Frequency of Obesity-Related Gene Variants in a European Population With Early-Onset, Severe Obesity

Presentation FC3.3

Jesús Argente, MD, PhD, presenting

Carel W. le Roux,[1] Jesus Dominguez-Riscart,[2] Maria Rosaria Licenziati,[3] Leandro Soriano-Guillén,[4] Belma Haliloglu,[5] Anjali Zalin,[6] Simona Filomena Madeo,[7] Patrick Sleiman,[8] Charles Savoie,[8] Liya Kerem,[9] Jesús Argente[10]

[1]Diabetes Complications Research Centre, University College Dublin, Ireland; [2]Instituto de Investigación e Innovación Biomédica de Cádiz, Hospital Universitario Puerta del Mar, Universidad de Cádiz, Cádiz, Andalusia, Spain; [3]Neuro-Endocrine Diseases and Obesity Unit, Department of Neurosciences, Santobono-Pausilipon Children's Hospital, Naples, Italy; [4]Hospital Universitario Fundación Jiménez Díaz, Universidad Autónoma de Madrid, Spain; [5]Department of Pediatrics and Pediatric Endocrinology and Diabetes, Marmara University Medical School, Istanbul, Turkey; [6]Barts Health NHS Trust, London, UK and Bedfordshire Hospitals NHS Foundation Trust, Bedford, UK; [7]Pediatric Unit, Department of Medical and Surgical Sciences of the Mother, Children and Adults, University of Modena, Italy; [8]Rhythm Pharmaceuticals, Inc., Boston, MA, USA; [9]Pediatric Endocrinology, Hadassah University Medical Center, Israel; [10]Department of Pediatrics & Pediatric Endocrinology, Universidad Autónoma de Madrid, University Hospital Niño Jesús, CIBER "Fisiopatología de la obesidad y nutrición" (CIBEROBN), Instituto de Salud Carlos III, IMDEA Institute, Madrid, Spain

DISCLOSURE STATEMENT

Jesús Argente

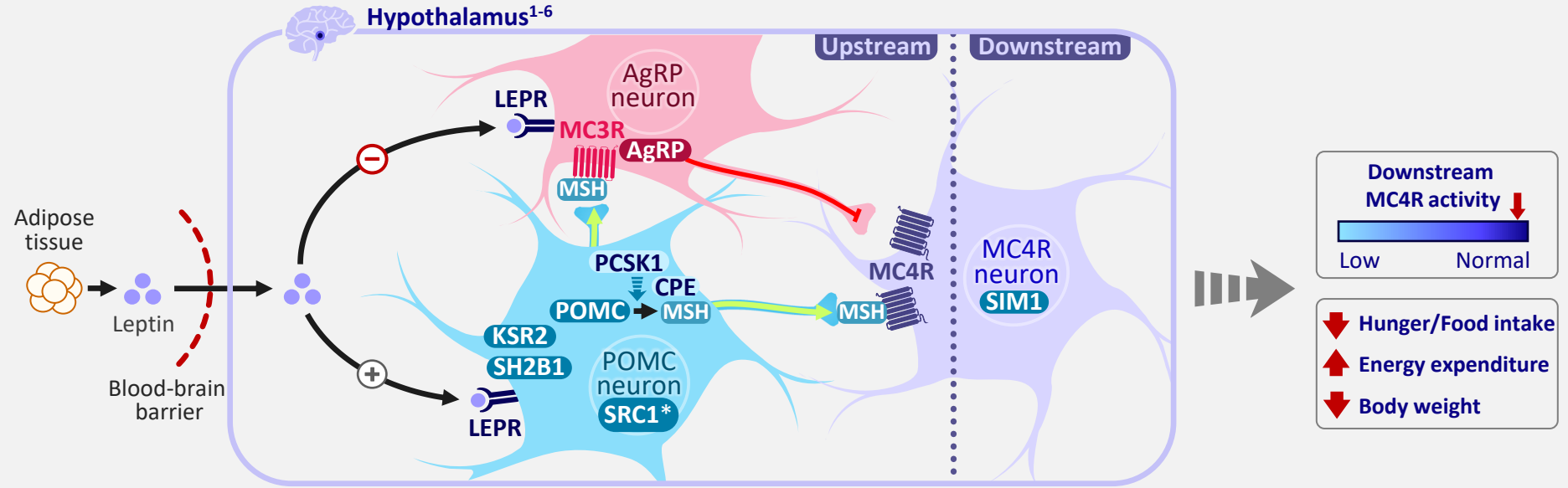
☒ I have the following potential conflicts of interest to report:

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

ESPE
European Society for Paediatric Endocrinology

Rare Genetic Variants Can Lead to Hyperphagia and Early-Onset, Severe Obesity

- Rare variants in key genes of the MC4R pathway, a regulator of energy balance, are associated with hyperphagia (pathologic, insatiable hunger) and early-onset, severe obesity[1-6]
- Patients with these variants often do not respond to traditional weight management strategies[7]



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.
*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.** Doche et al. *J Clin Invest*. 2012;122:4732-4736. **6.** Ghamari-Langroudi et al. *Sci Adv*. 2018;4:eaat0866. **7.** Clément et al. *Physiol Behav.* 2020;227:113134.

The Need for Genetic Testing

- Routine genetic testing can[1-5]
  - Improve identification and diagnosis of individuals with hyperphagia and obesity caused by rare genetic variants
  - Inform specialized management strategies or eligibility for clinical trials

- Hyperphagia and obesity caused by rare genetic variants are likely underdiagnosed owing to low rates and limited access to genetic testing in individuals with obesity[6,7]

ROAD®
RARE OBESITY ADVANCED DIAGNOSIS

A NO-CHARGE, GENETIC TESTING SOLUTION FOR RARE GENETIC DISEASES OF OBESITY

The Rare Obesity Advanced Diagnosis® (ROAD®) testing program aims to enhance genetic testing access for individuals with suspected rare genetic causes of obesity*

*For questions about the ROAD® genetic testing program, including questions regarding criteria for sending samples, please contact Unilabs at roadgenetic@unilabs.com.
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.** Ayers et al. *J Clin Endocrinol Metab*. 2018;103:2601-2612. **7.** Clément et al. *Physiol Behav*. 2020;227:113134.

Analysis Objectives and Design of the ROAD® Program

Objectives of current analysis:

- To assess the frequency of selected rare genetic variants in individuals with hallmark symptoms of potential underlying genetic causes of early-onset, severe obesity who were sequenced as part of the ROAD® genetic testing program

- No-charge 79-gene and 1–chromosomal region panel for individuals living in participating regions[a] 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

Genes and chromosomal region sequenced

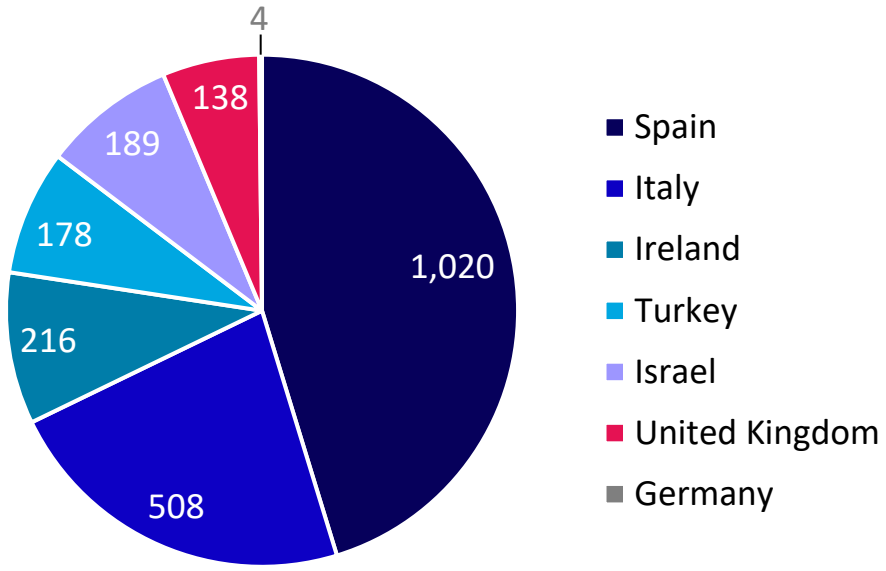
ADCY3	*ALMS1*	*BBS3*[b]	*BBS18*[c]	*AFF4*	*CREBBP*	*CUL4B*	*DNMT3A*
BBS1	*BBS10*	*BBS12*	*BBS2*	*DYRK1B*	*EP300*	*HTR2C*	*INPP5E*
BBS4	*BBS5*	*BBS7*	*BBS9*[d]	*ISL1*	*KIDINS220*	*MAGEL2*	*MECP2*
BDNF	*BBS21*[e]	*BBS14*[f]	*GNAS*	*MRAP2*	*NR0B2*	*NRP1*	*NRP2*
IFT172	*BBS19*[g]	*BBS20*[h]	*KSR2*	*PCNT*	*PHIP*	*PLXNA1*	*PLXNA2*
LEP	*LEPR*	*BBS17*[i]	*MC3R*	*PLXNA3*	*PLXNA4*	*PPARG*	*PROK2*
MC4R	*BBS6*[j]	*BBS13*[k]	*NCOA1*	*RAB23*	*RPGRIP1L*	*RPS6KA3*	*SEMA3A*
NTRK2	*PCSK1*	*PHF6*	*POMC*	*SEMA3B*	*SEMA3C*	*SEMA3D*	*SEMA3E*
RAI1	*BBS16*[l]	*SH2B1*	*SIM1*	*SEMA3F*	*SEMA3G*	*TBX3*	*TRPC5*
BBS11[m]	*BBS8*[n]	*BBS15*[o]	*CPE*	*TUB*	*UCP3*	*VPS13B*	16p11.2[p]

BBS, Bardet-Biedl syndrome; BMI, body mass index. ROAD, Rare Obesity Advanced Diagnosis. [a]Spain, Italy, Ireland, Turkey, Israel, the United Kingdom, and Germany. [b]*ARL6*. [c]*BBIP1*. [d]*PTHB1*. [e]*CFAP418*. [f]*CEP290*. [g]*IFT27*. [h]*IFT74*. [i]*LZTFL1*. [j]*MKKS*. [k]*MKS1*. [l]*SDCCAG8*. [m]*TRIM32*. [n]*TTC8*. [o]*WDPCP*. [p]Assessment for rearrangement of the 16p11.2 chromosomal region.

Baseline Characteristics of Sequenced Individuals

Parameter	Total (N=2,253)
Age, n (%)	
≥18 years	1,045 (46.4)
<18 years	1,208 (53.6)
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)

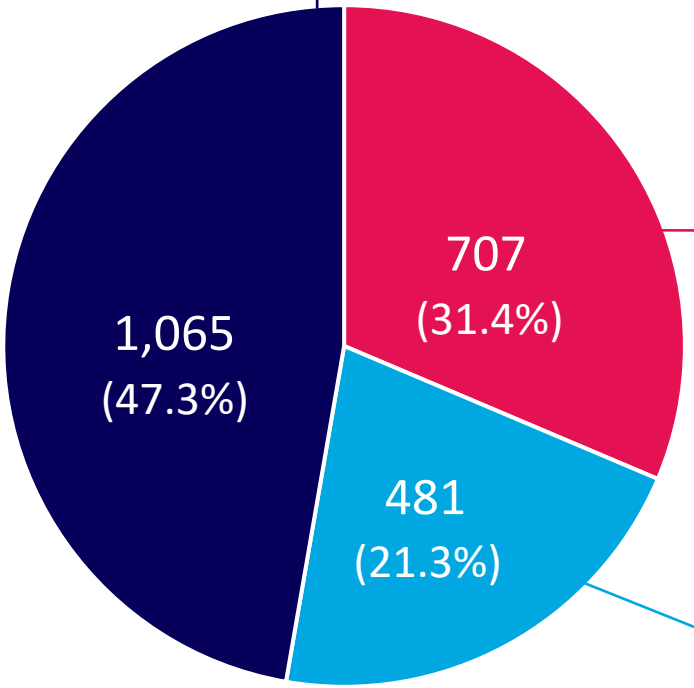
Location (N=2,253)



BMI, body mass index; SD, standard deviation.

Approximately 31% of Individuals Tested in ROAD® Had Variants Potentially Eligible for Targeted MC4R Treatment

Sequencing Yield



No variants identified

Variants potentially eligible for targeted MC4R treatment or individuals with variants being investigated in clinical trials

46 (2.0%) — Variants potentially eligible for targeted MC4R treatment

661 (29.3%) — Variants being investigated clinical trials

Variants in other genes supportive of a diagnosis of genetic obesity

Genes	Number of individuals
POMC biallelic	0
PCSK1 biallelic	2
LEPR biallelic	16
BBS-associated genes	28
EMANATE clinical trial eligible genes • *POMC/PCSK1/LEPR* heterozygous • *NCOA1/SH2B1** homozygous, heterozygous, or compound heterozygous	 15 80
DAYBREAK clinical trial eligible genes • Preidentified MC4R pathway–related genes *CPE, CREBBP, DNMT3A, HTR2C, ISL1, KSR2, LEP, MAGEL2, MC3R, MC4R, MECP2, MRAP2, NRP1, NRP2, PHIP, PLXNA1, PLXNA2, PLXNA3, PLXNA4, RPGRIP1L, SEMA3A, SEMA3B, SEMA3C, SEMA3D, SEMA3E, SEMA3F, SEMA3G, SIM1, TBX3, TRPC5, TUB*	566

*Including the chromosomal 16p11.2 deletion encompassing *SH2B1*.
BBS, Bardet-Biedl syndrome; MC4R, melanocortin-4 receptor.

Summary and Conclusions

- The ROAD® testing program offers enhanced genetic testing access for individuals with suspected rare genetic causes of obesity in key genes of the MC4R pathway
- In this cohort of individuals with early-onset, severe obesity or clinical signs of BBS, 52.7% carried variants of the MC4R pathway or of another type of genetic obesity disorder, which could inform specialized management strategies
  - Approximately one-third of individuals carried variants in *POMC*, *PCSK1*, *LEPR*, BBS-associated genes, or variants in other genes that are being investigated in clinical trials

Genetic testing may elucidate the etiology of early-onset, severe obesity and expedite transition to specialized care

BBS, Bardet-Biedl syndrome; MC4R, melanocortin-4 receptor.