Frequency of MC4R Pathway Variants in a European Cohort of Individuals With Early-Onset Severe Obesity

Presentation FC8.2

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DISCLOSURE STATEMENT

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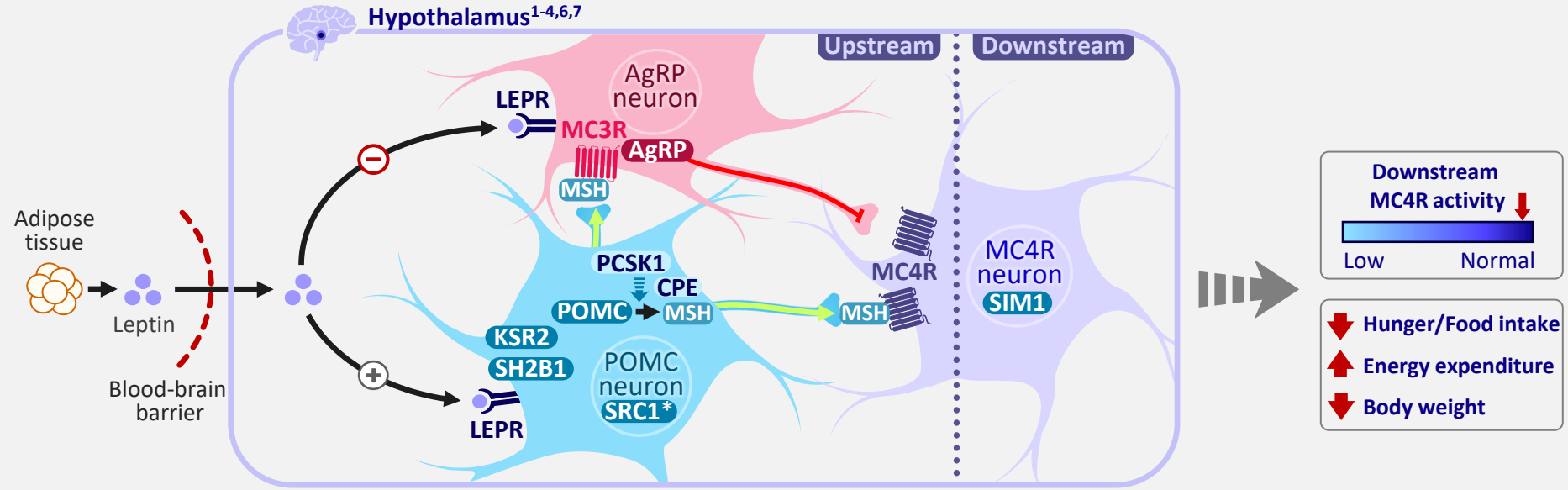
☒ I have the following potential conflicts of interest to report:

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

ESPE
European Society for Paediatric Endocrinology

Energy Balance Is Regulated by the Hypothalamic MC4R Pathway

- The MC4R pathway is critical for the regulation of hunger, energy balance, and body weight[1-3]
- Individuals who carry variants in MC4R pathway genes may present with hyperphagia (pathologic, insatiable hunger) and early-onset, severe obesity[4]
- Setmelanotide is an MC4R agonist indicated for chronic weight management in adult and pediatric patients aged ≥6 years with specific forms of monogenic or syndromic obesity[5]



AgRP, agouti-related peptide; CPE, carboxypeptidase E; KSR2, kinase suppressor of ras 2; LEPR, leptin receptor; MC3R, melanocortin-3 receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; SCR1, steroid receptor coactivator 1; SIM1, single-minded homolog 1; SH2B1, SH2B adaptor protein.
*The SRC1 protein is encoded by *NCOA1*.

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.** IMCIVREE (setmelanotide) injection [package insert]. Boston, MA: Rhythm Pharmaceuticals, Inc.; 2022. **6.** Doche et al. *J Clin Invest*. 2012;122:4732-4736. **7.** Ghamari-Langroudi et al. *Sci Adv*. 2018;4:eaat0866.

MC4R Pathway-Related Gene Variant Analyses of Individuals Sequenced as Part of the ROAD® Genetic Testing Program*

Objective: To determine the frequency of MC4R pathway–related variants potentially eligible for setmelanotide treatment in a European cohort of individuals with hallmark symptoms of potential underlying genetic causes of early-onset, severe obesity who were sequenced in the ROAD® genetic testing program

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

Eligibility

≤18 years of age with a BMI ≥97th

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

Evaluated subset of 11 MC4R pathway–related genes associated with genetic obesity

POMC, PCSK1, LEPR, NCOA1, SH2B1, MC4R, MC3R, CPE, LEP, KSR2, SIM1

Variant classification

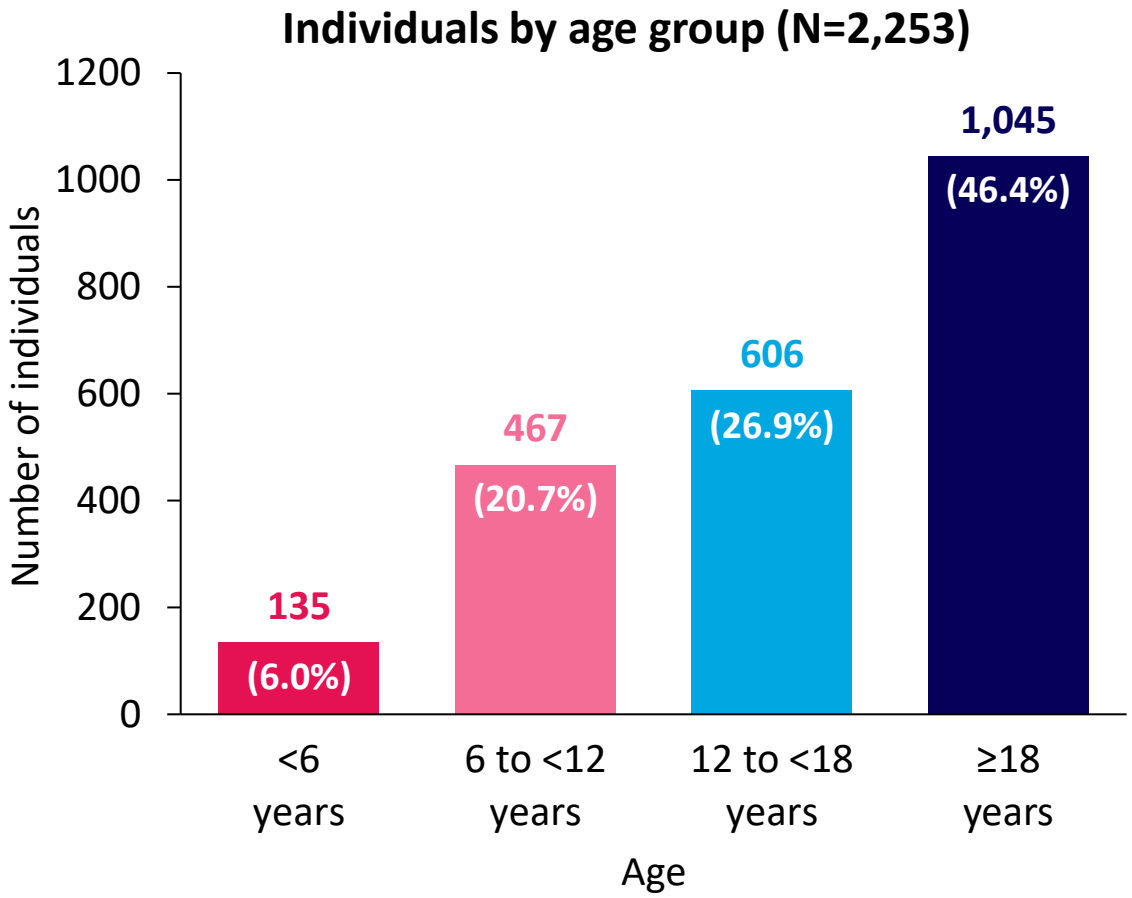
- Pathogenic (P)†
- Likely pathogenic (LP)†
- Variant of unknown significance (VUS)†
  - Suspected pathogenic (SP)
  - Uncertain
  - Suspected benign (SB)
- Risk‡

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

 *For questions about the ROAD® genetic testing program, including questions regarding criteria for sending samples, please contact Unilabs at roadgenetic@unilabs.com. †Variants were classified as P/LP/VUS according to American College of Medical Genetics criteria. ‡A nonrare variant (*PCSK1* p.N221D) that has been suggested to predispose carriers to obesity was included and is therefore categorized as "risk" according to American College of Medical Genetics criteria.

Baseline Characteristics of Sequenced Individuals

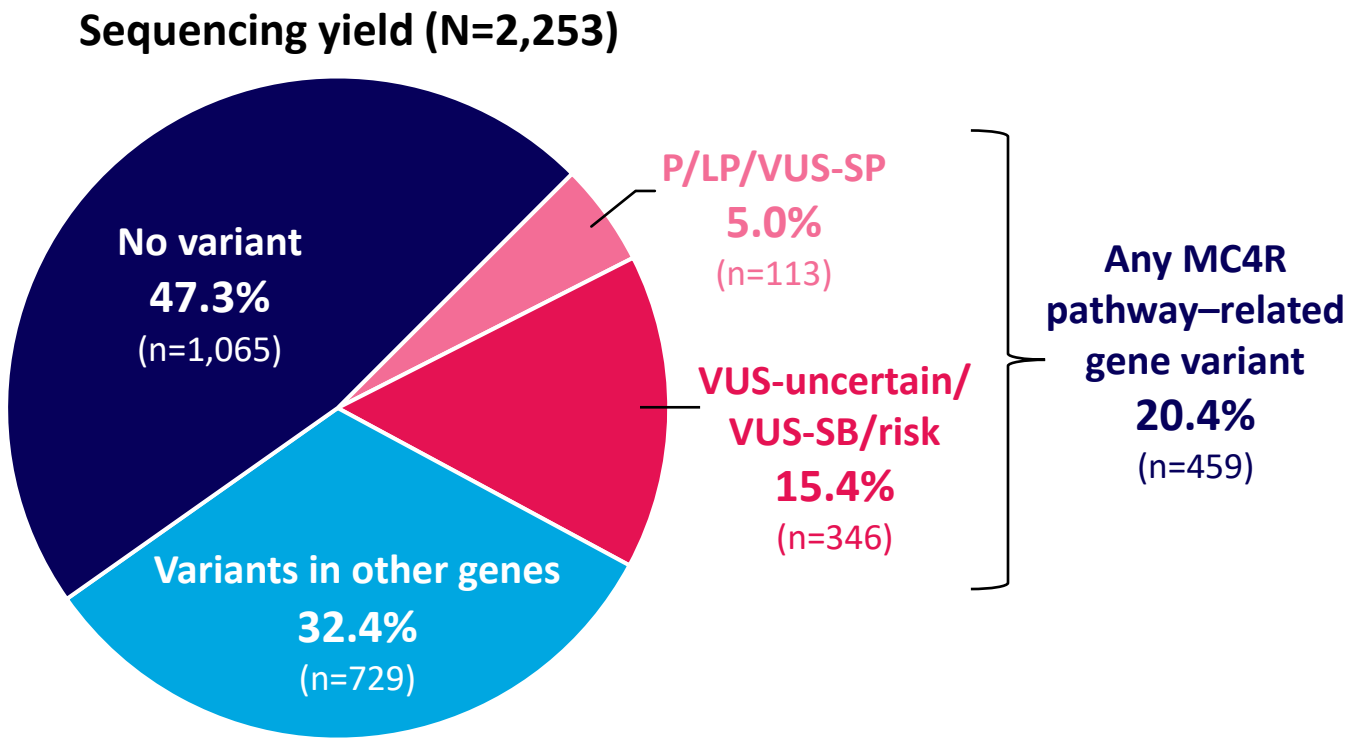
Parameter	Total (N=2,253)
Sex, n (%)	
Female	1,240 (55.0)
Male	1,010 (44.9)
Prefer not to disclose/not provided	3 (0.1)
Age of onset of obesity, mean (SD), y	6.9 (8.5)
BMI (patients aged ≥18 years), mean (SD), kg/m^2	**44.2 (8.5)**
BMI Z score (patients aged <18 years), mean (SD)	**3.4 (0.9)**
Location, n (%)	
Spain	1,020 (45.3)
Italy	508 (22.3)
Ireland	216 (9.6)
Turkey	178 (7.9)
Israel	189 (8.4)
United Kingdom	138 (6.1)
Germany	4 (0.2)



BMI, body mass index; SD, standard deviation.

Individuals Who Carried ≥1 Variant in the Evaluated Subset of MC4R Pathway–Related Genes

Overall, 20.4% of individuals carried ≥1 variant in the 11 evaluated MC4R pathway–related genes associated with obesity



- The variant frequency for key genes of interest (*POMC*, *PCSK1*, *LEPR*, *NCOA1*, and *SH2B1*) was 15.7%[1-4]
  - 7.3% included individuals with the *PCSK1* polymorphic p.N221D variant[5]

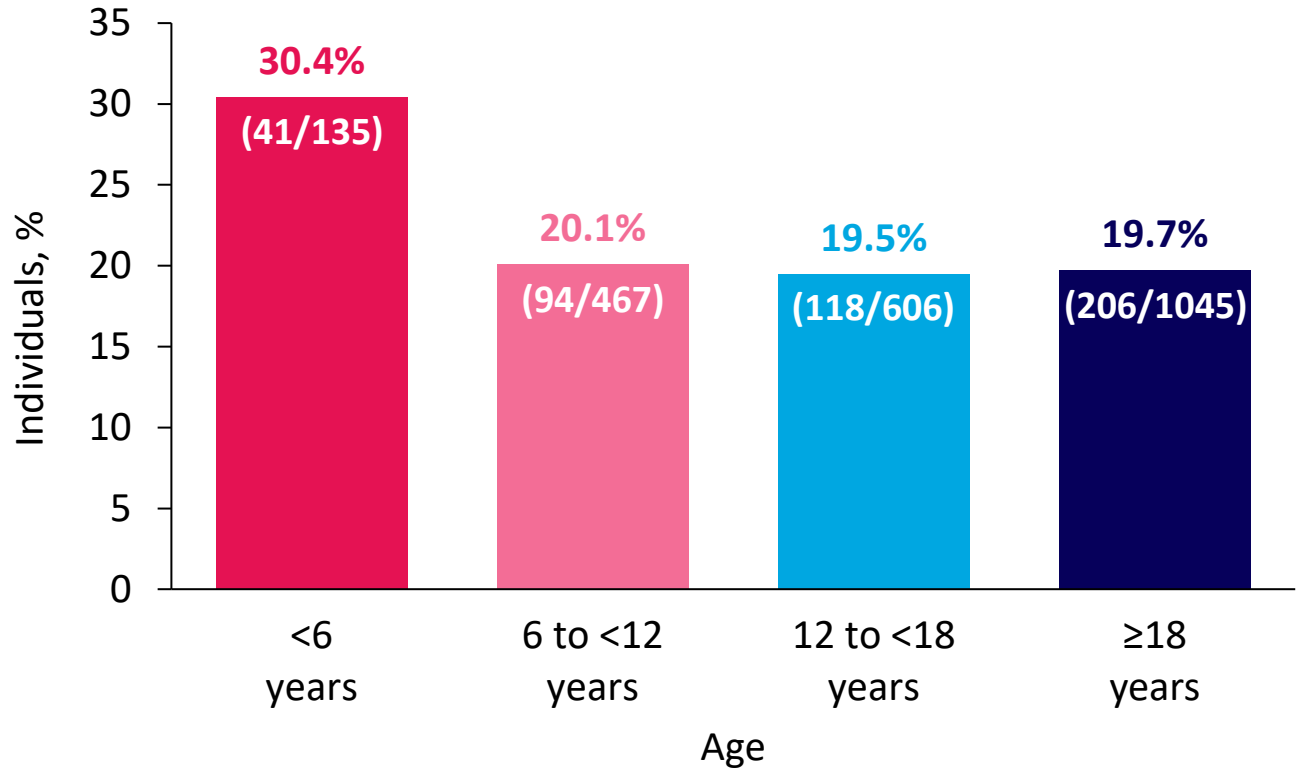
LP, likely pathogenic; MC4R, melanocortin-4 receptor; P, pathogenic; SB, suspected benign; SP, suspected pathogenic; VUS, variant of unknown significance.

1. Farooqi et al. Presented at ENDO 2022; June 11-14, 2022; Atlanta, GA. **2.** Clément et al. *Lancet Diabetes Endocrinol*. 2020;8:960-970. **3.** Farooqi et al. Presented at ENDO 2022; June 11-14, 2022; Atlanta, GA. **4.** Argente et al. Presented at ENDO 2022; June 11-14, 2022; Atlanta, GA. **5.** Ramos-Molina et al. *Prog Mol Biol Transl Sci*. 2016;140:47-74.

Individuals Who Carried ≥1 Variant in the Evaluated Subset of MC4R Pathway–Related Genes by Age Group

The <6 years age group had the highest proportion of individuals with variants in the 11 evaluated MC4R pathway–related genes, highlighting the utility of early genetic testing for identifying patients potentially eligible for targeted treatment

Proportion of tested individuals with MC4R pathway–related variant per age group



MC4R, melanocortin-4 receptor.

Summary and Conclusions

- In our large Europe-based cohort of individuals with hallmark symptoms of potential underlying genetic causes of hyperphagia and early-onset, severe obesity, 20.4% carried a variant in ≥1 of the 11 studied MC4R pathway–related genes, with 5.0% classified as P/LP/VUS-SP
- The ROAD® program contributes to the breadth of scientific evidence on variants of uncertain significance occurring in this population of individuals with obesity, which may contribute to confirmation of pathogenicity over time as more cases are identified
- Genetic testing identified MC4R pathway–related gene variants across all age groups, reinforcing the importance of genetic testing regardless of patient age
  - The highest incidence of selected MC4R pathway–related gene variants was in the <6 years age group, supporting early testing in patients with suspected MC4R pathway diseases
- The ongoing clinical trials EMANATE (NCT05093634) and DAYBREAK (NCT04963231) are currently assessing the effect of setmelanotide in individuals with variants in a subset of these genes
  - A response to setmelanotide in these trials may provide evidence that the underlying cause of obesity in these individuals is MC4R pathway impairment
- Further studies are needed to identify clinical characteristics that may be associated with MC4R pathway–related gene variants (eg, age of obesity onset, severity of obesity, presence of hyperphagia)

Genetic testing of individuals with severe obesity may be an important part of clinical care at any age to improve understanding of the disease etiology and identify those who may benefit from novel therapies

LP, likely pathogenic; MC4R, melanocortin-4 receptor; P, pathogenic; SP, suspected pathogenic; VUS, variant of unknown significance.