Free Communications 6: Fat, Metabolism And Obesity 1

FC6.2

Frequency of Bardet-Biedl syndrome variants in a population with early-onset obesity

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Frequency of Bardet-Biedl Syndrome variants in a population with early-onset obesity

Presentation FC6.2

Jesús Argente, MD, PhD, presenting

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DISCLOSURE STATEMENT

Jesús Argente
X I have the following potential conflicts of interest to report:

□ Research Contracts
X Consulting
□ Employment in the Industry
□ Stockholder of a healthcare company
□ Owner of a healthcare company
X Other(s) – speaking engagements for Rhythm Pharmaceuticals, Inc.

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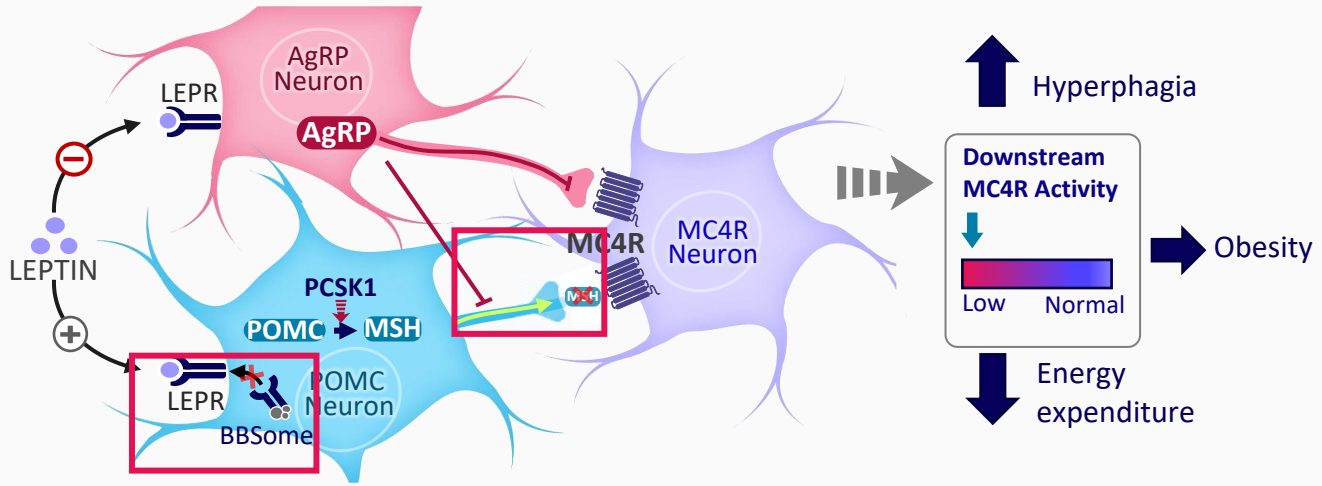
The central hypothalamus is a key regulator of energy balance, appetite and bodyweight[1-4]

- **The melanocortin-4 receptor (MC4R) pathway in the hypothalamus is critical for the regulation of hunger, energy balance, and body weight[1-3]**
- **Individuals who carry disruptive variants in MC4R pathway genes may present with hyperphagia (pathologic, insatiable hunger) and early-onset obesity[4]**
- **In patients with Bardet–Biedl syndrome (BBS), a rare, genetically heterogeneous, and highly pleiotropic disease, the immotile primary cilia are dysfunctional, leading to impairment of the MC4R pathway**

Hypothalamus[1–4,9,10]



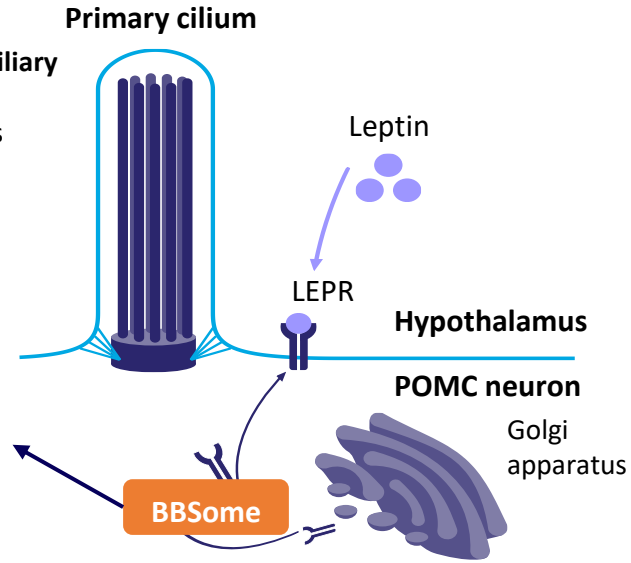
BBSome[5–8]

The BBSome **traffics intracellular proteins to ciliary membranes** and other membrane compartments

BBSome genes

BBS1 *BBS7*
BBS2 *BBS8*
BBS4 *BBS9*
BBS5 *BBS18*

- **Chaperonin complex**
  BBS6 *BBS12*
  BBS10
- **BBSome trafficking**
  BBS3 *BBS17*



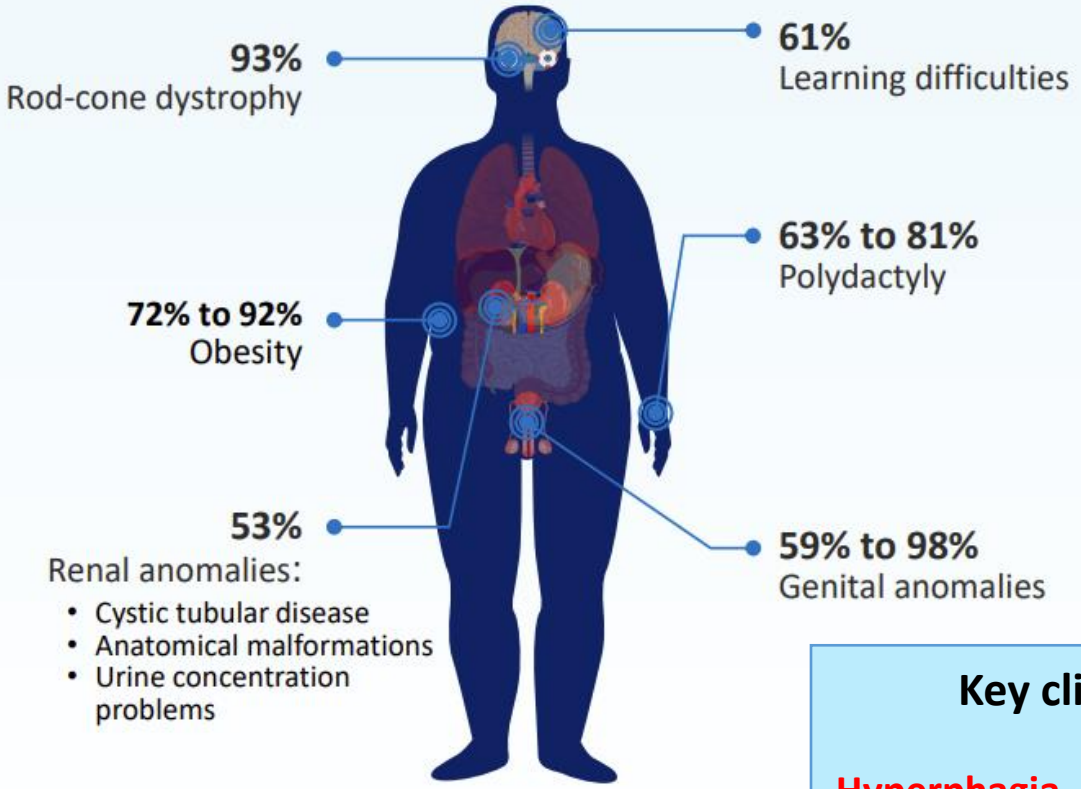
AgRP, agouti-related peptide; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin

1. Huvenne et al. *Obes Facts*. 2016;9:158-173. **2.** Yazdi et al. *PeerJ*. 2015;3:e856. **3.** Yang et al. *Nat Commun*. 2019;10:1718. **4.** Revelli et al. *Obesity (Silver Spring)*. 2011;19:1010-1018. **5.** Vaisse et al. *Cold Spring Harb Perspect Biol* 2016;9:a028217; **6.** Guo and Rahmouni. *Trends Endocrinol Metab*. 2011;22:286-293; **7.** Seo et al. *Hum Mol Genet*. 2009;18:1323-1331; **8.** Wang et al. *J Clin Invest*. 2021;131:e146287; **9.** Doche et al. *J Clin Invest*. 2012;122:4732-4736. **10.** Ghamari-Langroudi et al. *Sci Adv*. 2018;4:eaat0866.

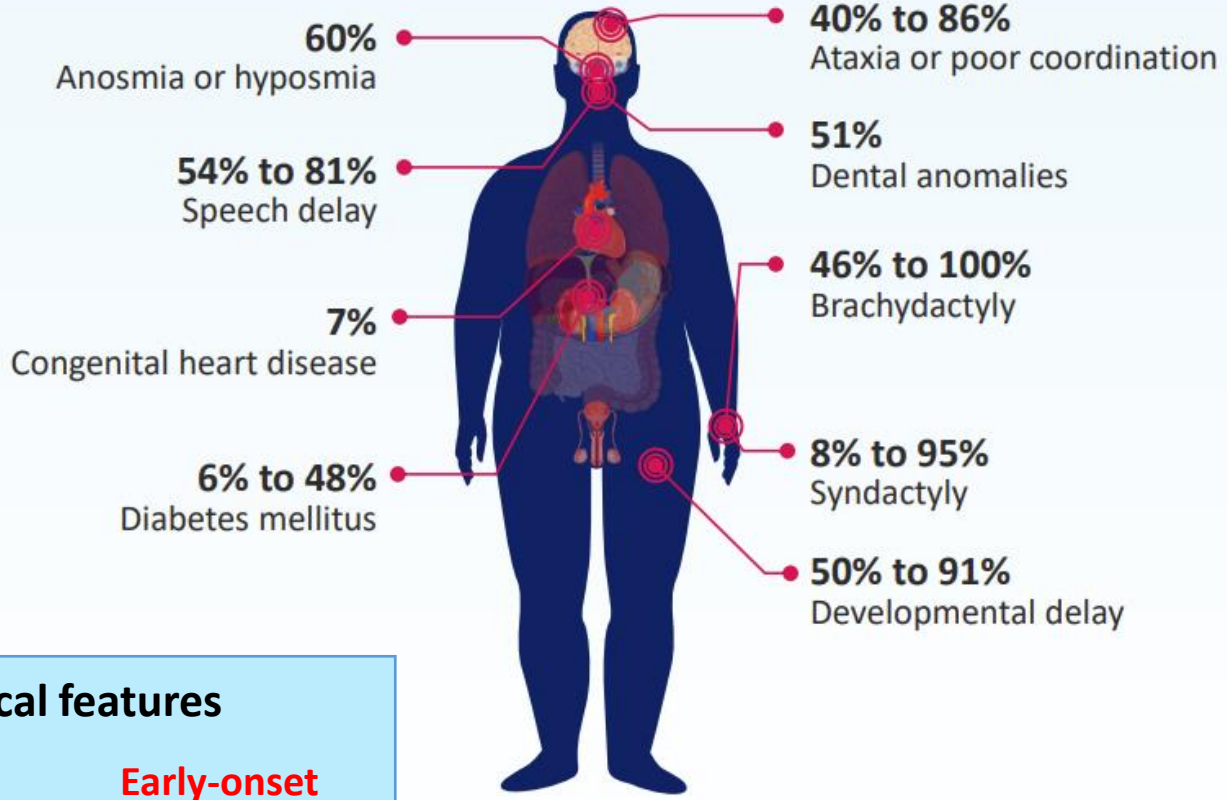
The presence and severity of clinical features are highly variable in BBS[1–4]

Onset of clinical manifestations is variable making diagnosis challenging, as not all symptoms might be present during early testing

Primary clinical features



Secondary clinical features



Key clinical features

Hyperphagia

Early-onset obesity

1. Forsythe E, et al. Eur J Hum Genet. 2013:21:8–13; 2. Forsythe E, et al. Front Pediatr 2018;6:1–8; 3; 3. Pomeroy J, et al. Pediatr Obes. 2021;16(2):e12703; 4. Poitou C, et al. Eur J Endocrinol. 2020;183;R149-R166.

Early identification of patients with BBS is essential for optimal disease management[1-4]

Early and routine genetic testing can…

Improve identification and diagnosis of individuals with hyperphagia and early-onset obesity caused by rare genetic variants[1–5]

Inform specialized management strategies or eligibility for clinical trials[1–5]

Hyperphagia and obesity caused by rare genetic variants are likely underdiagnosed due to low prevalence and limited access to genetic testing for individuals with obesity[7,8]

BBS, Bardet-Biedl syndrome.

1. Gregoric et al. *Front Endocrinol (Lausanne)*. 2021;12:689387. **2.** Styne et al. *J Clin Endocrinol Metab*. 2017;102:709-757. **3.** van der Valk et al. *Obes Rev*. 2019;20:795-804. **4.** Zorn et al. *Mol Cell Pediatr*. 2020;7:15. **5.** Huvenne et al. *Obes Facts*. 2016;9:158-173; **6.** Dollfus et al. *Eur J Hum Genet*. 2024:10.1038/s41431-024-01634-7; **7.** Ayers et al. *J Clin Endocrinol Metab*. 2018;103:2601-2612; **8.** Clément et al. *Physiol Behav*. 2020;227:113134.

The Rare Obesity Advanced Diagnosis (ROAD)® program

The ROAD® genetic testing program aims to encourage and support timely diagnosis by physicians of individuals with suspected rare MC4R pathway diseases

- **79-gene and 1–chromosomal region panel for individuals living in participating regions[a] and who meet eligibility criteria**
- **Testing is conducted by an ISO 15189 accredited clinical laboratory**

Eligibility

≤18 years of age with a BMI ≥97th percentile	OR	≥19 years of age with a BMI ≥40 kg/m² and a history of childhood obesity	OR
 Immediate family member of select, previously tested patients	OR	 Showing clinical symptoms of BBS	

[a]Germany, Greece, Ireland, Israel, Italy, Spain, Türkiye, the United Kingdom; Rare Obesity Advanced Diagnosis (ROAD) and its logo are registered trademarks of Rhythm Pharmaceuticals, Inc.
BMI, body mass index. ROAD, Rare Obesity Advanced Diagnosis.

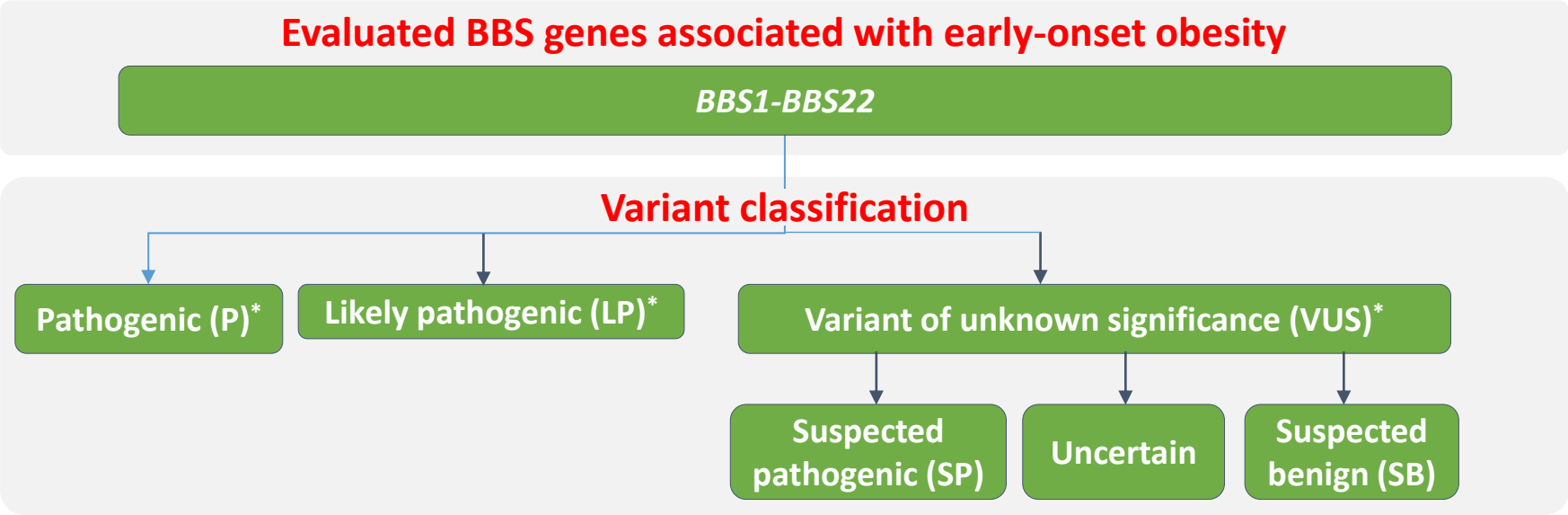
BBS gene variant analyses within ROAD®

Objective:

- To assess the frequency of BBS genetic variants in individuals with hallmark symptoms of potential underlying genetic causes of early-onset obesity who were sequenced as part of the ROAD® genetic testing program

Genes sequenced

BBS1	*BBS7*	*MKS1 (BBS13)*	*IFT27 (BBS19)*
BBS2	*TTC8 (BBS8)*	*CEP290 (BBS14)*	*IFT172 (BBS20)*
ARL6 (BBS3)	*PTHB1 (BBS9)*	*WDPCP (BBS15)*	*CFAP418 (BBS21)*
BBS4	*BBS10*	*SDCCAG8 (BBS16)*	*IFT74 (BBS22)*
BBS5	*TRIM32 (BBS11)*	*LZTFL1 (BBS17)*	
MKKS (BBS6)	*BBS12*	*BBIP1 (BBS18)*	

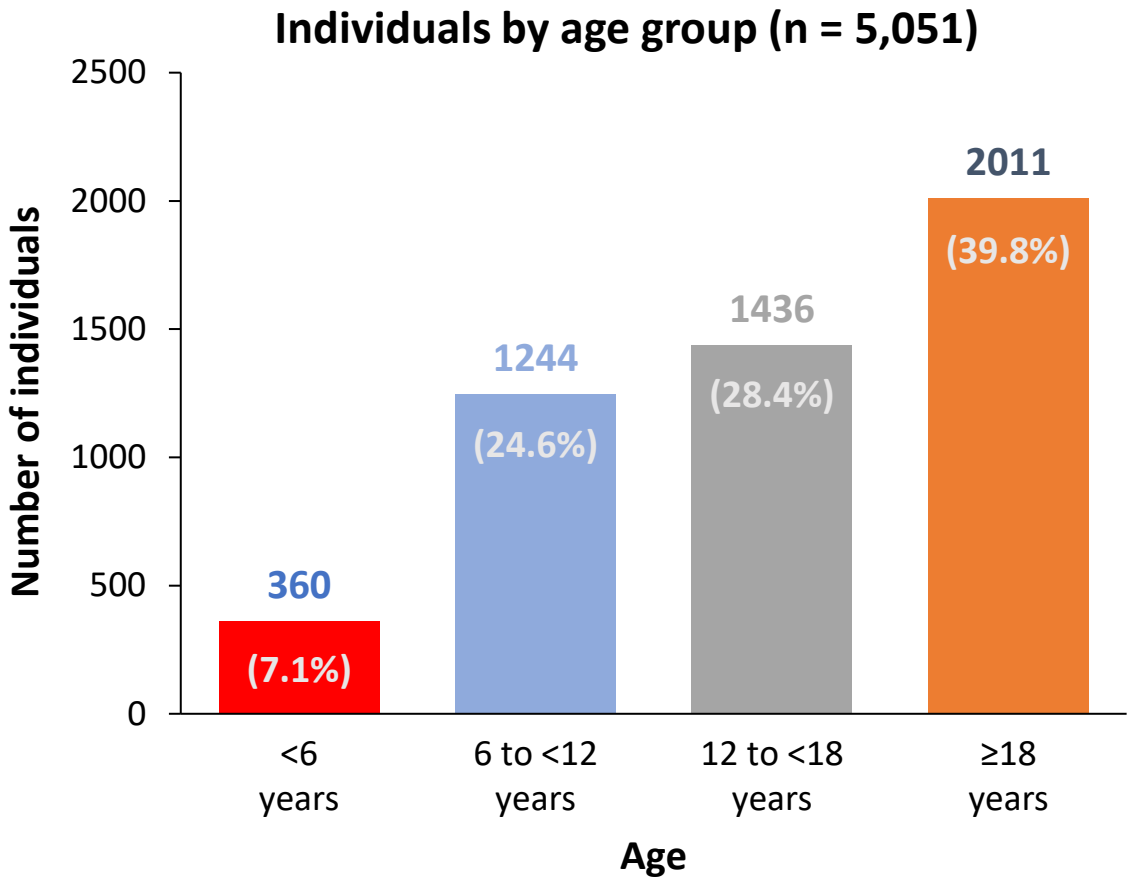


BBS, Bardet-Biedl syndrome; MC4R, melanocortin-4 receptor; ROAD, Rare Obesity Advanced Diagnosis.

*Variants were classified as P/LP/VUS according to American College of Medical Genetics criteria.

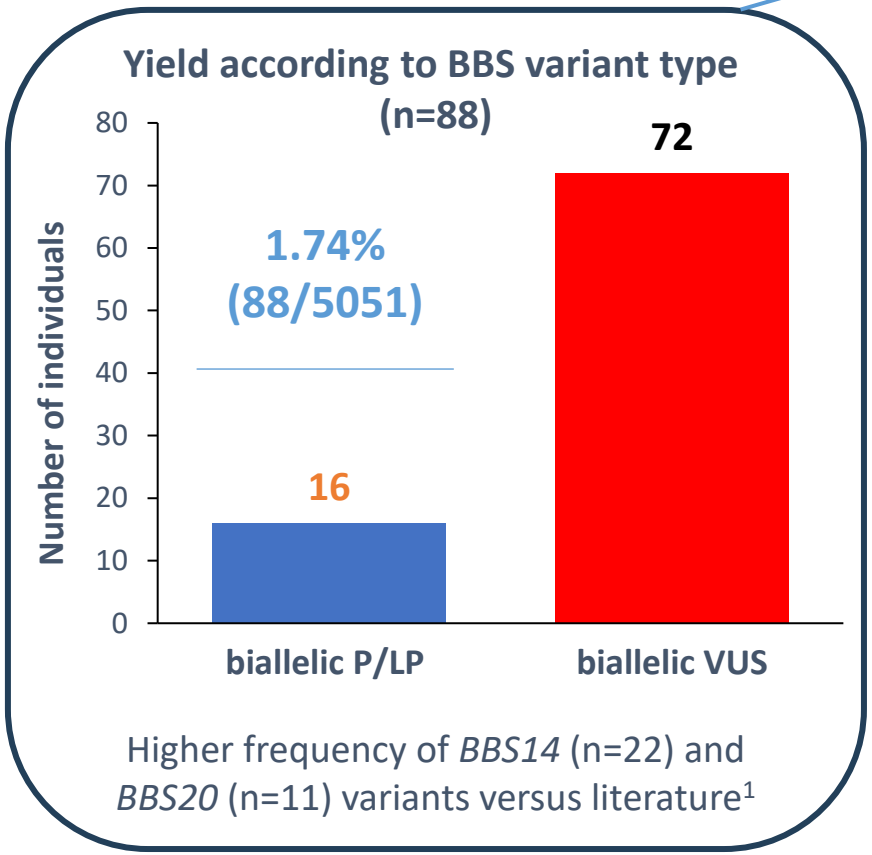
Baseline characteristics of total sequenced individuals

Parameter	Total (n = 5,051)
Sex, n (%)	
Female	2,763 (54.7)
Male	2,285 (45.2)
Prefer not to disclose/not provided	3 (0.1)
Age at time of testing, mean (SD)	23.0 (17.7)
Age at onset of obesity (n= 1,554), mean (SD)	8.0 (3.9)
BMI z-score (patients aged <18 years, n= 3026), mean (SD)	**3.6 (1.0)**
BMI (patients aged ≥18 years, n=1,936), mean (SD), kg/m^2	**43.7 (10.1)**
Location, n (% of tested individuals)	
Spain	1,834 (36.3)
Italy	1,291 (25.6)
Türkiye	653 (12.9)
Israel	501 (9.9)
United Kingdom	445 (8.8)
Ireland	250 (4.9)
Germany	76 (1.5)



BMI, body mass index; SD, standard deviation.

1.74% of tested individuals carried biallelic variants in one of 22 tested BBS genes and presented with early hyperphagia and obesity onset



Higher frequency of *BBS14* (n=22) and *BBS20* (n=11) variants versus literature[1]

Hyperphagia and weight parameters, mean (SD)

Age of hyperphagia onset	Age of obesity onset	BMI (≥18 years) BMI z-score (<18 years)
3.1 (2.8) years	4.8 (3.7) years	BMI: 41.6 (9.5) kg/m^2 BMI z-score: 3.8 (1.2)

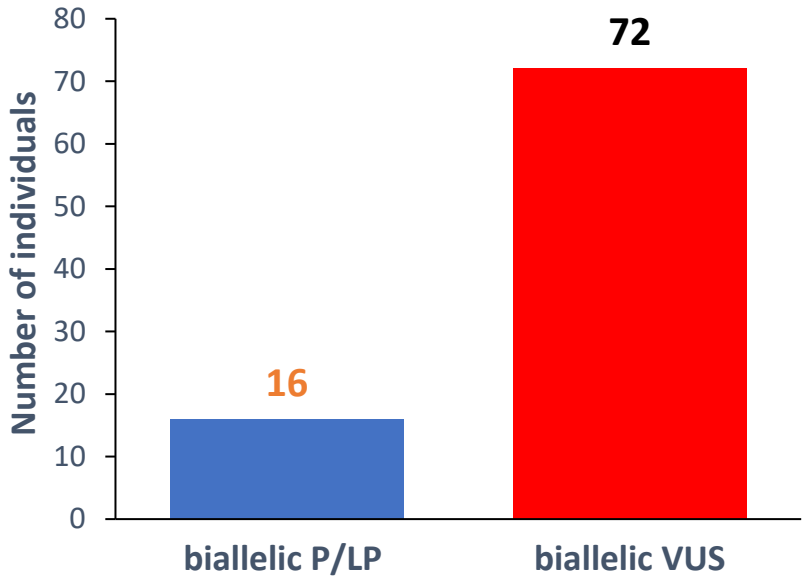
BBS, Bardet-Biedl syndrome; BMI, body mass index; P/LP, pathogenic/likely pathogenic; SD, standard deviation; VUS, variant of unknown significance.

1. Forsythe E, Beales PL. *Eur J Hum Genet.* 2013;21:8-13.

1.74% of tested individuals carried biallelic variants in one of 22 tested BBS genes; BBS was not suspected in most cases

Yield according to BBS variant type (n=88)

1.74%
(88/5051)



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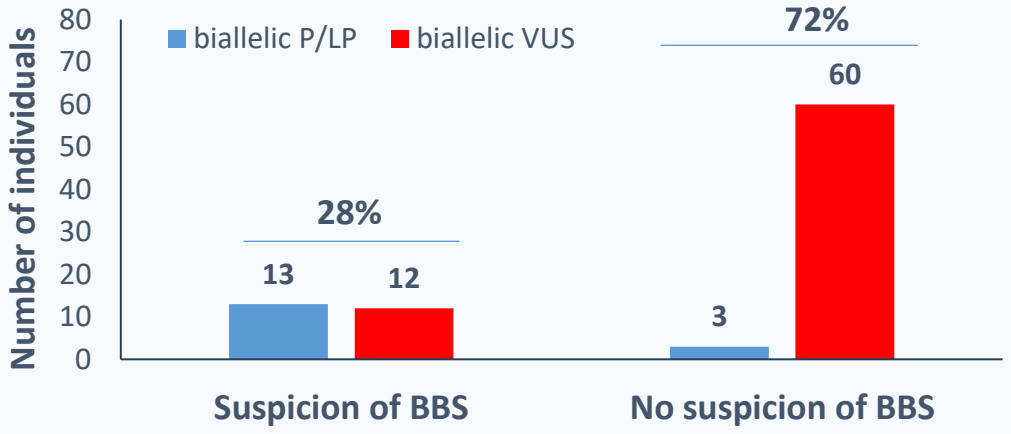
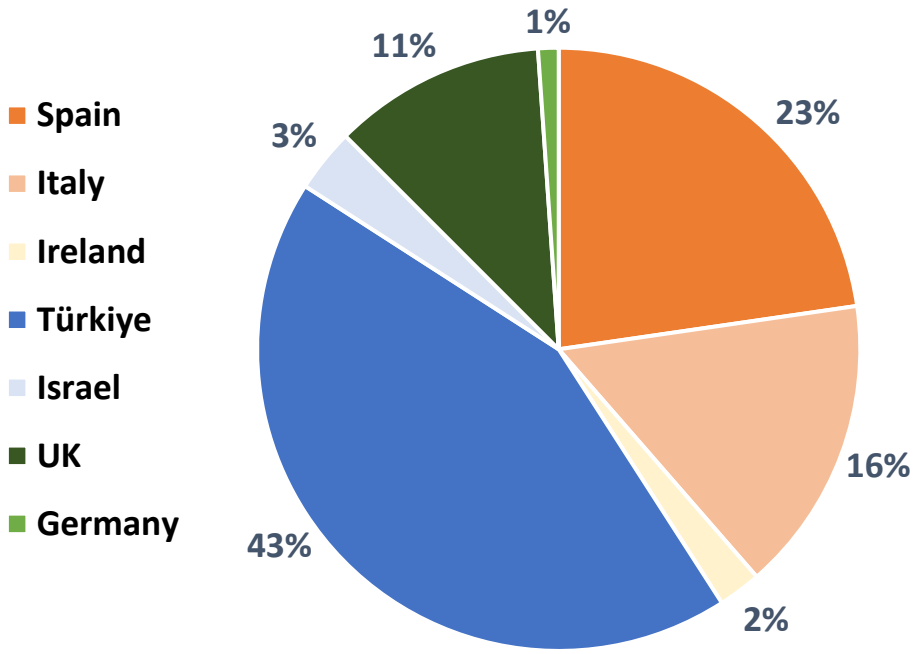
Number of patients with or without a suspicion of BBS at testing



BBS, Bardet-Biedl syndrome; BMI, body mass index; P/LP, pathogenic/likely pathogenic; SD, standard deviation; VUS, variant of unknown significance.

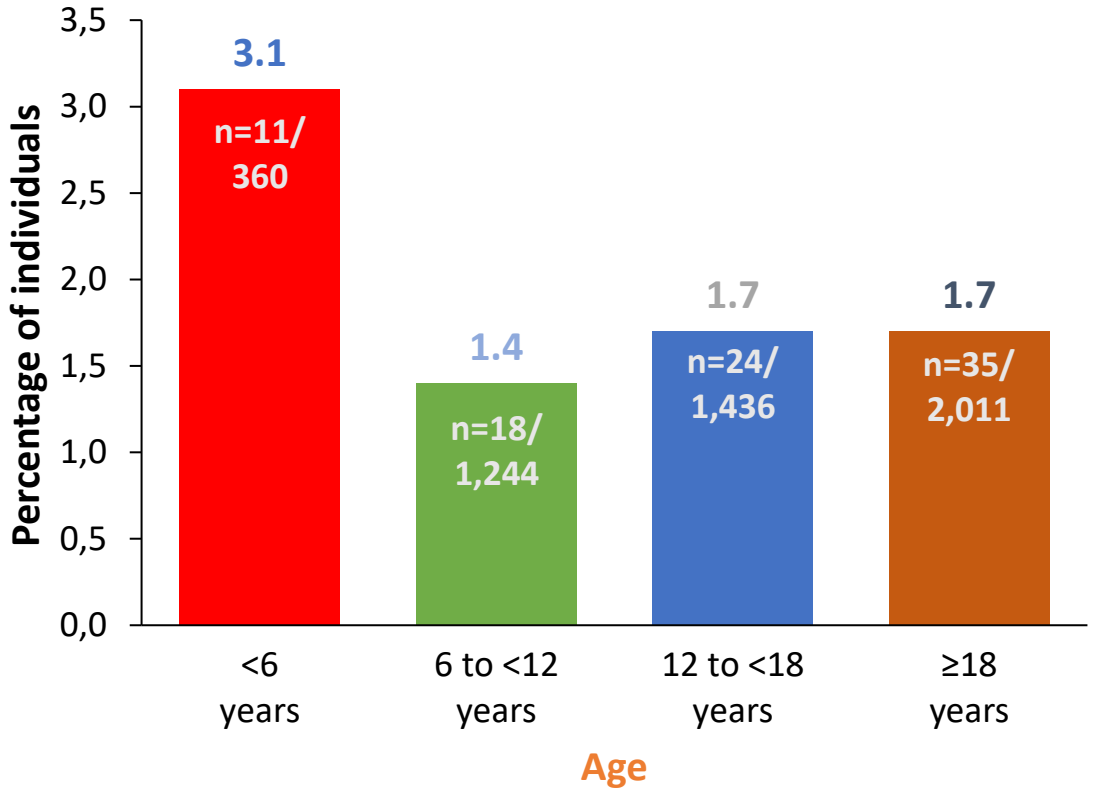
BBS diagnosis in patients <6 years of age

Percentage of individuals with BBS variants across locations (n = 88)



High frequency in Türkiye (5.82%; 38/653)

Percentage of individuals with BBS variants by age subgroups of the full cohort (n = 88/5,051)



BBS, Bardet-Biedl syndrome.

Summary and conclusions

- The ROAD® testing program encourages and supports timely diagnosis by physicians of individuals with suspected rare genetic causes of obesity in key genes of the MC4R pathway
- Among individuals tested, **1.74%** (88/5,051) carried a biallelic variant in one of 22 tested BBS genes
  - **Frequency in Türkiye (5.82%) was highest across locations**
- At diagnosis, not all patients had a clear BBS phenotype indicating that all BBS genes should be included in panels testing for early-onset obesity, not just those investigating suspected syndromic disease

Genetic testing of individuals with early-onset obesity can help improve disease etiology understanding and identify patients who could potentially benefit from specialized care

BBS, Bardet-Biedl syndrome; MC4R, melanocortin-4 receptor.