Frequency of MC4R Pathway Variants in a Large US Cohort of Patients With Severe Obesity

Presenting Author:
Ida Hatoum Moeller
imoeller@rhythmtx.com

Ida Hatoum Moeller,[1] Patrick Kleyn,[1] Patrick M. Sleiman,[2,3] Courtney Vaccaro,[2] Hakon Hakonarson,[2,3] Samira Bahl,[1] Tiago Antao,[1] Alastair S. Garfield[1]*

[1]Rhythm Pharmaceuticals, Inc., Boston, MA; [2]Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, PA; [3]Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

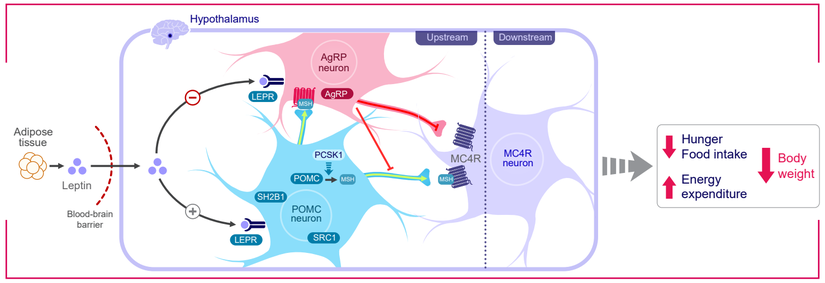
Summary

- **Overall, in our large US-based cohort of individuals with severe early-onset obesity, 15.6% of individuals carry a potentially clinically relevant variant in the melanocortin-4 receptor (MC4R) pathway genes *POMC, PCSK1, LEPR, SH2B1,* and *SRC1***
- **Understanding the role of these variants in the pathophysiology of obesity may improve the clinical care of individuals living with these rare genetic diseases of obesity**

Background

- The MC4R pathway is critical for the regulation of energy balance[1]
- When leptin binds to the leptin receptor on proopiomelanocortin (POMC) neurons in the hypothalamus, the POMC protein is cleaved by a protein encoded by *PCSK1* to form α melanocyte-stimulating hormone (αMSH). αMSH then activates the MC4R neuron, leading to a decrease in hunger and an increase in energy expenditure (Figure)[1-4]
- Variants within genes comprising this pathway, including *POMC, PCSK1, LEPR, SH2B1,* and *SRC1,* have well-established associations with severe obesity, and patients with heterozygous and/or biallelic mutations in these genes have demonstrated meaningful weight loss in a Phase 2 investigational study with the MC4R agonist setmelanotide[1,3-6]
- The frequency of variants in these genes have not yet been assessed systematically in a clinically relevant US population

Figure. Key genes involved in the MC4R pathway.[1-4]



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References: 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.** Doche et al. *J Clin Invest.* 2012;122:4732-4736. **5.** Farooqi et al. Presented at: Endocrine Society 2021; March 20, 2021; Virtual. **6.** Meeker et al. Presented at: Rhythm Pharmaceuticals R&D Event; January 26, 2021; Virtual.

Methods

- Through March 30, 2021, we sequenced *POMC, PCSK1, LEPR, SH2B1,* and *SRC1* exons and intron-exon boundaries in 35,276 US individuals with severe obesity (<18 years old: ≥97th percentile BMI for age; ≥18 years old: BMI ≥40 kg/m^2). Through September 14, 2021, this database included 41,425 individuals sequenced globally and 38,608 individuals sequenced within the United States; all analyses were performed on the 35,276 individuals sequenced through March 2021
- This cohort comprises individuals sequenced across multiple sequencing initiatives in the United States, including the Uncovering Rare Obesity® diagnostic genetic testing program, the Genetic Obesity Identification (GO-ID) study, and several biobank collaborations, including 9,683 patients from the Children's Hospital of Philadelphia (CHOP) biobank
- In the current analysis, we included rare variants classified as pathogenic/likely pathogenic (P/LP) or as a variant of uncertain significance (VUS) according to American College of Medical Genetics criteria. Given that high-impact variants (stop, frameshift, or splice site) may possibly have an impact on protein function, even if the variant does not meet full P/LP criteria, these variants were analyzed separately
- We additionally included one non-rare variant, *PCSK1* p.N221D, for which published functional and population studies suggest a potential contribution to obesity

Results

- 10.2% of individuals with severe obesity carried ≥1 rare variant in ≥1 of the 5 studied genes, including 0.7% who carried a P/LP or high impact variant and 9.5% who carried a VUS variant. An additional 5.4% carried the *PCSK1* p.N221D variant
- In the total population, 14.4% of individuals carried only one variant, while 1.2% carried >1 variant in ≥1 genes. The most common variant present with additional variants was the less rare *PCSK1* p.N221D variant
- The gene with the highest variant frequency was *POMC*, followed by *LEPR, SH2B1, SRC1,* and *PCSK1* (Table)
- Individuals sequenced through the community-focused clinical diagnostic tool (Uncovering Rare Obesity®) demonstrated a slightly higher frequency of P/LP/high-impact VUS and *PCSK1* p.N221D genotypes (1.2% and 6.9%, respectively), and a 9.8% frequency of VUS genotypes

Table. Variant Frequencies

	Total cohort (N=35,276)				Uncovering Rare Obesity® only (N=7,103)			
Gene	PLP	High-impact VUS	VUS	RISK[e]	PLP	High-impact VUS	VUS	RISK[e]
Total[a]	0.27%	0.45%	9.48%	5.37%	0.70%	0.51%	9.83%	6.88%
POMC[b]	0.05%	0.26%	2.40%		0.07%	0.25%	2.31%	
PCSK1[b]	0.05%	0.07%	1.83%	5.91%	0.11%	0.06%	1.83%	7.67%
LEPR[b]	0.06%	0.07%	2.44%		0.21%	0.08%	2.34%	
SRC1[b]	NA[c]	0.04%	1.95%		NA[c]	0.11%	2.37%	
SH2B1[b]	0.11%[d]	0.02%	1.96%		0.35%[d]	0%	2.20%	

[a]Removes individuals present in multiple genes/variant categories. Prioritized for P/LP/>high-impact VUS>VUS>RISK. [b]Individuals may be present in more than 1 gene/variant category; includes 1.2% of individuals present in more than one gene category overall, and 1.5% present in more than one gene category in Uncovering Rare Obesity® only. [c]No *SRC1* variants are deemed P/LP because of the gene being classified as a "gene of uncertain significance" clinically. [d]All P/LP *SH2B1* variants are 16p11.2 deletions, including deletion of *SH2B1*. [e]The only variant classified as "RISK" is p.N221D in *PCSK1*. NA, not applicable; PLP, pathogenic/likely pathogenic; VUS, variant of uncertain significance.

Conclusions

- Overall, in our large US-based cohort of individuals with severe, early-onset obesity, 15.6% of individuals carry a potentially clinically relevant variant in the MC4R pathway genes *POMC, PCSK1, LEPR, SH2B1,* or *SRC1*. Individuals sequenced through the course of clinical care as part of the Uncovering Rare Obesity® diagnostic genetic testing program had a slightly higher rate of variant frequency than the overall cohort
- The majority of observed variants were of uncertain significance. It is unknown whether these variants will ultimately be determined to impact protein function and affect phenotype. Individuals with variants impacting the MC4R pathway may benefit from treatment with the MC4R agonist setmelanotide
- Understanding the role of variants in the MC4R pathway in the pathophysiology of obesity may improve the clinical care of individuals living with these rare genetic diseases of obesity