Free Communications 11: Fat, Metabolism and Obesity 2

FC11.2.
Frequency of rare non-syndromic diseases in a population with early-onset obesity

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

Presentation FC11.2

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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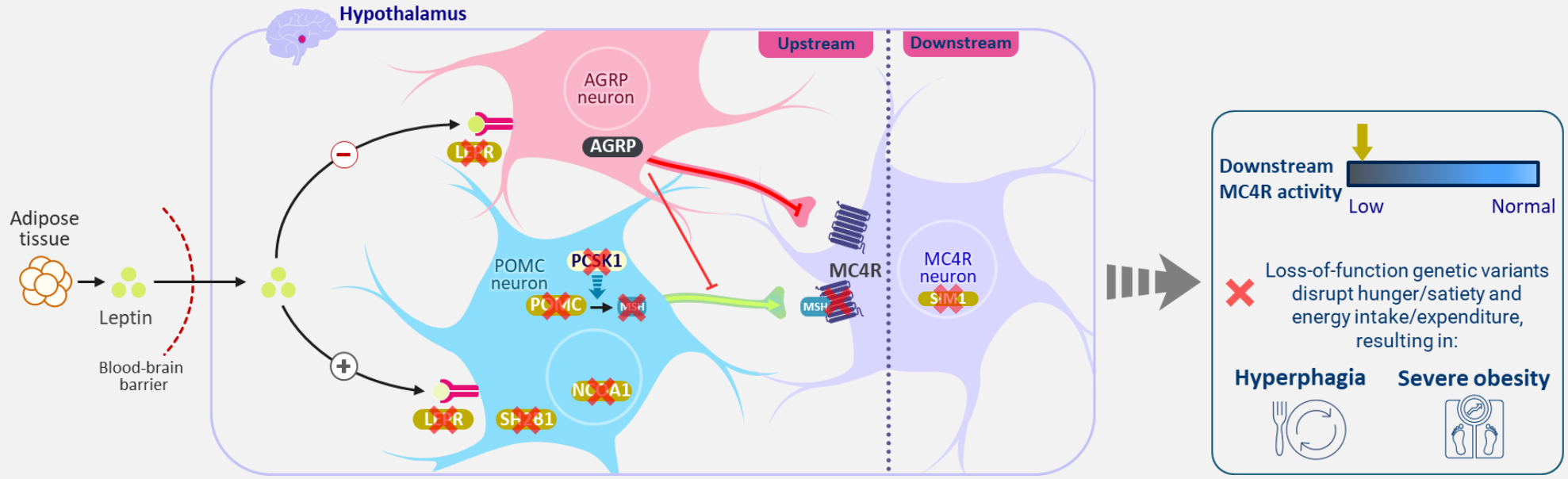
Impairment in the melanocortin-4 receptor (MC4R) pathway is a root cause of hyperphagia (pathological, insatiable hunger) and early-onset obesity[1–8]

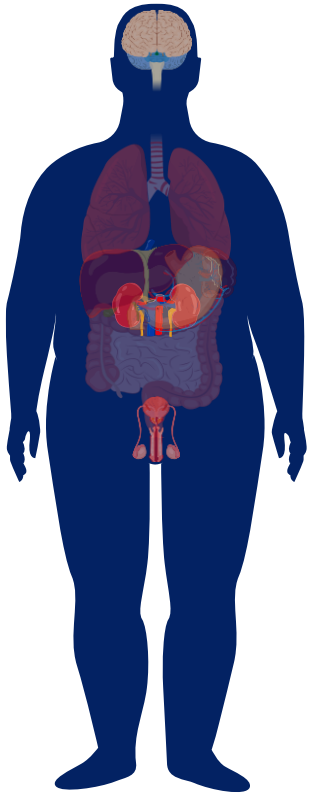
Loss-of-function variants in the MC4R pathway can lead to POMC, PCSK1 and LEPR deficiency, which may result in clinical features such as hyperphagia (pathologic, insatiable hunger) and early-onset obesity as well as hypogonadotropic hypogonadism, light or pale skin and red hair[9]



AgRP, agouti-related peptide; BBS, Bardet-Biedl syndrome; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; NCOA1, nuclear receptor coactivator 1; PCSK1, proprotein convertase subtilisin/kexin type 1; *POMC*, proopiomelanocortin; *SH2B1*, SH2B adaptor protein 1.

1. Montague CT, et al. *Nature.* 1997;387(6636):903–8; 2. Clement K, et al. *Nature*. 1998;392(6674):398–401; **3.** Krude H, et al. *Nat Genet*. 1998;19(2):155–7; **4.** Jackson RS, et al. *Nat Genet.* 1997;16(3):303–6; **5.** Farooqi IS, et al. *N Engl J Med*. 2003;348(12):1085–95; **6.** Bochukova EG, et al. *Nature.* 2010;463(7281):666–670; **7.** Doche ME, et al. *J Clin Invest.* 2012;122(12):4732–4736; **8.** Loos RJF and Yeo GSH. *Nat Rev Genet*. 2022;23:120–133; **9.** Malhotra S, et al. *J Pediatr Genet.* 2021;10:194–203.

Genetic testing is recommended to focus the diagnosis and treatment in patients with hyperphagia and early-onset obesity[1-4]



Identify patients

- **Hyperphagia**
- **Early-onset[a] obesity**
- **Other clinical characteristics of rare MC4R pathway diseases (ie, neurological abnormalities, growth abnormalities, endocrine abnormalities)**
- **Family history of notable weight differences between family members**

Genetic testing can aid in the diagnosis of rare MC4R pathway diseases

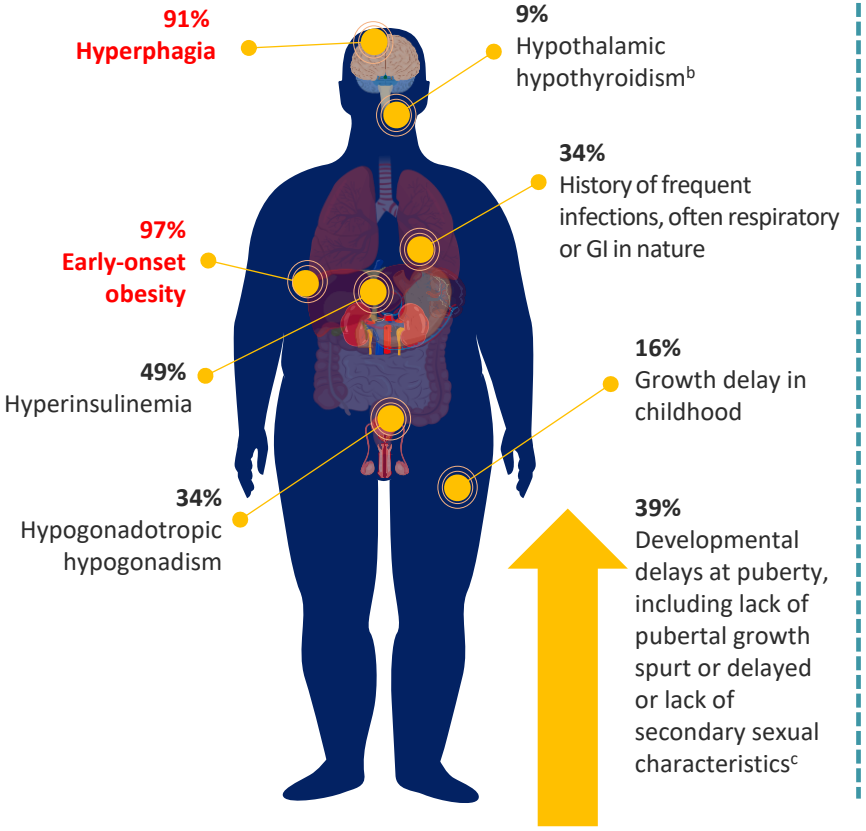
Genetically identifiable, non-syndromic[b]

- **POMC deficiency**
- **LEPR deficiency**
- **PCSK1 deficiency**
- **MC4R deficiency**
- **SRC1/NCOA1 deficiency**
- **SH2B1 deficiency**

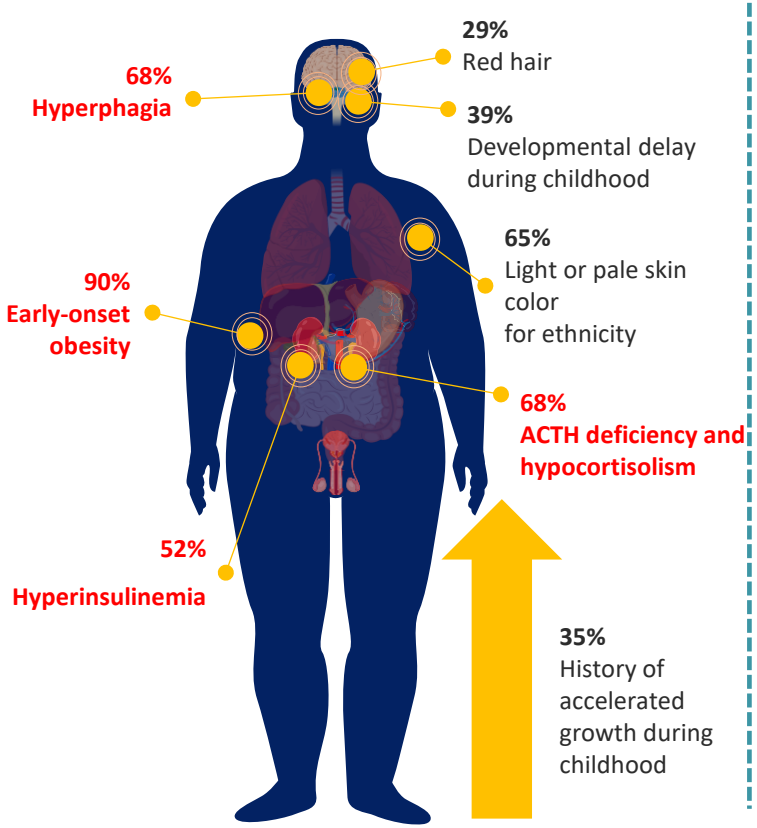
[a]Before 5 years of age. [b]Clinical Non-exhaustive list, summary of few non-syndromic gene variants but not all that were tested in the ROAD program.
LEPR, leptin receptor; MC4R, melanocortin-4 receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; SH2B1, Src homology 2 B adapter protein 1; SRC1, steroid receptor coactivator 1.
1. Styne DM, et al. *J Clin Endocrinol Metab*. 2017;102(3):709-757; 2. van der Valk ES, et al. *Obes Rev*. 2019;20(6):795-804; 3. Huvenne H, et al. *Obes Facts*. 2016;9(3):158-173; 4. Smith ACM, et al. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1310/. Last accessed: September 2024.

Clinical characteristics in patients with non-syndromic diseases driven by variants in *LEPR*, *POMC*, or *PCSK1* genes

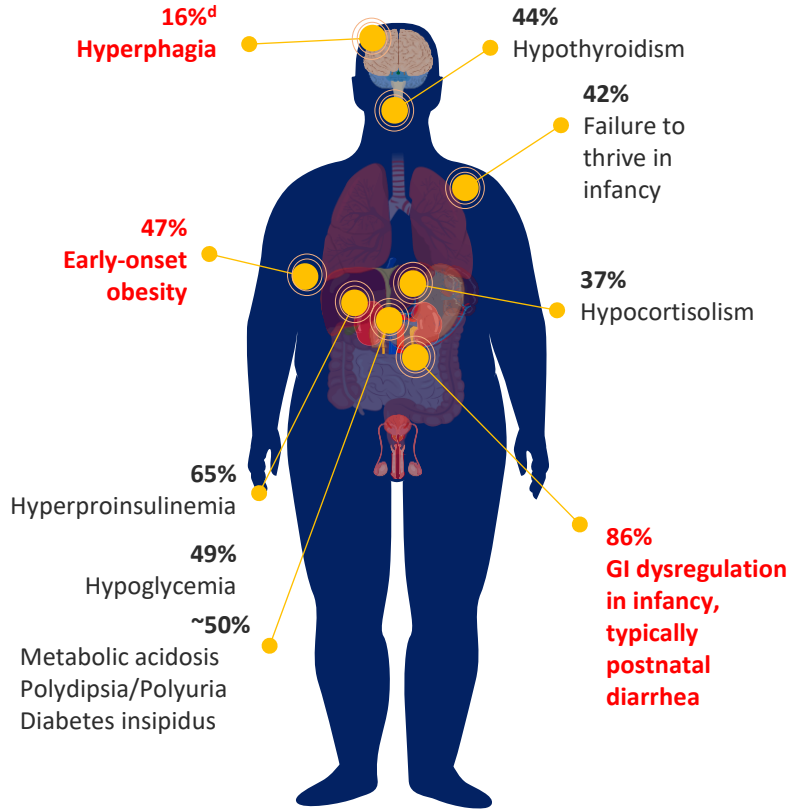
LEPR deficiency[1a]



POMC deficiency[1a]



PCSK1 deficiency[1a]



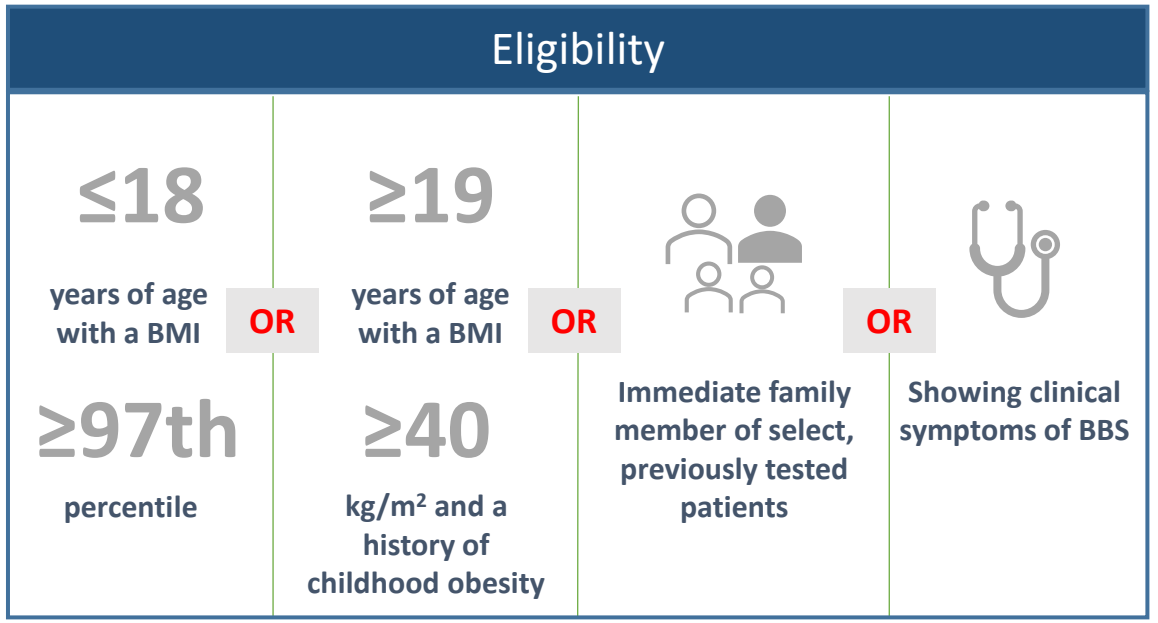
[a]Prevalence of characteristics based on an analysis of published case studies (n=76 individuals). Prevalence calculated by number of cases with the characteristic divided by total number of cases. [b]Thyroid function not noted in 67% of cases. [c]Delayed puberty and hypogonadotropic hypogonadism were separate categories in this analysis. [d]It is accepted in the literature that excess hunger is a characteristic of individuals with PCSK1 deficiency; however, patient hunger level, excess hunger, and hyperphagia were not mentioned as patient characteristics 79% of the time.

1. Argente et al. Poster presented at: 21st European Congress of Endocrinology (ECE); May 18-21, 2019; Lyon, France.

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**



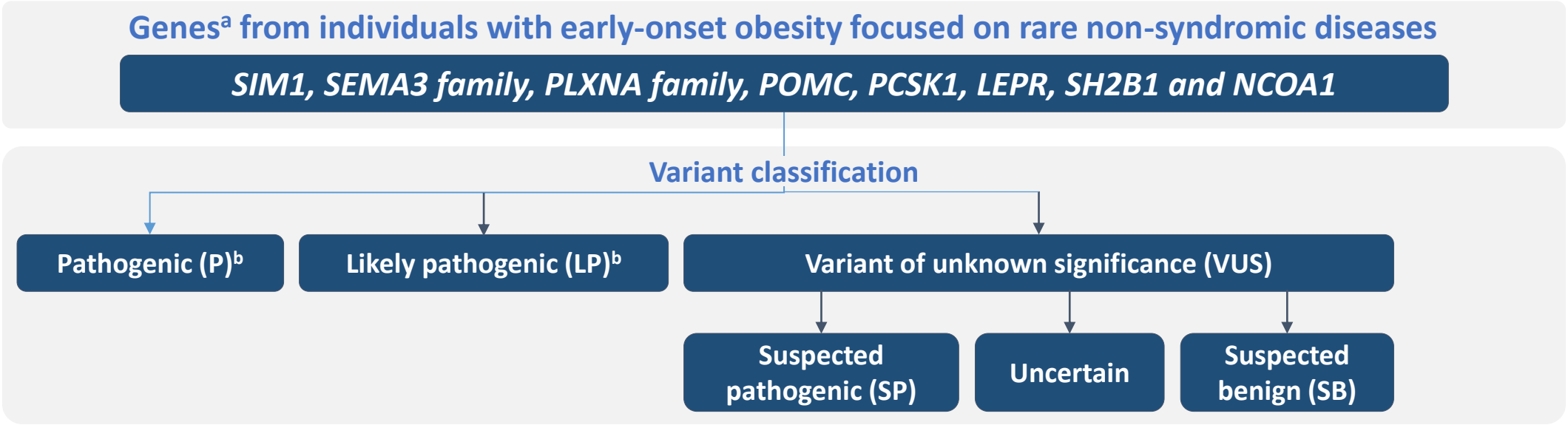
[a]Germany, Greece, Ireland, Israel, Italy, Spain, Türkiye, the United Kingdom; Rare Obesity Advanced Diagnosis (ROAD) and its logo are registered trademarks of Rhythm Pharmaceuticals, Inc.

Rare non-syndromic variant analyses within ROAD®

Objective:

- **To assess the frequency of selected rare non-syndromic diseases 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**

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

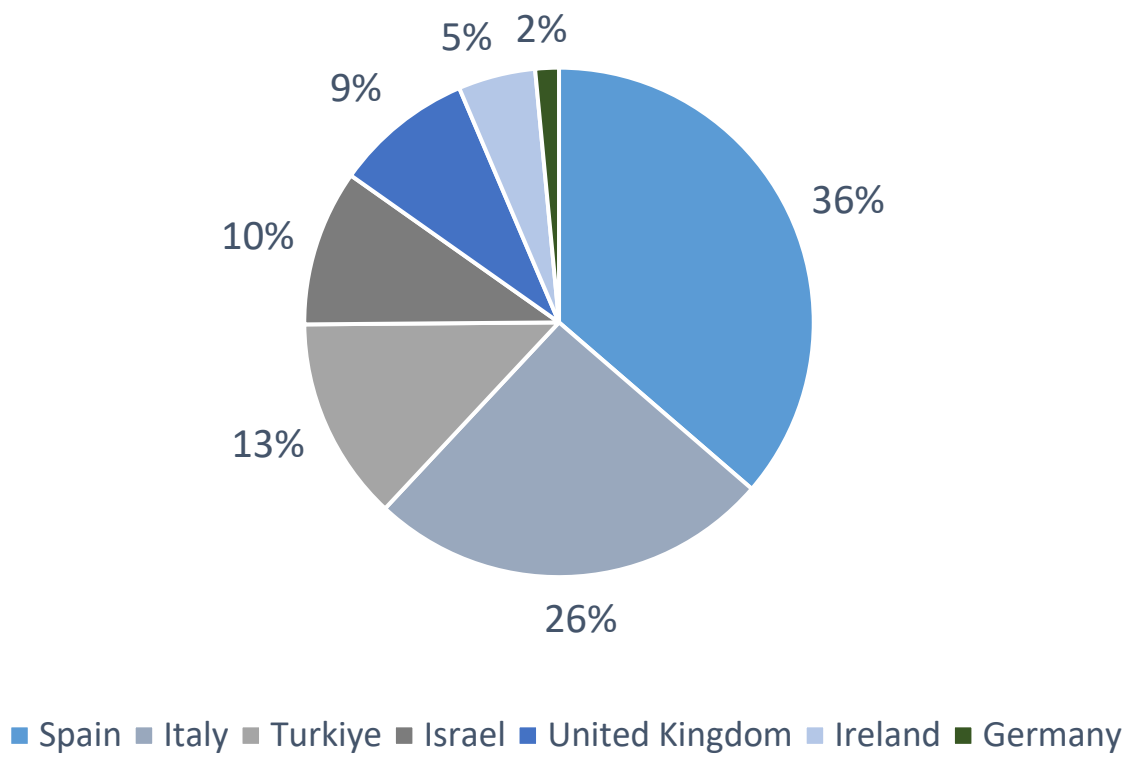


[a]Gene family members tested: SIM1; SEMA3 family (SEMA3A, SEMA3B, SEMA3C, SEMA3D, SEMA3E, SEMA3F, SEMA3G); PLXNA family (PLXNA1, PLXNA2, PLXNA3, PLXNA4); LEPR, POMC, PCSK1 (heterozygous and biallelic);
SH2B1 and NCOA1. Excluding PCSK1 p.(Asn221Asp) variant 435 occurrences in ROAD. Some of the variants could also be syndromic; [b]Variants were classified as P/LP/VUS according to American College of Medical Genetics criteria.
MC4R, melanocortin-4 receptor; LEPR, leptin receptor; NCOA1, Nuclear Receptor Coactivator 1; PCSK1, proprotein convertase subtilisin/kexin type 1; PLXNA, plexin A; POMC, proopiomelanocortin; ROAD, Rare Obesity Advanced Diagnosis; SEMA3, semaphorin 3; SH2B1, SH2B adaptor protein 1; SIM1, single-minded homolog 1.

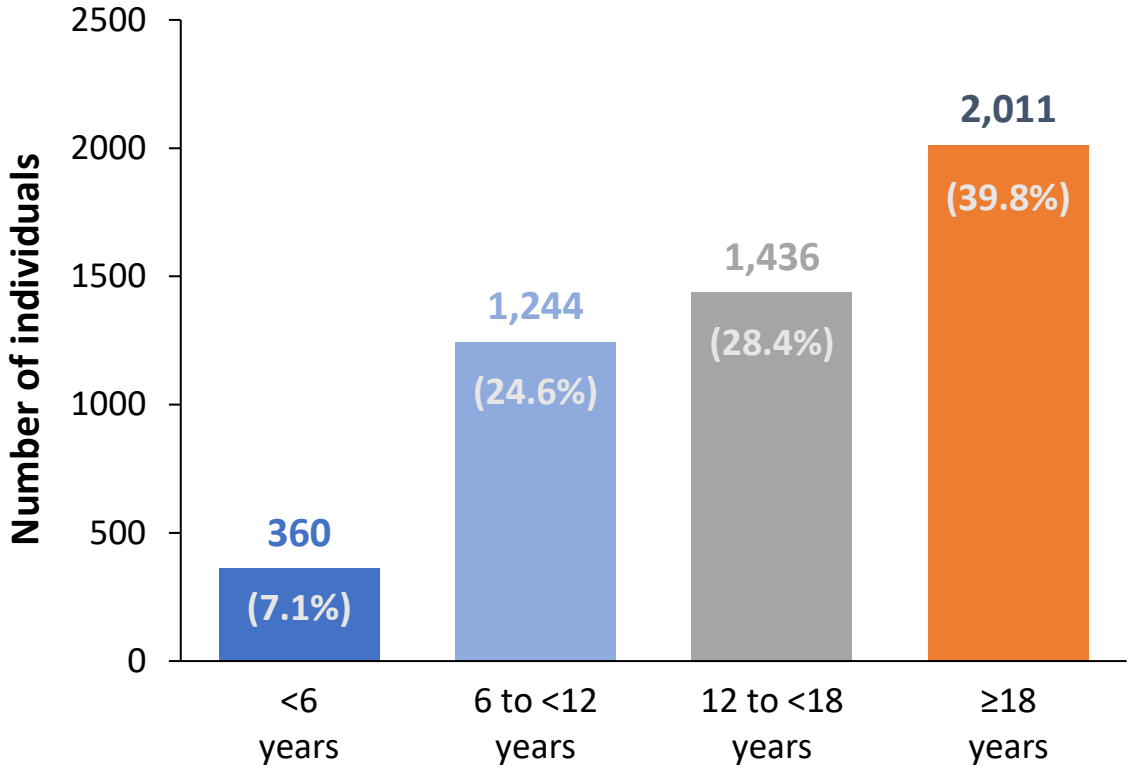
Baseline characteristics of total sequenced individuals

Female **54.7%** ; Male **45.2%** | Mean (SD) age at time of testing **23.0 (17.7)** years | Mean (SD) age at onset of obesity **8.0 (3.9)** years
Mean (SD) age of onset of hyperphagia **3.1 (3.7)** years | Mean (SD) BMI z-score **3.6 (1.0)** | Mean (SD) BMI **43.7 (10.1)** km/m^2

Individuals by location (%; n = 5,051)

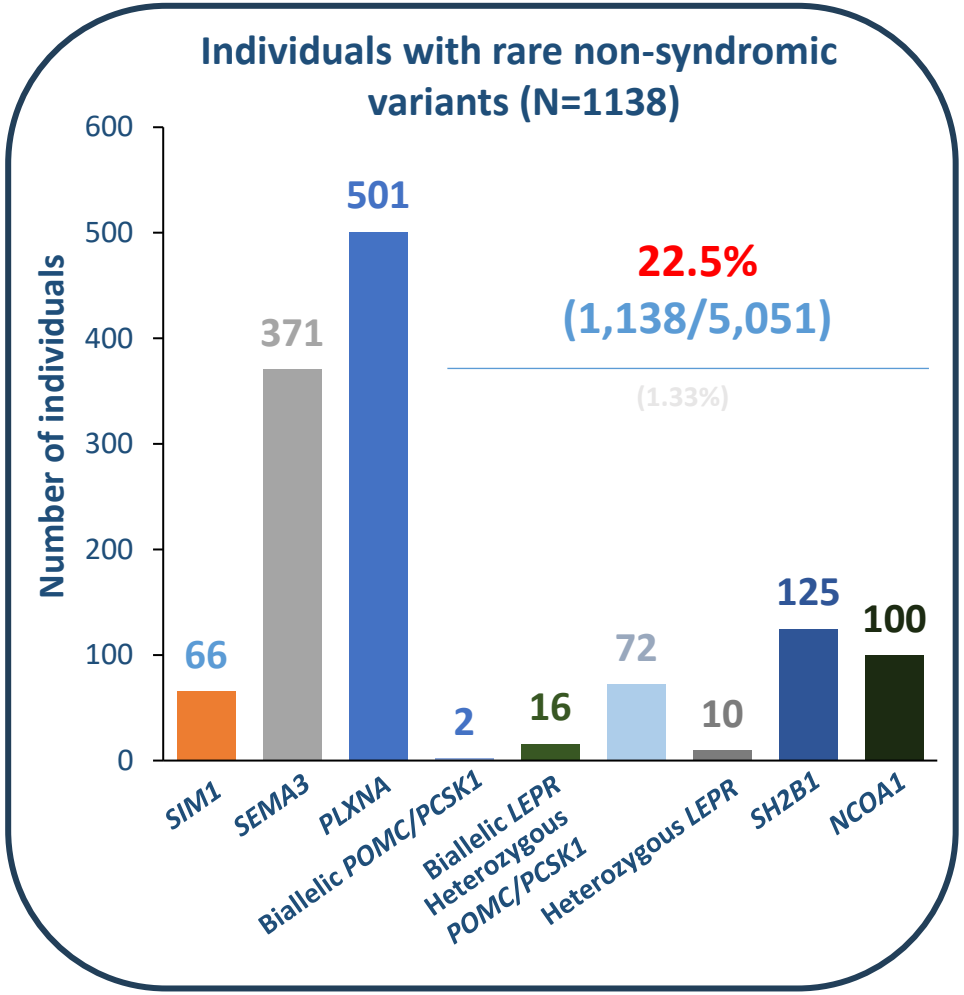


Individuals by age group (n =5,051)



BMI, body mass index; SD, standard deviation.

22.5% of individuals carried ≥1 gene variant potentially leading to disease from the non-syndromic panel and presented with early hyperphagia and obesity



Hyperphagia and weight parameters, mean (SD)

Age of hyperphagia onset	Age of obesity onset	BMI z-score (<18 years) BMI (≥18 years)
4.1 (4.0) years	5.2 (3.8) years	BMI z-score: 3.6 (1.1) BMI: 42.7 (10.2) kg/m^2

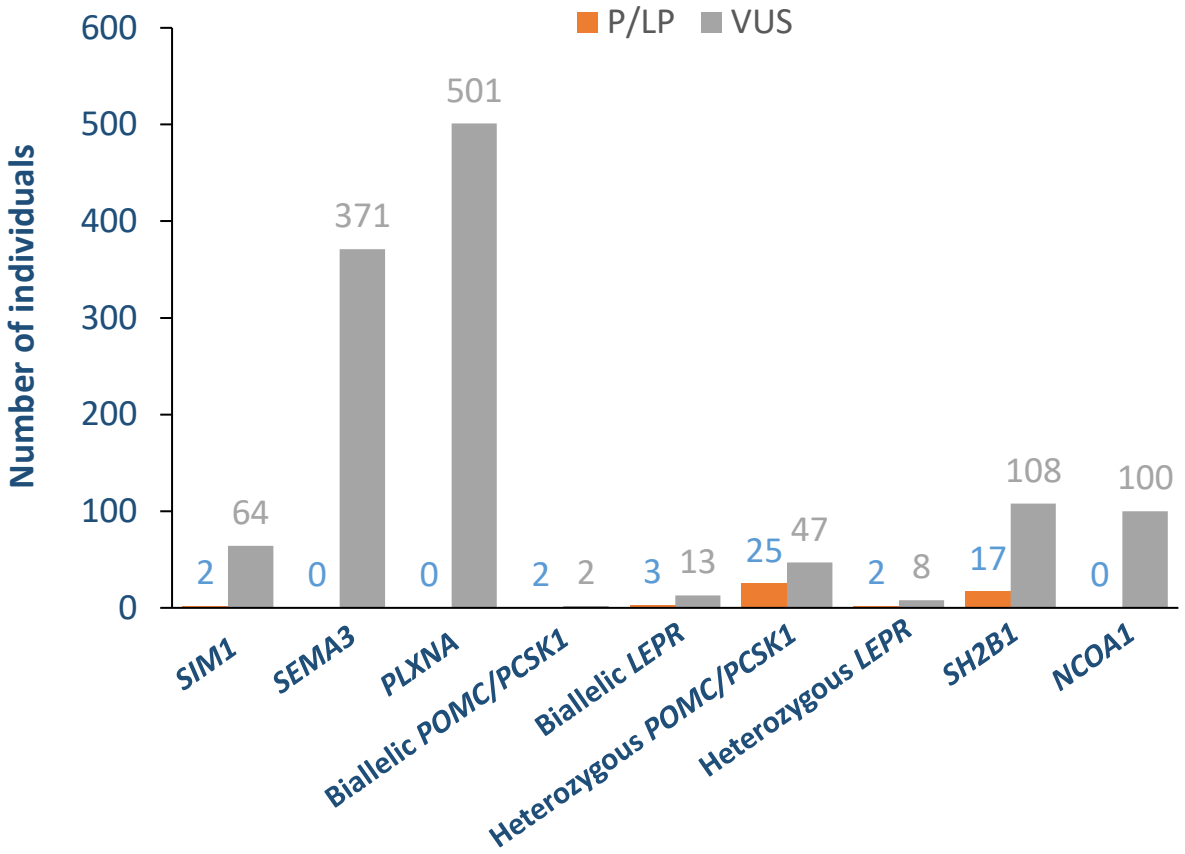
Early-onset hyperphagia and obesity

- The greatest BMI z-scores across the cohort were reported in individuals with biallelic *POMC/PCSK1* variants (4.2 mean BMI z-score) and biallelic *LEPR* variants (4.2 mean BMI z-score)
- Individuals with biallelic *LEPR* variants were associated with very early onset of hyperphagia and obesity (mean age 0.7 years for both)
- Mean age (SD) of hyperphagia and obesity onset:
  - Biallelic POMC/PCSK1: NR and 6.0 (5.7) years, respectively
  - Heterozygous POMC/PCSK1: 3.6 (3.1) years and 5.7 (3.6) years, respectively

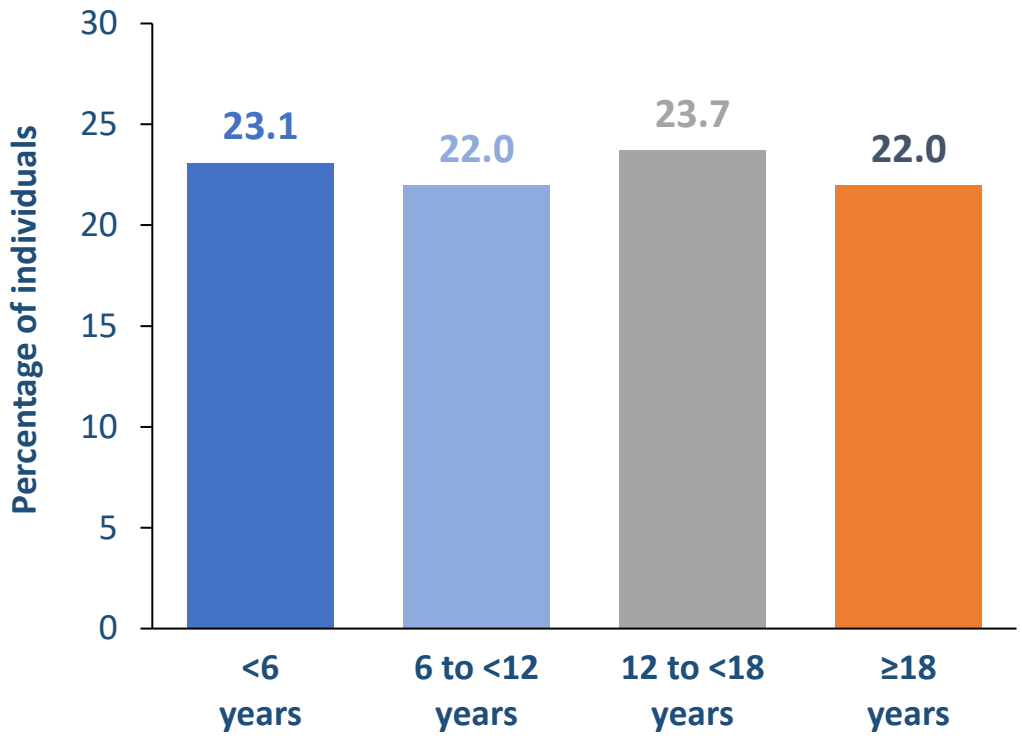
BMI, body mass index; LEPR, leptin receptor; NCOA1, Nuclear Receptor Coactivator 1; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; SD, standard deviation; SEMA3, semaphorin 3; SH2B1, SH2B adaptor protein 1; SIM1, single-minded homolog 1.

Frequency for P/LP and VUS variants potentially leading to disease were similar across all age groups with highest seen in paediatric cohort

Number of P/LP and VUS variants across gene variant types (N=1,138)



Percentage of individuals with variants by age subgroups of the full cohort (n = 1,138/5,051)



61.2% testing positive for non-syndromic variants were in the paediatric cohort

LEPR, leptin receptor; NCOA1, Nuclear Receptor Coactivator 1; PCSK1, proprotein convertase subtilisin/kexin type 1; P/LP, pathogenic/likely pathogenic; POMC, proopiomelanocortin; SD, standard deviation; SEMA3, semaphorin 3; SH2B1, SH2B adaptor protein 1; SIM1, single-minded homolog 1; VUS, variant of unknown significance.

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
- **22.5%** of tested individuals with early-onset obesity carried a P/LP/VUS variant in ≥1 of the studied *SIM1*, SEMA3 family, PLXNA family, *POMC*, *PCSK1*, *LEPR*, *SH2B1* and *NCOA1* genes
- Hyperphagia and obesity were seen earliest in patients with LEPR deficiency; these patients were also among those with the highest reported mean BMI z-score

Identification of genetic causes of early-onset obesity provides important insights in disease mechanisms and allows for a timely specialized care for patients with rare MC4R pathway diseases

LEPR, leptin receptor; MC4R, melanocortin-4 receptor; NCOA1, Nuclear Receptor Coactivator 1; PCSK1, proprotein convertase subtilisin/kexin type 1; P/LP, pathogenic/likely pathogenic; POMC, proopiomelanocortin; SEMA3, semaphorin 3; SH2B1, SH2B adaptor protein 1; SIM1, single-minded homolog 1; VUS, variant of unknown significance.