Diagnosing Bardet-Biedl Syndrome (BBS):

Take a closer look

Discover more about this clinically and genetically diverse disease and how it may present in your patients

Actor portrayal

BBS is a rare autosomal recessive ciliopathy that is clinically and genetically diverse[1]

Almost all major body systems contain primary cilia, which are vital to several biological processes[2,3]

BBS ciliary dysfunction impairs various systems throughout the body[1,2]

Brain[1,4]

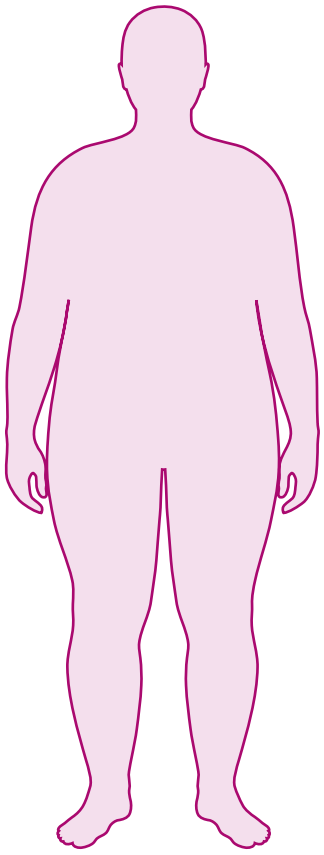
- Hyperphagia
- Early-onset obesity **72–92%**
- Cognitive impairment **61%**

Kidneys[1,5]

- Renal anomalies **53–82%**

Reproductive[1,6]

- Hypogonadism **59–98%**



Eyes[1,7]

- Rod-cone dystrophy/ retinitis pigmentosa **93%**

Skeletal[1]

- Polydactyly **63-81%**

Additional clinical features of BBS may include[1,8]:

- **Brain:** speech delay, developmental delay, ataxia/poor coordination, anosmia/hyposmia
- **Endocrine:** diabetes mellitus
- **Heart:** congenital heart disease
- **Skeletal:** dental anomalies, brachydactyly, syndactyly

Primary cilia dysfunction within each organ system contributes to the highly variable phenotype in BBS[9]

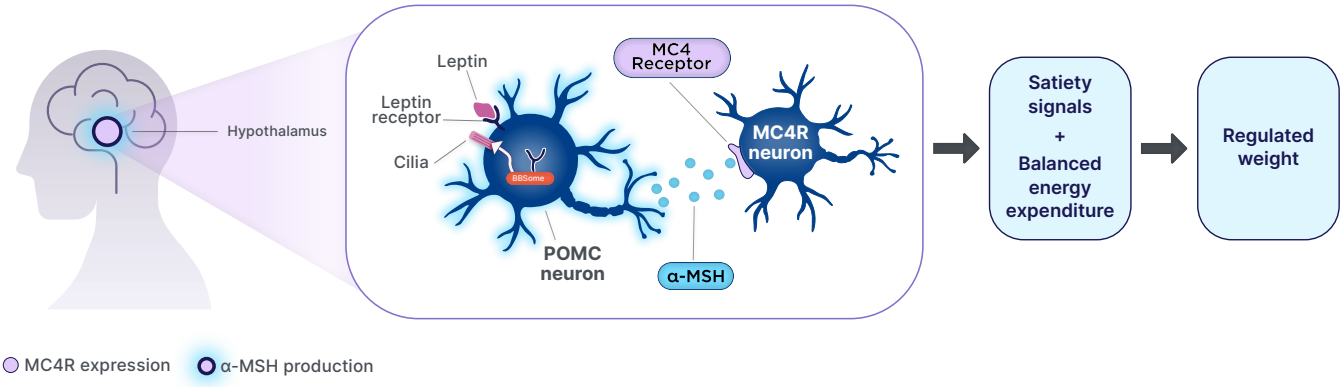
The MC4R pathway is a key signaling pathway in the hypothalamus that regulates hunger and energy expenditure

Functional MC4R pathway activity[2,4,10]

The BBSome plays a central role in cilia function, including trafficking of the leptin receptors (LEPR) to allow leptin activation and satiety signaling.

Leptin binding to the LEPR triggers a signaling cascade, including secretion of alpha-melanocyte stimulating hormone (α-MSH) from the POMC neuron. α-MSH binds to the MC4 receptor.

Activation of the MC4R pathway regulates hunger and satiety, and energy expenditure, so weight and energy remain in balance.



MC4R expression | α-MSH production

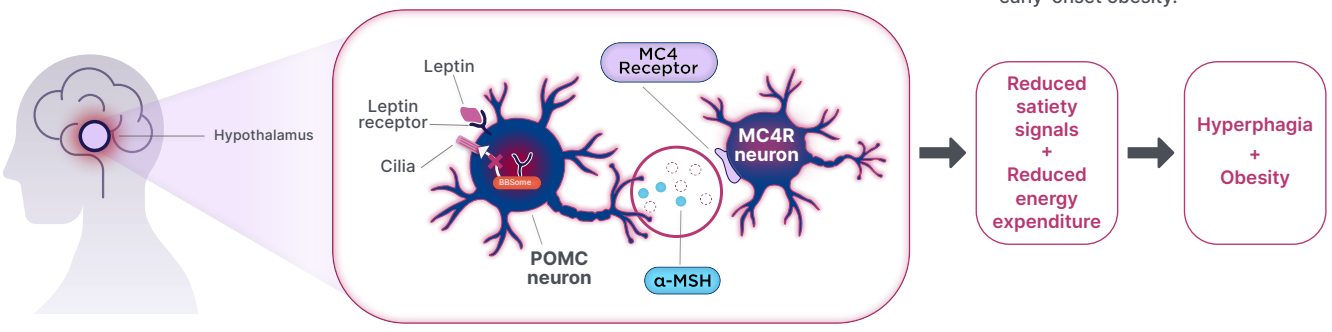
Impaired MC4R pathway activity[2,4,10,11]

Unlike general obesity, a root cause of obesity in BBS is impairment of the MC4R pathway which can occur due to ciliary dysfunction

In people with BBS, a variant in one or more *BBS* genes can disrupt the BBSome. This causes ciliary dysfunction and disruption of LEPR signaling.

Alpha-melanocyte-stimulating hormone (α-MSH) production is impaired, or deficient, preventing activation of the MC4 receptor.

Impairment of the MC4R pathway leads to decreased satiety signaling, hyperphagia, and reduced energy expenditure. This often leads to early-onset obesity.



MC4R expression | Decreased α-MSH production

BBSome: A complex of proteins formed by a host of *BBS* genes | Cilia: A structure that plays an important role in cell signaling, protein trafficking, tissue formation, cell motility, and homeostasis | Leptin: A satiety hormone | MC4R: melanocortin-4 receptor | POMC: proopiomelanocortin

How BBS can present in your practice

MOST COMMON CLINICAL FEATURES	CLINICAL MANIFESTATIONS	POTENTIAL ASSESSMENTS
Hyperphagia[12]	**A chronic, pathological condition characterized by insatiable hunger and impaired satiety, accompanied by:** • Persistent abnormal food-seeking behavior • Prolonged time to satiation and shortened duration of satiety • Prolonged hunger	• Hyperphagia questionnaires • Follow up with patients/caregivers regarding behaviors around food
Obesity[4,8,13,14]	• **Early-onset obesity, typically diffuse in children and truncal in adults** • Normal birth weight, followed by rapid weight gain	• Growth chart • Track patients' BMI/BMI Z-score over time
Visual impairment[6–8,15]	• Rod-cone dystrophy atypical retinitis pigmentosa. Symptoms include: – Night blindness – Photophobia – Loss of central and color vision – Overall loss of visual acuity – Legal blindness • Less common features may include: – Astigmatism – Strabismus – Cataracts – Color blindness – Macular edema and degeneration	• Opthalmologic consultation – Electroretinography test (older children and adults)
Cognitive impairment[7,15]	• Developmental delay (gross motor, fine motor, speech*/language) • Mild to moderate learning difficulties • Behavioral problems (immaturity, frustration, obsessive/compulsive nature, poor concentration/hyperactivity) • Gaze avoidance **See* Speech delays and deficits *on the next page*	• Developmental and/or neurocognitive assessment • Routine developmental assessments from early childhood to adulthood • Neuropsychiatric evaluation if signs/symptoms of atypical behaviors or mood disorder
Renal anomalies[7,8,15–18]	• Cystic tubular disease • Anatomical malformations • Urinary tract abnormalities • Hypertension • Chronic renal failure • Polyuria/polydipsia • Chronic tubulointerstitial nephritis • Glomerular defects • Anatomical malformations at birth, including parenchymal cysts, calyceal cysts, calyceal clubbing and blunting, horseshoe kidney, fetal lobulation, scarring, unilateral renal agenesis, dysplastic kidneys, bladder obstruction, hydronephrosis, ectopic kidney, renal calculi, and vesicoureteral reflux	• Renal ultrasound • Blood pressure (24-hour monitoring, if needed) • Laboratory assessments including eGFR, CBC, serum electrolytes, creatine, BUN, cystatin C • Nephrology review
Digit abnormalities[8,15]	• Postaxial polydactyly • Less common features may include: – Brachydactyly – Syndactyly	Physical examination or discussion with older patients/caregivers as extra digits are typically surgically removed in early childhood

(**Most common clinical features** cont'd on next page)

How BBS can present in your practice (cont'd)

MOST COMMON CLINICAL FEATURES	CLINICAL MANIFESTATIONS	POTENTIAL ASSESSMENTS
Genitourinary abnormalities[6–8,15]	**In males:** • Hypogonadism • Micropenis, small-volume testes, maldescent of testes, cryptorchidism, hypogonadotropic hypogonadism, delayed puberty, infertility **In females:** • Uterine, fallopian, ovarian, or vaginal hypoplasia	• Laboratory tests (if indicated due to delayed puberty) – Follicle-stimulating hormone – Luteinizing hormone – Estrogen **In females:** • Pelvic ultrasound to assess for malformations of uterus, fallopian tubes, ovaries, and vagina

ADDITIONAL CLINICAL FEATURES	CLINICAL MANIFESTATIONS	POTENTIAL ASSESSMENTS
Dental anomalies[7,17]	• Crowding • Malocclusion/micrognathia • Enamel hypoplasia • Discoloration • Microdontia • Taurodontism or short roots • Hypodontia • High-arched or deep palate • Periodontal disease	• Dental exam
Congenital heart disease[8,15]	**Abnormalities are highly variable. Examples include:** • Valvular stenosis • Patent ductus arteriosus • Cardiomyopathy	• Echocardiogram • Abdominal ultrasound to assess for laterality defects
Speech delays and deficits[7,8,19–21]	• High-pitched nasal speech/poor articulation • Unintelligible speech before age of 4 • Palatal incoordination • Consonant omissions/substitutions • Poor language interpretation	• Ages and Stages Questionnaires • Language Development Survey • MacArthur-Bates Communicative Development Inventories
Neurological deficits[7,8]	• Ataxia • Clumsiness • Poor coordination and balance • Abnormal gait	
Diabetes Mellitus[1,7,22]	• Non-insulin-dependent diabetes	• Fasting plasma levels of: – Glucose – Insulin • Other biochemical metrics, such as: – HbA1c – Homeostatic model assessment of insulin resistance

BBS has a highly variable phenotype with key identifiable features[1]

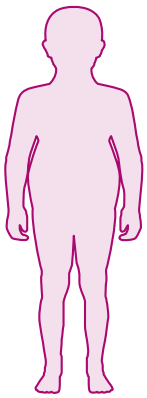
BBS is clinically and genetically diverse, so not all people with BBS will present the same way or with all of these most common features[1]

	Birth	**First years of life** (0 to 5 years)	**Early childhood** (up to 10 years)	**Adolescence to adulthood** (>10 years)
Polydactyly[8,15]	Extra digits (postaxial)	Typically surgically removed		
Renal anomalies[16]	Anatomical malformations	Progressive kidney disease	Polyuria/Polydipsia	Chronic kidney disease
Hyperphagia and early-onset obesity[8,13,23,24]	Normal birth weight	Rapid weight gain leading to early-onset, severe obesity, unusual food seeking	Hyperphagia and severe obesity persist	Continued hyperphagia and severe obesity persist, presenting as truncal obesity for adults
Cognitive impairment[7,8]		Developmental delay, speech delay	Specialized schooling needs, behavioral difficulties	Learning difficulties
Visual impairment[8,25]			Progressive vision loss, night blindness	Legal blindness
Hypogonadism[7,8]				Delayed puberty, genital anomalies

Due to the multisystemic nature of BBS, it may be diagnosed by various specialists from childhood to adulthood

Recognizing BBS

In children[26]

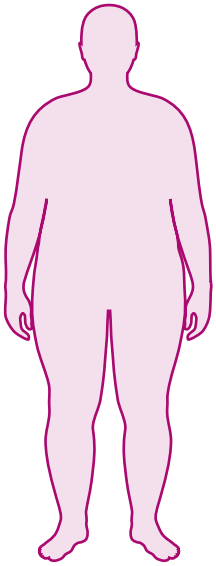


Due to the progressive onset of clinical symptoms, patients may not meet the diagnostic criteria early in life, leading to a potential delay in diagnosis

- Therefore, genetic testing may play a critical diagnostic role in young children

Diagnosing patients as early as possible is key to reducing their weight gain trajectory and managing associated obesity outcomes. It may also help reduce the burden of hyperphagia.

In adults[7,26,27]



Many people with BBS over 30 years may not have been diagnosed as children due to the following limitations:

- Clinical diagnosis: Clinical diagnosis criteria were newly defined when they were children; clinical recognition of the syndrome also remains low due to variability in phenotypical presentation
- Genetic confirmation: In 1999, only 4 of the current *BBS* genes had been identified; also, there has been historically low genetic testing utilization due to a lack of availability, insurance coverage, and treatment for BBS

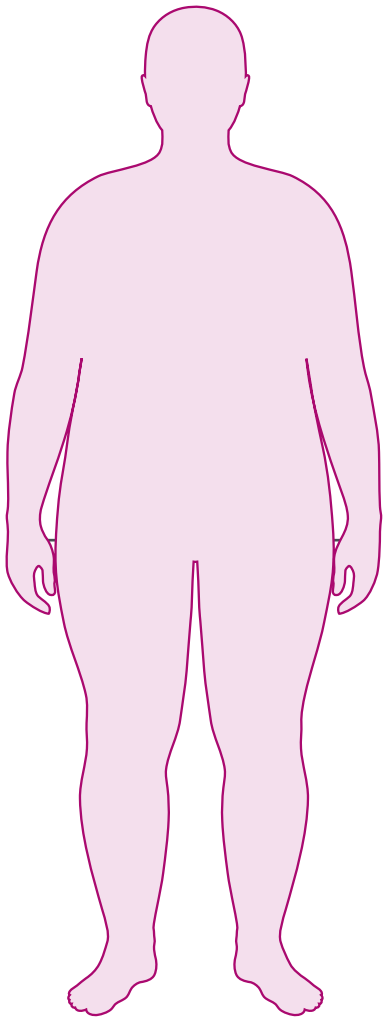
It is important to recognize the symptoms of BBS in adults to ensure they are diagnosed appropriately.

BBS is clinically and genetically diverse[1]

Factors to consider when clinically diagnosing BBS

Clinical manifestations[8]

- BBS is a ciliopathy with a highly variable phenotype and clinical features that vary greatly across individuals and evolve over time
- Some features may present more mildly or slowly depending on the gene variant and other factors



Genetics[1,28]

- Genetic testing for BBS can provide additional diagnostic information to help inform your diagnosis; for more information, visit **UncoveringRareObesity.com**
- Results should be integrated into the overall clinical assessment of the patient and do not equate to a diagnosis on their own; additionally, variant interpretation may change over time as the information about the genetics of BBS continues to evolve

Patient history

- Review patients' complete medical history; some clinical manifestations of BBS may have been previously treated and/or not recognized as a symptom of BBS

Family findings[1,15]

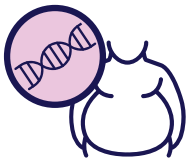
- Family members have an increased risk of inheriting a pathogenic *BBS* gene
- Once one family member is diagnosed, others should be evaluated for BBS as well
- Phenotype can vary between family members

Consider the complete patient presentation when making a diagnosis

Dedicated ICD-10 code for BBS—Q87.83

Expand your perspective on BBS

Factors to consider when diagnosing BBS



BBS is a rare autosomal recessive ciliopathy[1]

- Impairment of the MC4R pathway is a root cause of hyperphagia and early-onset obesity, 2 common features of BBS[2,4]
- Other common features may include visual impairment, cognitive impairment, renal anomalies, polydactyly, and hypogonadism[8,11]

BBS is clinically and genetically diverse, so consider the complete patient presentation[1]

- BBS is a multisystemic disorder with a highly variable phenotype that can evolve over time[1]
- Clinical manifestations, genetics, patient history, and family findings should all be considered when making a diagnosis

To learn more about a treatment for obesity due to BBS **CLICK HERE**

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