Bardet-Biedl syndrome

Bardet-Biedl syndrome (BBS) is a rare, autosomal disease resulting from genetic variants within the BBS family of genes.

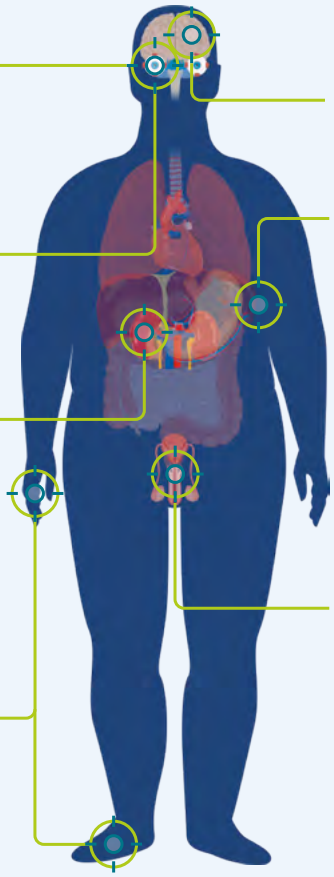
This disease presents with a variety of clinical features, some of which are present from birth, while others evolve over time. These features are attributed to impairments in the melanocortin-4 receptor (MC4R) pathway.[1]

Solomon, living with BBS

Prevalence:

Prevalence estimates may increase as more healthcare providers become aware of the clinical features of BBS and genetically test to aid in clinical diagnosis[3]

Key clinical features of BBS[1,4,5]



Hyperphagia
(pathological, insatiable hunger leading to obsessive food-seeking behaviours and abnormal food intake)

93%
Rod-cone dystrophy

53%
Renal anomalies

63% to 81%
Polydactyly

61%
Learning difficulties

72% to 92%
Obesity

59% to 98%
Genital anomalies

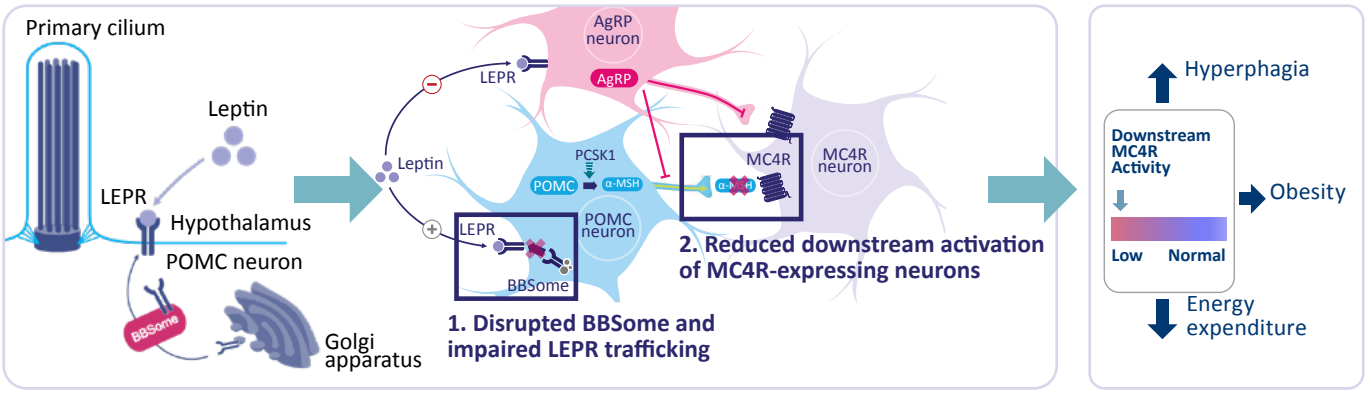
Percentages represent frequency of feature appearance among individuals diagnosed with BBS. The clinical features vary greatly in presence and severity.[1]

26 genes and 4 modifier loci associated with BBS are involved in the MC4R pathway.[5]

Eight BBS proteins form a stable complex, the BBSome, which contributes to cilia development and function by trafficking intracellular proteins to ciliary membranes and potentially to other membrane compartments.[6]

Variants in BBS genes disrupt the BBSome, resulting in ciliary defects and impaired signalling of receptors that regulate body weight, such as LEPR.[6-10]

This disrupts LEPR signalling, reducing activation of MC4R-expressing neurons, and can lead to hyperphagia and early-onset obesity.[6-10]



Abbreviations: AgRP, agouti-related peptide; α-MSH, α-melanocyte-stimulating hormone; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; NPY, neuropeptide Y; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

The European Reference Networks (ERN) diagnostic criteria prioritise genetic testing and streamline clinical criteria for diagnosis of BBS, which may support more accurate diagnosis[5]

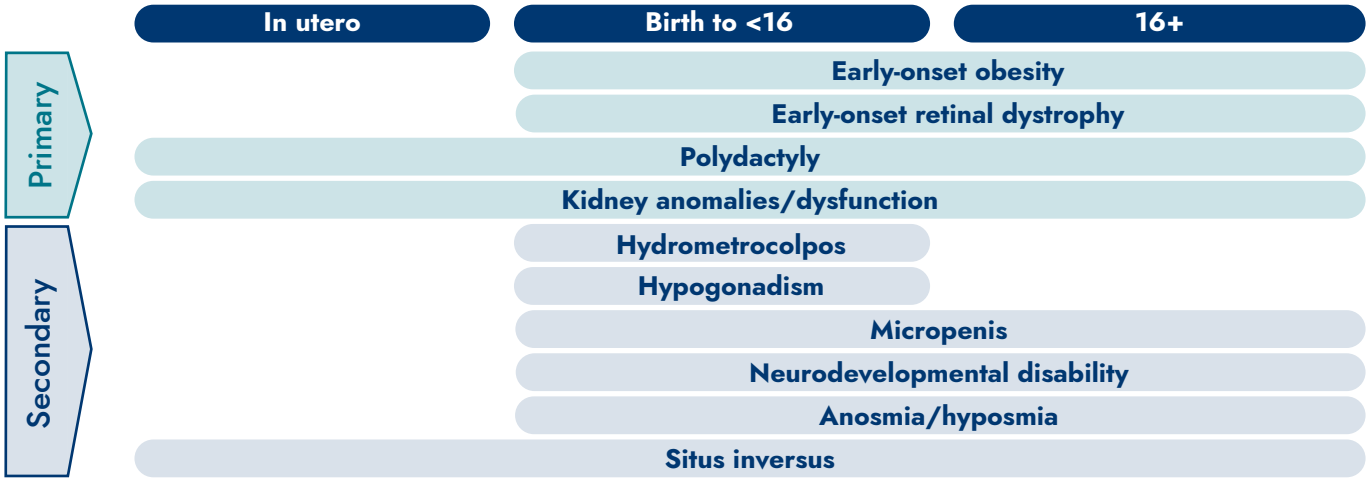
Requirements for BBS diagnosis

Patient age	With high level of confidence	With high level of confidence, when genetic testing not available	With moderate level of confidence
In utero	Positive foetus BBS genetic test + 1 PRIMARY feature		Positive affected sibling BBS genetic test + 1 (patient) PRIMARY feature OR 2 (patient) PRIMARY + 1 (patient) SECONDARY features
0-16 Birth to <16 years	Positive BBS genetic test + 1 PRIMARY feature	At least 4 PRIMARY features OR At least 3 PRIMARY + 2 SECONDARY features	If genetic testing not available, positive affected sibling BBS genetic test + 2 (patient) PRIMARY features
16+ From 16 years old and adult	Positive BBS genetic test + retinal dystrophy + 1 other PRIMARY feature	Retinal dystrophy + at least 3 other PRIMARY features OR Retinal dystrophy + at least 2 other PRIMARY features + at least 3 other SECONDARY features	If genetic testing not available, positive affected sibling BBS genetic test + 2 (patient) PRIMARY features

Clinical features relevant to age stratification[5]

Hyperphagia is recognised as an issue in most children and adolescents and routine monitoring, for example using the hyperphagia Dykens questionnaire, is recommended

Early-onset obesity, especially if retinal dystrophy is present, should prompt for BBS genetic testing



Genetic confirmation[11-13]

A genetic diagnosis of BBS can make a significant difference to an individual's life by:

- Improving access to appropriate care
- Empowering the individual and carers to understand the root cause of their disease and make informed decisions about their care
- Reducing the social stigma of obesity and providing coping strategies for managing stigmatisation
- Allowing for preventive or prophylactic screening of associated conditions

References: 1. Forsythe E, et al. *Front Pediatr.* 2018;6:23. 2. Tsang SH, et al. *Advances in Experimental Medicine and Biology.* 2018:1085. 3. Suspitsin EN, Imyanitov EN. *Mol Syndromol.* 2016;7:62–71. 4. Forsythe E, et al. *Eur J Hum Genet.* 2013:21:8–13. 5. Dollfus H, et al. *Eur J Hum Genet.* 2024;32(11):1347–1360. 6. Guo DF and Rahmouni K. *Trends Endocrinol Metab.* 2011;22(7):286–293. 7. Seo S, et al. *Hum Mol Genet.* 2009;18(7):1323–1331. 8. Wang L, et al. *J Clin Invest.* 2021;131(8):146287. 9. Loos RJF and Yeo GSH. *Nat Rev Gens.* 2022;23:120–13. 10. Yazdi FT, et al. *Peer J.* 2015;3:e856; 11. Styne DM, et al. *J Clin Endocrinol Metab.* 2017;102(3):709–757. 12. August GP, et al. *J Clin Endocrinol Metab.* 2008;93(12):4576–4599. 13. Kleinendorst L, et al. *BMJ Case Rep.* 2017:bcr2017221067.

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