Not all obesity is the same

Environmental factors[1-3]

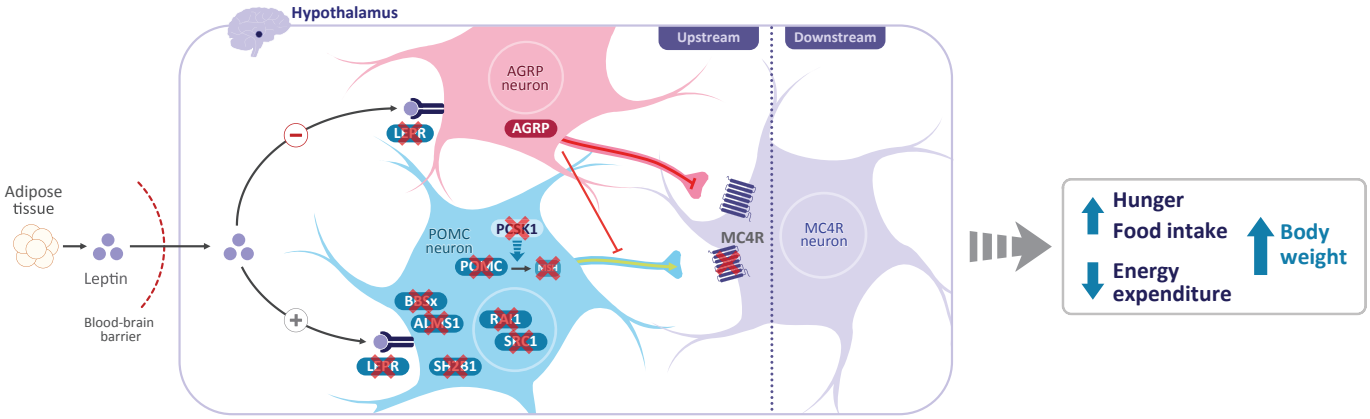
- Diet and overeating
- Lack of sleep
- Increased stress
- Physical inactivity
- Medications

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 at age 2 to 5 years.

A link and QR code for Prescribing Information and Adverse Event reporting information can be found on page 3

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]**
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

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.

References:
1. Muñoz Yáñez C, et al. *Austin J Nutr Metab.* 2017;4(3):1052. **2.** National Heart, Lung, and Blood Institute. https://www.nhlbi.nih.gov/health-topics/overweight-and-obesity. Accessed February 2024. **3.** Domecq JP, et al. *J Clin Endocrinol Metab.* 2015;100(2):363-370. **4.** Speliotes EK, et al. *Nat Genet.* 2010;42(11):937-948. **5.** da Fonseca ACP, et al. *J Diabetes Complications.* 2017;31(10):1549-1561. **6.** Yazdi FT, et al. *PeerJ.* 2015;3:e856. **7.** Burns B, et al. *Hum Mol Genet.*2010;19(20):4026-4042. **8.** Lu Q, et al. *J Mol Endocrinol.* 2019;62(1):37-46. **9.** Vaisse C, et al. *Cold Spring Harb Perspect Biol.* 2017;9(7):a028217. **10.** Huvenne H, et al. *Obes Facts.* 2016;9(3):158-173. **11.** Coll AP, et al. *J Clin Endocrinol Metab.* 2004;89(6):2557-2562. **12.** Styne DM, et al. *J Clin Endocrinol Metab.* 2017;102(3):709-757. **13.** Mendiratta MS, et al. *Int J Pediatr Endocrinol.* 2011;2011(1):5. **14.** Argente J, et al. *Endocr Abstr.* 2019;63:P976. **15.** Farooqi IS, O'Rahilly S. *J Endocrinol.* 2014;223(1):T63-T70. **16.** Thaker V V. *Adolesc Med State Art Rev.* 2017;28(2):379-405. **17.** Forsythe E, Beales PL. *Eur J Hum Genet.* 2013;21(1): 8-13. **18.** Cacciottolo TM, et al. *QJM.* 2019;112(9):724-729. **19.** Yang Y, et al. *Nat Commun.* 2019;10(1):1718. **20.** Doche ME, et al. *J Clin Invest.* 2012;122(12):4732-4736. **21.** van der Valk ES, et al. *Obes Rev.* 2019;20(6):795-804.

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Adverse events should be reported.
Reporting forms and information can be found at:
yellowcard.mhra.gov.uk
Adverse events should also be reported to Rhythm Pharmaceuticals Netherlands B.V., Radarweg 29, 1043NX Amsterdam, Netherlands.
Tel: +31 20 8546071.