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Bardet-Biedl
Syndrome
(*BBS1, BBS2, BBS10*)



Frequently Used Abbreviations: **BBS:** Bardet-Biedl Syndrome; **LMS:** Laurence-Moon Syndrome

Introduction

Bardet-Biedl Syndrome (BBS) is defined by a range of primary and secondary features.¹ The syndrome's hallmark is retinal degeneration; other primary features are postaxial polydactyly, obesity, hypogenitalism, renal malformations, and learning disabilities. Since none of the diverse symptoms of BBS by itself is diagnostic of the disorder and many of the symptoms only become apparent over time, diagnosis of the BBS is often delayed until about nine years of age, when visual problems first appear. Definitive diagnosis of BBS at a younger age would enable parents to understand and compensate for their child's learning disabilities, developmental delays, or behavioral problems, and to help prepare their child for an adult life in blindness. Early diagnosis of BBS would also allow patients to be monitored for renal malformations, which are a leading cause of morbidity and mortality in individuals with BBS, but often remain unnoticed until renal failure occurs.²

BBS has been associated with mutations in any one of several genes (*BBS1*, *BBS2*, *ARL6* (*BBS3*), *BBS4*, *BBS5*, *MKKS* (*BBS6*), *BBS7*, *TTC8* (*BBS8*), *PTHB1* (*BBS9*), *BBS10*, *TRIM32* (*BBS11*), *BBS12*).³⁻¹⁶ Among the known BBS genes, *BBS1*, *BBS2*, and *BBS10* are believed to account for the greatest proportions of BBS, about 23%, 8%, and 20%, respectively, of all cases.^{14,17}

Genetic testing for BBS can confirm a diagnosis reached on the basis of current clinical criteria. In addition, genetic testing of infants with postaxial polydactyly for BBS-associated mutations in *BBS1*, *BBS2*, or *BBS10* can help to detect up to half of all cases of BBS at a very young age. Genetic testing can also facilitate carrier detection, genetic counseling, and the early diagnosis of affected family members.

Causes of BBS

BBS is a pleiotropic disorder with mostly monogenic causes. While different BBS genes code for different classes of proteins, such as chaperonin-like proteins (*BBS6*, *BBS10*, and *BBS12*),^{9,10,14,16} an E3 ubiquitin ligase (*BBS11*),¹⁵ or an ADP-ribosylation factor (*BBS3*),^{5,6} all BBS gene products are believed to be involved in intracellular trafficking or, more specifically, intraflagellar transport (IFT).^{18,19} IFT is the active transport of proteins along the microtubules – long, hollow protein cylinders – that form the “skeleton” inside of cilia. Cilia are hair-like cellular appendages serving a wide variety of cellular functions. Motile cilia are able to perform repeated beating motions and are responsible for the mobility of sperm cells and for the transport of fluids over epithelial cells. Directional movement of fluid over the cell surface is important for such diverse functions as clearing the lungs of mucus and determining right-left asymmetry during embryonic development. Non-motile cilia are involved in sensory perception and play a role in processes such as photoreception in the vertebrate retina, olfaction, and detection of fluid movement over cell surfaces in kidney epithelial cells.

IFT is necessary for both formation and maintenance of cilia. Defects in IFT have been implicated in male infertility, polycystic kidney disease, retinal degeneration, and disturbances in embryonic development.²⁰ Given the ubiquity of IFT in mammalian cells and the varied roles of cilia in different cell types, association of BBS with

mutations in IFT components may explain the pleiotropic phenotype of the disorder.

Clinical Presentation of BBS

BBS is associated with a range of primary and secondary features.¹ Type and severity of symptoms can vary both between and within families.²¹ Visual problems, which usually start with night blindness at about 8 years of age, affect virtually all individuals with BBS and typically lead to blindness in the second or third decade. Postaxial polydactyly occurs in about 70% of cases and can affect only one or several limbs. Most males (90%) with BBS suffer from hypogonadism; in females, complex genitourinary malformation may occur. Obesity develops in about 50% of individuals with BBS, often during the first year of life. Renal abnormalities are a major cause of morbidity and early mortality, leading to chronic renal failure in 5% of patients; they affect about half of all individuals with BBS, but are often underdiagnosed. Mild to moderate learning disabilities are seen in about 60% of individuals with BBS, and about half of all BBS patients are partially or completely anosmic.²²

In addition to these primary features, a number of secondary symptoms have been associated with BBS (see table).

Prenatal presentation of BBS with polydactyly and kidney anomalies may resemble that of Meckel Syndrome or “Meckel-like” Syndrome in the absence of encephalocele.²³

Table: Features of Bardet-Biedl Syndrome

Primary Features of BBS

- Retinal dystrophy
- Postaxial polydactyly
- Obesity
- Hypogonadism
- Renal abnormalities
- Learning disabilities

Secondary Features of BBS

- Developmental delay
- Behavioral problems
- Neurological problems
- Speech disorder
- Brachy-, syn-, or clinodactyly
- Dental anomalies
- Nephrogenic diabetes insipidus
- Diabetes mellitus
- Hypertension
- Anosmia

The names Bardet-Biedl Syndrome and Laurence-Moon Syndrome are often used interchangeably or together (Laurence-Moon-Biedl-(Bardet) Syndrome) to describe BBS. However, Laurence-Moon Syndrome (LMS) is defined as a separate entity characterized by retinal degeneration, mental retardation, hypogonadism, and spastic paraplegia, although a recent study questions this distinction between LMS and BBS.²⁴

Diagnosis of BBS

Diagnosis of BBS is currently based on the presence of four primary features or three primary and two secondary features. The average age at diagnosis is 9 years, when visual problems first become apparent, but diagnosis after the age of 50 has also been reported.²⁵ It has been suggested that BBS may be significantly underdiagnosed.²⁵

Genetic testing for BBS can confirm a diagnosis of BBS reached on the basis of clinical features. In addition, genetic testing for mutations in BBS genes can allow a diagnosis of BBS in infants with postaxial polydactyly. Postaxial polydactyly occurs at a frequency of about 1:1,500 in the general population.²⁶ In whites, postaxial polydactyly is mostly syndromic; in individuals of African descent, it can also be linked to autosomal dominant mutations and tends to be more common. In African American infants, genetic testing for BBS may therefore only be indicated if postaxial polydactyly is accompanied by one other symptom of BBS.

Treatment of BBS

There is no cure for BBS. However, early diagnosis of BBS can allow the patient to be monitored for the typical symptoms of BBS, so that management or treatment of individual symptoms can be initiated as soon as possible.

Genetics of BBS

Inheritance of BBS is mainly autosomal recessive. In some cases, digenic inheritance has been reported, where mutations in two different BBS genes are necessary for expression of the phenotype.^{17,27,28} In some of these cases, mutations in a second BBS gene may not be necessary for disease manifestation, but rather may potentiate the phenotype caused by two recessive mutations in the primarily affected BBS gene.²⁹

Mutations in *BBS6* have also been associated with McKusick Kaufman Syndrome, which is characterized by vaginal atresia with hydrometrocolpos, postaxial polydactyly, and congenital heart defects. McKusick Kaufman Syndrome is typically reported in very young children and shows recessive inheritance.³⁰ Consequently, *BBS6* is also known as *MKKS*.

Genetic Testing for BBS

The Bardet-Biedl Syndrome Evaluation detects mutations in *BBS1*, *BBS2*, and *BBS10*, which have been associated with 23%, 8%, and 20%, respectively, of BBS cases. Genetic testing can confirm a diagnosis of BBS reached on the basis of clinical features, or may identify BBS in infants with

postaxial polydactyly. Genetic testing can also facilitate carrier detection, genetic counseling, and the early diagnosis of affected family members. Diagnosis of BBS at a young age enables parents to recognize and understand their child's problems, such as behavioral and learning disabilities and developmental delays, and to seek appropriate help early. Early diagnosis of BBS also allows patients to be monitored for renal malformations, which are a leading cause of morbidity and mortality in individuals with BBS, but often remain unnoticed until renal failure occurs.

For the current number of variants in *BBS1*, *BBS2*, and *BBS10*, please visit <http://www.correlagen.com/fields/endocrinology/endocrinology.jsp>

How Is Genetic Testing for BBS Performed?

DNA for sequencing is obtained from leukocytes present in a small blood sample. The coding sequences of *BBS1*, *BBS2*, and *BBS10* are amplified in a highly specific manner through a polymerase chain reaction (PCR), and all PCR products are fully sequenced. Sequencing results are interpreted, and a detailed result report is sent to the patient's physician.

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For information on ordering the Bardet-Biedl Syndrome (*BBS1*, *BBS2*, *BBS10*) Evaluation, #887 call Athena Diagnostics' Customer Service Representatives at

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