Rhythm is a biopharmaceutical company dedicated to a greater understanding of rare genetic diseases of obesity

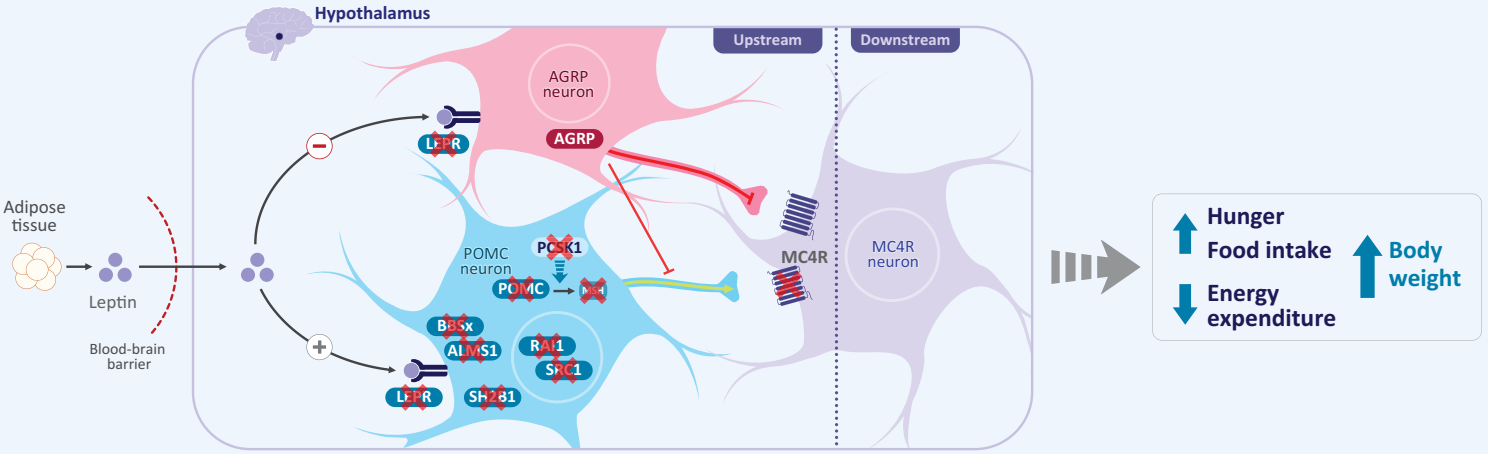
Not all obesity is the same

Environmental factors[1-3]
- Diet and overeating
- Lack of sleep
- Increased stress
- Physical inactivity
- Medications

Genetic factors[4]
- Common genetic variants
- Impairment of gene expression or function
- Rare genetic variants

Rare genetic variants within the MC4R pathway—a key pathway responsible for regulating hunger—may result in impaired neuronal signaling, leading to rare genetic diseases of obesity[5-10]

Impaired MC4R pathway



Abbreviations: AGRP, agouti-related protein; ALMS1, Alström syndrome 1; BBS, Bardet-Biedl syndrome; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; RAI1, retinoic acid induced 1; SH2B1, Src homology 2 B adapter protein 1; SRC1, steroid receptor coactivator 1.

Individuals with rare genetic diseases of obesity are often affected with early-onset, severe obesity and hyperphagia[10]

Early-onset, severe obesity[a]

Hyperphagia (insatiable hunger)

[a]Early onset is typically at age 2 to 5 years.

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Rare genetic diseases of obesity present with a variety of clinical characteristics, but early-onset, severe obesity and hyperphagia are common features

	Disease and Estimated Number of Individuals Affected[11]						
	POMC deficiency[12-15] 100-500 (US)	**LEPR deficiency**[16,17] 500-2000 (US)	**Bardet-Biedl syndrome**[10,18] 1500-2500 (US)	**Alström syndrome**[19-22] 500-1000 (worldwide)	**MC4R deficiency**[13,16,23] 10,000[a] (US)	**SRC1 deficiency**[8,24,25,b] >23,000 (US)	**SH2B1 deficiency**[26] >24,000 (US)
Clinical Characteristics							
Early-onset, severe obesity	✓	✓	✓	✓	✓	✓	✓
Hyperphagia	✓	✓	✓	✓	✓	✓	✓
Growth abnormalities	✓	✓		✓	✓		✓
Endocrine abnormalities	✓	✓	✓	✓	✓	✓	✓
Renal disease			✓	✓			
Visual impairments			✓	✓			
Cognitive or developmental impairments			✓	✓			
Cardiovascular defects			✓	✓			
Other possible characteristics	• Red/orange hair • Light or pale skin	• Severe bacterial infections	• Polydactyly	• Audiopathy			

[a]Estimated number of individuals in the US with rescuable variants of the MC4R.
[b]Hyperphagia was observed in mouse models of SRC1 deficiency.

Genetic testing along with evaluation of clinical presentation may aid in the diagnosis of a rare genetic disease of obesity[13,27]

Consider specific genetic testing in individuals (children or adults) with:

- Early-onset, severe obesity (before 5 years of age)
- Hyperphagia
- Other clinical characteristics of rare genetic diseases of obesity
- Family history of notable weight differences between family members

If you think your patient may have a rare genetic disease of obesity and would like more information on genetic testing, please visit:

UncoveringRareObesity.com

Abbreviations: LEPR, leptin receptor; MC4R, melanocortin-4 receptor; POMC, proopiomelanocortin; SH2B1, Src homology 2 B adapter protein 1; SRC1, steroid receptor coactivator 1.

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