The association of clinical features of Bardet-Biedl syndrome (BBS) in a large population of patients with obesity and a positive genetic test for biallelic BBS variants

P1202

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Related poster: EP1757 – Clinical features associated with pathogenic or likely pathogenic biallelic Bardet-Biedl syndrome gene variants in a large population of patients with obesity

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Conclusions

- In the Rare Obesity Advanced Diagnosis (ROAD)™ programme, cognitive impairment and visual impairment were the most frequently reported key Bardet-Biedl syndrome (BBS) clinical features among individuals with obesity who underwent genetic testing
- Individuals with biallelic BBS pathogenic/likely pathogenic (P/LP) genetic variants exhibited the highest frequency and greatest burden of key BBS clinical features compared with those with biallelic BBS variants of uncertain significance (VUS), other gene variants, and negative tests
- These findings suggest that obesity, in combination with ≥1 key BBS clinical feature (cognitive impairment, polydactyly, visual impairment, renal dysfunction, genitourinary abnormalities), may be associated with an increased likelihood of underlying biallelic BBS P/LP variants, and support consideration of genetic testing – irrespective of age – to facilitate earlier identification of BBS and appropriate disease management

Background

- In individuals living with BBS, a rare, genetically heterogeneous disease, dysfunction of the primary cilia may lead to melanocortin-4 receptor (MC4R) pathway disruption resulting in hyperphagia and early-onset obesity[1–6]
- Clinical presentation varies, with key clinical features of BBS including obesity, cognitive impairment, polydactyly, visual impairment, renal dysfunction, and genitourinary abnormalities[7]

Objectives

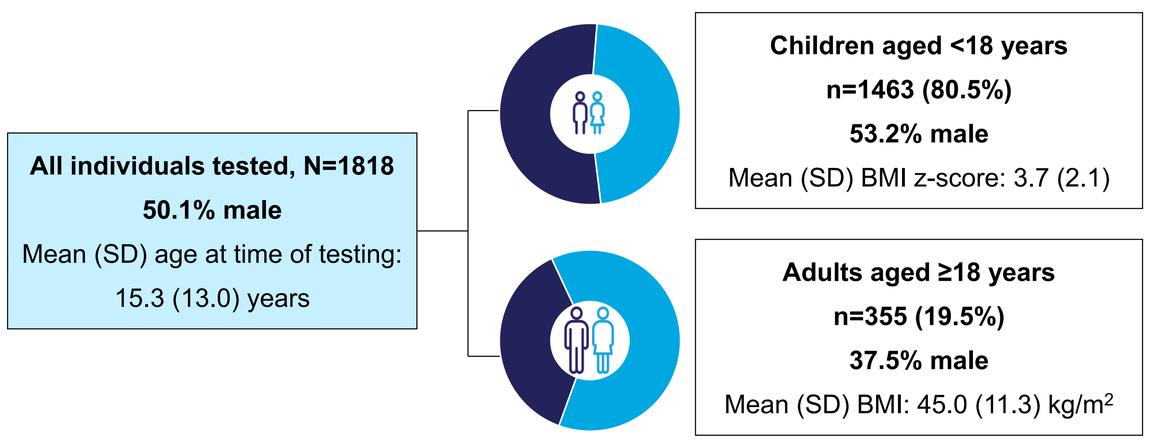
- The ROAD™ genetic testing programme is available in selected countries in Europe and the Middle East and aims to identify individuals with suspected rare MC4R pathway diseases
- In this analysis, the frequency of biallelic BBS gene variants and associated clinical features of BBS were assessed using data from the ROAD™ programme

Methods

- Variants in genes associated with BBS were classified as P/LP or VUS according to the American College of Medical Genetics (ACMG) criteria[8]
- The genetic testing panel encompassed 88 genes (including 30 BBS-associated genes) plus Ch16p11.2
- Eligible individuals included those with obesity, were aged ≤18 years with BMI ≥97th percentile for age and sex or aged ≥19 years with BMI ≥40.0 kg/m^2, and a history of childhood obesity
- Key clinical features of BBS were captured on the test requisition forms
- Data were analysed from 22 August 2024 to 13 January 2026

Results

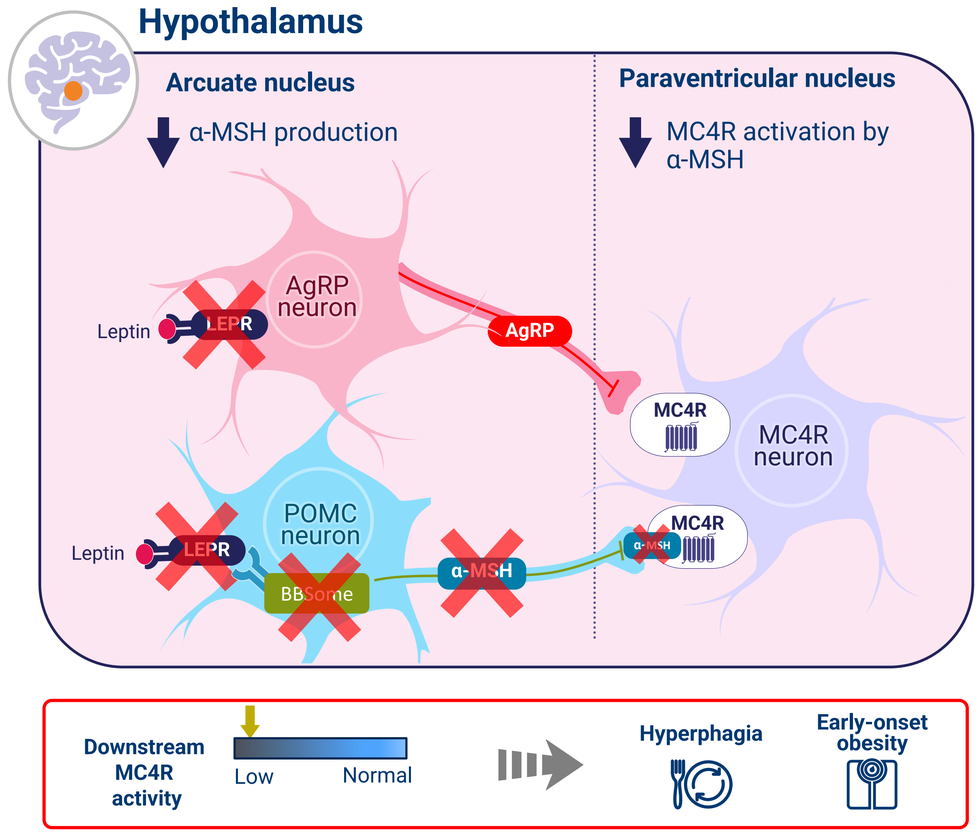
In total, 1818 individuals were included, the majority of whom were aged <18 years



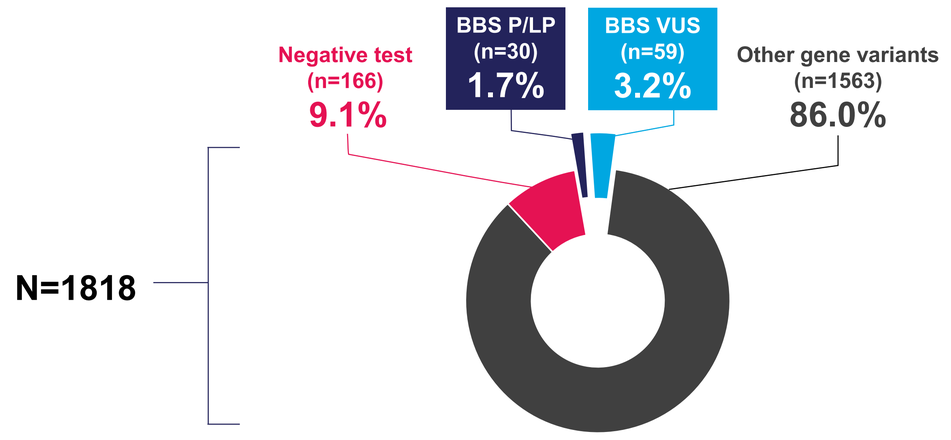
Among individuals with obesity, cognitive impairment and visual impairment were the most frequently reported key BBS clinical features, with the highest frequency in individuals with biallelic BBS P/LP variants

	Cognitive impairment	Polydactyly	Visual impairment	Renal dysfunction	Genitourinary abnormalities
BBS P/LP (n=30)	**80.0%** (n=24)	**80.0%** (n=24)	**66.7%** (n=20)	**33.3%** (n=10)	**23.3%** (n=7)
BBS VUS (n=59)	**32.2%** (n=19)	**3.4%** (n=2)	**3.4%** (n=2)	**0.0%** (n=0)	**3.4%** (n=2)
Other gene variants (n=1563)	**27.8%** (n=435)	**0.8%** (n=12)	**5.5%** (n=86)	**1.3%** (n=21)	**4.5%** (n=70)
Negative test (n=166)	**24.7%** (n=41)	**0.6%** (n=1)	**6.6%** (n=11)	**2.4%** (n=4)	**4.8%** (n=8)
Total (N=1818)	**28.5%** (n=519)	**2.1%** (n=39)	**6.5%** (n=119)	**1.9%** (n=35)	**4.8%** (n=87)

MC4R pathway disruption in BBS[1–6]



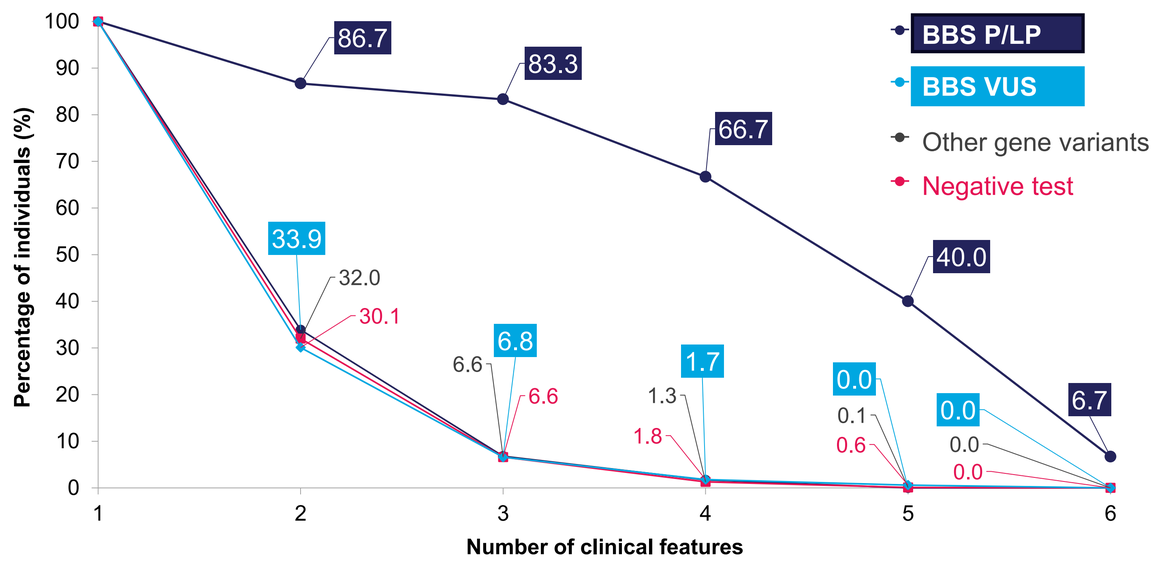
Overall, 89 individuals (4.9%) had biallelic P/LP/VUS variants within a single BBS gene



Scan the QR code in the top right corner for a list of genes in each group (supplementary table S1).

All individuals tested were pre-screened by an HCP based on a clinical suspicion of obesity. A negative test was defined as no reportable variants in the ROAD gene panel. The "other gene variants" category included individuals with any other variant not defined as BBS P/LP/VUS, encompassing variants of all ACMG pathogenicity classifications.[8]

Among individuals with obesity, biallelic BBS P/LP variants were associated with a higher frequency of key BBS clinical features and greater cumulative symptom burden compared with biallelic BBS VUS, other gene variants, and negative tests



Abbreviations: α-MSH, alpha melanocyte-stimulating hormone; ACMG, American College of Medical Genetics and Genomics; AgRP, agouti-related peptide; BBS, Bardet-Biedl syndrome; BBSome, complex of 8 BBS proteins; BMI, body mass index; HCP, healthcare professional; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; P/LP, pathogenic/likely pathogenic; POMC, proopiomelanocortin; ROAD, Rare Obesity Advanced Diagnosis; SD, standard deviation; VUS, variant(s) of uncertain significance.

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