Not all obesity is the same

Environmental factors[1-3]

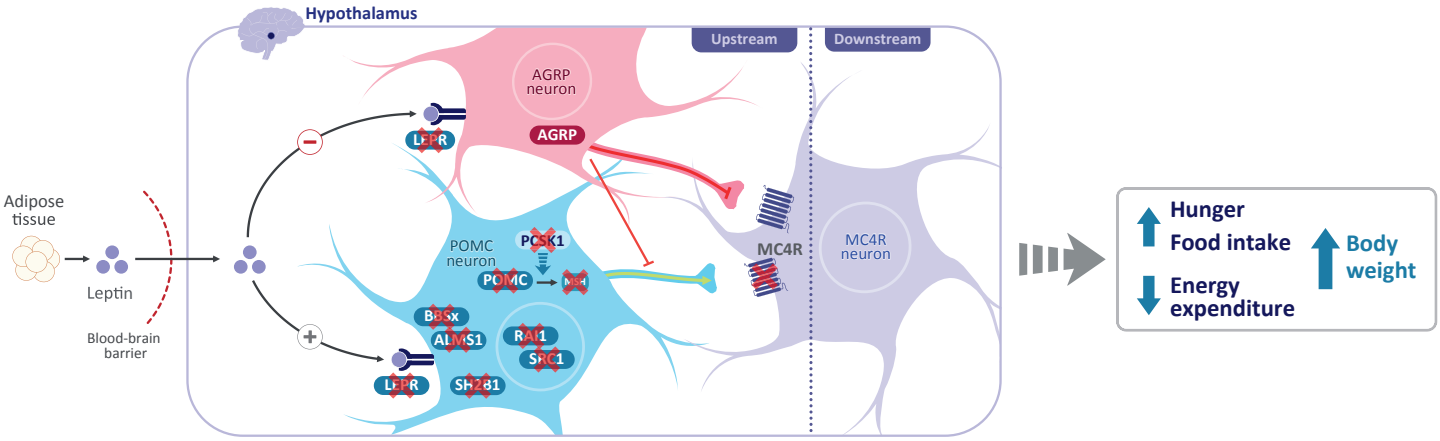
- Diet and overeating
- Lack of sleep
- Increased stress
- Physical inactivity
- Medications

Genetic factors[4]

- Common genetic variants
- Impairment of gene expression or function
- Rare genetic variants

Rare genetic variants within the hypothalamic melanocortin-4 receptor (MC4R) pathway — a key pathway responsible for regulating hunger and energy expenditure — may result in impaired neuronal signaling, leading to rare MC4R pathway disease[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 MC4R pathway diseases are often affected with hyperphagia and early-onset, severe obesity[10]

Hyperphagia
(insatiable hunger)

Early-onset, severe obesity[a]

[a] Early-onset is typically before 5 years of age.

Rare MC4R pathway diseases present a variety of clinical characteristics, but hyperphagia and early-onset, severe obesity are common features

		Rare genetic disease[11]				
		POMC deficiency[11-14]	LEPR deficiency[15,16]	Bardet-Biedl syndrome[10,17]	SRC1 deficiency[8,18,19,a]	SH2B1 deficiency[20]
Cardinal Symptoms	**Hyperphagia**	✓	✓	✓	✓	✓
	Early-onset, severe obesity	✓	✓	✓	✓	✓
Symptoms	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		

[a] Hyperphagia was observed in mouse models of SRC1 deficiency.

Genetic testing along with evaluation of clinical presentation may aid in the diagnosis of rare MC4R pathway diseases[12,21]

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

- Hyperphagia
- Early-onset, severe obesity (before 5 years of age)
- Other clinical characteristics of rare MC4R pathway diseases
- Family history of notable weight differences between family members

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

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