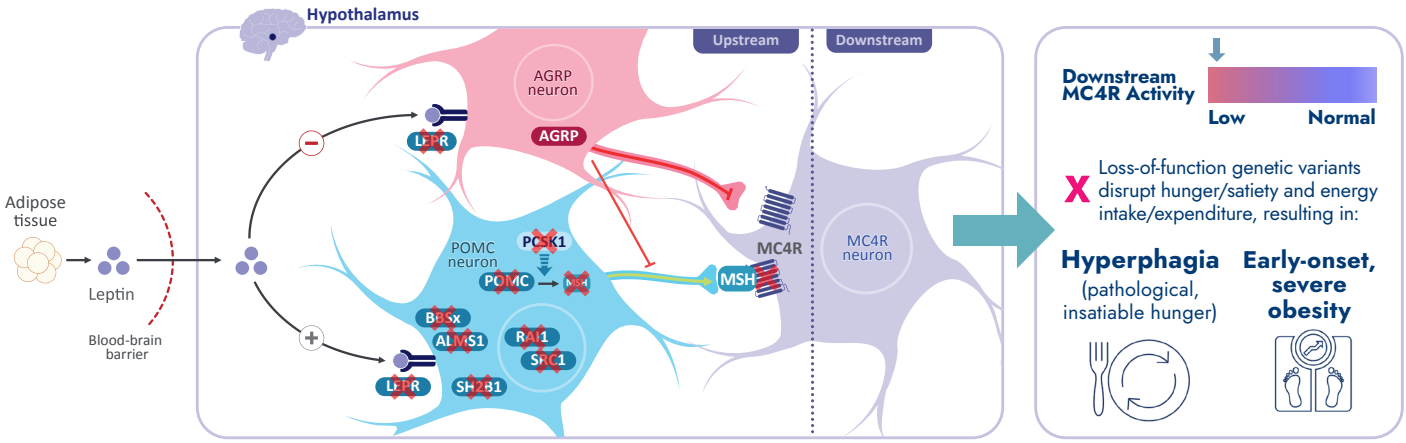
# Rare melanocortin-4 receptor pathway diseases

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<br>· 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

**References:** 1. Yazdi FT, et al. *Peer J*. 2015;3:e856. 2. Loos RJF and Yeo GSH. *Nat Rev Gens*. 2022;23:120–13. 3. Montague CT, et al. *Nature*. 1997;387(6636):903–8. 4. Clement K, et al. *Nature*. 1998;392(6674):398–401. 5. Krude H, et al. *Nat Genet*. 1998;19(2):155–7. 6. Jackson RS, et al. *Nat Genet*. 1997;16(3):303. 7. Doche ME, et al. *J Clin Invest*. 2012;122(12):4732–4736. 8. Hampl SE, et al. *Pediatrics*. 2023;151(2):e2022060640. 9. Huvenne H, et al. *Obes Facts*. 2016;9(3):158–173. 10. van der Valk ES, et al. *Obes Rev*. 2019;20(6):795–804. 11. Malhotra S, et al. *J Pediatr Genet*. 2021;10(3):194-203. 12. Coll AP, et al. *J Clin Endocrinol Metab*. 2004;89(6):2557–2562. 13. Styne DM, et al. *J Clin Endocrinol Metab*. 2017;102(3):709–757. 14. Farooqi IS and O'Rahilly S. *J Endocrinol*.2014;223(1):T63–T70. 15. Thaker V V. *Adolesc Med State Art Rev*. 2017;28(2):379–405. 16. Forsythe E and Beales PL. *Eur J Hum Genet*. 2013;21(1): 8–13. 17. Lu Q, et al. J Mol *Endocrinol*. 2019;62(1):37–46. 18. Yang Y, et al. *Nat Commun*. 2019;10(1):1718.

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