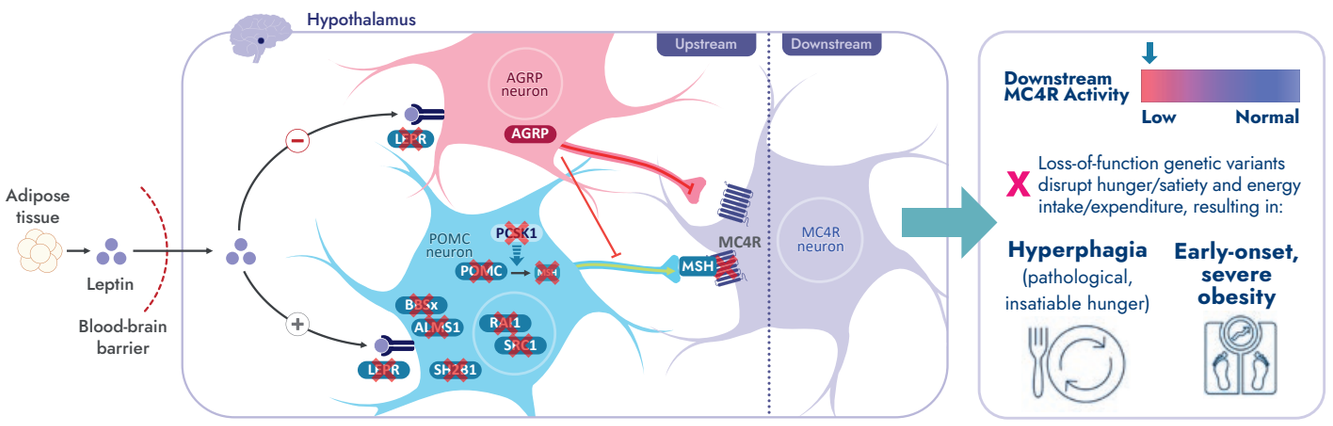
Rare melanocortin-4 receptor pathway diseases

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 signalling, leading to rare MC4R pathway diseases.[1,2]

Impaired MC4R pathway[1,3-7]



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 often experience hyperphagia and early-onset, severe obesity.[8,9]

Hyperphagia

Early-onset, severe obesity[a]

a) Defined as having a BMI ≥120% of the 95th percentile and onset before the age of 5.

Rare MC4R pathway diseases present a variety of clinical features, but hyperphagia and early-onset, severe obesity are considered cardinal symptoms.[10,11]

		Rare genetic disease				
		POMC deficiency[10,11,13]	**LEPR deficiency[10,14,15]**	**Bardet-Biedl syndrome[10-16]**	**SRC1 deficiency[17,18,a]**	**SH2B1 deficiency[7]**
Cardinal Symptoms	**Hyperphagia**	✓	✓	✓	✓	✓
	Early-onset, severe obesity	✓	✓	✓	✓	✓
Clinical Features	Cardiovascular defects			✓		
	Cognitive or developmental impairments			✓		
	Endocrine abnormalities	✓	✓	✓	✓	✓
	Growth abnormalities	✓	✓			✓
	Renal disease			✓		
	Visual impairments			✓		
	Other possible characteristics	· Red/orange hair · Light or pale skin	· Severe bacterial infections	· Polydactyly		

a) Hyperphagia was observed in mouse models of SRC1 deficiency.

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

Genetic testing along with evaluation of clinical presentation may aid in the diagnosis of rare MC4R pathway diseases.[10,13]

Consider specific genetic testing in individuals (children or adults) with:[10,13]

- Hyperphagia
- Early-onset, severe obesity
- Other clinical characteristics of rare MC4R pathway diseases
- Family history of notable weight differences between family members

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