Age at onset of hyperphagia and/or obesity as key predictors of a positive genetic test for POMC, PCSK1 or LEPR deficiency or BBS

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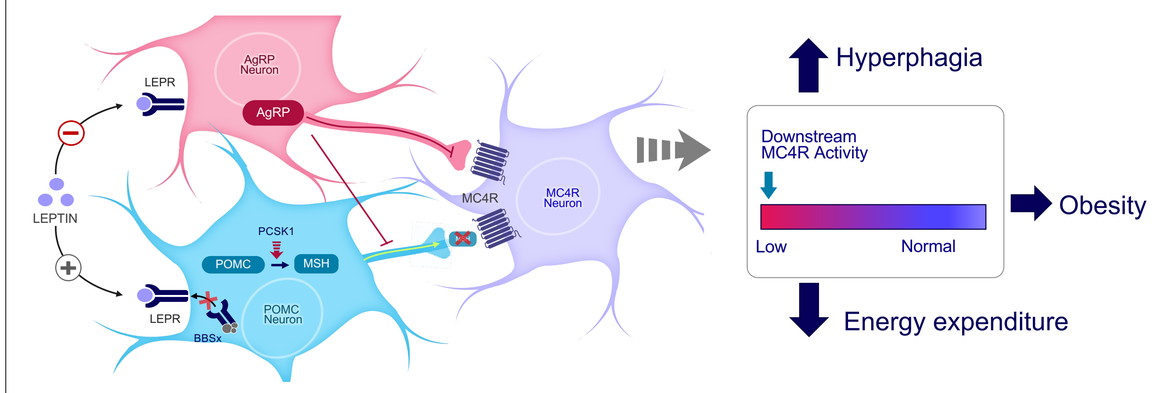
Introduction about MC4R, hyperphagia, and obesity

- Genetic variants in the melanocortin-4 receptor (MC4R) pathway can lead to hyperphagia and early-onset obesity



AgRP, agouti-related peptide; BBS, Bardet-Biedl syndrome, LEPR, leptin receptor; MSH, melanocyte-stimulating hormone; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

Rare Obesity Advanced Diagnosis (ROAD)® genetic testing programme

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

Objective

To assess the frequency of selected rare genetic variants in individuals with hallmark symptoms of potential underlying genetic causes of early-onset obesity

Programme eligibility

≤18 years of age with a BMI **≥97th** percentile

OR

≥19 years of age with a BMI **≥40** kg/m² and a history of childhood obesity

OR

Immediate family member of select, previously tested patients

OR

Showing clinical symptoms of BBS

BMI, body mass index.

- Gene panel included 88 genes and 1 chromosomal region

Genetic testing results

Gene	Heritance	Patients with a PLP variant, n	Patients with a VUS variant, n	Total	% of tested population N=6,169
Key genes of interest					
POMC/PCSK1 (Bial)	AR	0	3	3	0.05
LEPR (Bial)	AR	4	13	17	0.28
BBS1-22	AR	29	83	112	1.82
Total		**33**	**99**	**132**	**2.14**
Other genes tested					
POMC/PCSK1 (het)	AR – het effect	71	184	255	4.13
LEPR (het)	AR – het effect	2	52	54	0.88
SIM1	AD	2	72	74	1.20
SEMA3 family	AD	0	434	434	7.04
PLXNA family	AD	0	587	587	9.52
SH2B1	AD	22	137	159	2.58
NCOA1	AD	0	111	111	1.80
TBX3	AD	0	65	65	1.05
PHIP	AD	5	70	75	1.22
MAGEL2	AD	4	22	26	0.42
ALSM1	AR	14	35	49	0.79
Total		**120**	**1,769**	**1,889**	**30.62**

AD, autosomal dominant; AR autosomal recessive; Bial, biallelic variant; het, heterozygous variant; PLP, pathogenic/likely pathogenic; VUS, variant of uncertain significance.

Patient characteristics

Gene	*POMC/PCSK1* (biallelic*) N=3	*LEPR* (biallelic*) N=17	*BBS1-22* (biallelic*) N=112	Negative test† N=2,749
% of tested population (N=6,169)	0.05	0.28	1.82	40.2
Sex, male, n (%)	2 (66.7%)	7 (43.8%)	56 (50.0%)	1,239 (45.1)
Age at time of testing, years, mean (SD)	23.4 (17.2)	15.7 (16.6)	18.5 (14.3)	22.4 (17.4)
BMI z-score, mean (SD); n (patients <18 years)	**4.41 (0.28) n=2**	**4.22 (1.17) n=9**	**3.72 (1.00) n=67**	**3.59 (0.96) n=1,698**
BMI, kg/m², mean (SD); n (patients ≥18 years)	**40.1 (n/a) n=1**	**43.3 (16.8) n=4**	**40.8 (9.1) n=41**	**44.4 (9.7) n=1,001**
Age at onset of hyperphagia, years, mean (SD)	**n/a n=0**	**0.7 (1.0) n=12**	**3.1 (2.7) n=66**	**4.5 (4.3) n=2,130**
Age at onset of obesity, years, mean (SD)	**5.7 (4.0) n=3**	**0.7 (0.9) n=15**	**4.7 (3.6) n=67**	**5.4 (3.8) n=2,469**

* Genetic variants found include pathogenic, likely pathogenic variants and variants of uncertain significance; † Defined as a negative outcome for any of the gene variants tested.

SD, standard deviation.

Predictors of a positive genetic test for POMC (including *PCSK1*) or LEPR deficiencies, or BBS

Patient group	BMI z-score, n* (<18 years)	BMI, n* (≥19 years)	Age at hyperphagia onset, n	Age at obesity onset, n
Patients with a positive test for *POMC/PCSK1/LEPR/BBS1-22*	78	46	78	85
Patients with a negative test†	1,698	1,001	2,130	2,469
	P=0.6681	P=0.0232	**P=0.0001‡**	**P=0.0007‡**

Early onset of hyperphagia or obesity is a predictor of a positive test for biallelic variants in *BBS1-22, POMC, PCSK1,* and *LEPR* genes

*Number of patients with a BMI/BMI z-score available at time of testing; †Defined as a negative outcome for any of the variants tested; ‡Linear regression analysis with age at onset of hyperphagia or obesity, BMI, or BMI z-score as continuous variable. P<0.01 was considered significant.

Key take-aways

- Genetic variants in the MC4R pathway can lead to hyperphagia and early-onset obesity
- Age at onset of hyperphagia and age at onset of obesity are key predictors for a positive genetic test of biallelic variants in *POMC, PCSK1*, or *LEPR*, or in *BBS1-22* genes
- All patients with hyperphagia and early-onset obesity should have access to genetic testing
- **Genetic testing of individuals with early-onset hyperphagia and/or obesity may be crucial at any age to improve understanding of the disease etiology of rare MC4R pathway diseases and identify those who may be eligible for targeted therapies**

Discussion

- This real-world analysis was subject to the presence of missing data
- All individuals tested had some form of early-onset obesity as part of the eligibility criteria; in those who tested negative for the gene panel, other gene variants may be involved in the disease etiology

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For more information, please contact us at EU_Medinfo@rhythmtx.com

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