

# **Bardet-Biedl Syndrome**

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# Disclosures

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# Bardet-Biedl Syndrome (BBS)

**BBS is a rare genetic disease of the primary cilia with pleiotropic features<sup>1,2</sup>**

- Early onset obesity beginning in infancy with life-long implications
  - Retinal degeneration with significant risk for blindness
  - Chronic kidney disease with kidney failure most often occurring before 20 years of age
  - Learning difficulties and impaired cognitive health
  - Post-axial polydactyly and diverse musculoskeletal anomalies
  - Endocrinopathies (hypogonadism, hypothyroidism and T2DM)
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- ❖ Estimated incidence is 1:160,000 in northern European populations
  - ❖ Incidence in North American is suspected to be similar
  - ❖ BBS is particularly common in certain regions and populations such as Newfoundland and the Hmong and Mennonite/Amish populations

1. Forsythe E, Beales PL. Bardet-Biedl syndrome. Eur J Human Genet. 2013 Jan; 21(1):8-13.

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# The genetics of BBS<sup>1</sup>

- BBS is autosomal recessive disease resulting from variants in more than 25 unique genes
- The unifying biological mechanism underlying BBS is disordered primary cilia regulation and/or function.<sup>1</sup>
- The role of the cilia in different cells, tissues and organs result in diverse cellular dysregulation
  - Impaired melanocortin-4 signaling in the hypothalamus<sup>2,3</sup>
  - Disruption of photoreceptors in the eye<sup>3</sup>
  - Altered vascular responsiveness<sup>4</sup>

## Known genes causing BBS

BBS type	Gene name
BBS1	BBS1
BBS2	BBS2
BBS3	ARL6
BBS4	BBS4
BBS5	BBS5
BBS6	MKKS
BBS7	BBS7
BBS8	TTC8
BBS9	PHTB1
BBS10	BBS10
BBS11	TRIM32
BBS12	BBS12
BBS13	MKS1
BBS14	CEP290
BBS15	WDPCP
BBS16	SDCCAG8
BBS17	LZTFL1
BBS18	BBIP1
BBS19	IFT27
BBS20	IFT74
BBS21	CFAP418
BBS22	NPHP1
BBS23	IFT172
BBS24	SCAPER
BBS25	SCLT1

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4. Weihbrecht K, Goar WA, Pak T, et al. Keeping an Eye on Bardet-Biedl Syndrome: A Comprehensive Review of the Role of Bardet-Biedl Syndrome Genes in the Eye. *Med Res Arch.* 2017;5(9):10.18103

# Clinical Conditions Similar to BBS<sup>1</sup>

Other diseases may resemble BBS but have clinical differences that are considered by healthcare providers when establishing a differential diagnosis.

Condition	Description
<b>Laurence-Moon syndrome (LMS)</b>	LMS is a rare autosomal recessive condition defined by visual degeneration compounded with pituitary dysfunction. The pituitary gland serves to regulate the major chemicals that drive body processes, ranging from growth and metabolism to reproduction potential. LMS is characterized by childhood neurological problems including loss of control over movement and loss of peripheral nerve function, which can result in a stiffness-contraction of the limbs. Intellectual disabilities may be associated but are poorly defined.
<b>Alström syndrome</b>	Alstrom syndrome is a rare autosomal recessive disease characterized by vision and hearing abnormalities, childhood obesity, diabetes mellitus, and slowly progressive kidney dysfunction.
<b>Meckel syndrome</b>	Meckel syndrome, also known as Meckel-Gruber syndrome, is inherited as an autosomal recessive disorder. This rare condition is characterized by abnormalities affecting several organ systems of the body.
<b>McKusick-Kaufman syndrome (MKKS)</b>	MKKS is inherited as an autosomal recessive trait. It is an extremely rare genetic disease characterized by the presence of an extra finger near the pinky or an extra toe near the fifth toe (postaxial polydactyly), congenital heart defects, and, in females, a collection of watery fluid in the uterus and vagina called “hydrometrocolpos” that results in dilation of the organs.
<b>Biemond II syndrome</b>	Biemond II syndrome is inherited as an autosomal recessive trait. This syndrome is an extremely rare genetic disorder characterized by absence of tissue from the colored portion of the eye (iris coloboma), intellectual disability, obesity, genitourinary abnormalities, and an extra finger near the pinky or an extra toe near the fifth toe (postaxial polydactyly).
<b>Prader-Willi syndrome</b>	Prader-Willi syndrome is a genetic disorder characterized by weak resting muscle strength (hypotonia), feeding difficulties, and failure to gain weight through infancy (failure to thrive). In later childhood, features of the disorder include short stature, genital abnormalities and an excessive appetite. All individuals with Prader-Willi syndrome have some degree of cognitive impairment that ranges from borderline normal with learning disabilities to severe intellectual disabilities.

1. National Organization for Rare Disorders (NORD). Rare Disease Database. Bardet-Biedl Syndrome. Accessed on April 26, 2021 at <https://rarediseases.org/rare-diseases/bardet-biedl-syndrome/>

# BBS is diagnosed clinically<sup>1</sup>

To properly diagnose BBS, providers rely on the identification of **four** of the primary characteristics, **or three** primary characteristics and at least **two** secondary characteristics.

## Primary Characteristics:

- Retinal degeneration
- Obesity
- Polydactyly
- Male hypogonadism
- Renal anomalies
- Learning disabilities

## Secondary Characteristics:

- Speech disorder/delay
- Strabismus/cataracts/astigmatism
- Brachydactyly, syndactyly
- Developmental delay
- Polyuria/polydipsia
- Ataxia/poor coordination/imbalance
- Mild spasticity (especially lower extremities)
- Dental crowding/hypodontia/small roots/high arched palate
- Diabetes mellitus
- Left ventricular hypertrophy/congenital heart disease
- Hepatic fibrosis

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# Genetic Testing and Treatment<sup>1</sup>

- BBS is a clinical diagnosis however confirmatory genetic testing is ideal.<sup>1</sup>
  - 15-20% of individuals meeting BBS diagnostic criteria do not have confirmatory genetic findings.
- BBS impacts multiple organ systems; therefore, comprehensive multidisciplinary clinics staffed by providers familiar with BBS are ideal.<sup>1</sup>
- Overweight/obesity and hyperphagia are present in > 90% of individuals with BBS.<sup>2</sup>
  - Effective obesity interventions offers significant benefits to ameliorate other manifestations of disease in BBS including T2DM, dyslipidemia, hypertension and self-image.<sup>3</sup>
- Therapies including stem cell and gene replacement (subretinal, systemic) are being explored and may provide life changing benefits to individuals with BBS.<sup>4</sup>

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# Conclusion

- BBS is a rare genetic disease with pleiotropic effects<sup>1</sup>
- The condition is diagnosed based on clinical features however genetic confirmation is possible in ~80% of affected individuals<sup>1</sup>
- Other diseases may resemble BBS; therefore, for the full benefit of research opportunities and targeted therapies implementation it is critical to correctly identify BBS as a unique disease<sup>1,2,3</sup>
- Optimal care for individuals with BBS is ideally provided in multispecialty clinics designed to meet patient needs however increased awareness of the complex healthcare needs of individuals with BBS; identification of affected individuals; and personalized care is essential<sup>1,4,5</sup>

1. Forsythe E, Beales PL. Bardet-Biedl syndrome. *Eur J Human Genet.* 2013 Jan; 21(1):8-13

2. National Organization for Rare Disorders (NORD). Rare Disease Database. Bardet-Biedl Syndrome. Accessed on April 26, 2021 at <https://rarediseases.org/rare-diseases/bardet-biedl-syndrome/>

3. National Center for Advancing Translational Sciences, Genetic and Rare Disease Information Center: Bardet Biedl Syndrome. Accessed 1/25/2022 at <https://rarediseases.info.nih.gov/diseases/6866/bardet-biedl-syndrome>

4 Forsythe E, et al. *Front Pediatr.* 2018;6(23):1-8.

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