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[1]

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BBS IS A RARE AUTOSOMAL RECESSIVE CILIOPATHY THAT IS CLINICALLY AND GENETICALLY DIVERSE[1,2]

Almost all major body systems contain primary cilia, which are vital to several biological processes[32,33]

BBS ciliary dysfunction impairs various systems throughout the body[32]

Brain[4,15,16]

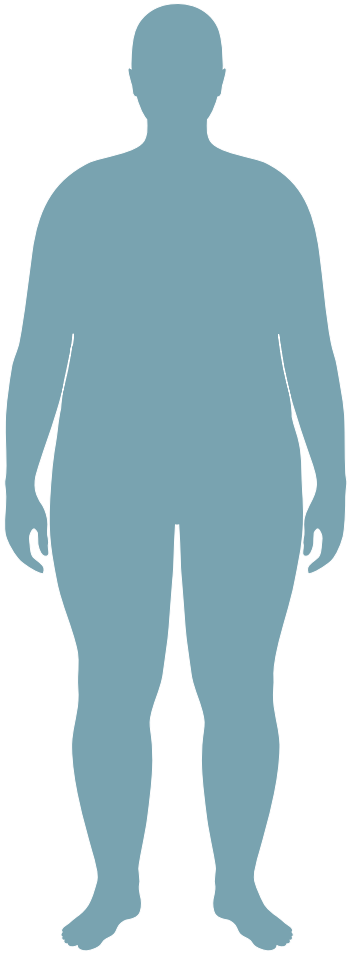
- **Hyperphagia and consequent obesity**
- **Cognitive impairment**

Kidney[15,32]

- **Renal anomalies**

Reproductive[13]

- **Hypogonadism**



Eyes[5,13]

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

Skeletal[5]

- **Postaxial polydactyly**

Additional clinical features of BBS may include[5,15,23]

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

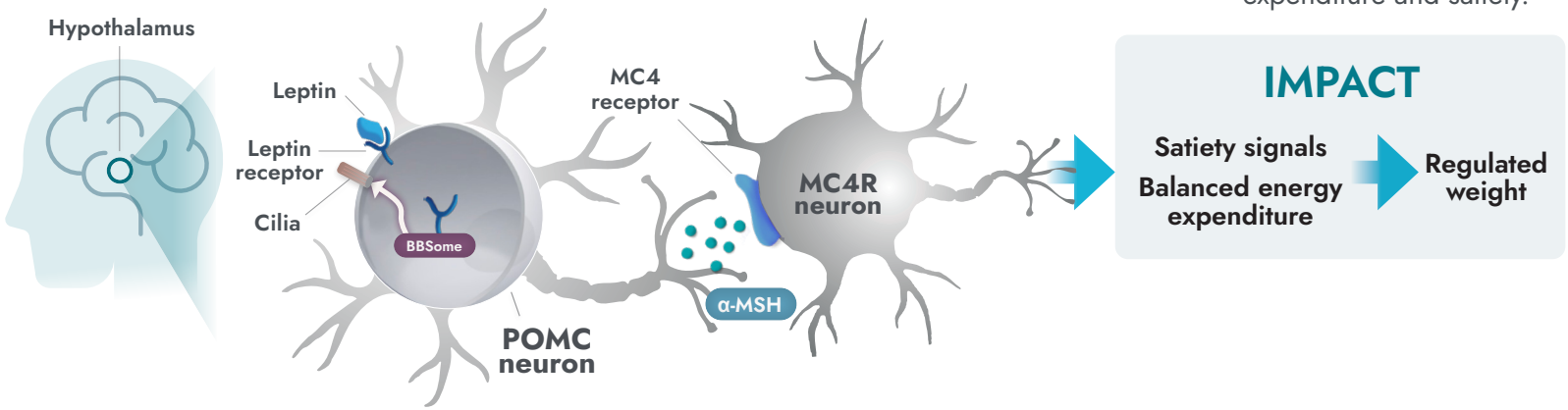
Primary cilia dysfunction within each organ system contributes to the highly variable phenotype in BBS[34]

THE MC4R PATHWAY IN THE HYPOTHALAMUS IS A KEY NEURONAL PATHWAY IN REGULATING HUNGER, CALORIC INTAKE, AND ENERGY EXPENDITURE[4]

Functional MC4R pathway activity[4,32,35,36]

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 LEPR triggers a signaling cascade, including secretion of alpha-melanocyte-stimulating hormone (α-MSH) from the POMC neuron, which binds to the MC4 receptor to regulate energy expenditure and satiety.

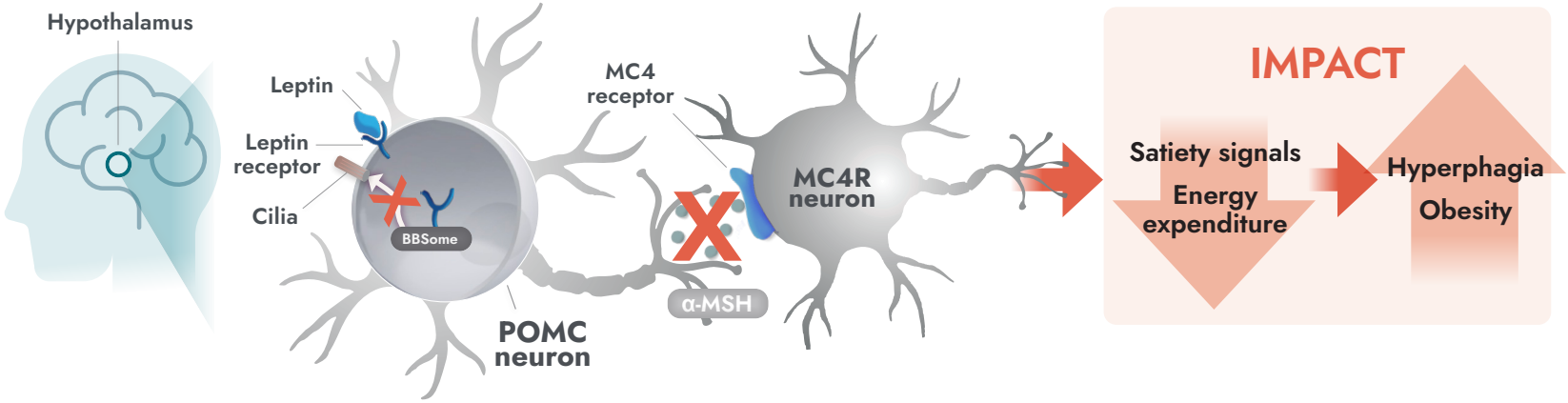


Ciliary dysfunction in the hypothalamus leads to MC4R pathway impairment, which is a root cause of hyperphagia and obesity in BBS[4,32]

Impaired MC4R pathway activity[4,35,36]

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

Alpha-melanocyte-stimulating hormone (α-MSH) production is impaired or deficient, preventing activation of the MC4 receptor, therefore impairing regulation of energy expenditure and satiety signaling.



BBSome: A complex of proteins formed by a host of BBS genes[37] | **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[4,7,8]	• Pathological, insatiable hunger • Long time to satiation • Shorter duration of satiation	• Prolonged feeling of hunger • Severe preoccupation with food and distress if denied food, often associated with abnormal food-seeking behaviors	• Utilizing hyperphagia questionnaires, following up with patients/caregivers regarding their behaviors around food
Obesity[5,10-12]	• Early-onset truncal obesity • Normal birth weight, followed by rapid weight gain		• Growth chart, tracking patients' BMI/ BMI Z-score over time
Visual impairment[5,13-15]	• Rod-cone dystrophy/retinitis pigmentosa (including night blindness, photophobia, legal blindness, diminution of color, overall loss of visual acuity)	• Less common features may include: – Strabismus – Astigmatism – Cataracts – Color blindness – Macular edema and degeneration – Optic atrophy	• Electroretinography test (for retinitis pigmentosa only)
Cognitive impairment[15,16]	• Developmental delay (gross motor, fine motor, speech/ language) • Mild to moderate learning difficulties • Speech delays, poor articulation, poor language interpretation	• Behavioral problems (immaturity, frustration, obsessive/compulsive nature, poor concentration/ hyperactivity) • Gaze avoidance • Lack of abstract thought	• 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[5,15,18-20]	• Cystic tubular disease • Anatomical malformations • Urinary tract abnormalities • Hypertension • Chronic renal failure • Transplantation • Polyuria/polydipsia • Chronic tubulointerstitial nephritis • Glomerular defects	• Urinary concentrating 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	• Regular monitoring/testing of renal function is recommended to diagnose and treat CKD early to prevent morbidity and mortality • Ultrasound scan, isotope renography, labs (raised plasma urea and creatinine levels), intravenous pyelogram, renal ultrasonography, renal biopsy

Digit abnormalities[5]	• Postaxial polydactyly • Brachydactyly • Syndactyly		• Physical examination or discussion with older patients/caregivers because extra digits are typically surgically removed in early childhood
Genitourinary abnormalities[5,13,15,16]	**In males:** • Hypogonadism • Micropenis, small-volume testes, maldescent of testes, cryptorchidism, hypogonadotropic hypogonadism, delayed puberty, infertility	**In females:** • Uterine, fallopian, ovarian, or vaginal hypoplasia or atresia • Low fertility rates	• Check follicle-stimulating hormone, luteinizing hormone, estrogen, and testosterone levels if indicated due to delayed puberty • Pelvic ultrasound in females to assess for malformations of uterus, fallopian tubes, ovaries, and vagina

Additional clinical features	Clinical manifestations		Potential assessments
Dental anomalies[5,15,23]	• Crowding • Malocclusion/micrognathia • Enamel hypoplasia • Discoloration	• Microdontia • Taurodontism or short roots • High-arched or deep palate • Periodontal disease	• Dental exam
Congenital heart disease[5]	• Valvular stenosis • Patent ductus arteriosus • Cardiomyopathy		• Echocardiogram, chest x-ray
Speech delay[5,38-40]	• High-pitched nasal speech • Speech delay and deficits • Unintelligible speech		• Assessments, such as Ages and Stages Questionnaires, the Language Development Survey, and the MacArthur-Bates Communicative Development Inventories
Neurological deficits[5,15,16]	• Ataxia • Clumsiness • Poor coordination and balance		• MRI

BBS HAS A HIGHLY VARIABLE PHENOTYPE WITH KEY IDENTIFIABLE FEATURES[5]

BBS is clinically and genetically diverse, so not all people with BBS will present the same way or with all of these features[1,2]

	Birth	First years of life (0 to 5 years)	Early childhood (up to 10 years)	Adolescence to adulthood (>10 years)
Postaxial polydactyly[5,16,21,22,27]	Extra digits (postaxial)	Typically surgically removed		
Renal anomalies[5,16,18]	Anatomical malformations	Progressive kidney disease	Polyuria/Polydipsia	Chronic kidney disease
Hyperphagia and obesity[4,5,7,28,29]	Normal birth weight	Rapid weight gain leading to early-onset, severe obesity, unusual food seeking	Hyperphagia and severe obesity persists	Continued severe obesity and hyperphagia persist, presenting as truncal obesity for adults
Cognitive impairment[5,15]		Developmental delay, speech delay	Specialized schooling needs, behavioral difficulties	Learning difficulties
Visual impairment[5,30]			Progressive vision loss, night blindness	Legal blindness
Hypogonadism[5,15]				Delayed puberty, genital anomalies

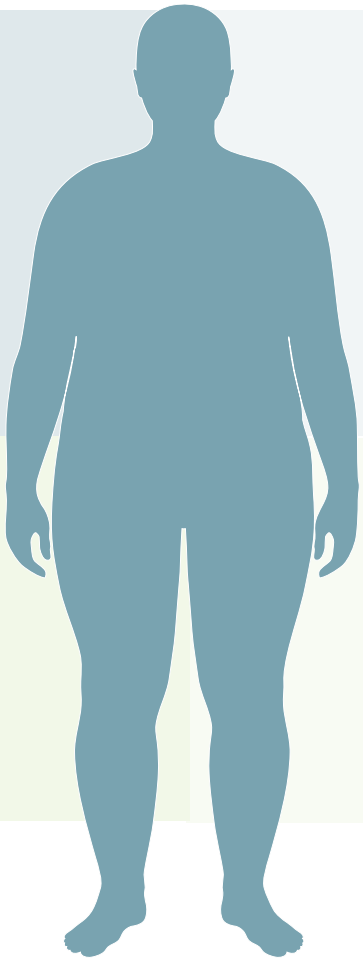
Due to the multisystemic nature of BBS, it may be diagnosed by various specialists from childhood to adulthood

BBS IS CLINICALLY AND GENETICALLY DIVERSE

Factors to consider when diagnosing BBS

Clinical manifestations[1,2,5]

- 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 gene variant and other factors



Genetics[1]

- 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 around the genetics of BBS continue 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[2,16]

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

Announcing the ICD-10 code for BBS **Q87.83**—effective as of October 1, 2023

Consider the complete patient presentation when making a diagnosis

EXPAND YOUR PERSPECTIVE ON BBS

BBS is a rare autosomal recessive ciliopathy[1,2]

- Impairment in the MC4R pathway is a root cause of hyperphagia and obesity, 2 common features of BBS[4]
- Other common features may include visual impairment, cognitive impairment, renal anomalies, postaxial polydactyly, and hypogonadism[2,5,6]

BBS is clinically and genetically diverse, so consider the complete patient presentation[1,2]

- BBS is a multisystemic disorder with a highly variable phenotype that can evolve over time[1,5]
- Clinical manifestations, genetics, patient history, and family findings should all be considered when making a diagnosis

Click here to learn about a treatment for obesity due to BBS

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