Bardet biedl syndrome

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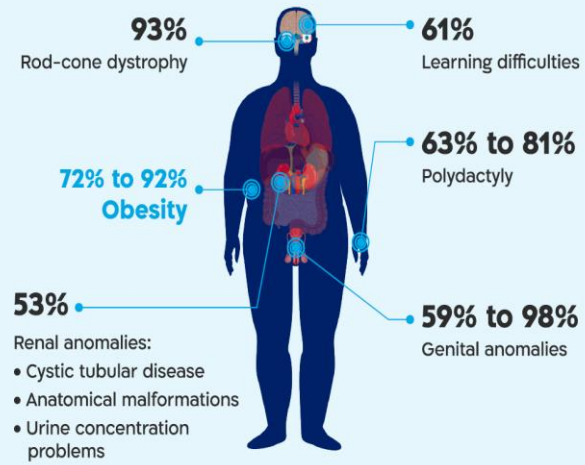
Introduction

- In 1866, Laurence and Moon described a family of four siblings with retinal dystrophy, obesity, and cognitive deficit.
- Bardet and Biedl later reported separately on further similarly affected individuals who in addition had post-axial polydactyly
- The condition was coined Laurence–Moon–Bardet–Biedl syndrome.
- BBS is now the standard term in common usage.

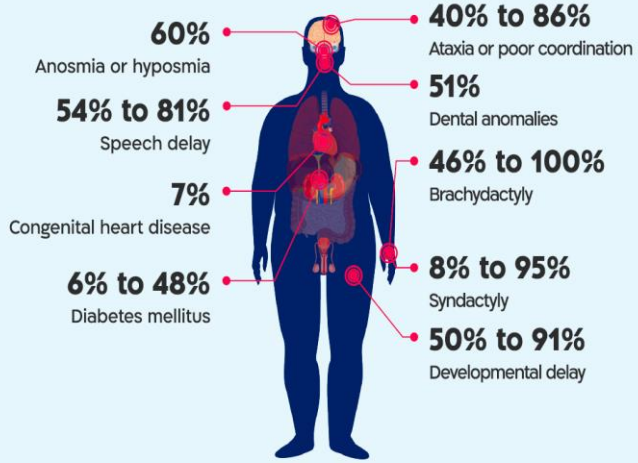
Epidemiology

- The prevalence in North America and Europe, ranges between 1:120,000 and 1:160,000 individuals.
- In some isolated communities, due to increased marriages among consanguineous, it is far higher: 1:13,500 among Bedouins and 1:3700 in Faroe Islands.

Primary Clinical Manifestations[3]

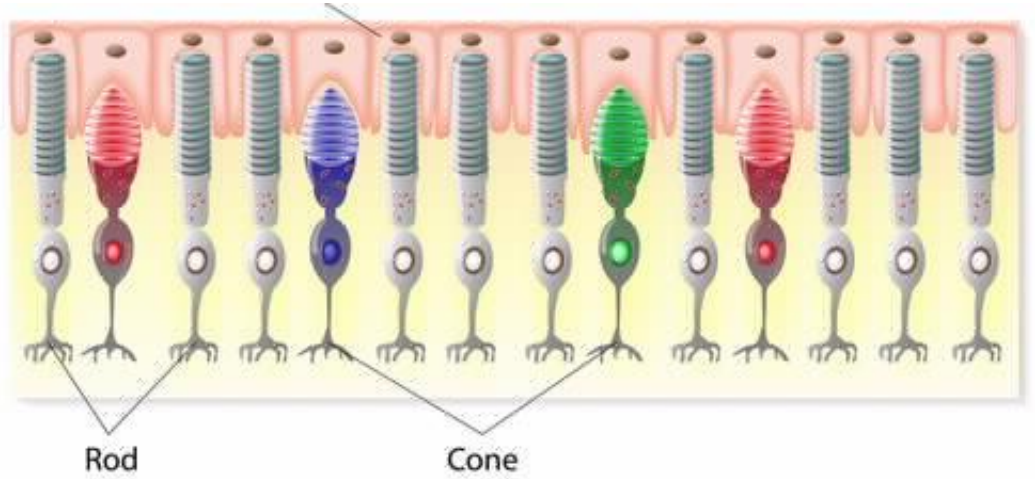


Secondary Clinical Manifestations[3,4]



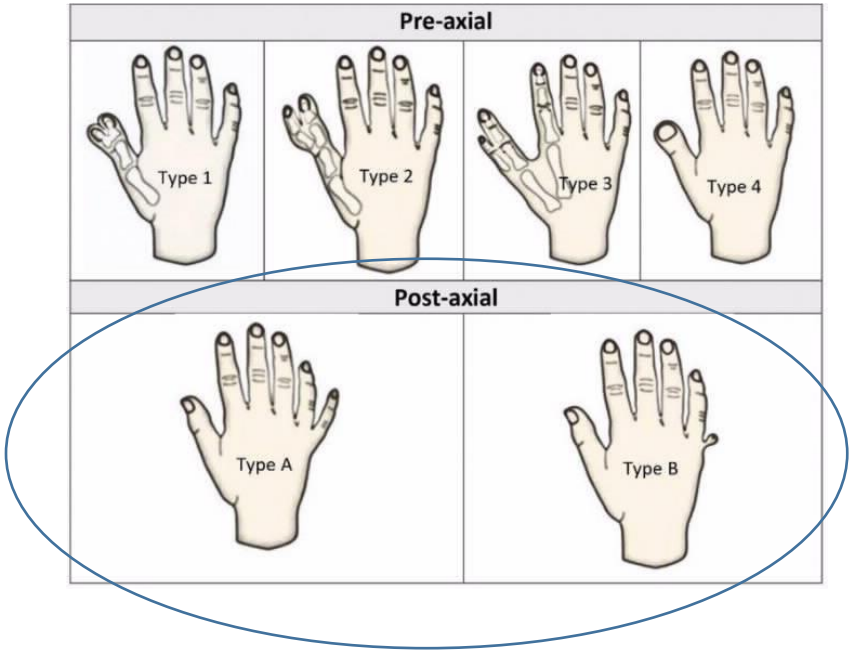
Retinal Dystrophy

- Atypical retinitis pigmentosa with early macular involvement.
- Primary loss of rod photoreceptors is followed by later demise of cone photoreceptors.
- The clinical manifestation is gradual onset of night blindness, followed by photophobia and loss of color vision.



polydactyly

- Post-axial polydactyly is common (63-81%) and may be the only obvious dysmorphic feature at birth.
- Polydactyly can be present in all four limbs (21%), only on the hands (8%) or only on the feet (21%).



Obesity

- Incidence is reported to be 72–92% in the BBS population.
- Birth weight is usually within the normal range
- One-third of those with a normal birth weight develop obesity by the age of one year
- Pathogenesis is multifactorial and includes both central and peripheral control of energy expenditure.

Hypogonadism

- Hypogonadism or genitourinary abnormalities are present in 59% of BBS subjects.
- Patients can manifest delayed onset of secondary sexual characteristics
- Males may have cryptorchidism (9%), micropenis and small volume testes
- Female have often irregular menstrual cycle and polycystic ovaries and may have malformed uterus, vaginal atresia and other genital anomalies

Renal

- In a recent French study, renal abnormalities were documented in 82% of the BBS cohort including 33 BBS patients
- Kidney abnormalities in BBS are both anatomical and functional
- Anatomic lesions include fetal lobulation, cystic dysplasia, small kidneys, horseshoe and ectopic/duplex/absent kidneys
- Polyuria/polydypsia linked to a vasopressin-resistant urinary concentration defect is present in approximately one-third of patients.
- Low urinary tract defects, as neurogenic bladder, bladder outflow obstruction or vesicoureteral reflux have been reported in 5–10% of adults.
- Urinary tract infections are frequently reported.

Renal

- Renal tubular acidosis and Fanconi syndrome are rarely associated. Glomerular signs are consistently absent.
- In some cases, the first renal manifestation may be chronic or end-stage renal disease (ESRD)
- According to O'Dea et al., 25% of BBS patients have chronic renal failure by age 48 and 10% develop ESRD in childhood or adolescence
- Renal transplantation has been successfully performed. The major problem in these patients is the exacerbation of severe obesity
- Hypertension may be observed early in life and is present in 30–50% of patients by age 34 and globally in two-thirds of the patients

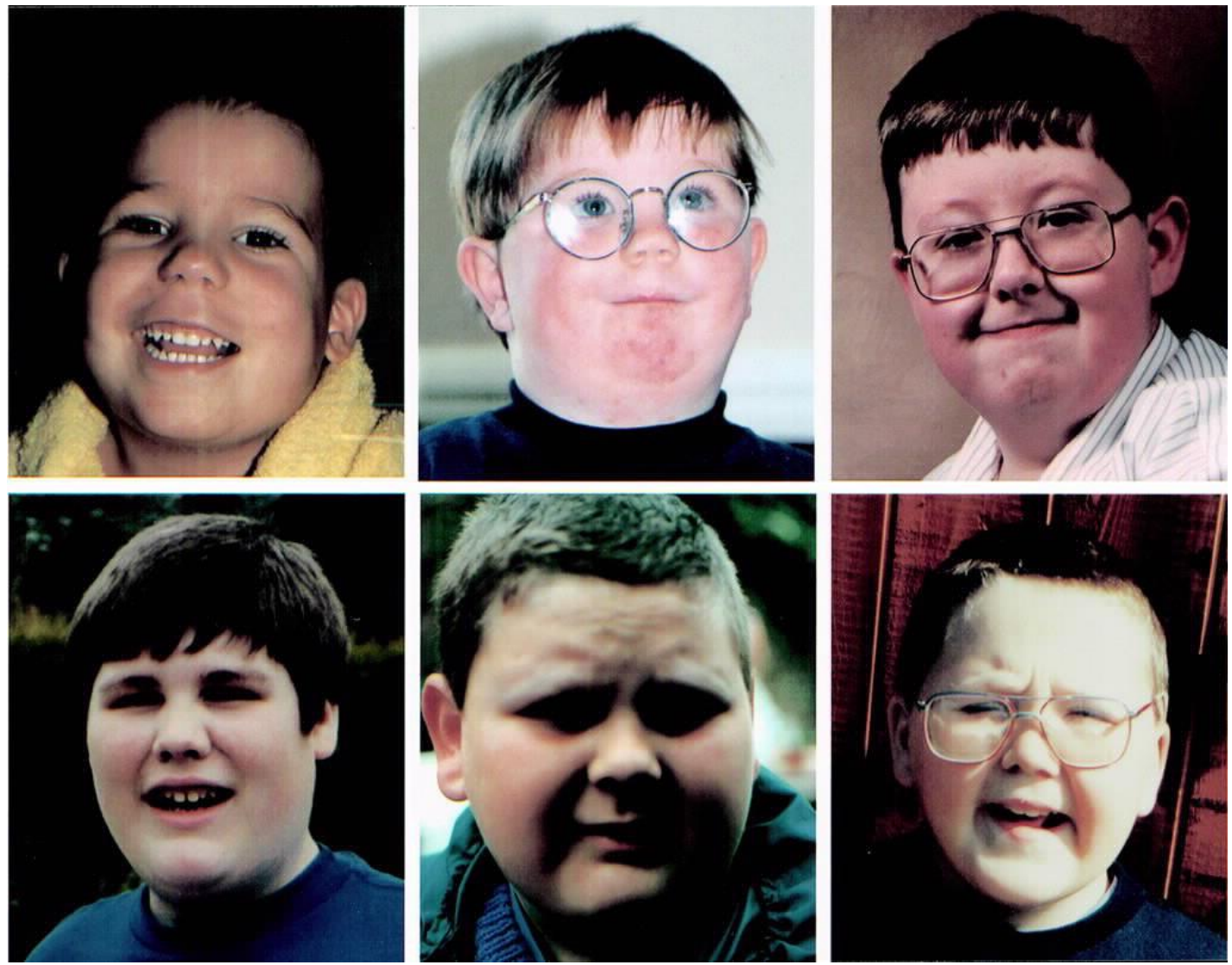
Other manifestations

- Global developmental delay and cognitive deficit are common in BBS.
- Behavioral anomalies have an incidence of 33%. Autism-related signs were present in 77% of participants
- Cardiac abnormalities (7-50%) include valvular stenoses, patent ductus arteriosis and cardiomyopathies
- GI involvement including liver disease
- Anosmia

Diagnosis

The diagnosis of BBS is based on clinical criteria published by Beales et al. and requires the presence of at least **four primary features or three primary features and two secondary features**

Primary Diagnostic Features	**Secondary Diagnostic Features**	**Described BBS Features Non Included in the Diagnostic Criteria**
Retinal Degeneration	Strabismus, cataracts, and astigmatism	Cutaneous Dermatoses
Obesity	Metabolic/endocrine abnormalities (metabolic syndrome, subclinical hypothyroidism, polycystic ovary s.)	Hearing loss
Postaxial polydactyly	Brachydactyly/syndactyly	Asthma
Renal Anomalies	Anosmia/olfactory dysfunction	Dysregulated immune and hematopoietic systems
Learning Disabilities	Neurodevelopmental abnormalities (developmental delay, speech delay, epilepsy, behavioral disturbances, ataxia/poor coordination, mild spasticity)	Musculoskeletal abnormalities
Hypogonadism and Genitourinary Abnormalities	Liver and other gastrointestinal diseases (Hirschsprung disease, inflammatory bowel disease, celiac disease)	
	Cardiovascular and thoraco-abdominal abnormalities	



Genetics

Table 2 Known Causative Genes of Human Bardet–Biedl Syndrome[88,144,145]

Gene	Name	Chromosomal Coordinate	Localization of the Protein in the Cell	Tissue Specificity	Protein Function
BBS1	Bardet-Biedl syndrome 1	11q13.2	Cilium and basal body	Low	Component of BBSome complex
BBS2	Bardet-Biedl syndrome 2	16q13	Cilium and basal body	Low	Component of BBSome complex
BBS3/ARL6	Bardet-Biedl syndrome 3/ ADP ribosylation factor like GTPase 6	3q11.2	Cilium, basal body, transition zone and cytosol	Low	GTP-binding protein involved in ciliary trafficking[146]
BBS4	Bardet-Biedl syndrome 4	15q24.1	Cilium and basal body	Low	Component of BBSome complex
BBS5	Bardet-Biedl syndrome 5	2q31.1	Basal body	Low	Component of BBSome complex
BBS6/MKKS	Bardet-Biedl syndrome 6/ MKKS centrosomal shuttling protein	20p12.2	Cilium and basal body	Low	Chaperonin like protein assisting BBSome formation
BBS7	Bardet-Biedl syndrome 7	4q27	Cilium and basal body	Low	Component of BBSome complex
BBS8/TTC8	Bardet-Biedl syndrome 8/ tetratricopeptide repeat domain 8	14q31.3	Cilium, IFT and basal body	Low	Component of BBSome complex
BBS9	Bardet-Biedl syndrome 9	7p14.3	Cilium	Low	Component of BBSome complex
BBS10	Bardet-Biedl syndrome 10	12q21.2	Basal body	Low	Chaperonin like protein assisting BBSome formation
BBS11/TRIM32	Bardet- Biedl syndrome 11- tripartite motif containing 32	9q33.1	Intermediate filaments	Low	E3 ubiquitin ligase; it promotes degradation of several targets[147]
BBS12	Bardet-Biedl syndrome 12	4q27	Basal body	Low	Chaperonin like protein assisting BBSome formation
BBS13/MKS1	Bardet-Biedl syndrome 13/MKS transition zone complex subunit 1	17q22	Basal body	Low	Component of the tectonic-like complex localized at the transition zone of primary cilium[148]
BBS14/CEP290	Bardet-Biedl syndrome 14/centrosomal protein 290	12q21.32	Basal body and centrosome	Low	Centrosomal protein involved in primary cilium formation[149]
BBS15/WDPCP	Bardet-Biedl syndrome 15/WD repeat containing planar cell polarity effector	2p15	Cytosol, axoneme and plasma membrane,	Low	Controls ciliogenesis[150]
BBS16/SDCCAG8	Bardet-Biedl syndrome 16/SHH signaling and ciliogenesis regulator SDCCAG8	1q43-q44	Basal body, transition zone and centriole	Low	Involved in ciliogenesis and Sonic Hedgehog signaling pathway
BBS17/LZTFL1	Bardet-Biedl syndrome 17/leucine zipper transcription factor like 1	3p21.31	Cilium and basal body	Mainly in lymphoid tissue	Regulator of BBSome trafficking and Sonic Hedgehog signalling[151]
BBS18/BBIP1	Bardet-Biedl syndrome 18/BBSome interacting protein 1	10q25.2	Cytosol	Mainly in testis	Component of BBSome complex
BBS19/IFT27	Bardet-Biedl syndrome 19/intraflagellar transport 27	22q12.3	Cilium, IFT and basal body	Low	Intraflagellar trafficking (IFT-B) component[151]
BBS20/IFT172	Bardet-Biedl syndrome 20/ intraflagellar transport 172	2p23.3	Vesicles	Low	Intraflagellar trafficking (IFT-B) component[152]
BBS21/ CFAP418/ C8orf37	Bardet-Biedl syndrome 21/ cilia and flagella associated protein 418	8q22.1	Basal body and ciliary root	Low	Unknown[153]
BBS22/IFT74	Bardet-Biedl syndrome 22/ intraflagellar transport 74	9p21.2	Cilium, IFT and basal body	Low	Intraflagellar trafficking (IFT-B) component[152]
CEP19	Centrosomal protein 19	3q29	Centrosome	Low	Recruits the RABL2B GTPase to the ciliary base and intraflagellar transport (IFT) complex B[154]
NPHP1	Nephrocystin 1	2q13	Transition zone	Mainly in skeletal muscle	Cell-matrix signaling at focal adhesions[155]
SCAPER	S-phase cyclin A associated protein in the ER	15q24.3	Endoplasmic reticulum and ciliary tip	Low	Ciliary dynamics and disassembly[156]
SCLT1	Sodium channel and clathrin linker 1	4q28.2	Centriole	Low	Component of distal appendages which anchor the cilium to the plasma membrane, involved in ciliogenesis[157]

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REVIEW

Bardet-Biedl Syndrome: Current Perspectives and Clinical Outlook

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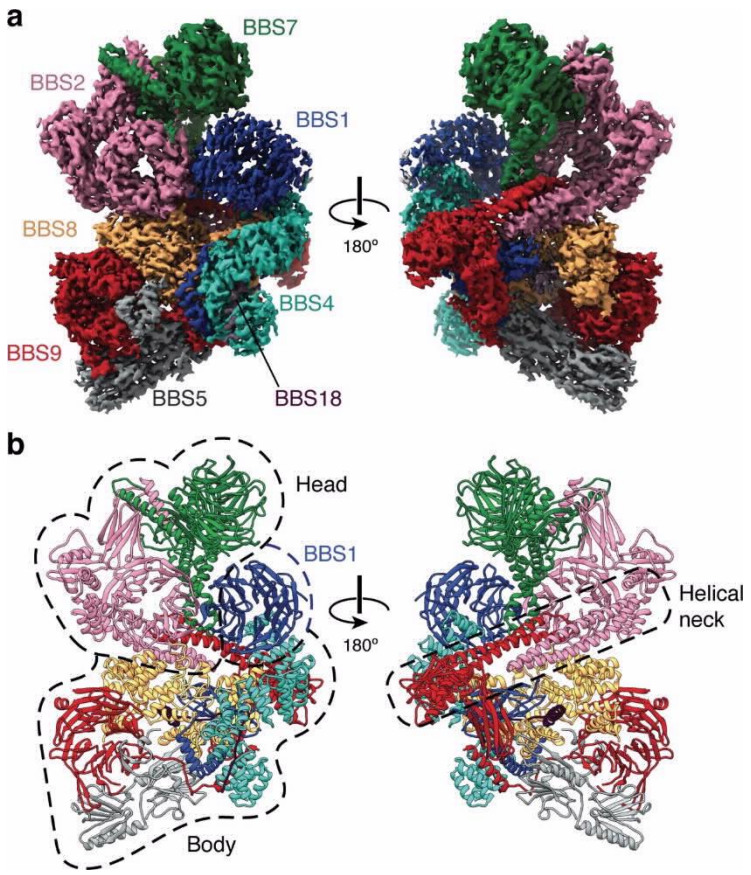
Genetics

- Inheritance is traditionally considered autosomal recessive
- About 50% of diagnosis in the western countries are due to mutations in three genes: *BBS1, BBS2* and *BBS10*.
- *BBS1, BBS3*, and *BBS4* mutations are commonly reported in Saudi Arabia

אצלנו

מוטציה
BBS4 c.77-1421_221-1229del5784
BBS4 c.77-1421_221-1229del5784
BBS4 c.77-1421_221-1229del5784
BBS4
BBS4 c.884G>C
BBS3 -ARL6 c.3757G>A
BBS3 -ARL6 c.3757G>A
BBS10 c.310_311del Glu104Lysfs*7
BBS4 c.884G>C
BBS2 V56G
BBS4 c.884G>C p.Arg295Pro
BBS3 -ARL6 c.3757G>A
BBS2 V75G
BBS4 c.424G>A/N
BBS4 c.424G>A/N
BBS4 c.424G>A/N

Bbsome complex



Bbsome complex

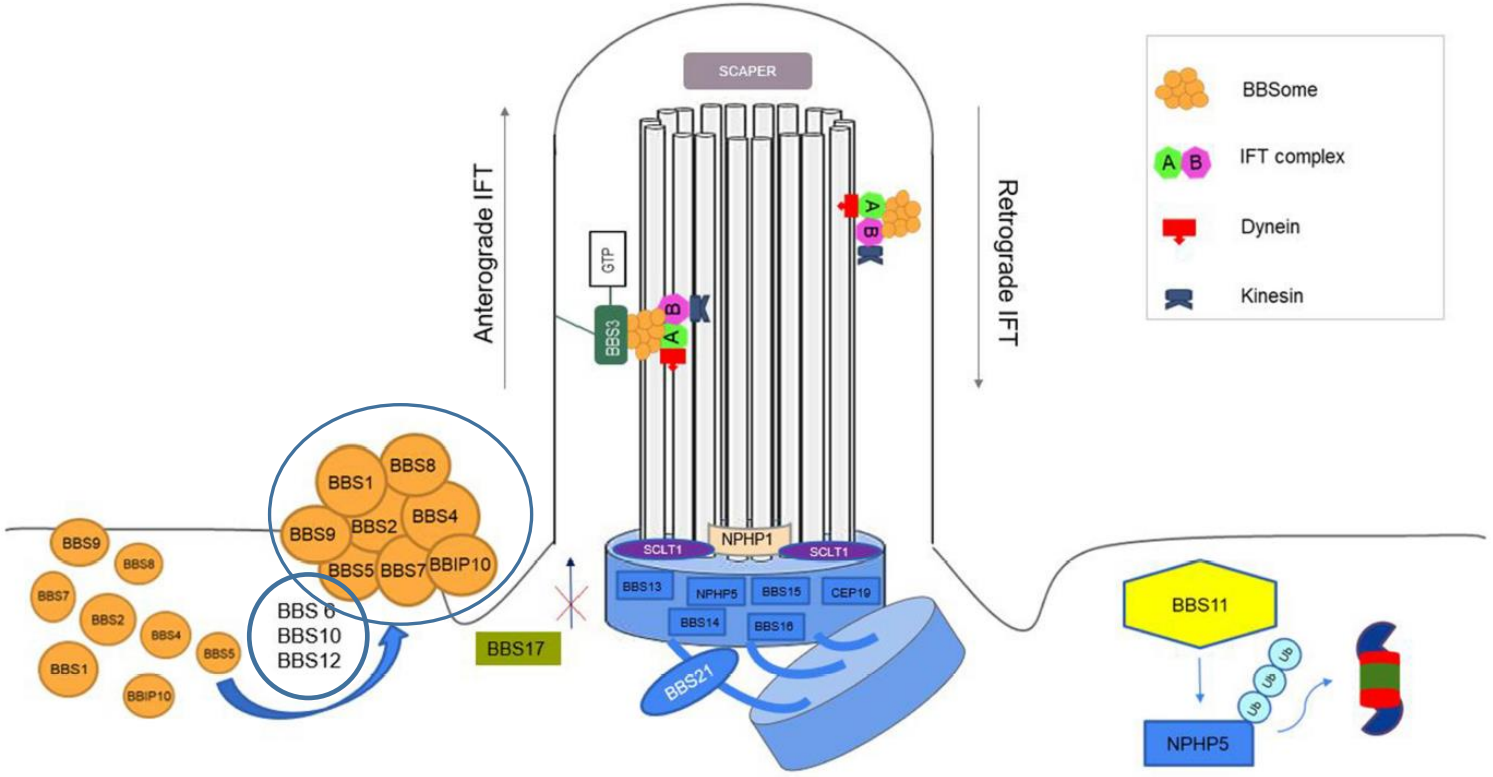
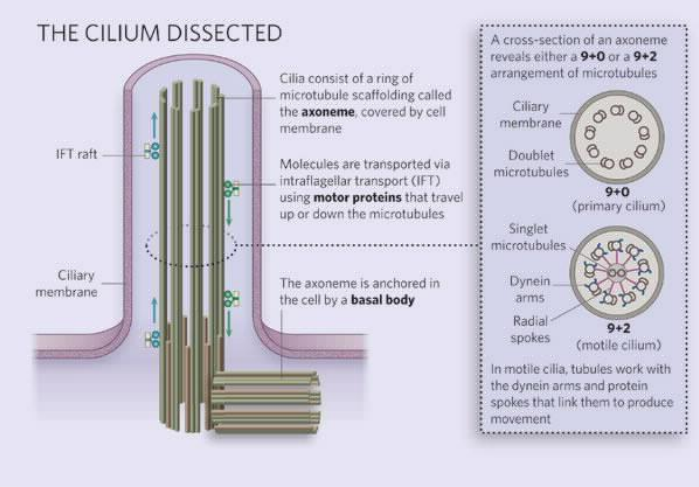
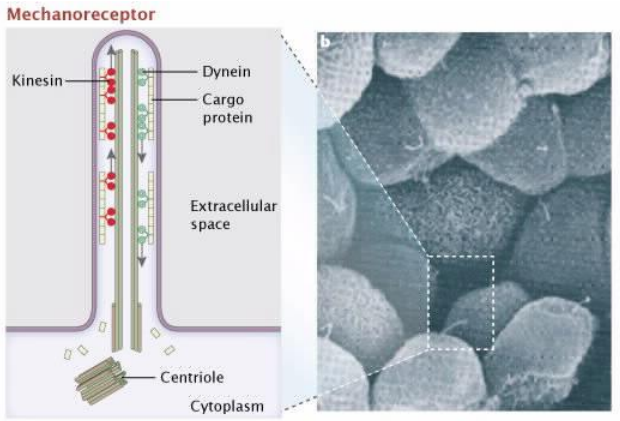


Figure 1 Diagram of Bardet Biedl syndrome (BBS) proteins and their relationship with the primary cilium. The BBSome complex, constituted by BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, BBS9 and BBIP1 (represented on the left), is assembled with the assistance of chaperonin-like proteins (BBS6, BBS10 and BBS12). The link between BBSome and BBS3 GTPase protein allows the intraflagellar transport. On the other hand, the link to BBS17 keeps the BBSome at basal body level. IFT-A complex mediates retrograde trafficking from the tip of cilia to the base, powered by dynein. IFT-B complex (which includes BBS19 and BBS20, not shown in figure) mediates anterograde trafficking, powered by kinesin. BBS11, as shown on the right, favors protein ubiquitination.

Primary cilia

- The PC is a dynamic organelle acting as an antenna sensing external stimuli
- Its structure consists of a microtubule-based axoneme
- The PC contains at least 600 different proteins
- There is no evidence of protein synthesis within cilia, thus ciliary proteins depend on transport
- Abnormal transport impairs cilia function - ciliopathy



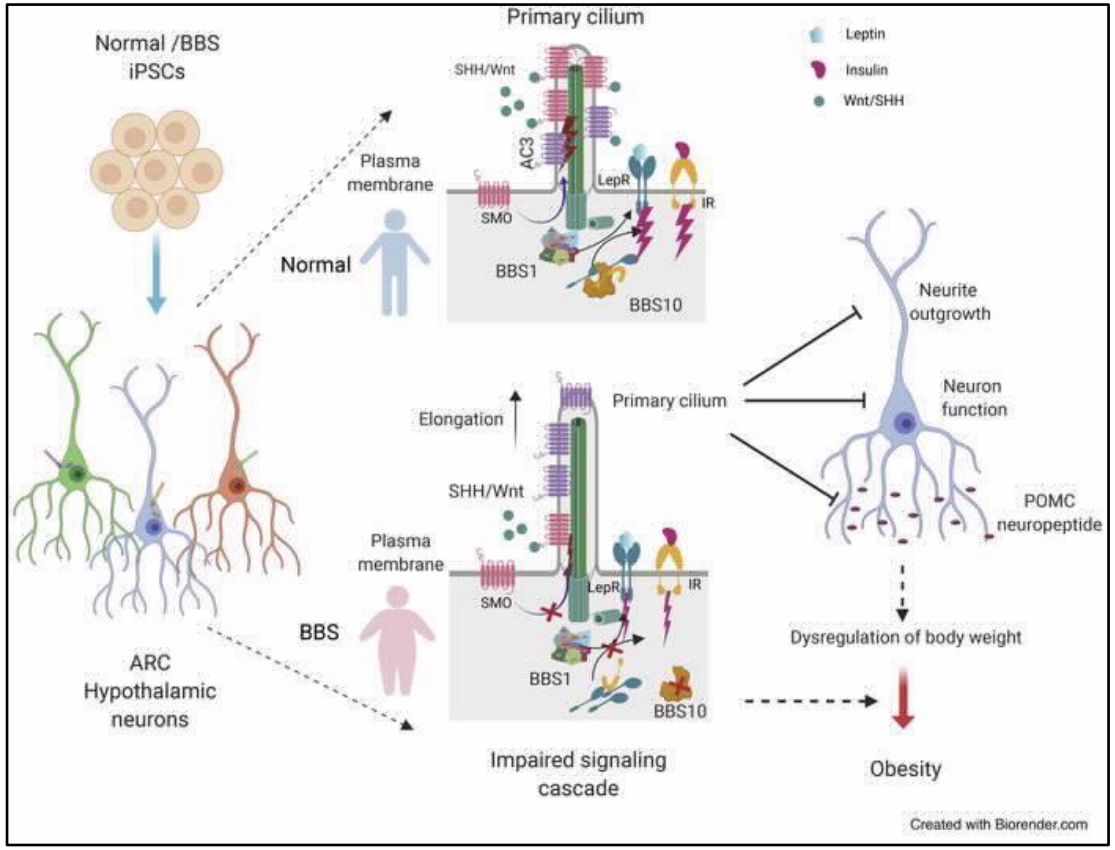


Ciliopathies

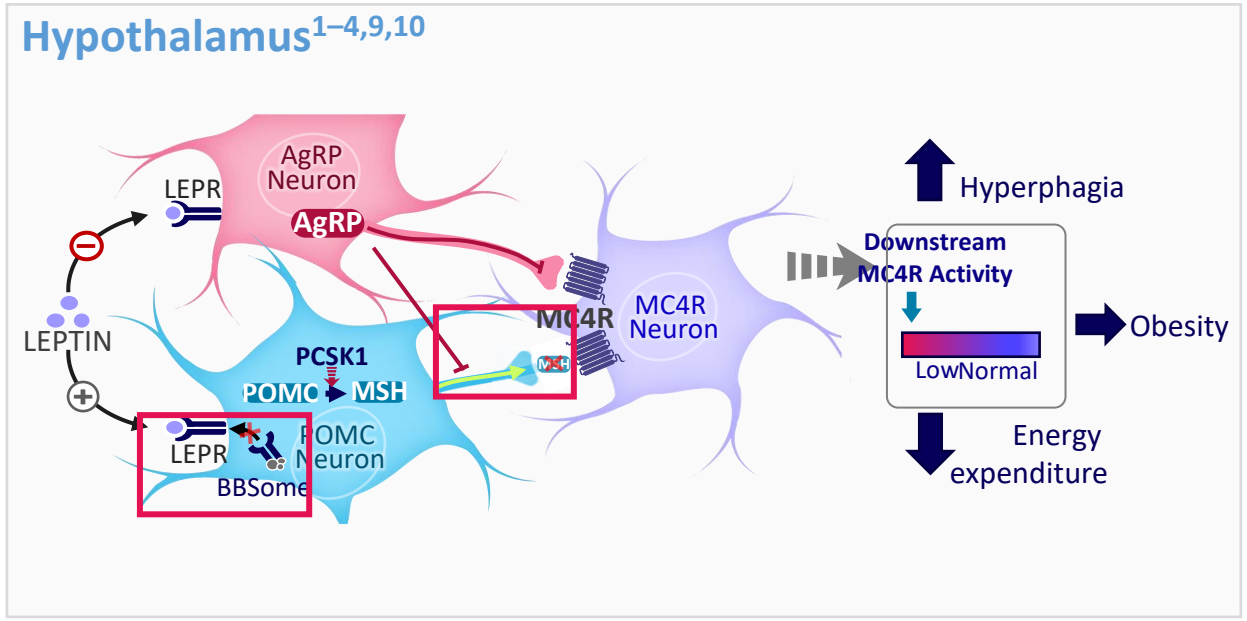
Condition	OMIM	Gene(s)	Systems/organs affected
Alström syndrome[8][1]	203800	*ALMS1*	
Asphyxiating thoracic dysplasia (Jeune syndrome)[8][23]	208500		
Bardet–Biedl syndrome[8][7][10]	209900	*BBS1, BBS2, ARL6, BBS4, BBS5, MKKS, BBS7, TTC8, BBS9, BBS10, TRIM32, BBS12*	
Ellis–van Creveld syndrome[23]	225500	*EVC, EVC2*	
Joubert syndrome[8][10]	213300	*INPP5E, TMEM216, AHI1, NPHP1, CEP290, TMEM67, RPGRIP1L, ARL13B, CC2D2A, BRCC3*	Brain
Leber congenital amaurosis[23]	204000	*GUCY2D, RPE65*	
McKusick–Kaufman syndrome[23]	236700	*MKKS*	
Meckel–Gruber syndrome[8][10][24]	249000	*MKS1, TMEM67, TMEM216, CEP290, RPGRIP1L, CC2D2A*	Liver, heart, bone
Nephronophthisis[8][7][10]	256100	*NPHP1, INVS, NPHP3, NPHP4, IQCB1, CEP290, GLIS2, RPGRIP1L*	Kidney
Orofaciodigital syndrome 1[1][7]	311200	*OFD1*	
Polycystic kidney disease[8][7] (ADPKD and ARPKD)[25]	173900	*PKD1, PKD2, PKHD1*	Kidney
Primary ciliary dyskinesia (Kartagener syndrome)[8]	244400	*DNAI1, DNAH5, TXNDC3, DNAH11, DNAI2, KTU, RSPH4A, RSPH9, LRRC50*	
Senior–Løken syndrome[7]	266900	*NPHP1, NPHP4, IQCB1, CEP290, SDCCAG8*	Eye
Sensenbrenner syndrome (cranioectodermal dysplasia)[23]	218330	*IFT122*	
Short rib–polydactyly syndrome[23]	613091	*DYNC2H1*	
?	?	*IFT88*	Novel form of congenital anosmia, reported in 2012[26]

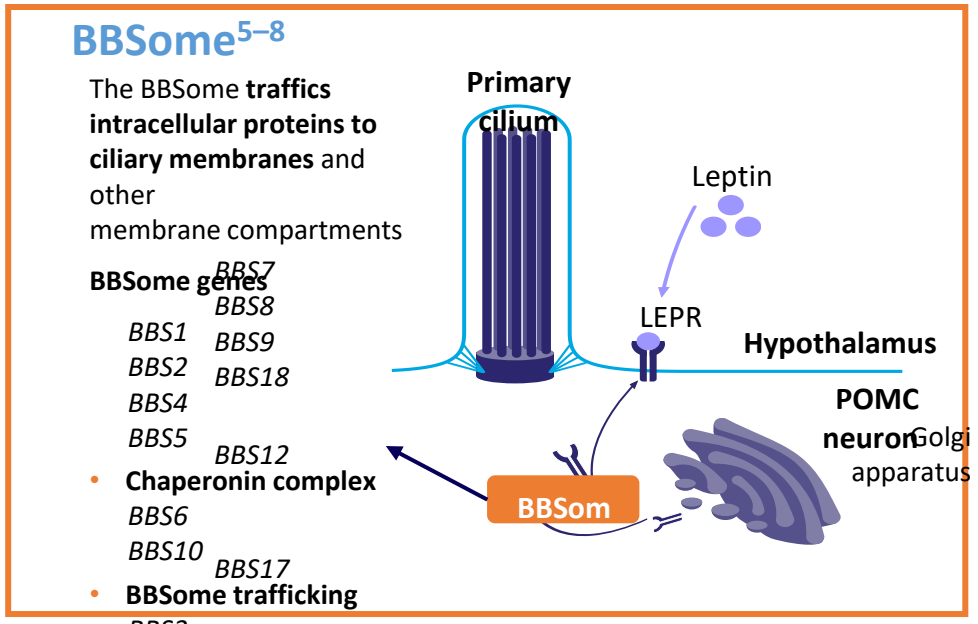
Suggested mechanisms for obesity in BBS

- Abnormal trafficking of proteins to the PC and to the plasma membrane.
- Insulin resistance
- leptin resistance
- Central and peripheral



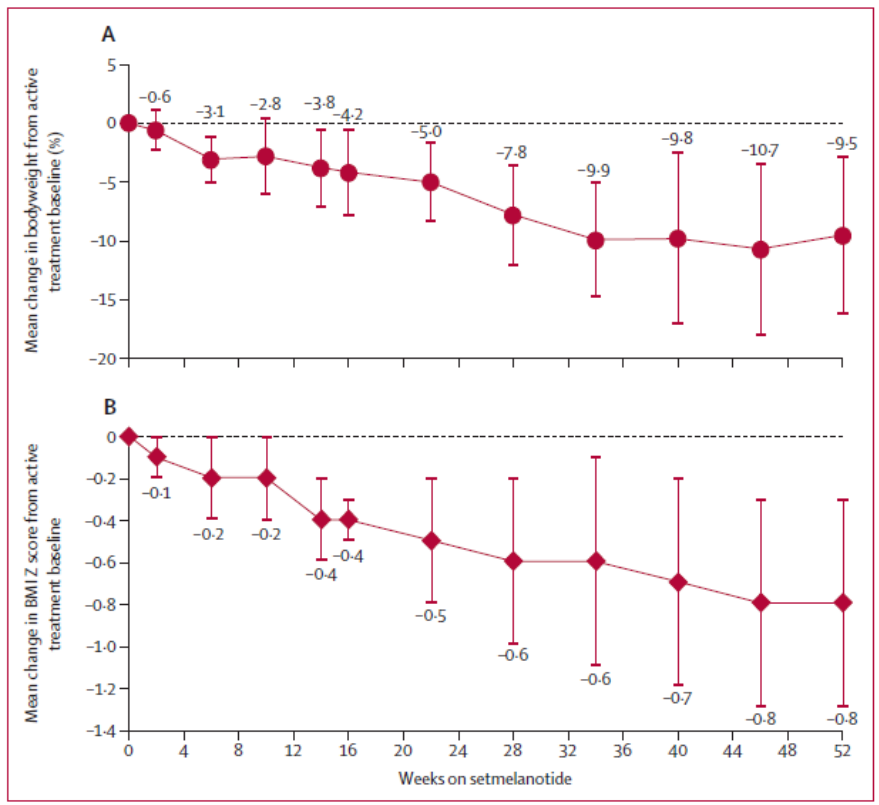
Setmelanotide – MC4R agonist





Efficacy and safety of setmelanotide, a melanocortin-4 receptor agonist, in patients with Bardet-Biedl syndrome and Alström syndrome: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial with an open-label period

Andrea M Haqq, Wendy K Chung, Hélène Dollfus, Robert M Haws, Gabriel Á Martos-Moreno, Christine Poitou, Jack A Yanovski, Robert S Mittleman, Guojun Yuan, Elizabeth Forsythe, Karine Clément, Jesús Argente



	Active treatment baseline	Week 52	Change from active treatment baseline	Percentage change from active treatment baseline
12 years or older (n=28)				
Bodyweight, kg	115·9 (26·7)	108·5 (27·0)	−7·4 (8·2); p<0·0001	−6·5 (7·0); p<0·0001
Maximal hunger score*	7·0 (1·9)	4·9 (2·5)	−2·1 (2·0); p=0·0010	−30·5 (26·5); p=0·0004
Reached ≥25% reduction	..	57·1% (28·9 to 82·3); p<0·0001	..	..
≥1 point reduction	..	10 (71%)	..	..
≥2 point reduction	..	6 (43%)	..	..
All ages (≥6 years; n=31)				
Waist circumference, cm†	117·9 (18·0)	110·3 (21·0)	−7·2 (7·4)	−6·3 (7·4)
Body fat, kg‡	51·1 (18·9)	43·1 (16·3)	−5·6 (12·0)	−11·3 (26·3)
Lean muscle, kg‡	58·9 (14·1)	57·6 (12·4)	−1·2 (3·9)	−2·0 (6·5)
Lipids, mmol/L§				
Total cholesterol	4·4 (1·0)	3·9 (0·9)	−0·3 (0·4)	−6·1 (10·6)
HDL cholesterol	1·1 (0·2)	1·1 (0·2)	0·1 (0·1)	5·3 (11·6)
LDL cholesterol	3·0 (1·0)	2·6 (0·9)	−0·2 (0·4)	−7·8 (16·8)
Triglycerides	1·9 (0·9)	1·4 (0·8)	−0·2 (0·6)	−9·6 (32·5)
18 years or older (n=15)				
Bodyweight, kg	128·4 (16·6)	119·0 (20·6)	−9·4 (9·4); p=0·0008	−7·6 (−7·1); p=0·0005
BMI, kg/m²¶	46·4 (5·9)	43·3 (7·2)	−4·2 (3·3)	−9·1 (6·8)
Younger than 18 years (n=16)				
BMI, kg/m²‖	37·4 (9·4)	34·2 (10·1)	−3·4 (2·1)	−9·5 (6·4)
BMI Z score‖	3·7 (1·3)	3·0 (1·5)	−0·8 (0·5)	..
≥0·2 point reduction	..	12 (86%)	..	..
≥0·3 point reduction	..	14 (71%)	..	..
95th BMI percentile	144·5 (35·8)	126·8 (37·1)	−17·3 (7·7)	..

Data are the mean (SD) or mean (95% CI), unless stated otherwise. *Patients ≥12 years old without cognitive impairment and with hunger scores at active treatment baseline and Week 52 (n=14). †Patients with measurements at active treatment baseline (n=31) and week 52 (n=25). ‡Patients with measurements at active treatment baseline (n=29), week 52 (n=18), and both (n=17). §Patients with measurements at active treatment baseline (n=31) and week 52 (n=23). ¶Patients with measurements at active treatment baseline (n=15) and week 52 (n=12). ‖Patients with measurements at active treatment baseline (n=16) and week 52 (n=14).

***Table 3*: Changes in anthropometric and metabolic parameters after setmelanotide treatment in pivotal patients with Bardet-Biedl syndrome (n=32)**

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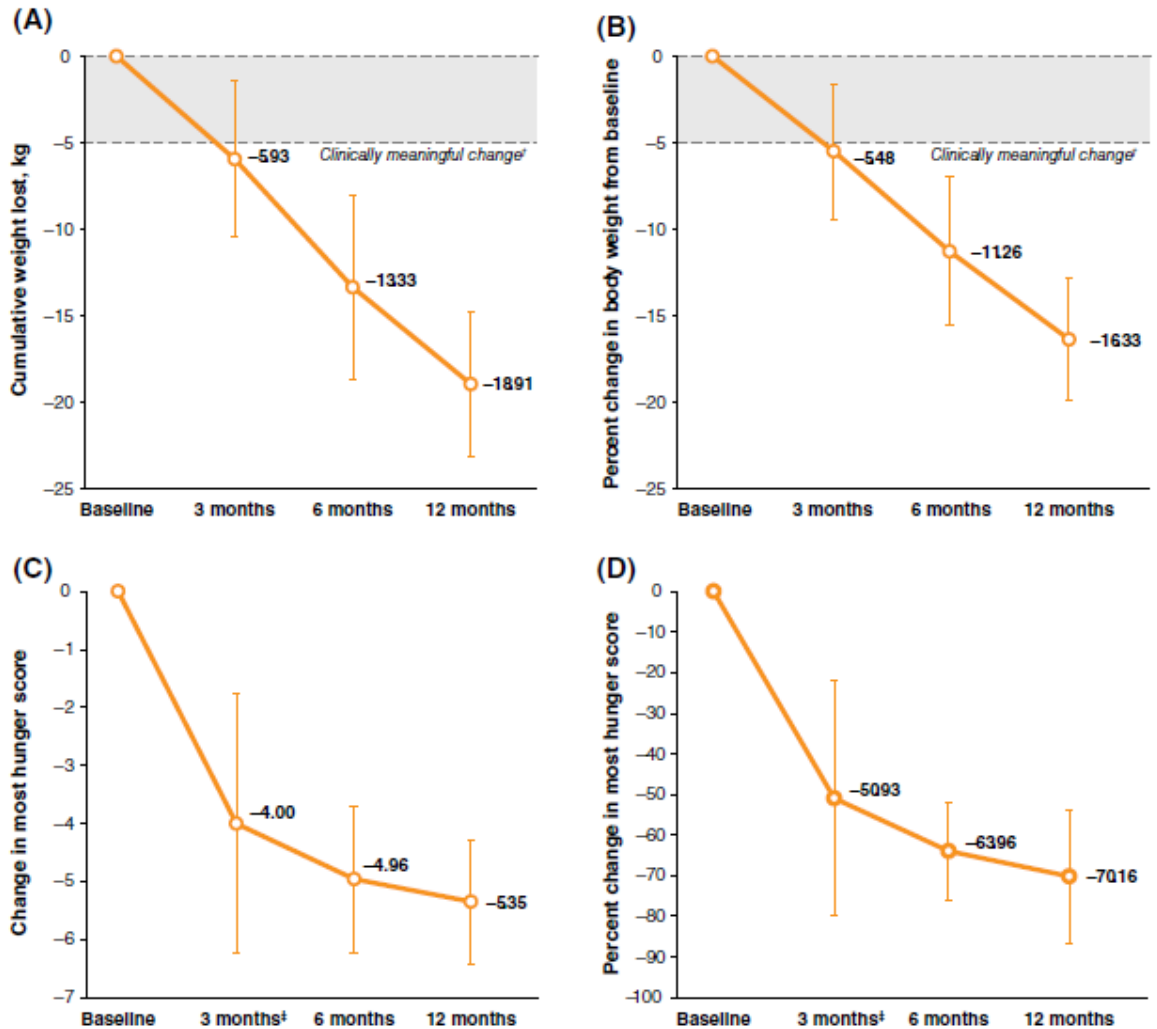
ORIGINAL ARTICLE

WILEY

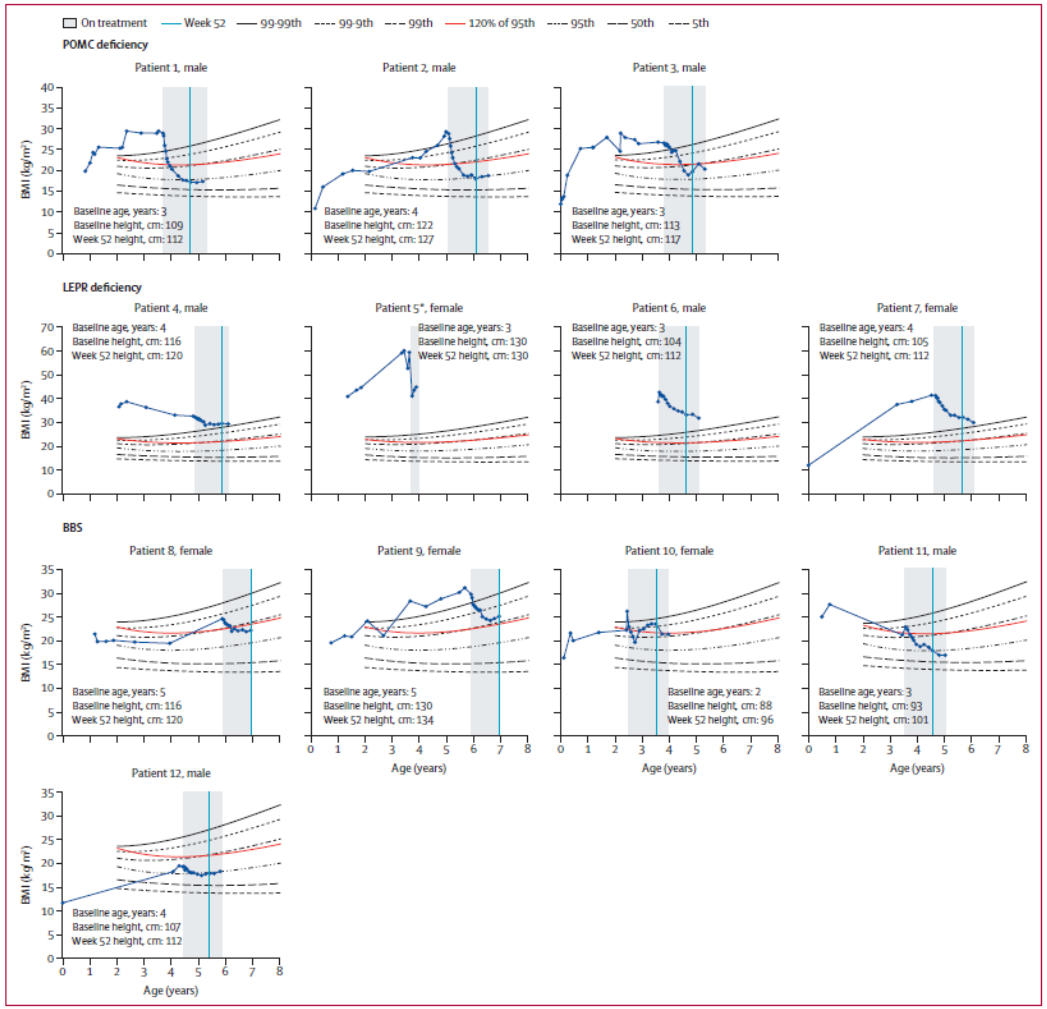
Effect of setmelanotide, a melanocortin-4 receptor agonist, on obesity in Bardet-Biedl syndrome

Robert Haws MD[1] | Sheila Brady MSN[2] | Elisabeth Davis BA[2] | Kristina Fletty BS[1] | Guojun Yuan PhD[3] | Gregory Gordon MD[3] | Murray Stewart MD[3] | Jack Yanovski MD[2]



Setmelanotide in patients aged 2–5 years with rare MC4R pathway-associated obesity (VENTURE): a 1 year, open-label, multicenter, phase 3 trial

Jesús Argente, Charles F Verge, Uzoma Okorie, Ilene Fennoy, Megan M Kelsey, Casey Cokkinias, Cecilia Scimia, Hak-Myung Lee, I Sadaf Farooqi



	POMC or LEPR deficiency (n=7)	BBS (n=5)	Overall (N=12)
Percentage reaching a 0·2-point decrease or more in BMI Z score† from baseline to week 52			
Patients, n/N (%)	6/7 (86%)	4/5 (80%)	10/12 (83%)
95% CI	48·7–97·4	37·6–96·4	58·7–99·8
BMI change from baseline at week 52			
Baseline			
Patients, n/N	7/7	5/5	12/12
BMI, mean (SD), kg/m²	34·3 (7·1)	23·7 (3·5)	29·9 (7·9)
Week 52			
Patients, n/N	6/7	5/5	11/12
Absolute change in BMI, kg/m²	−8·2 (3·2)	−2·4 (2·2)	−5·6 (4·1)
Percentage change in BMI	−26% (11)	−10% (9)	−18% (13)
Weight-related outcomes change from baseline at week 52			
Patients, n/N	6/7	5/5	11/12
WHO BMI Z score	−5·2 (1·9)	−1·3 (1·2)	−3·4 (2·5)
CDC BMI Z score‡	−2·2 (1·3)	−0·8 (0·8)	−1·6 (1·3)
%BMI_{95}	−47·6 (17·3)	−14·5 (13·9)	−32·5 (22·9)
Waist circumference, cm	−12·4 (7·8)	−2·0 (5·9)	−7·7 (8·6)
Weight, kg	−7·1 (5·1)	−0·3 (3·0)	−4·0 (5·4)
Height, cm	5·1 (2·2)	6·0 (2·0)	5·5 (2·1)
Hunger response§ change from baseline at week 52			
Patients' caregiver responses, n/N	6/7	5/5	11/12
Much less hungry	5/6 (83%)	2/5 (40%)	7/11 (64%)
Somewhat less hungry	1/6 (17%)	2/5 (40%)	3/11 (27%)
No change	0	0	0
Somewhat more hungry	0	0	0
Much more hungry	0	1/5 (20%)	1/11 (9%)
Caregiver burden change from baseline at week 52			
n/N	6/7	5/5	11/12
ZBI global score	−13·2 (10·9)	−13·2 (9·6)	−13·2 (9·8)

Data are n (%) or mean (SD) unless otherwise specified. %BMI_{95}=percent of the 95th BMI percentile. BBS=Bardet-Biedl syndrome. CDC=US Centers for Disease Control. LEPR=leptin receptor. POMC=proopiomelanocortin. ZBI=Zarit Burden Interview. *Safety population defined as patients who received one dose or more of setmelanotide. †Per WHO methodology. ‡Post hoc analysis. §In response to the question, "How hungry has your child acted in the past 7 days compared to before starting this study?".

Table 2: **Primary, secondary, and exploratory efficacy outcomes (safety population*)**


THANK YOU!