Free Communications 11 (FC11.1): Fat, Metabolism and Obesity

Frequency of rare syndromic diseases in a population with early-onset obesity

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DISCLOSURE STATEMENT

Melania Manco, MD, PhD

□ I have the following potential conflicts of interest to report:

- □ Research Contracts
- □ Consulting
- □ Employment in the Industry
- □ Stockholder of a healthcare company
- □ Owner of a healthcare company
- □ Other(s) – *please include details*

□ I declare that I have no potential conflict of interest.

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Presentation FC11.1

Melania Manco, MD, PhD, presenting

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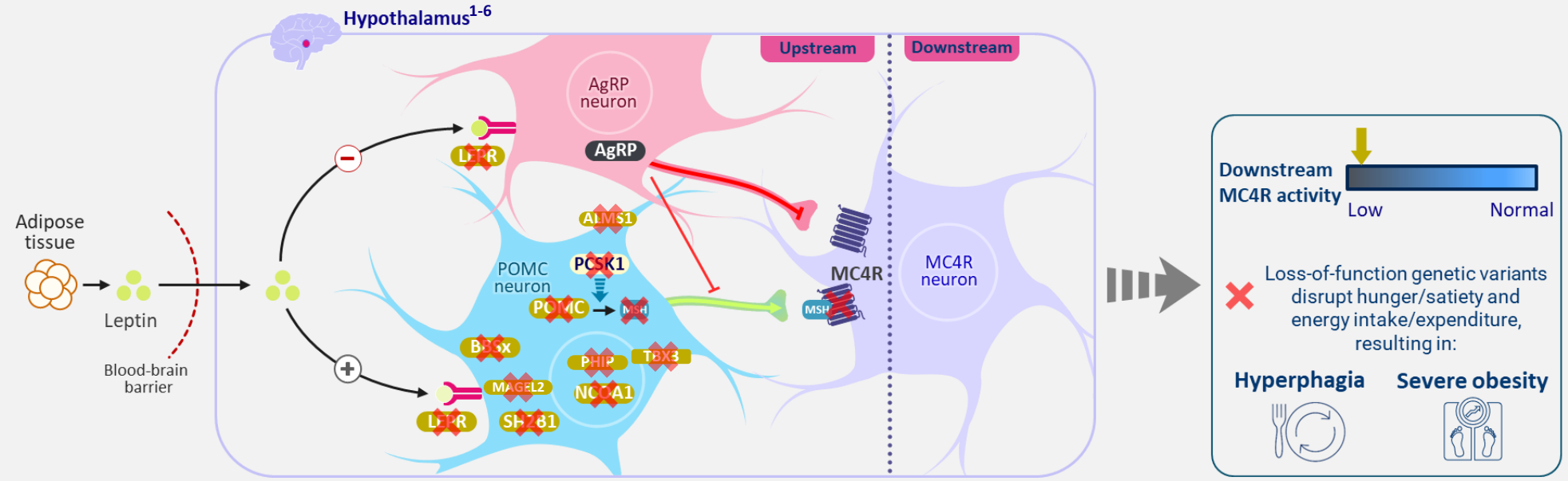
The central hypothalamus is a key regulator of energy balance, appetite and bodyweight[1-4]

- The hypothalamic melanocortin-4 receptor (MC4R) pathway 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, as well as neurodevelopmental delay or dysmorphic features[4,5]
- Patients with these variants often do not respond to traditional weight management strategies[6]



AgRP, agouti-related peptide; ALMS1, Alström syndrome protein 1; BBS, Bardet-Biedl syndrome; LEPR, leptin receptor; *MAGEL2,* melanoma-associated antigen gene L2; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; *NCOA1*, Nuclear Receptor Coactivator 1; *PCSK1*, proprotein convertase subtilisin/kexin type 1; *PHIP*, pleckstrin homology domain interacting protein; *POMC*, proopiomelanocortin; *TBX3*, T-box transcription factor.

1. Huvenne H, et al. *Obes Facts*. 2016;9(3):158–173; **2.** Yazdi FT, et al. *PeerJ.* 2015;3:e856; **3.** Yang Y, et al. *Nat Commun*. 2019;10(1718):10.1038/s41467-019-08737-6; **4.** Revelli JP, et al. *Obesity (Silver Spring).* 2011;19(5):1010–1018; **5.** Sohn Y, et al. *Ann Pediatr Endocrinol Metab*. 2022;27(3):169–175; **6.** Clément K, et al. *Physiol Behav.* 2020;227:113134.

Gene variants associated with rare syndromic diseases are linked with multiple syndromes

ALMS1[1–4]

- *ALMS1* encodes a protein found in cilia. Loss of this protein may **disrupt cilia structure and function which impacts on LEPR trafficking**
- *ALMS1* variants are associated with **Alström Syndrome**

Phenotypes

- Excessive weight gain
- Retinopathy
- Renal disease
- Developmental delay
- Audiopathy
- Cardiovascular defects
- Insulin resistance
- Genital anomalies

MAGEL2[5–11]

- *MAGEL2* encodes a **ubiquitin ligase enhancer**. Disrupted expression leads to **defective leptin sensing in POMC neurons**
- Gene variants associated with obesity have been identified in **Prader-Willi syndrome** and **Schaaf-Yang syndrome**

Phenotypes

- Hyperphagia
- Excessive weight gain
- Intellectual disability
- Sleep apnea
- Hypogonadism

PHIP[12–14]

- *PHIP* encodes a protein that acts as a **transcriptional regulator** that **enhances POMC transcription**
- Some ***PHIP* variants** associated with obesity **repress *POMC* transcription;** variants are associated with **Chung-Jansen syndrome**

Phenotypes

- Hyperphagia
- Early-onset obesity
- Insulin resistance
- Developmental delay and behavioural problems
- Learning difficulties
- Dysmorphic features

TBX3[15–18]

- *TBX3* encodes a **transcription factor** important for limb development and directs postnatal neuronal fate
- *TBX3* is critical for **defining POMC identity**; *TBX3* variants may affect energy balance and are associated with **Ulnar-Mammary syndrome**

Phenotypes

- Obesity
- Hypogonadism
- Posterior limb deficiencies
- Apocrine/mammary gland hypoplasia
- Abnormal dentition
- Delayed puberty in males
- Genital anomalies

BBS[19–25]

- **26 BBS genes have been identified to date.** These encode proteins critical for the structure and function of cilia
- BBS gene variants lead to ciliary dysfunction, which may disrupt **LEPR signaling and downstream activation of MC4R neurons**

Phenotypes

- Hyperphagia
- Early-onset obesity
- Rod-cone dystrophy
- Renal anomalies
- Learning difficulties
- Polydactyly
- Genital anomalies

ALMS1, Alström syndrome protein 1; BBS, Bardet-Biedl syndrome; LEPR, leptin receptor; MAGEL2, melanoma-associated antigen gene L2; PHIP, pleckstrin homology domain interacting protein; POMC, proopiomelanocortin; TBX3, T-box transcription factor.

1. Forsythe E, Beales PL. *Eur J Hum Genet.* 2013;21:8–13; **2.** Forsythe E, Gunay-Aygun, M. *Gene Reviews*. 2023. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1363. Last accessed July 2023; **3.** Vaisse C, et al. *Cold Spring Harb Perspect Biol.* 2017;9:a028217; **4.** Seo S, et al. *Hum Mol Genet.* 2009;18:1323–1331; **5.** Maillard J, et al. *Hum Mol Genet.* 2016;25:3208–3215; **6.** Mercer RE, et al. *PLoS Genet.* 2013;9:e1003207; **7.** Pravdivyi I, et al. *Hum Mol Genet.* 2015;24:4276–4283; **8.** Patak J, et al. *Clin Genet.* 2019;96:493–505; **9.** McCarthy J, et al. *Am J Med Genet A.* 2018;176:2564–2574; **10.** Negishi Y, et al. *Orphanet J Rare Dis.* 2019;14:277; **11.** Schaaf CP, et al. *Nat Genet.* 2013;45:1405–1408; **12.** Marenne G, et al. *Cell Metab.* 2020;31:1107–1119; **13.** Webster E, et al. *Cold Spring Harb Mol Case Stud.* 2016;2:a001172; **14.** Podcheko A, et al. *Mol Cell Biol.* 2007;27:6484–6496; **15.** Yazdi FT, et al. *PeerJ*. 2015;3:e856; **16.** Sanz E, et al. *J Neurosci.* 2015;35:5549–5556; **17.** Quarta C, et al. *Nat Metab.* 2019;1:222–235; **18.** Galazzi E, et al. *Endocr Connect.* 2018;7:1432–1441; **19.** Dollfus H, et al. *Eur J Hum Genet.* 2024:10.1038/s41431-024-01634-7; **20.** Guo and Rahmouni. *Trends Endocrinol Metab*. 2011;22:286–293; **21.** Seo S, et al. *Hum Mol Genet*. 2009;18:1323–1331; **22.** Forsythe E, et al. *Eur J Hum Genet*. 2013:21:8–13; **23.** Forsythe E, et al. *Front Pediatr* 2018;6:1–8; 3; **24.** Pomeroy J, et al. *Pediatr Obes*. 2021;16(2):e12703; **25.** Poitou C, et al. *Eur J Endocrinol.* 2020;183;R149-R166.

Early identification of patients with rare syndromic variants 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]

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/m^2 and a history of childhood obesity

OR

Immediate family member of select, previously tested patients

OR

Showing clinical symptoms of BBS

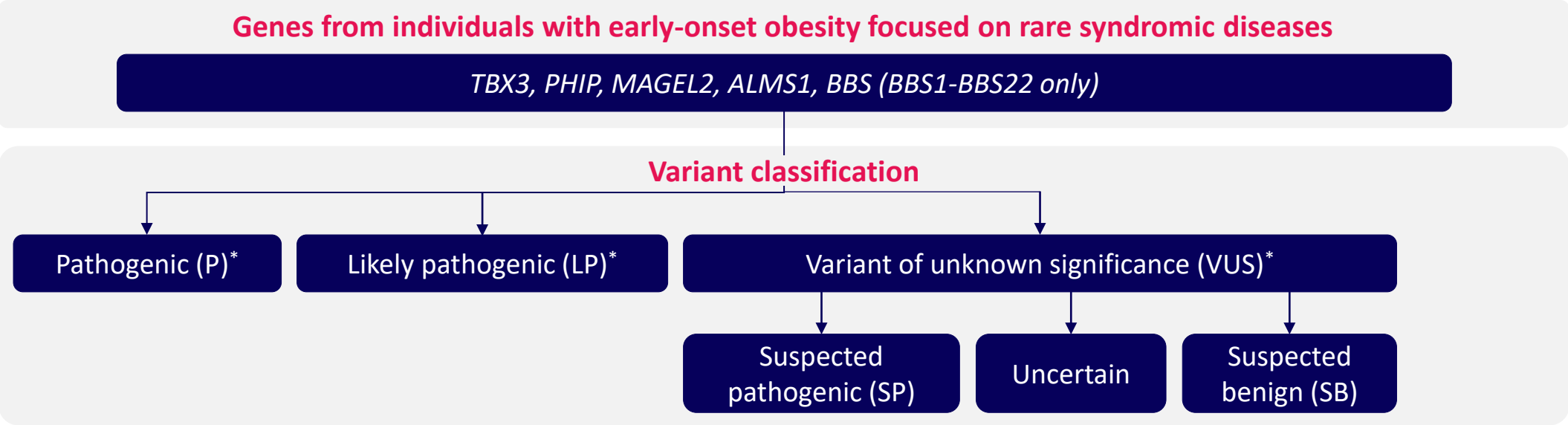
[a]Germany, Greece, Ireland, Israel, Italy, Spain, Türkiye, the United Kingdom; Rare Obesity Advanced Diagnosis (ROAD) and its logo are registered trademarks of Rhythm Pharmaceuticals, Inc.
BMI, body mass index; MC4R, melanocortin-4 receptor; ROAD, Rare Obesity Advanced Diagnosis.

Rare syndromic gene variant analysis within ROAD®

Objective:

- To assess the frequency of selected rare syndromic diseases in individuals with hallmark symptoms of potential underlying genetic causes of early-onset obesity, using ROAD data

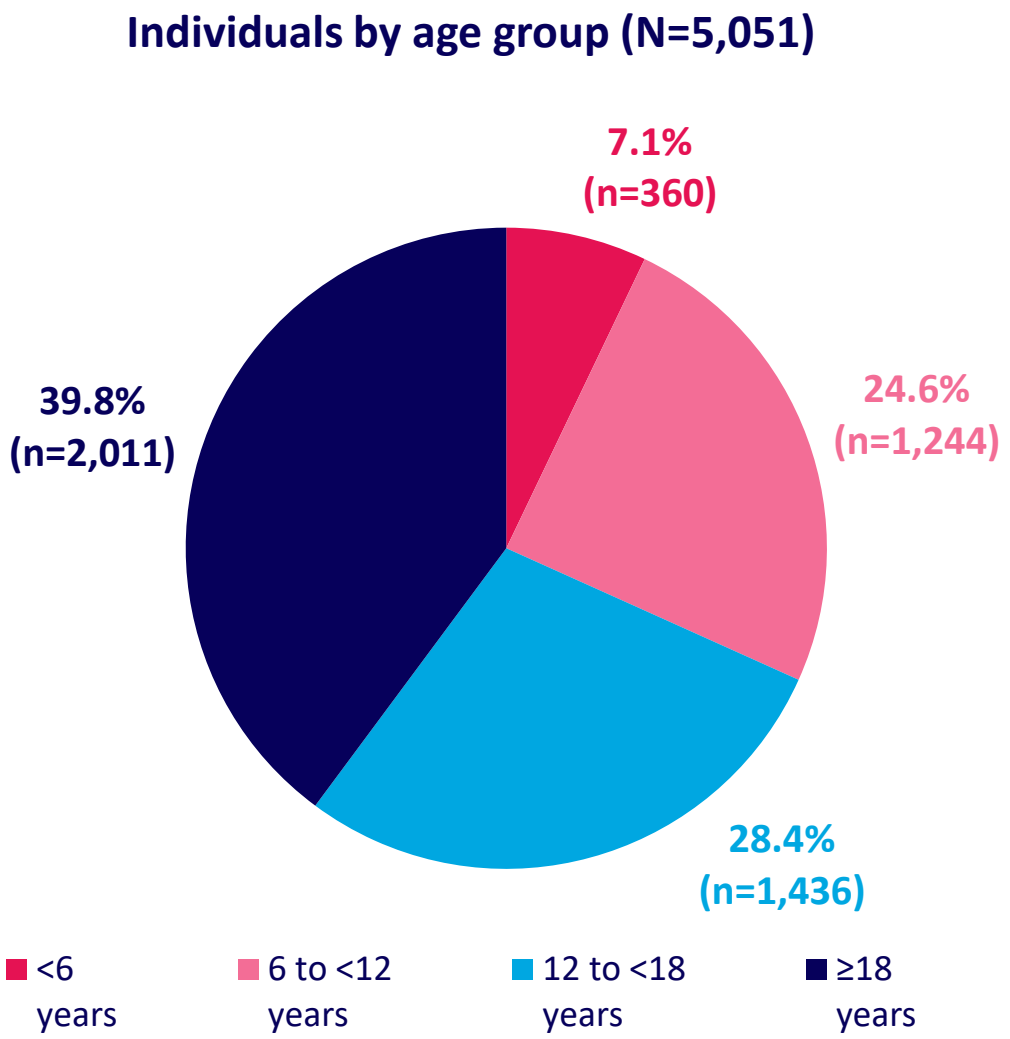
- Healthcare professionals ordered ROAD® genetic testing for individuals with early-onset obesity located in Germany, Greece, Ireland, Israel, Italy, Spain, Türkiye, the United Kingdom.



*Variants were classified as P/LP/VUS according to American College of Medical Genetics criteria.
ALMS1, Alström syndrome protein 1; BBS, Bardet-Biedl syndrome; MAGEL2, melanoma-associated antigen gene L2; MC4R, melanocortin-4 receptor; PHIP, pleckstrin homology domain interacting protein; TBX3, T-box transcription factor.

Baseline characteristics of total sequenced individuals

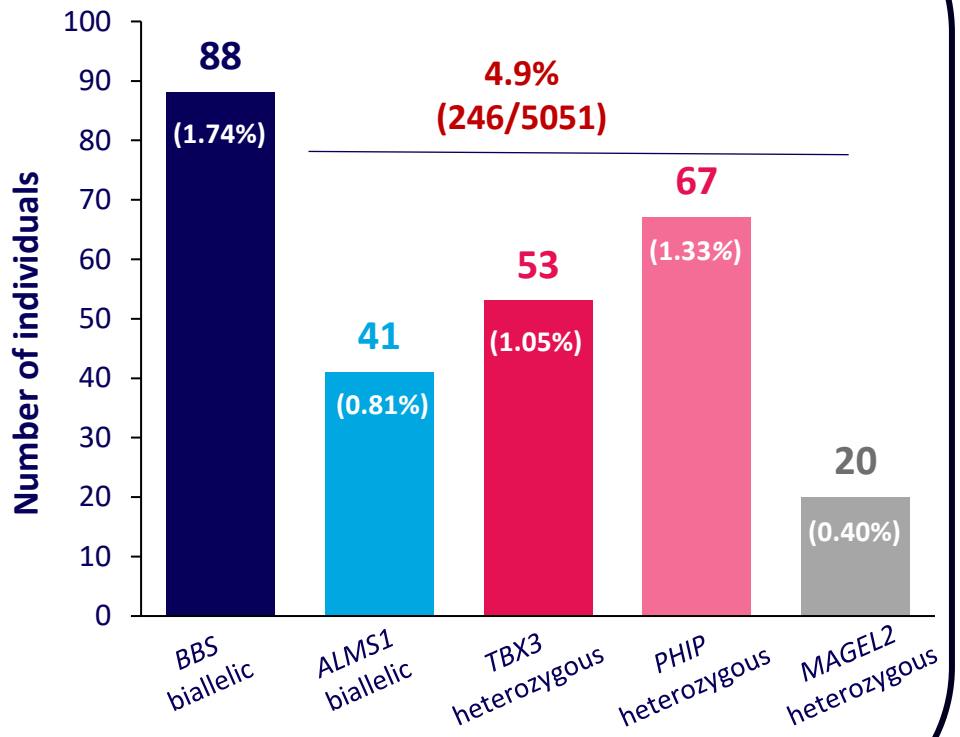
Parameter	Total (N=5,051)
Sex, n (%)	
Female	2,763 (54.7)
Male	2,285 (45.2)
Prefer not to disclose/not provided	3 (0.1)
Age at time of testing, mean (SD)	23.0 (17.7)
Age at onset of obesity (n=1,554), mean (SD)	8.0 (3.9)
BMI z score (patients aged <18 years, n=3,026), mean (SD)	**3.6 (1.0)**
BMI (patients 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.

4.9% of tested individuals carried a variant potentially leading to disease and presented with early hyperphagia and obesity onset

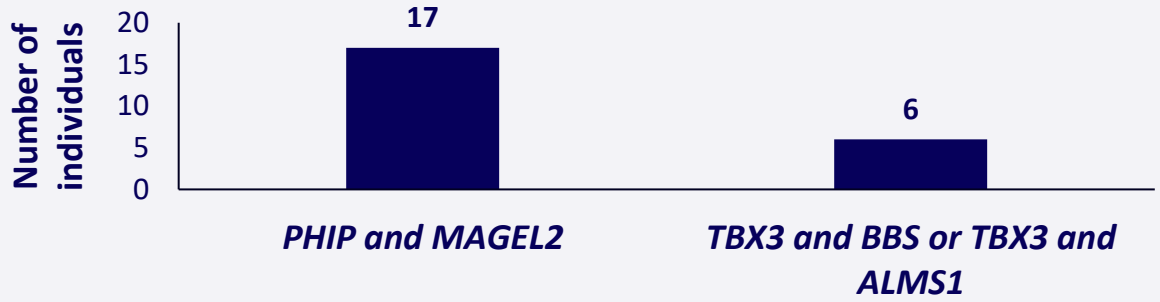
Individuals with rare syndromic variants* (N=246)



Hyperphagia and weight parameters, mean (SD)

Age of hyperphagia onset	Age of obesity onset	BMI z-score (<18 years) BMI (≥18 years)
3.8 (2.4) years	4.7 (3.7) years	BMI z-score: 3.5 (1.1) BMI: 41.4 (10.6) kg/m^2

Individuals with multiple gene variants



Two patients with *TBX3* variants were also *LEPR* biallelic

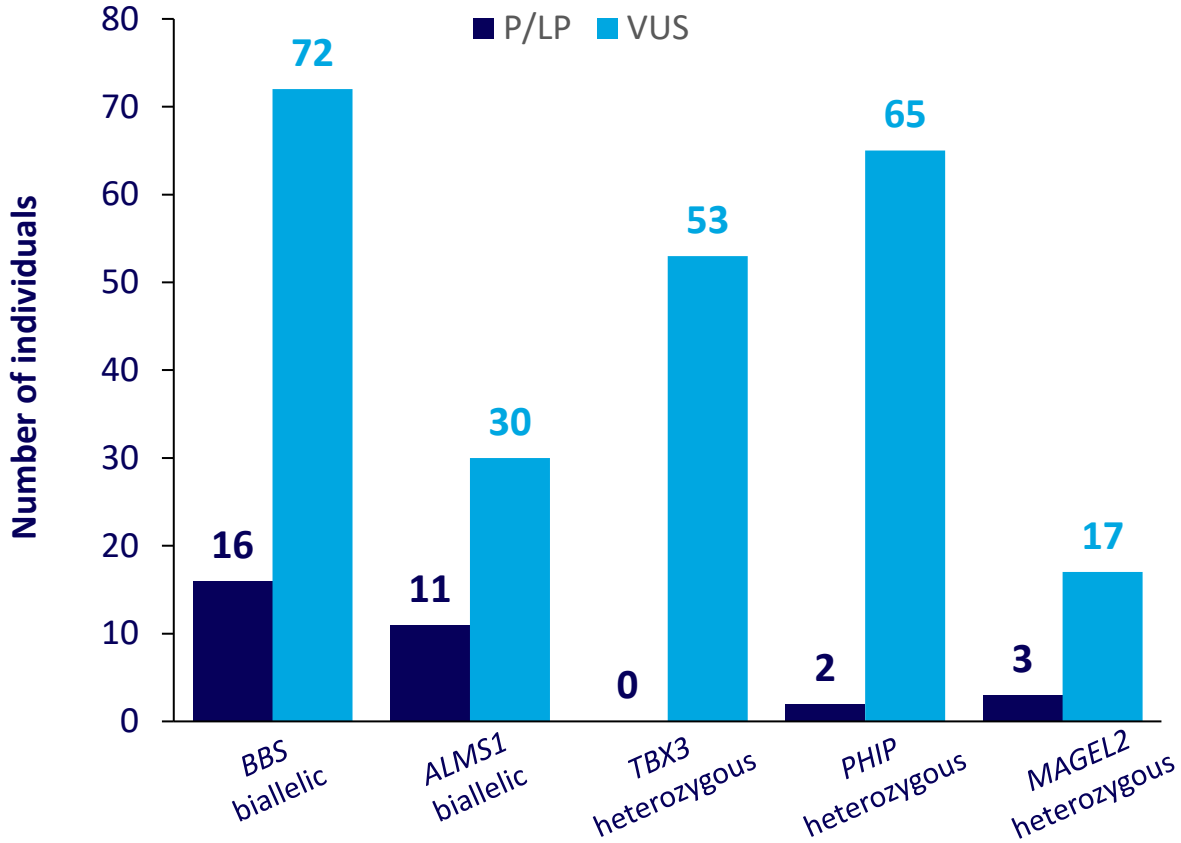
*Some individuals tested demonstrated a variant in multiple genes.

Inheritance: BBS, autosomal recessive; TBX3, autosomal dominant; PHIP, autosomal dominant; MAGEL2, autosomal dominant; ALSM1, autosomal recessive.

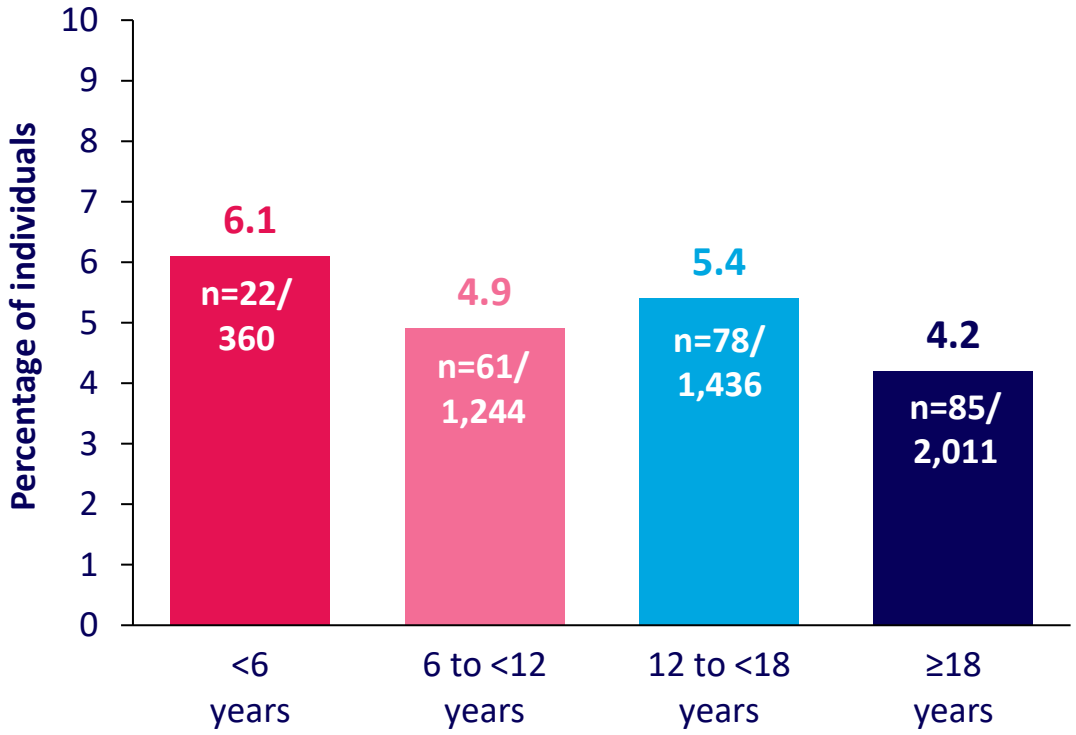
ALMS1, Alström syndrome protein 1; BBS, Bardet-Biedl syndrome; BMI, body mass index; LEPR, leptin receptor; MAGEL2, melanoma-associated antigen gene L2; PHIP, pleckstrin homology domain interacting protein; SD, standard deviation; TBX3, T-box transcription factor.

Frequency for P/LP and VUS variants potentially leading to disease were similar across all age groups with highest seen in patients <6 years

Number of P/LP and VUS variants across gene types (N=246)



Percentage of individuals with rare variants in syndromic genes by age subgroups of the full cohort (N=246/5,051)



Inheritance: BBS, autosomal recessive; TBX3, autosomal dominant; PHIP, autosomal dominant; MAGEL2, autosomal dominant; ALSM1, autosomal recessive.
ALMS1, Alström syndrome protein 1; BBS, Bardet-Biedl syndrome; MAGEL2, melanoma-associated antigen gene L2; P/LP, pathogenic/likely pathogenic; PHIP, pleckstrin homology domain interacting protein; TBX3, T-box transcription factor; VUS, variant of unknown significance.

Summary and conclusions

- 4.9% of tested individuals carried a biallelic or heterozygous P/LP/VUS variant in ≥1 of the tested rare syndromic variants (*ALMS1*, *BBS*, *MAGEL2*, *PHIP*, or *TBX3* genes)
  - Variants in these genes are associated with many debilitating syndromes and currently have no effective targeted treatment
- While the highest rates with P/LP/VUS were seen in individuals <6 years, it was observed across all age groups, highlighting the need for early recognition and genetic testing
  - By testing patients of with early-onset obesity with selected gene panel, a genetic cause might be identified, allowing improved disease awareness and disease management
- 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

Early identification of patients affected by rare MC4R pathway diseases may aid in effective management and reduced disease burden for patients and families with timely specialized care

AS, Alström Syndrome; BBS, Bardet-Biedl syndrome; MAGEL2, melanoma-associated antigen gene L2; P/LP, pathogenic/likely pathogenic; PHIP, pleckstrin homology domain interacting protein; TBX3, T-box transcription factor; VUS, variant of unknown significance.