An Evidence-based Framework to Evaluate Melanocortin-4 Receptor (MC4R) Pathway Relevance for Obesity-associated Genes

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Presenting Author:
Bhavik P. Shah
bshah@rhythmtx.com

Megan E. Vogel, Ida H. Moeller, Alastair S. Garfield,* Bhavik P. Shah
Rhythm Pharmaceuticals, Boston, MA, United States

Summary

- **The outlined framework provides:**
  - **Robust means of selecting melanocortin-4 receptor (MC4R) pathway–relevant genes**
  - **Support of clinical investigation of setmelanotide responsiveness in an additional 31 "Very Strong/Strong" genes, including *LEP*, *SIM1*, *MRAP2*, and *KSR2***
- **The evidence-based framework presented here is supported by clinical data that demonstrate significant weight and hunger score reductions following setmelanotide treatment in patients with obesity due to variants in 6 genes, all initially classified as "Very Strong" or "Strong"**
- **The DAYBREAK trial is a Phase 2 clinical trial that will evaluate setmelanotide in patients with specific variants in 1 of these 31 genes**

Introduction

- The MC4R pathway serves as the principal regulator of mammalian energy balance by modulating energy intake and expenditure[1]
- Defects in genes associated with the MC4R pathway can result in rare genetic diseases of obesity[1]
- Genetic testing is needed to aid in the diagnosis of individuals with such diseases, which can lead to specialized management strategies or identification of eligibility for clinical studies[1-4]
- Clinical data in patients with genetic defects in the MC4R pathway indicate that setmelanotide can effectively reduce weight and hunger scores in scientifically rationalized subpopulations with obesity in which MC4R pathway deficit is a factor contributing to obesity[5-8]

Objectives

- To identify genetically defined patient populations most likely to benefit from long-term setmelanotide therapy using an evidence-based framework that was designed to assess the relevance of genes to the MC4R pathway

Methods

Gene candidate selection process

- Rhythm utilizes a core set of nonclinical (experimental) and clinical (human genetics) evidence to evaluate the functional association between a gene and the MC4R pathway (Figure 1, Table 1)

Figure 1. Overall approach

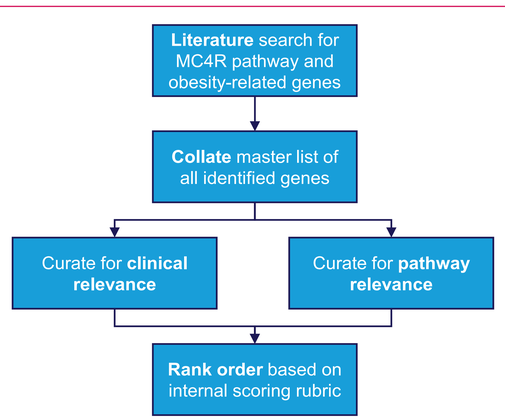


Table 1. Evidence for assessing MC4R pathway relevance

		Evidence	Evidence Type	Description
Nonclinical (Experimental)		Gene expression	Neuroanatomy	Is the gene expressed in the hypothalamus of pathway-relevant cell types?
		Molecular/ Cellular function	In vitro/In vivo	Does the gene have a functional connection to known pathway gene or cell types?
		Physiologic function	Disease model phenotype	Does the gene have a role in energy balance or body weight regulation in preclinical models?
		Functional rescue	Pharmacological rescue of phenotype (in vivo)	Can MC4R agonism rescue obesity phenotype in preclinical models with gain or loss of function in the candidate gene?
Clinical (Genetics)	Weight	Human disease relevance	Genetic epidemiology	Is the gene implicated in regulating human body weight?

- This approach is adapted from the National Institutes of Health ClinGen gene-disease clinical validity framework[9], which is the evolving standard for the identification of disease-associated genes (Table 2)
- Genetic evidence helps define a gene's contribution to human obesity
- Experimental evidence assesses a gene's involvement in the function of MC4R pathway

Table 2. Putative MC4R pathway genes can be stratified by strength of association based on a rationalized scoring rubric

Nonclinical				Clinical	
Gene Expression	Molecular/ Cellular Function	Physiological Function	Functional Rescue	Genetic Epidemiology	Strength Tiers
✓	✓	✓	✓	✓	Very Strong
✓	✓	✓		✓	Strong
✓	✓			✓	Moderate
✓				✓	Weak

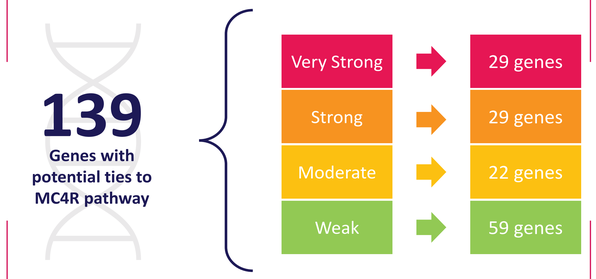
- The cumulative weight of evidence informs a semiquantitative score that enables rank ordering of genes into 4 strength-based tiers: "Very Strong," "Strong," "Moderate," and "Weak"
- The nature, quantity, and quality of evidence required for each tier builds upon that of the previous tier, with higher ranked genes being most likely to define patient populations potentially responsive to long-term setmelanotide treatment

RESULTS

Identified gene candidates

- Based on a comprehensive literature review, 139 genes with potential ties to the MC4R pathway were identified and rank ordered into strength-based tiers (Figure 2)

Figure 2. Number of MC4R pathway–relevant genes and their ranking



- A list of MC4R pathway–relevant "Very Strong" and "Strong" genes with a broad spectrum of biological functions is provided (Table 3)
- Clinically meaningful reductions in weight and hunger score following treatment with setmelanotide have been demonstrated in patients with obesity due to variants in 6 genes
  - 80% (8/10) of patients with a biallelic variant in *POMC* or *PCSK1* and 45% (5/11) of patients with a biallelic variant in *LEPR* achieved ≥10% reduction in body weight after ~1 year of setmelanotide treatment in two Phase 3 trials[5]
  - 34.5% (11/31) of patients with Bardet-Biedl syndrome (BBS) or Alström syndrome (aged ≥12 years) achieved ≥10% reduction in body weight after ~1 year of setmelanotide treatment in a Phase 3 trial; all of the patients who achieved this reduction had BBS[6]
    - Mean (standard deviation) percent change in body weight among those with BBS aged ≥18 years was −9.4% (8.2%) at Week 52. Mean (standard deviation) BMI Z score change in those with BBS aged <18 years was −0.8 (0.4) at Week 52[6]
  - 42.9% (15/25) of patients with an *SH2B1* variant or 16p11.2 deletion, which involves the *SH2B1* gene, and 30% (9/30) of patients with a variant in *SRC1* achieved ≥5% reduction in body weight (in those aged ≥18 years) or ≥0.15 reduction in BMI Z score (in those aged <18 years) after 3 months of setmelanotide treatment in a Phase 2 trial[7,8]
  - *POMC*, *PCSK1*, *LEPR*, *BBSx*, *SH2B1*, and *SRC1* were initially classified as "Very strong" or "Strong" MC4R pathway–relevant genes, lending credence to this framework for the selection of patient populations most likely to benefit from long-term setmelanotide therapy

Table 3. MC4R pathway–relevant gene set for "Very Strong" and "Strong" genes

	Gene	Gene Expression	Molecular/ Cellular Function	Physiological Function	Functional Rescue	Genetic Epidemiology	Setmelanotide Responsiveness
Very Strong	*POMC*	✓	✓	✓	✓	✓	✓
	LEPR	✓	✓	✓	✓	✓	✓
	*BBSx**	✓	✓	✓	✓	✓	✓
	KSR2	✓	✓	✓	✓	✓	
	LEP	✓	✓	✓	✓	✓	
	MRAP2	✓	✓	✓	✓	✓	
	SIM1	✓	✓	✓	✓	✓	
	HTR2C	✓	✓	✓	✓	✓	
Strong	*PCSK1*	✓	✓	✓		✓	✓
	NCOA1 (SRC1)	✓	✓	✓		✓	✓
	SH2B1	✓	✓	✓		✓	✓
	MC4R	✓	✓	✓		✓	
	MC3R	✓		✓	✓	✓	
	CPE	✓	✓	✓		✓	
	TBX3	✓	✓	✓		✓	
	MAGEL2	✓	✓	✓	✓	✓	
	CREBBP	✓	✓	✓		✓	
	TUB	✓	✓	✓		✓	
	*SEMA***	✓	✓	✓		✓	
	RPGRIP1l	✓	✓	✓		✓	
	ISL1	✓	✓	✓		✓	
	MECP2	✓	✓	✓		✓	
	PHIP	✓	✓	✓		✓	
	TRPC5	✓	✓	✓		✓	
	DNMT3A	✓	✓	✓		✓	

*Comprises a family of 22 genes. **Comprises a family of 13 genes.

*Alastair S. Garfield was an employee of Rhythm Pharmaceuticals, Inc., at the time of abstract submission.

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References: 1. Huvenne et al. *Obes Facts*. 2016;9:158-173. **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.** Clement et al. *Lancet Diabetes Endocrinol*. 2020;8:960-970. **6.** Haws et al. Poster presented at: Pediatric Endocrine Society Annual Meeting; April 30-May 3, 2021; Virtual. **7.** Argente et al. Presented at: European Society for Paediatric Endocrinology; September 22-26, 2021; Virtual. **8.** Farooqi et al. Presented at: European Society for Paediatric Endocrinology; September 22-26, 2021; Virtual. **9.** Strande et al. *Am J Hum Genet*. 2017;100:895-906.