badano JL, Mah AK, Beales PL, Davidson WS, Johnsen RC, Audeh M, Plasterk RH, Baillie DL, Katsanis N, Quarmby LM, Wicks SR, Leroux MR. Loss of C. elegans BBS-7 and BBS-8 protein function results in cilia defects and compromised intraflagellar transport. Genes Dev. 2004;18:1630–42. [PubMed: 15231740]

BLUMEL J, KNIKER WT. Laurence-Moon-Bardet-Biedl syndrome: review of the literature and a report of five cases including a family group with three affected males. Tex Rep Biol Med. 1959;17:391–410. [PubMed: 13801723]

Borgstrom MK, Riise R, Tornqvist K, Granath L. Anomalies in the permanent dentition and other oral findings in 29 individuals with Laurence-Moon-Bardet-Biedl syndrome. J Oral Pathol Med. 1996;25:86–9. [PubMed: 8667262]

BURN RA. Deafness and the Laurence-Moon-Biedl syndrome. Br J Ophthalmol. 1950;34:65–88. [PubMed: 15405352]

Campo RV, Aaberg TM. Ocular and systemic manifestations of the Bardet-Biedl syndrome. Am J Ophthalmol. 1982;94:750–6. [PubMed: 7180914]

Carmi R, Rokhlina T, Kwitek-Black AE, Elbedour K, Nishimura D, Stone EM, Sheffield VC. Use of a DNA pooling strategy to identify a human obesity syndrome locus on chromosome 15. Hum Mol Genet. 1995;4:9–13. [PubMed: 7711739]

Cassart M, Eurin D, Didier F, Guibaud L, Avni EF. Antenatal renal sonographic anomalies and postnatal follow-up of renal involvement in Bardet-Biedl syndrome. Ultrasound Obstet Gynecol. 2004;24:51–4. [PubMed: 15229916]

Chiang AP, Beck JS, Yen HJ, Tayeh MK, Scheetz TE, Swiderski RE, Nishimura DY, Braun TA, Kim KY, 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: 16606853]

Chiang AP, Nishimura D, Searby C, Elbedour K, Carmi R, Ferguson AL, Secrist J, Braun T, Casavant T, Stone EM, Sheffield VC. Comparative genomic analysis identifies an ADP-ribosylation factor-like gene as the cause of Bardet-Biedl syndrome (BBS3). Am J Hum Genet. 2004;75:475–84. [PubMed: 15258860]

Cramer B, Green J, Harnett J, Johnson GJ, McManamon P, Farid N, Pryse-Phillips W, Parfrey PS. Sonographic and urographic correlation in Bardet-Biedl syndrome (formerly Laurence-Moon-Biedl syndrome). Urol Radiol. 1988;10:176–80. [PubMed: 3072750]

Croft JB, Swift M. Obesity, hypertension, and renal disease in relatives of Bardet-Biedl syndrome sibs. Am J Med Genet. 1990;36:37–42. [PubMed: 2333905]

Dar P, Sachs GS, Carter SM, Ferreira JC, Nitowsky HM, Gross SJ. Prenatal diagnosis of Bardet-Biedl syndrome by targeted second-trimester sonography. Ultrasound Obstet Gynecol. 2001;17:354–6. [PubMed: 11339197]

David A, Bitoun P, Lacombe D, Lambert JC, Nivelon A, Vigneron J, Verloes A. Hydrometrocolpos and polydactyly: a common neonatal presentation of Bardet-Biedl and McKusick-Kaufman syndromes. J Med Genet. 1999;36:599–603. [PubMed: 10465109]

Elbedour K, Zucker N, Zalzstein E, Barki Y, Carmi R. Cardiac abnormalities in the Bardet-Biedl syndrome: echocardiographic studies of 22 patients. Am J Med Genet. 1994;52:164–9. [PubMed: 7802002]

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: 15314642]

Farag TI, Teebi AS. Bardet-Biedl and Laurence-Moon syndromes in a mixed Arab population. Clin Genet. 1988;33:78–82. [PubMed: 3359670]

Fath MA, Mullins RF, Searby C, Nishimura DY, Wei J, Rahmouni K, Davis RE, Tayeh MK, Andrews M, Yang B, Sigmund CD, Stone EM, Sheffield VC. Mkks-null mice have a phenotype resembling Bardet-Biedl syndrome. Hum Mol Genet. 2005;14:1109–18. [PubMed: 15772095]

Fauser S, Munz M, Besch D. Further support for digenic inheritance in Bardet-Biedl syndrome. J Med Genet. 2003;40:104. [PubMed: 12920096]

Fralick RA, Leichter HE, Sheth KJ. Early diagnosis of Bardet-Biedl syndrome. Pediatr Nephrol. 1990;4:264–5. [PubMed: 2400655]

Frosk P, Weiler T, Nylen E, Sudha T, Greenberg CR, Morgan K, Fujiwara TM, Wrogemann K. Limb-girdle muscular dystrophy type 2H associated with mutation in TRIM32, a putative E3-ubiquitin-ligase gene. Am J Hum Genet. 2002;70:663–72. [PubMed: 11822024]

Fulton AB, Hansen RM, Glynn RJ. Natural course of visual functions in the Bardet-Biedl syndrome. Arch Ophthalmol. 1993;111:1500–6. [PubMed: 8240105]

Garber SJ, de Bruyn R. Laurence-Moon-Biedl syndrome: renal ultrasound appearances in the neonate. Br J Radiol. 1991;64:631–3. [PubMed: 1873665]

Garstecki DC, Borton TE, Stark EW, Kennedy BT. Speech, language, and hearing problems in the Laurence-Moon-Biedl syndrome. J Speech Hear Disord. 1972;37:407–13. [PubMed: 5057257]

Grace C, Beales P, Summerbell C, Jebb SA, Wright A, Parker D, Kopelman P. Energy metabolism in Bardet-Biedl syndrome. Int J Obes Relat Metab Disord. 2003;27:1319–24. [PubMed: 14574341]

Green JS, Parfrey PS, Harnett JD, Farid NR, Cramer BC, Johnson G, Heath O, McManamon PJ, O'Leary E, Pryse-Phillips W. The cardinal manifestations of Bardet-Biedl syndrome, a form of Laurence-Moon-Biedl syndrome. N Engl J Med. 1989;321:1002–9. [PubMed: 2779627]

Harnett JD, Green JS, Cramer BC, Johnson G, Chafe L, McManamon P, Farid NR, Pryse-Phillips W, Parfrey PS. The spectrum of renal disease in Laurence-Moon-Biedl syndrome. N Engl J Med. 1988;319:615–8. [PubMed: 3412378]

Heon E, Westall C, Carmi R, Elbedour K, Panton C, Mackeen L, Stone EM, Sheffield VC. Ocular phenotypes of three genetic variants of Bardet-Biedl syndrome. Am J Med Genet A. 2005;132:283–7. [PubMed: 15690372]

Hichri H, Stoetzel C, Laurier V, Caron S, Sigaudy S, Sarda P, Hamel C, Martin-Coignard D, Gilles M, Leheup B, Holder M, Kaplan J, Bitoun P, Lacombe D, Verloes A, Bonneau D, Perrin-Schmitt F, Brandt C, Besancon AF, Mandel JL, Cossee M, Dollfus H. Testing for triallelism: analysis of six BBS genes in a Bardet-Biedl syndrome family cohort. Eur J Hum Genet. 2005;13:607–16. [PubMed: 15770229]

Hurley RM, Dery P, Norady MB, Drummond KN. The renal lesion of the Laurence-Moon-Biedl syndrome. J Pediatr. 1975;87:206–9. [PubMed: 1151560]

Iannaccone A, Mykytyn K, Persico AM, Searby CC, Baldi A, Jablonski MM, Sheffield VC. Clinical evidence of decreased olfaction in Bardet-Biedl syndrome caused by a deletion in the BBS4 gene. Am J Med Genet A. 2005;132:343–6. [PubMed: 15654695]

Jacobson SG, Borruat FX, Apathy PP. Patterns of rod and cone dysfunction in Bardet-Biedl syndrome. Am J Ophthalmol. 1990;109:676–88. [PubMed: 2346197]

Karmous-Benailly H, Martinovic J, Gubler MC, Sirot Y, Clech L, Ozilou C, Auge J, Brahimi N, Etchevers H, Detrait E, Esculpavit C, Audollent S, Goudefroye G, Gonzales M, Tantau J, Loget P, Joubert M, Gaillard D, Jeanne-Pasquier C, Delezoide AL, Peter MO, Plessis G, Simon-Bouy B, Dollfus H, Le Merrer M, Munnich A, Encha-Razavi F, Vekemans M, Attie-Bitach T. Antenatal presentation of Bardet-Biedl syndrome may mimic Meckel syndrome. Am J Hum Genet. 2005;76:493–504. [PubMed: 15666242]

Katsanis N. The oligogenic properties of Bardet-Biedl syndrome. Hum Mol Genet 13 Spec No. 2004;1:R65–71. [PubMed: 14976158]

Katsanis N, Ansley SJ, Badano JL, Eichers ER, Lewis RA, Hoskins BE, Scambler PJ, Davidson WS, Beales PL, Lupski JR. Triallelic inheritance in Bardet-Biedl syndrome, a Mendelian recessive disorder. Science. 2001;293:2256–9. [PubMed: 11567139]

Katsanis N, Beales PL, Woods MO, Lewis RA, Green JS, Parfrey PS, Ansley SJ, Davidson WS, Lupski JR. Mutations in MKKS cause obesity, retinal dystrophy and renal malformations associated with Bardet-Biedl syndrome. Nat Genet. 2000;26:67–70. [PubMed: 10973251]

Katsanis N, Eichers ER, Ansley SJ, Lewis RA, Kayserili H, Hoskins BE, Scambler PJ, Beales PL, Lupski JR. BBS4 is a minor contributor to Bardet-Biedl syndrome and may also participate in triallelic inheritance. Am J Hum Genet. 2002;71:22–9. [PubMed: 12016587]

Kim JC, Badano JL, Sibold S, Esmail MA, Hill J, Hoskins BE, Leitch CC, Venner K, Ansley SJ, Ross AJ, Leroux MR, Katsanis N, Beales PL. The Bardet-Biedl protein BBS4 targets cargo to the pericentriolar region and is required for microtubule anchoring and cell cycle progression. Nat Genet. 2004;36:462–70. [PubMed: 15107855]

Kim JC, Ou YY, Badano JL, Esmail MA, Leitch CC, Fiedrich E, Beales PL, Archibald JM, Katsanis N, Rattner JB, Leroux MR. MKKS/BBS6, a divergent chaperonin-like protein linked to the obesity disorder Bardet-Biedl syndrome, is a novel centrosomal component required for cytokinesis. J Cell Sci. 2005;118:1007–20. [PubMed: 15731008]

Klein D. Diverse clinical and genetic varieties of the Bardet-Biedl syndrome. Rev Otoneuroophtalmol. 1968;40:125–44. [PubMed: 5743337]

Klein D, Ammann F. The syndrome of Laurence-Moon-Bardet-Biedl and allied diseases in Switzerland. Clinical, genetic and epidemiological studies. J Neurol Sci. 1969;9:479–513. [PubMed: 5367041]

Kulaga HM, Leitch CC, Eichers ER, Badano JL, Lesemann A, Hoskins BE, Lupski JR, Beales PL, Reed RR, Katsanis N. Loss of BBS proteins causes anosmia in humans and defects in olfactory cilia structure and function in the mouse. Nat Genet. 2004;36:994–8. [PubMed: 15322545]

Li JB, Gerdes JM, Haycraft CJ, Fan Y, Teslovich TM, May-Simera H, Li H, Blacque OE, Li L, Leitch CC, Lewis RA, Green JS, Parfrey PS, Leroux MR, Davidson WS, Beales PL, Guay-Woodford LM, Yoder BK, Stormo GD, Katsanis N, Dutcher SK. Comparative genomics identifies a flagellar and basal body proteome that includes the BBS5 human disease gene. Cell. 2004;117:541–52. [PubMed: 15137946]

Linne T, Wikstad I, Zetterstrom R. Renal involvement in the Laurence-Moon-Biedl syndrome. Functional and radiological studies. Acta Paediatr Scand. 1986;75:240–4. [PubMed: 3962657]

Lorda-Sanchez I, Ayuso C, Sanz R, Ibanez A. Does Bardet-Biedl syndrome have a characteristic face? J Med Genet. 2001;38:E14. [PubMed: 11333870]

McLoughlin TG, Shanklin DR. Pathology of Laurence-Moon-Bardet-Biedl syndrome. J Pathol Bacteriol. 1967;93:65–79. [PubMed: 4382110]

Meeker WR Jr, Nighbert EJ. Association of cystic dilatation of intrahepatic and common bile ducts with Laurence-Moon-Biedl-Bardet syndrome. Am J Surg. 1971;122:822–4. [PubMed: 5127736]

Mehrotra N, Taub S, Covert RF. Hydrometrocolpos as a neonatal manifestation of the Bardet-Biedl syndrome [letter; comment]. Am J Med Genet. 1997;69:220. [PubMed: 9056566]

Moore SJ, Green JS, Fan Y, Bhogal AK, Dicks E, Fernandez BA, Stefanelli M, Murphy C, Cramer BC, Dean JC, Beales PL, Katsanis N, Bassett AS, Davidson WS, Parfrey PS. Clinical and genetic epidemiology of Bardet-Biedl syndrome in Newfoundland: a 22-year prospective, population-based, cohort study. Am J Med Genet A. 2005;132:352–60. [PubMed: 15637713]

Mykytyn K, Braun T, Carmi R, Haider NB, Searby CC, Shastri M, Beck G, Wright AF, Iannaccone A, Elbedour K, Riise R, Baldi A, Raas-Rothschild A, Gorman SW, Duhl DM, Jacobson SG, Casavant T, Stone EM, Sheffield VC. Identification of the gene that, when mutated, causes the human obesity syndrome BBS4. Nat Genet. 2001;28:188–91. [PubMed: 11381270]

Mykytyn K, Mullins RF, Andrews M, Chiang AP, Swiderski RE, Yang B, Braun T, Casavant T, Stone EM, Sheffield VC. Bardet-Biedl syndrome type 4 (BBS4)-null mice implicate Bbs4 in flagella formation but not global cilia assembly. Proc Natl Acad Sci U S A. 2004;101:8664–9. [PubMed: 15173597]

Mykytyn K, Nishimura DY, Searby CC, Beck G, Bugge K, Haines HL, Cornier AS, Cox GF, Fulton AB, Carmi R, Iannaccone A, Jacobson SG, Weleber RG, Wright AF, Riise R, Hennekam RC, Luleci G, Berker-Karauzum S, Biesecker LG, Stone EM, Sheffield VC. Evaluation of complex inheritance involving the most common Bardet-Biedl syndrome locus (BBS1). Am J Hum Genet. 2003;72:429–37. [PubMed: 12524598]

Mykytyn K, Nishimura DY, Searby CC, Shastri M, Yen HJ, Beck JS, Braun T, Streb LM, Cornier AS, Cox GF, Fulton AB, Carmi R, Luleci G, Chandrasekharappa SC, Collins FS, Jacobson SG, Heckenlively JR, Weleber RG, Stone EM, Sheffield VC. Identification of the gene (BBS1) most commonly involved in Bardet-Biedl syndrome, a complex human obesity syndrome. Nat Genet. 2002;31:435–8. [PubMed: 12118255]

Mykytyn K, Sheffield VC. Establishing a connection between cilia and Bardet-Biedl Syndrome. Trends Mol Med. 2004;10:106–9. [PubMed: 15106604]

Nadjmi B, Flanagan MJ, Christian JR. Laurence-Moon-Biedl syndrome, associated with multiple genitourinary tract anomalies. Am J Dis Child. 1969;117:352–6. [PubMed: 5765158]

Nakamura F, Sasaki H, Kajihara H, Yamanoue M. Laurence-Moon-Biedl syndrome accompanied by congenital hepatic fibrosis. J Gastroenterol Hepatol. 1990;5:206–10. [PubMed: 2103400]

Nishimura DY, Fath M, Mullins RF, Searby C, Andrews M, Davis R, Andorf JL, Mykytyn K, Swiderski RE, Yang B, Carmi R, Stone EM, Sheffield VC. Bbs2-null mice have neurosensory deficits, a defect in social dominance, and retinopathy associated with mislocalization of rhodopsin. Proc Natl Acad Sci U S A. 2004;101:16588–93. [PubMed: 15539463]

Nishimura DY, Searby CC, Carmi R, Elbedour K, Van Maldergem L, Fulton AB, Lam BL, Powell BR, Swiderski RE, Bugge KE, Haider NB, Kwitek-Black AE, Ying L, Duhl DM, Gorman SW, Heon E, Iannaccone A, Bonneau D, Biesecker LG, Jacobson SG, Stone EM, Sheffield VC. Positional cloning of a novel gene on chromosome 16q causing Bardet-Biedl syndrome (BBS2). Hum Mol Genet. 2001;10:865–74. [PubMed: 11285252]

Nishimura DY, Swiderski RE, Searby CC, Berg EM, Ferguson AL, Hennekam R, Merin S, Weleber RG, Biesecker LG, Stone EM, Sheffield VC. Comparative genomics and gene expression analysis

identifies BBS9, a new Bardet-Biedl syndrome gene. Am J Hum Genet. 2005;77:1021–33. [PubMed: 16380913]

O'Dea D, Parfrey PS, Harnett JD, Hefferton D, Cramer BC, Green J. The importance of renal impairment in the natural history of Bardet- Biedl syndrome. Am J Kidney Dis. 1996;27:776–83. [PubMed: 8651240]

Pagon RA, Haas JE, Bunt AH, Rodaway KA. Hepatic involvement in the Bardet-Biedl syndrome. Am J Med Genet. 1982;13:373–81. [PubMed: 7158637]

Pazour GJ, Witman GB. The vertebrate primary cilium is a sensory organelle. Curr Opin Cell Biol. 2003;15:105–10. [PubMed: 12517711]

Price D, Gartner JG, Kaplan BS. Ultrastructural changes in the glomerular basement membrane of patients with Laurence-Moon-Biedl-Bardet syndrome. Clin Nephrol. 1981;16:283–8. [PubMed: 7318262]

Ramirez N, Marrero L, Carlo S, Cornier AS. Orthopaedic manifestations of Bardet-Biedl syndrome. J Pediatr Orthop. 2004;24:92–6. [PubMed: 14676542]

Riise R. The cause of death in Laurence-Moon-Bardet-Biedl syndrome. Acta Ophthalmol Scand Suppl. 1996;219:45–7. [PubMed: 8741118]

Riise R, Andreasson S, Borgastrom MK, Wright AF, Tommerup N, Rosenberg T, Tornqvist K. Intrafamilial variation of the phenotype in Bardet-Biedl syndrome. Br J Ophthalmol. 1997;81:378–85. [PubMed: 9227203]

Riise R, Andreasson S, Wright AF, Tornqvist K. Ocular findings in the Laurence-Moon-Bardet-Biedl syndrome. Acta Ophthalmol Scand. 1996;74:612–7. [PubMed: 9017053]

Riise R, Tornqvist K, Wright AF, Mykytyn K, Sheffield VC. The phenotype in Norwegian patients with Bardet-Biedl syndrome with mutations in the BBS4 gene. Arch Ophthalmol. 2002;120:1364–7. [PubMed: 12365916]

Ross AJ, May-Simera H, Eichers ER, Kai M, Hill J, Jagger DJ, Leitch CC, Chapple JP, Munro PM, Fisher S, Tan PL, Phillips HM, Leroux MR, Henderson DJ, Murdoch JN, Copp AJ, Eliot MM, Lupski JR, Kemp DT, Dollfus H, Tada M, Katsanis N, Forge A, Beales PL. Disruption of Bardet-Biedl syndrome ciliary proteins perturbs planar cell polarity in vertebrates. Nat Genet. 2005;37:1135–40. [PubMed: 16170314]

Roussel B, Leroux B, Gaillard D, Fandre M. Laurence-Moon-Bardet-Biedl syndrome, chronic diffuse tubulo-interstitial nephritis and liver involvement. Helv Paediatr Acta. 1985;40:405–13. [PubMed: 4086314]

Rudling O, Riise R, Tornqvist K, Jonsson K. Skeletal abnormalities of hands and feet in Laurence-Moon-Bardet-Biedl (LMBB) syndrome: a radiographic study. Skeletal Radiol. 1996;25:655–60. [PubMed: 8915050]

Runge P, Calver D, Marshall J, Taylor D. Histopathology of mitochondrial cytopathy and the Laurence-Moon-Biedl syndrome. Br J Ophthalmol. 1986;70:782–96. [PubMed: 3778863]

Schachat AP, Maumenee IH. Bardet-Biedl syndrome and related disorders. Arch Ophthalmol. 1982;100:285–8. [PubMed: 7065946]

Slavotinek AM, Biesecker LG. Phenotypic overlap of McKusick-Kaufman syndrome with Bardet-Biedl syndrome: a literature review. Am J Med Genet. 2000;95:208–15. [PubMed: 11102925]

Slavotinek AM, Stone EM, Mykytyn K, Heckenlively JR, Green JS, Heon E, Musarella MA, Parfrey PS, Sheffield VC, Biesecker LG. Mutations in MKKS cause Bardet-Biedl syndrome. Nat Genet. 2000;26:15–6. [PubMed: 10973238]

Slavotinek AM, Searby C, Al-Gazali L, Hennekam RC, Schrander-Stumpel C, Orcana-Losa M, Pardo-Reoyo S, Cantani A, Kumar D, Capellini Q, Neri G, Zackai E, Biesecker LG. Mutation analysis of the MKKS gene in McKusick-Kaufman syndrome and selected Bardet-Biedl syndrome patients. Hum Genet. 2002;110:561–7. [PubMed: 12107442]

Srinivas V, Winsor GM, Dow D. Urologic manifestations of Laurence-Moon-Biedl syndrome. Urology. 1983;21:581–3. [PubMed: 6868229]

Stoetzel C, Laurier V, Davis EE, Muller J, Rix S, Badano JL, Leitch CC, Salem N, Chouery E, Corbani S, Jalk N, Vicaire S, Sarda P, Hamel C, Lacombe D, Holder M, Odent S, Holder S, Brooks AS, Elcioglu NH, Da Silva E, Rossillion B, Sigaudy S, de Ravel TJ, Lewis RA, Leheup B, Verloes A, Amati-Bonneau P, Megarbane A, Poch O, Bonneau D, Beales PL, Mandel JL, Katsanis N, Dollfus

H. BBS10 encodes a vertebrate-specific chaperonin-like protein and is a major BBS locus. Nat Genet. 2006;38:521–4. [PubMed: 16582908]

Stoetzel C, Muller J, Laurier V, Davis EE, Zaghloul NA, Vicaire S, Jacquelin C, Plewniak F, Leitch CC, Sarda P, Hamel C, de Ravel TJ, Lewis RA, Friederich E, Thibault C, Danse JM, Verloes A, Bonneau D, Katsanis N, Poch O, Mandel JL, Dollfus H. 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;80:1–11. [PubMed: 17160889]

Stoler JM, Herrin JT, Holmes LB. Genital abnormalities in females with Bardet-Biedl syndrome. Am J Med Genet. 1995;55:276–8. [PubMed: 7726222]

Stone DL, Slavotinek A, Bouffard GG, Banerjee-Basu S, Baxevanis AD, Barr M, Biesecker LG. Mutation of a gene encoding a putative chaperonin causes McKusick-Kaufman syndrome. Nat Genet. 2000;25:79–82. [PubMed: 10802661]

Tieder M, Levy M, Gubler MC, Gagnadoux MF, Broyer M. Renal abnormalities in the Bardet-Biedl syndrome. Int J Pediatr Nephrol. 1982;3:199–203. [PubMed: 7141791]

Tsuchiya R, Nishimura R, Ito T. Congenital cystic dilation of the bile duct associated with Laurence-Moon-Biedl-Bardet syndrome. Arch Surg. 1977;112:82–4. [PubMed: 831679]

Uguralp S, Demircan M, Cetin S, Sigirci A. Bardet-Biedl syndrome associated with vaginal atresia: a case report. Turk J Pediatr. 2003;45:273–5. [PubMed: 14696812]

Wickner S, Maurizi MR, Gottesman S. Posttranslational quality control: folding, refolding, and degrading proteins. Science. 1999;286:1888–93. [PubMed: 10583944]

Chapter Notes

Revision History

- 6 March 2007 (cd) Revision: correction, Table 2
- 5 January 2007 (cd) Revision: *BBS12* gene 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 updated posted to live Web site
- 17 October 2003 (pb) Revision: change in test availability
- 14 July 2003 (me) Review posted to live Web site
- 22 January 2003 (pb) Original submission

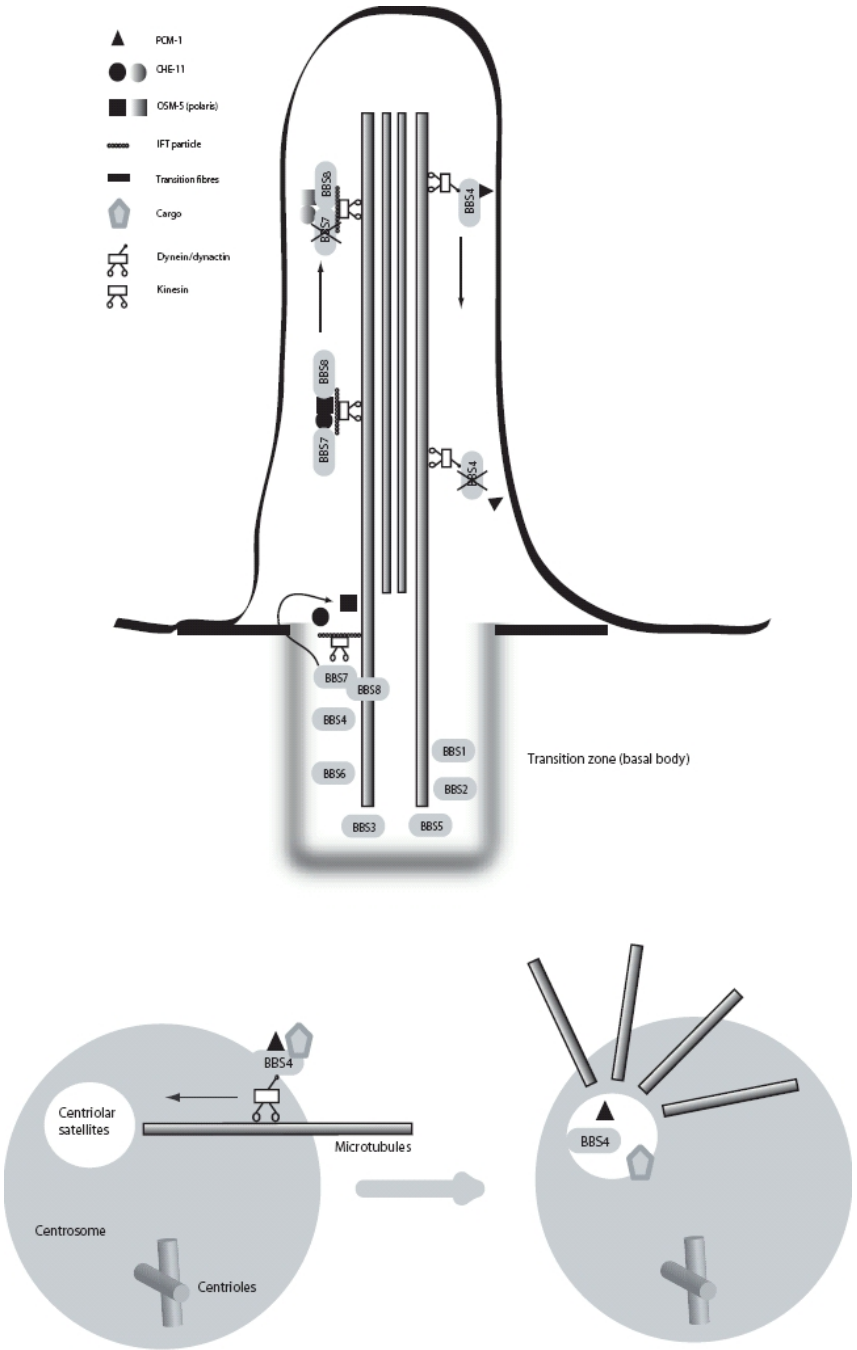

Figure 1. Schematic of the putative role of BBS proteins. The diagram amalgamates data accrued from several organisms and thus represents an idealized cell system. All BBS proteins have been placed in the transition zone (basal body), centrosome, and/or ciliary axoneme. There is additional evidence for the role of BBS7 and BBS8 in facilitating the selective assembly of IFT proteins into IFT particles. Knock-down of either BBS7 or BBS8 (only BBS7 is illustrated) results in diminished levels of CHE-11 and OSM-5 (polaris) in the ciliary axoneme, culminating in shortening. BBS4 through its direct interaction with $p150^{glued}$ subunit of dynactin probably behaves as an adapter assisting the loading of cargo (such as PCM-1) onto the IFT particles and subsequent transport to the centriolar satellites (in the centrosome and

the basal body). Given that the primary structure of BBS6 is similar to the group II chaperonins, we may speculate that its role is to process proteins prior to IFT assembly and loading as well as microtubule-dependent membrane trafficking.

Table 3. *BBS1* Pathologic Allelic Variants

Gene	Mutation	Exon	Reference
BBS1	p.E549X homozygote	16	Mykytyn et al 2002
BBS1	p.M390R homozygote	12	Mykytyn et al 2002
BBS1	p.M390R homozygote	12	Mykytyn et al 2002
BBS1	p.M390R heterozygote p.E549X heterozygote	12 16	Mykytyn et al 2002
BBS1	p.M390R heterozygote p.E549X heterozygote	12 16	Mykytyn et al 2002
BBS1	p.E549X heterozygote IVS4+1G>A	16 4	Mykytyn et al 2002
BBS1	p.Y284fsX288 homozygote	10	Mykytyn et al 2002
BBS1	p.M390R 27 homozygotes	12	Mykytyn et al 2002
BBS1	c.(-3)_37del heterozygote p.M390R heterozygote	1 12	Mykytyn et al 2003
BBS1	p.Y113X heterozygote p.M390R heterozygote	4 12	Mykytyn et al 2003
BBS1	V114fsX150 heterozygote p.L518P heterozygote	4 12	Mykytyn et al 2003
BBS1	p.I200_T201del p.M390R heterozygote	8 12	Mykytyn et al 2003
BBS1	p.Y284fsX288 heterozygote p.M390R heterozygote	16 12	Mykytyn et al 2003
BBS1	p.M347fsX373 heterozygote p.M390R heterozygote	11 12	Mykytyn et al 2003
BBS1	p.C377_F378delfsX412 homozygote	11	Mykytyn et al 2003
BBS1	p.R440X heterozygote p.M390R heterozygote	13 12	Mykytyn et al 2003
BBS1	p.L505fsX556 heterozygote p.M390R heterozygote	15 12	Mykytyn et al 2003
BBS1	p.L518P heterozygote p.M390R heterozygote	15 12	Mykytyn et al 2003
BBS1	p.H35R, 1 mutant allele		Beales et al 2003
BBS1	p.K53E, 1 mutant allele		Beales et al 2003
BBS1	p.L75fsX98, 1 mutant allele		Beales et al 2003
BBS1	p.Y133X, 1 mutant allele		Beales et al 2003
BBS1	p.Q128X, 1 mutant allele		Beales et al 2003
BBS1	p.R146X, 4 mutant alleles		Beales et al 2003
BBS1	p.D148N, 4 mutant alleles		Beales et al 2003
BBS1	p.E234K, 1 mutant allele		Beales et al 2003
BBS1	IVS9-3C>G, 2 mutant alleles		Beales et al 2003
BBS1	p.Y284fsX288, 3 mutant alleles		Beales et al 2003
BBS1	p.Q291X, 1 mutant allele		Beales et al 2003
BBS1	p.G305S, 4 mutant alleles		Beales et al 2003
BBS1	p.389delI, 1 mutant allele		Beales et al 2003

BBS1	p.M390R, 74 mutant alleles		Beales et al 2003
BBS1	p.R429X, 1 mutant allele		Beales et al 2003
BBS1	p.Y434S, 1 mutant allele		Beales et al 2003
BBS1	p.R440X, 2 mutant alleles		Beales et al 2003
BBS1	IVS13-2A>G, 2 mutant alleles		Beales et al 2003
BBS1	p.R483X, 1 mutant allele		Beales et al 2003
BBS1	p.L503H, 1 mutant allele		Beales et al 2003
BBS1	p.L505fsX556, 1 mutant allele		Beales et al 2003
BBS1	p.L518Q, 1 mutant allele		Beales et al 2003
BBS1	p.L548fsX579, 1 mutant allele		Beales et al 2003
BBS1	p.E549X, 1 mutant allele		Beales et al 2003

.0001 BBS1, E549X. This mutation was found in homozygous form in all affected individuals from a consanguineous Puerto Rican family [Mykytyn et al 2002]. In addition, affected members of two other Puerto Rican families were compound heterozygotes with respect to E549X and M390R [Mykytyn et al 2002]. Futhermore, all affected individuals of a further Puerto Rican family were found to be compound heterozygous for E549X and a G to A transition at the +1 position of the splice donor site in exon 4 (IVS4+1G>A) [Mykytyn et al 2002]. Furthermore, this nonsense mutation was also identified in one mutant allele in a cohort of 259 individuals with BBS [Beales et al 2003.

.0002 BBS1, M390R. This mutation was identified in homozygous form in all affected members of a Puerto Rican family [Mykytyn et al 2002]. Two other Puerto Rican families carried this mutation and the E549X in compound heterozygosity [Mykytyn et al 2002]. In addition, 22 out of 60 unrelated probands of mostly northern European ancestry with BBS had at least one copy; 16 were homozygous for the variant [Mykytyn et al 2002]. In a subsequent mutation survey, a total of 129 BBS probands were screened for the M390R mutation, 39 had at least one copy, 27 of whom were homozygous, indicating that this mutation was involved in 30% of the cohort [Mykytyn et al 2003]. In a further study of 259 individuals with BBS, a total of 74 M390R mutant alleles were identified, with M390R contributing to 18% of the cohort and involved in 79% of all families with BBS1 mutations [Beales et al 2003].

.0003 BBS1, IVS4+1G>A. All affected individuals of a Puerto Rican family were found to be compound heterozygotes for E549X and a G to A transition at the +1 position of the splice donor site in exon 4 [Mykytyn et al 2002].

.0004 BBS1, Y284fsX288. All affected members of a consanguineous Turkish family carried this frameshift mutation in homozygous form [Mykytyn et al 2002].

.0005 BBS1,c.(-3)_37del. This mutation wasidentified in compound heterozygous form with the M390R mutation in a BBS proband [Mykytyn et al 2003].

.0006 BBS1, p.Y113X. This nonsense mutation was identifiedin compound heterozygous form with the M390R mutation in a BBS proband [Mykytyn et al 2003].

.0007 BBS1, V114fsX150. This frameshift mutation was identifiedin compound heterozygous form with the L518P mutation in a BBS proband (Mykytyn et al. 2003).

.0008 BBS1,p.I200_T201del. This two aminoacid deletion within exon 8 was identified in compound heterozygous form withthe M390R mutation in an individual with BBS [Mykytyn et al 2003].

.0009 BBS1,p.Y284fsX288. This frameshiftmutation was identified in compound heterozygous form with the M390R mutation in a BBS proband [Mykytyn et al 2003]. It was also identified in three mutant alleles in a cohort of 259 individuals with BBS [Beales et al 2003].

.0010 BBS1,p.M347fsX373. This frameshift mutation was identified in compound heterozygous form with the M390R mutation in a BBS proband [Mykytyn et al 2003]. It was also identified in three mutant alleles in a cohort of 259 individuals with BBS [Beales et al 2003].

.0011 BBS1,p.C377_F378delfsX412. This frameshift mutation was identified in homozygous form in a BBS proband [Mykytyn et al 2003].

.0012 BBS1, p.R440X heterozygote. This nonsense mutation was identified in compound heterozygous form with the M390R mutation in a BBS proband [Mykytyn et al 2003].

.0013 BBS1,p.L505fsX556. This frameshift mutation was identified in compound heterozygous form with the M390R mutation in a BBS proband [Mykytyn et al 2003]).

.0014 BBS1, p.L518P. This amino acid substitution was identified in 3 BBS probands (Mykytyn et al. 2003). Two of these individuals were compound heterozygotes: one with the M390R mutation; the otherwith the V114fsX150 mutation [Mykytyn et al 2003].

.0015 BBS1, p.H35R. This mutation resulting in an amino acid substitution was identified in one mutant allele in a cohort of 259 individuals with BBS [Beales et al 2003].

.0016 BBS1, p.K53E. This mutation resulting in an amino acid substitution was identified in one mutant allele in a cohort of 259 individuals with BBS [Beales et al 2003].

.0017 BBS1, p.L75fsX98. This mutation resulting in a frameshift and the introduction of a premature stop codon was identified in one mutant allele in a cohort of 259 individuals with BBS [Beales et al 2003].

.0018 BBS1, p.Y113X. This nonsense mutation was identified in one mutant allele in a cohort of 259 individuals with BBS [Beales et al 2003].

.0019 BBS1, p.Q128X. This nonsense mutation was identified in one mutant allele in a cohort of 259 individuals with BBS [Beales et al 2003].

.0020 BBS1, p.R146X. This nonsense mutation was identified in four mutant alleles in a cohort of 259 individuals with BBS [Beales et al 2003].

.0021 BBS1, p.D148N. This mutation resulting in an amino acid substitution was identified in four mutant alleles in a cohort of 259 individuals with BBS [Beales et al 2003].

.0022 BBS1, p.E234K. This mutation resulting in an amino acid substitution was identified in one mutant allele in a cohort of 259 individuals with BBS [Beales et al 2003].

.0023 BBS1, IVS9-3C>G. A C to G nucleotide substitution was identified in the splice acceptor site of exon 10 in two mutant alleles in a cohort of 259 individuals with BBS [Beales et al 2003].

.0024 BBS1, p.Q291X. This nonsense mutation was identified in one mutant allele in a cohort of 259 individuals with BBS [Beales et al 2003].

.0025 BBS1, p.G305S. This mutation resulting in an amino acid substitution was identified in four mutant alleles in a cohort of 259 individuals with BBS [Beales et al 2003].

.0026 BBS1, p.389delI. This three base pair deletion resulting in the deletion of an isoleucine in exon 12 of BBS1 was identified in one mutant allele in a cohort of 259 individuals with BBS...0027 BBS1, p.R429X [Beales et al 2003].

.0028 BBS1, p.Y434S. This mutation resulting in an amino acid substitution was identified in four mutant alleles in a cohort of 259 individuals with BBS [Beales et al 2003].

.0029 BBS1, p.R440X. This nonsense mutation was identified in two mutant alleles in a cohort of 259 individuals with BBS [Beales et al 2003].

.0030 BBS1, IVS13-2A>G. This one base pair A to G substitution was identified in the splice acceptor site of exon 14 in two mutant alleles in a cohort of 259 individuals with BBS [Beales et al 2003].

.0031 BBS1, p.R483X. This nonsense mutation was identified in one mutant allele in a cohort of 259 individuals with BBS [Beales et al 2003].

.0032 BBS1, p.L503H. This mutation resulting in an amino acid substitution was identified in one mutant allele in a cohort of 259 individuals with BBS [Beales et al 2003].

.0033 BBS1, p.L505fsX556. This mutation resulting in a frameshift and the introduction of a premature stop codon was identified in one mutant allele in a cohort of 259 individuals with BBS [Beales et al 2003].

.0034 BBS1, pL518Q. This mutation resulting in an amino acid substitution was identified in one mutant allele in a cohort of 259 individuals with BBS [Beales et al 2003].

.0035 BBS1, p.L548fsX579. This mutation resulting in a frameshift and the introduction of a premature stop codon was identified in one mutant allele in a cohort of 259 individuals with BBS [Beales et al 2003].

Table 4. *BBS2* Normal Allelic Variants

Gene	Sequence Change	Exon	Coding Frequency	References
BBS2	p.I123V	3	Not done	Nishimura et al 2001
BBS2	p.V471V	12	Not done	Nishimura et al 2001

Table 5. *BBS2* Pathologic Allelic Variants

Gene	Mutation	Exon	Reference
BBS2	p.I314fsX324 homozygote	8	Nishimura et al 2001
BBS2	p.V75G homozygote	2	Nishimura et al 2001
BBS2	p.Y24X homozygote	1	Katsanis et al 2001
BBS2	p.Y24X heterozygote	1	Katsanis et al 2001
BBS2	p.Q59X heterozygote	2	Katsanis et al 2001
BBS2	p.Q59X heterozygote	2	Katsanis et al 2001
BBS2	p.Y24X heterozygote	1	Katsanis et al 2001
BBS2	p.R275X homozygote	8	Katsanis et al 2001
BBS2	p.R315W homozygote	9	Katsanis et al 2001
BBS2	p.D170fsX171 homozygote	4	Katsanis et al 2001
BBS2	p.C210fsX246 homozygote	6	Katsanis et al 2001
BBS2	p.D104A heterozygote	2	Katsanis et al 2001
BBS2	p.R634P heterozygote	15	Katsanis et al 2001
BBS2	p.D104A heterozygote	2	Katsanis et al 2001
BBS2	IVS1-1G>C heterozygote		Katsanis et al 2001
BBS2	p.V158fsX200 heterozygote	4	Katsanis et al 2001
BBS2	p.N70S heterozygote	2	Katsanis et al 2001
BBS2	p.L168fsX170 heterozygote	4	Katsanis et al 2001
BBS2	p.R216X heterozygote	6	Katsanis et al 2001
BBS2	p.T558I homozygote	14	Katsanis et al 2002
BBS2	p.N70S heterozygote	3	Katsanis et al 2000, 2001
BBS2	p.T558I homozygote	14	2001

.0001 BBS2 I314fsX324. All affected members of a consanguineous Bedouin family were found to carry a homozygous deletion of a single nucleotide in exon 8 [Nishimura et al 2001].

.0002 BBS2, V75G. All affected members of a large inbred Bedouin BBS kindred were found to carry a non-conservative valine to glycine substitution in exon 2 of BBS2 [Nishimura et al 2001]. The valine at this position is conserved in human, bovine, rabbit, rat, mouse and zebrafish BBS2 orthologues and this variant was postulated to be the disease-causing mutation, despite there being a second variant carried on the same chromosome (I123V).

.0003 BBS2, Y24X. This mutation was identified in the homozygous form in two unrelated individuals with BBS [Katsanis et al 2001]. One of those individuals also carried a heterozygous A242S mutation in BBS6 (see tri-allelic inheritance, section X). Y24X was also identified in compound heterozygosity with the Q59X mutation, in an individual who additionally had a heterozygous Q147X mutation within the BBS6 gene ([Katsanis et al 2001]; see tri-allelic inheritance).

.0004 BBS2, Q59X. One affected individual identified was a compound heterozygote for Q59X and Y24X in the BBS2 gene [Katsanis et al 2001]. A further mutation was identified in this individual: Q147X in BBS6.

.0009 BBS2, R275X. A homozygous arginine to termination mutation at codon 275 was identified in an individual with BBS [Katsanis et al 2001].

.0006 BBS2, R315W. A homozygous arginine to tryptophan mutation at codon 315 was identified in an individual with BBS [Katsanis et al 2001].

.0007 BBS2, D170fsX171. A homozygous frameshift mutation at codon 170 resulting in a termination codon at residue 171 was identified in an individual with BBS [Katsanis et al 2001].

.0008 BBS2, C210fsX246. A homozygous frameshift mutation at codon 210 resulting in a termination codon at residue 246 was identified in an individual with BBS [Katsanis et al 2001].

.0009 BBS2, D104A. One individual with BBS was identified who was compound heterozygous for an aspartic acid to alanine substitution at codon 104 of BBS2, and an arginine to proline substitution at codon 634 [Katsanis et al 2001]. This mutation was also identified in heterozygous form in an individual with BBS who was linked to the BBS1 locus.

.0010 BBS2, R634P. One individual with BBS was identified who was compound heterozygous for an arginine to proline substitution at codon 634 and an aspartic acid to alanine substitution at codon 104 of BBS2 [Katsanis et al 2001].

.0011 BBS2, IVS-1G>C. An affected individual identified was heterozygous for a G to C substitution at the -1 position of the intron 1 splice acceptor site [Katsanis et al 2001].

.0012 BBS2, V158fsX200. An affected individual linked to the BBS1 locus was found to carry a heterozygous frameshift mutation at codon 158, resulting in a premature stop codon at residue 200 [Katsanis et al 2001].

.0013 BBS2, N70S. An individual with BBS who was homozygous for a missense mutation in the BBS6 gene (Y37C) was found to additionally carry a heterozygous asparagines to serine substitution in the BBS2 gene [Katsanis et al 2001].

.0014 BBS2, L168fsX200. An individual with BBS was found to be a compound heterozygote for two mutations within the BBS2 gene: a frameshift mutation at codon 168 resulting in a stop codon at residue 170; and a nonsense mutation at codon 216 resulting in the introduction of a premature termination codon [Katsanis et al 2001]. A heterozygous C499S mutation in the BBS6 gene was identified in the same individual.

.0015 BBS2 R216X. An individual with BBS was found to be a compound heterozygote for two mutations within the BBS2 gene: the first a nonsense mutation at codon 216 resulting in the introduction of a premature termination codon; the second a frameshifting mutation at codon 168 resulting in a stop codon at residue 170 [Katsanis et al 2001]. A heterozygous C499S mutation in the BBS6 gene was identified in the same individual.

.0016 BBS2 T558I. A homozygous threonine to isoleucine mutation at codon 558 of the BBS2 gene was identified in an individual with BBS [Katsanis et al 2001]. The same individual was later also identified to have a homozygous A364E mutation in the BBS4 gene [Katsanis et al 2002].

Table 6. *BBS4* Normal Allelic Variants

Gene	Sequence Change	Exon	Coding Frequency	References
BBS4	c.-17C/A	1	Not done	Katsanis et al 2002
BBS4	c.42G/A; nil	1	A allele present in one individual and in 0/84 controls	Katsanis et al 2002
BBS4	c.-6A/G	3	G allele present in one individual and in 0/81 controls	Katsanis et al 2002
BBS4	c.91G/A; nil	4	Not done	Katsanis et al 2002
BBS4	c.8A/C; nil	5	C allele present in one individual and in 0/93 controls	Katsanis et al 2002
BBS4	c.28insA	5		Katsanis et al 2002
BBS4	c.17C/T	6		Katsanis et al 2002
BBS4	c.1061C/T	13		Katsanis et al 2002
BBS4	c.20C/T	13		Katsanis et al 2002
BBS4	c.18C/T	15	C allele present in one individual and in 0/93 controls	Katsanis et al 2002
BBS4	c.-45C/T	16		Katsanis et al 2002
BBS4	c.1561G/C	16	C allele present in one individual and in 0/87 controls	Katsanis et al 2002

Table 7. *BBS4* Pathologic Allelic Variants

Gene	Mutation	Exon	Reference
BBS4	p.A364E homozygote	13	Katsanis et al 2002
BBS4	c.77-220del homozygote	Exons 3-4	Mykytyn et al 2001
BBS4	c.77-220del homozygote	Exons 3-4	Mykytyn et al 2001
BBS4	p.R295P homozygote	12	Mykytyn et al 2001
BBS4	IVS4+1G>C homozygote	4	Mykytyn et al 2001
BBS4	p.V195fsX209 heterozygote	8	Mykytyn et al 2001
BBS4	IVS6-2A>C homozygote	7	Mykytyn et al 2001
BBS4	IVS3-2A>C homozygote	4	Katsanis et al 2001
BBS4	p.A364E homozygote	13	Katsanis et al 2001
BBS4	p.L327p heterozygote	12	Katsanis et al 2001
BBS4	p.N165H heterozygote	8	Katsanis et al 2002
BBS4	p.S457I heterozygote	15	Katsanis et al 2002

.0001 BBS4 77-220del. A homozygous 6-kb deletion resulting in the removal of the whole of exons 3 and 4 was identified in all individuals affected with BBS from two families: an Italian and an Israeli Arab family [Mykytyn et al 2001]. The deletion breakpoints occurred within Alu elements in introns 2 and 4 and haplotype analysis suggested that the mutation arose independently in the two families.

.0002 BBS4 R295P. All affected individuals of a large inbred Bedouin kindred were found to carry a homozygous arginine to proline missense mutation within exon 12 of BBS4 [Mykytyn et al 2001].

.0003 BBS4 IVS4+1G>C. A homozygous G to C substitution at the -2 position of the splice donor site of intron 4 was identified in the two affected siblings from a European BBS family [Mykytyn et al 2001].

.0004 BBS4 V195fsX209. A heterozygous two-base pair insertion in exon 8 of the BBS4 gene was identified in a small non-consanguineous BBS family which is predicted to result in a premature stop codon at residue 209 [Mykytyn et al 2001]. Sequence analysis of the coding region did not reveal a second mutation within the BBS4 gene in this family.

.0005 BBS4 IVS6-2A>C. A homozygous A to C substitution at the -2 position of the splice acceptor site of intron 6 was identified in the two affected siblings from a European BBS family [Mykytyn et al 2001].

.0006 BBS4 IVS3-2A>G. In a consanguineous family from Saudi Arabia the affected individual was found to carry a homozygous A to G substitution at the -2 position of the splice acceptor site of intron 3 [Katsanis et al 2002].

.0007 BBS4 A364E. A homozygous missense mutation resulting in an alanine to glutamine substitution was detected in an affected individual from a consanguineous Kurdish family [Katsanis et al 2002]. Furthermore, the affected individual had previously been shown to be homozygous for a T558I mutant BBS2 allele [Katsanis et al 2001], which may suggest that the disease is inherited in a tetra-allelic pattern in this family.

.0008 BBS4 L327P. A non-conservative leucine to proline substitution was identified in heterozygous form in affected members from a BBS family [Katsanis et al 2002]. With the absence of functional data on the BBS4 protein, it is unclear whether this change is a pathogenic alteration.

.0009 BBS4 N165H. A non-conservative asparagine to histidine substitution was identified in heterozygous form in affected members from a BBS family [Katsanis et al 2002]. With the absence of functional data on the BBS4 protein, it is unclear whether this change is a pathogenic alteration.

.0010 BBS4 S457I. A non-conservative serine to isoleucine substitution was identified in heterozygous form in affected members from a BBS family [Katsanis et al 2002]. With the absence of functional data on the BBS4 protein, it is unclear whether this change is a pathogenic alteration.

Table 8. *MKKS/BBS6* Normal Allelic Variants

Gene	Sequence Change	Exon	Coding Frequency	References
BBS6/MKKS	c.-675_674ins [GTGGCGGCCT]	1A	2.25%	Slavotinek et al 2002
BBS6/MKKS	c.-74G>A	3	0/94	Slavotinek et al 2002
BBS6/MKKS	c.117C>T; nil	3	Not done	Slavotinek et al 2002
BBS6	p.G49V	3	8.3%	Stone et al 2000
BBS6	c.534C>T; nil	3	Not done	Slavotinek et al 2002
BBS6	p.R517C	6	6.3%	Stone et al 2000
BBS6	p.G532V	6	6.4%	Stone et al 2000

Table 9. *MKKS/BBS6* Pathologic Allelic Variants

Gene	Mutation	Exon	Reference
BBS6	p.A242S heterozygote	3	Katsanis et al 2001
BBS6	p.Q147X heterozygote	3	Katsanis et al 2001
BBS6	p.Q147X heterozygote	3	Katsanis et al 2001
BBS6	p.Y37C homozygous	3	Katsanis et al 2001
BBS6	p.C499S heterozygote	6	Katsanis et al 2001
MKKS	p.H84Y homozygote	3	Stone et al 2000
MKKS	p.A242S homozygote	3	Stone et al 2000
MKKS	p.Y37C heterozygote	3	Stone et al 2000
MKKS	p.W405fsX413 heterozygote	5	Stone et al 2000
BBS6	p.Y37C homozygote	3	Katsanis et al 2000, 2001
BBS6	p.D143fsX157 heterozygote	3	Katsanis et al 2000
BBS6	p.L227P heterozygote	3	Katsanis et al 2000
BBS6	p.F94fsX103 homozygote	3	Katsanis et al 2000, Slavotinek et al 2000
BBS6	p.D143fsX157 homozygote	3	Katsanis et al 2000, Slavotinek et al 2000
BBS6	p.F94fsX103 heterozygote	3	Katsanis et al 2000
BBS6	p.D143fsX157 heterozygote	3	Katsanis et al 2000
BBS6	p.T57A heterozygote	3	Katsanis et al 2000
BBS6	p.G52D heterozygote	3	Slavotinek et al 2000
BBS6	p.Y264X heterozygote	3	Slavotinek et al 2000
BBS6	p.A242S heterozygote	3	Beales et al 2001
BBS6	p.A242S heterozygote	3	Slavotinek et al 2000
BBS6	p.Q147X homozygote	3	Beales et al 2001
BBS6	p.D285A homozygote	3	Beales et al 2001
BBS6	p.R518H homozygote	6	Beales et al 2001
BBS6	p.I32M homozygote	3	Beales et al 2001
BBS6	p.S235P homozygote	3	Beales et al 2001
BBS6	p.C499S homozygote	6	Beales et al 2001
BBS6	p.S511A homozygote	6	Beales et al 2001
BBS6	c.431-441del homozygote	3	Slavotinek et al 2002
BBS6	c.876-877 insCCTG heterozygote	3	Slavotinek et al 2002
BBS6	p.G345E homozygote	4	Slavotinek et al 2002
BBS6	p.R155L	3	Slavotinek et al 2002
BBS6	p.I339V	4	Slavotinek et al 2002

.0001 BBS6, H84Y. A homozygous histidine to tyrosine missense mutation was found together with A242S in all affected Amish individuals with McKusick-Kaufman syndrome [Stone et al 2000]. It has been predicted that this substitution may disrupt protein function by interfering with ATP hydrolysis in the equatorial domain of the protein.

.0002 BBS6, A242S. A homozygous alanine to serine missense mutation was found together with H84Y in all affected Amish individuals with Mckusick-Kaufman syndrome [Stone et al 2000]. However, unlike H84Y, this mutation has not been predicted to disrupt protein function. It has also been found in one unaffected control from Newfoundland [Beales et al 2001], in heterozygous form in an individual with BBS who had

hypothyroidism [Slavotinek et al 2002], and in affected and unaffected siblings in a Newfoundland family [Katsanis et al 2001]. It has been proposed that either this allele is actually a rare polymorphism, or else that BBS arises through multiallelic inheritance [Katsanis et al 2001].

.0003 BBS6, Y37C. A tyrosine to cysteine missense mutation was found in an infant with MKKS in compound heterozygous form along with a two base pair deletion in exon 5 (W405fsX413) [Stone et al 2000]. Y37C was also identified in homozygous form in an individual with BBS who carried an additional mutation in the BBS2 gene (N70S) [Katsanis et al 2001].

.0004 BBS6, W405fsX413. This two base pair deletion in exon 5 of the BBS6 gene was found in compound heterozygous form with Y37C in an infant with MKKS [Stone et al 2000].

.0005 BBS6, D143fsX157. This mutation is a complex deletion that predicts the introduction of a premature termination codon at residue 157 of the BBS6 gene and was identified in homozygous form in all affected individuals from two Newfoundland BBS families [Katsanis et al 2000]. In addition, it was also found in compound heterozygous form in an affected individual together with D143fsX157, and with L227P in an affected individual from Newfoundland [Katsanis et al 2000].

.0006 BBS6, L227P. This missense mutation was found in compound heterozygous form in an affected individual from Newfoundland together with D143fsX157 [Katsanis et al 2000].

.0007 BBS6, F94fsX103. This mutation has been identified in the homozygous form in all affected individuals from three BBS families from Newfoundland [Katsanis et al 2000, Slavotinek et al 2000]. In addition, it was also found in compound heterozygous form in an affected individual together with D143fsX157 [Katsanis et al 2000].

.0008 BBS6, T57A. This missense mutation was identified in heterozygous form in an individual with BBS and was not found in 192 control chromosomes [Katsanis et al 2000].

.0009 BBS6, G52D. A Hispanic BBS proband was found to be a compound heterozygote for a glycine to aspartic acid missense mutation (G52D), and a nonsense mutation (Y264X) in BBS6 [Slavotinek et al 2000].

.0010 BBS6, Y264X. A Hispanic BBS proband was found to be a compound heterozygote for a nonsense mutation (Y264X), and a missense mutation (G52D) in BBS6 [Slavotinek et al 2000].

.0011 BBS6, Q147X. This nonsense mutation was identified in heterozygous form in an individual with BBS who also carried two nonsense mutations in the BBS2 gene (Y24X & Q59X) [Beales et al 2001, Katsanis et al 2001].

.0012 BBS6, D285A. This missense mutation was identified in homozygous form in affected individuals from a BBS pedigree [Beales et al 2001].

.0013 BBS6, R518H. This missense mutation was identified in homozygous form in affected individuals from a BBS pedigree [Beales et al 2001].

.0014 BBS6, I32M. This missense mutation was identified in homozygous form in affected individuals from a BBS pedigree [Beales et al 2001]. It was suggested that this would result in the introduction of an alternative methionine start codon.

.0015 BBS6, S235P. This missense mutation was identified in homozygous form in affected individuals from a BBS pedigree [Beales et al 2001]. It was suggested that this change would result in a structural change to the BBS6 protein.

.0016 BBS6, C499S. This missense mutation was identified in homozygous form in an individual with BBS along with two other nonsense mutations in the BBS6 gene (L168fsX170 and R216X) [Katsanis et al 2001].

.0017 BBS6, S511A. This missense mutation was identified in homozygous form in affected individuals from a BBS pedigree [Beales et al 2001].

.0018 BBS6, c.431-441del. A homozygous deletion of 10 base pairs in exon 3 of the BBS6 gene that predicts a frameshift resulting in a premature stop codon at residue 152 was identified in an individual with BBS [Slavotinek et al 2002].

.0019 BBS6, c.876-877insCCTG. A heterozygous insertion of 4 base pairs in exon 3 of BBS6 was identified that predicts a frameshift resulting in a premature stop codon at residue 327 in an individual with atypical BBS [Slavotinek et al 2002].

.0020 BBS6, p.G345E. This homozygous missense mutation was identified in an individual with BBS [Slavotinek et al 2002].

.0021 BBS6, p.R155L. This missense mutation was identified in heterozygous form in an individual with BBS [Slavotinek et al 2002].

.0022 BBS6, p.I339V. This missense mutation was identified in heterozygous form in an individual with BBS [Slavotinek et al 2002].

Table 10. *BBS7* Pathologic Allelic Variants

Gene	Mutation	Exon	Reference
BBS7	p.H323R homozygous	10	Badano et al 2003
BBS7	p.H323R homozygous	10	Badano et al 2003
BBS7	p.T2111 homozygous	6	Badano et al 2003
BBS7	K237fsX296 homozygous	7	Badano et al 2003

.0001 BBS7 H323R. This amino acid substitution was identified in the homozygous state in all affected individuals from two unrelated BBS pedigrees [Badano et al 2003].

.0002 BBS7 T211I. This amino acid substitution was identified in the homozygous state in all individuals in a consanguineous BBS pedigree [Badano et al 2003]. All affected family members additionally carried a E234K heterozygous change in the BBS1 gene, raising the possibility of complex inheritance between BBS7 and BBS1 [Badano et al 2003].

.0003 BBS7 K237fsX296. A 4 base pair deletion within exon 7of the BBS7 gene, resulting in the introduction in a premature stop codon within exon 9, was identified in the homozygous state in the only affected individual in a BBS family from Saudi Arabia.