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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Related poster: P1202 – 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

Conclusions

- In the Rare Obesity Advanced Diagnosis (ROAD)™ programme, cognitive impairment and polydactyly were the most frequently reported key clinical features among individuals living with obesity and Bardet-Biedl syndrome (BBS) biallelic pathogenic/likely pathogenic (P/LP) genetic variants
- Among individuals with obesity, a history of polydactyly in combination with renal or genitourinary anomalies was associated with a >80% likelihood of testing positive for a biallelic BBS P/LP genetic variant
- These findings support consideration of genetic testing, irrespective of age, in individuals with obesity and ≥1 key BBS clinical feature (cognitive impairment, polydactyly, visual impairment, renal dysfunction, genitourinary abnormalities), as identification of an underlying genetic cause may facilitate earlier identification of BBS, informing clinical decision-making and appropriate disease management

Background

- BBS is a rare disease marked by genetic and clinical heterogeneity. It is caused by dysfunction of the primary cilia, which may disrupt melanocortin-4 receptor (MC4R) pathway signalling and lead to hyperphagia, decreased energy expenditure, and early-onset obesity[1–6]
- Clinical presentation is highly variable, with key clinical features of BBS including obesity, cognitive impairment, polydactyly, visual impairment, renal dysfunction, and genitourinary abnormalities[7]

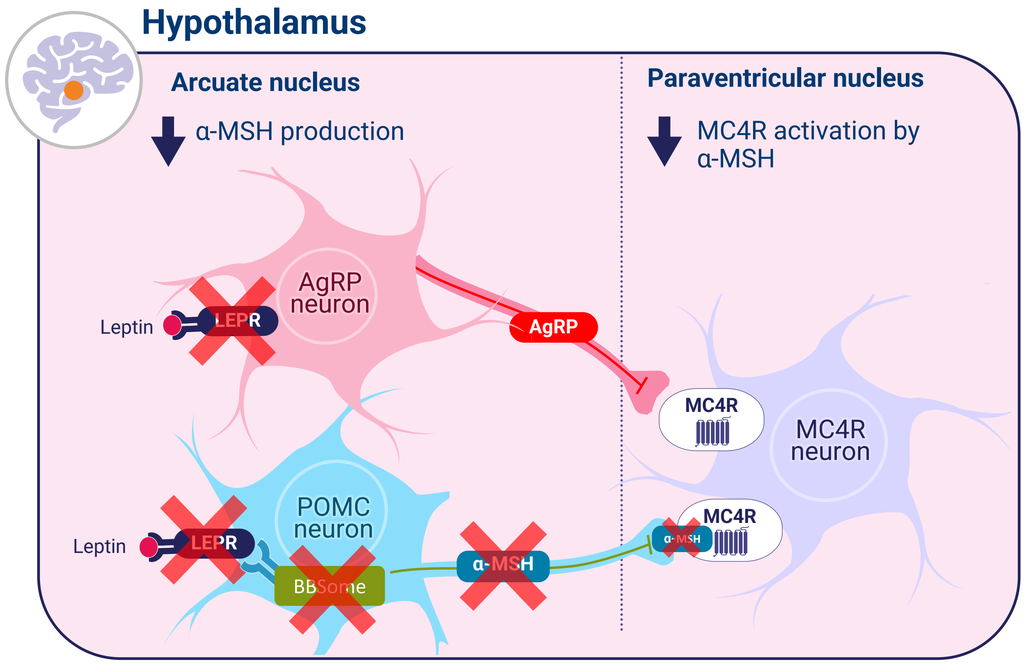
Objectives

- 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 prevalence of BBS key clinical features was evaluated in individuals with biallelic BBS P/LP genetic variants 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

MC4R pathway disruption in BBS[1–6]



Results

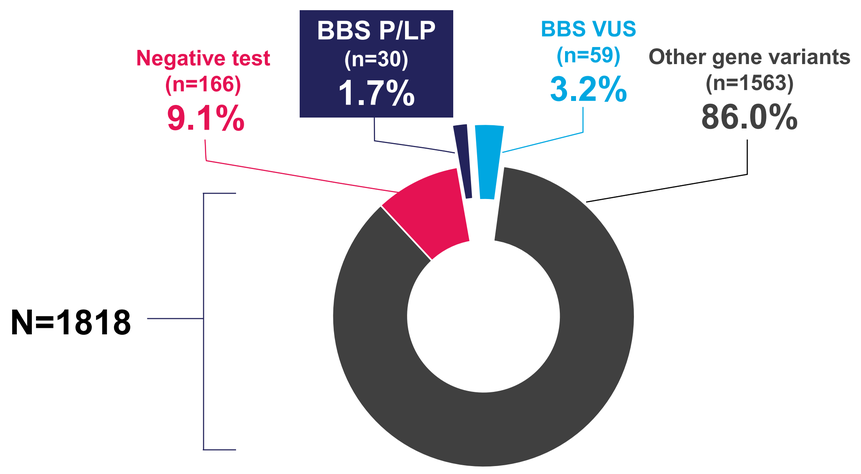
In total, 1818 individuals were included, the majority of whom were aged <18 years

All individuals tested, N=1818
50.1% male
Mean (SD) age at time of testing: 15.3 (13.0) years

Children aged <18 years
n=1463 (80.5%)
53.2% male
Mean (SD) BMI z-score: 3.7 (2.1)

Adults aged ≥18 years
n=355 (19.5%)
37.5% male
Mean (SD) BMI: 45.0 (11.3) kg/m^2

Overall, 30 individuals (1.7%) had a biallelic P/LP variant 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).

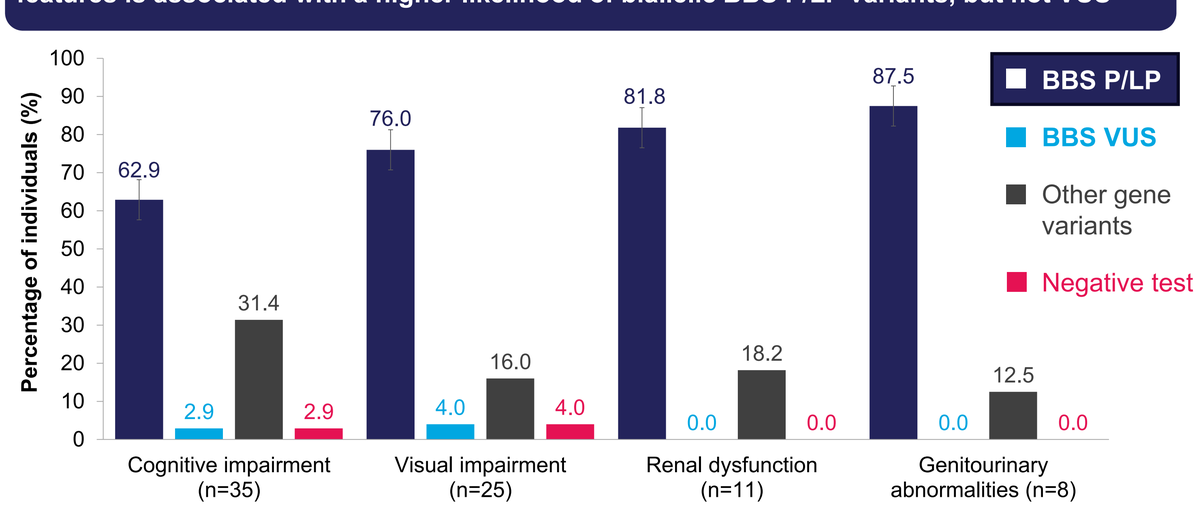
All individuals tested were pre-screened by an HCP based on a clinical suspicion of obesity. A negative test was defined as no reportable variants in the ROAD gene panel. The "other gene variants" category included individuals with any other variant not defined as BBS P/LP/VUS, encompassing variants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

Among individuals with obesity, cognitive impairment and polydactyly were the most frequently reported key BBS clinical features in individuals with biallelic BBS P/LP variants compared with all individuals tested

	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)
Total (N=1818)	**28.5%** (n=519)	**2.1%** (n=39)	**6.5%** (n=119)	**1.9%** (n=35)	**4.8%** (n=87)

Scan the QR code in the top right corner for further details (supplementary figure S1).

Among individuals with obesity and polydactyly, co-occurrence of additional key BBS clinical features is associated with a higher likelihood of biallelic BBS P/LP variants, but not VUS



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.

Disclosures: APG is a consultant for Rhythm Pharmaceuticals, Inc.; has been a consultant for Novo Nordisk, Eli Lilly, Bramble Partners, Evidera, Helsinn Healthcare, Idera Pharmaceuticals, Soleno Therapeutics, Tonix Pharmaceuticals, and Veda Ventures; has been an advisory board member for Millendo Therapeutics and Radius Health; has been a member of the Data Safety Monitoring Committee for Novo Nordisk; has received speaker honoraria from Novo Nordisk, Eli Lilly, and Rhythm Pharmaceuticals, Inc.; has been a Principal Investigator for clinical trials sponsored by Millendo Therapeutics, Rhythm Pharmaceuticals, Inc., and Soleno Therapeutics; and has received research funding from Novo Nordisk; **JD-R** has received compensation for speaking engagements, and/or institutional study funding from Rhythm Pharmaceuticals, Inc., as a clinical investigator; **GRU, EW, MM** have no conflicts of interest to disclose; **EK** has served as co-investigator in the "Setmelanotide Phase 2 Treatment trial in patients with rare genetic disorders of obesity", sponsored by Rhythm Pharmaceuticals, Inc.; **CS and PS** are employees of Rhythm Pharmaceuticals, Inc. and have received salary and stock options for their employment; **BH** is a member of the national BBS and monogenic obesity advisory board for Rhythm Pharmaceuticals, Inc.; **MY** has participated on advisory boards for Rhythm Pharmaceuticals, Inc.; **JA** has received compensation for speaking engagements, and/or institutional study funding from Rhythm Pharmaceuticals, Inc. as a clinical investigator, and has participated in the BBS advisory board for Rhythm Pharmaceuticals, Inc.

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