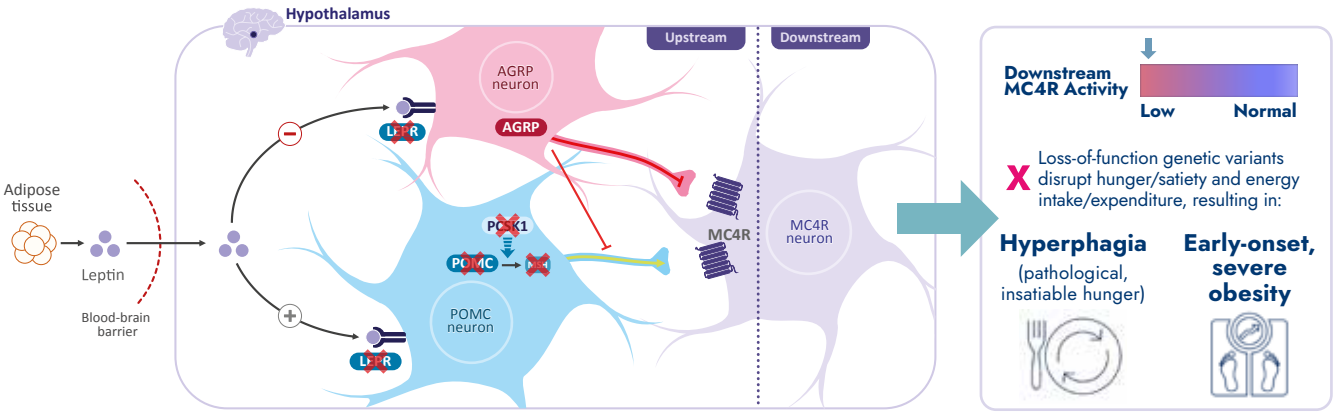
Leptin receptor deficiency and proopiomelanocortin deficiency

Leptin receptor (LEPR) deficiency and proopiomelanocortin (POMC) deficiency are caused by rare genetic variants within the melanocortin-4 receptor (MC4R) pathway - a key pathway responsible for regulating hunger.[1-3]

They are autosomal recessive diseases caused by variants of the *LEPR* or *POMC* genes.[1]

Impaired MC4R pathway[1-3]



Abbreviations: AGRP, agouti-related protein; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

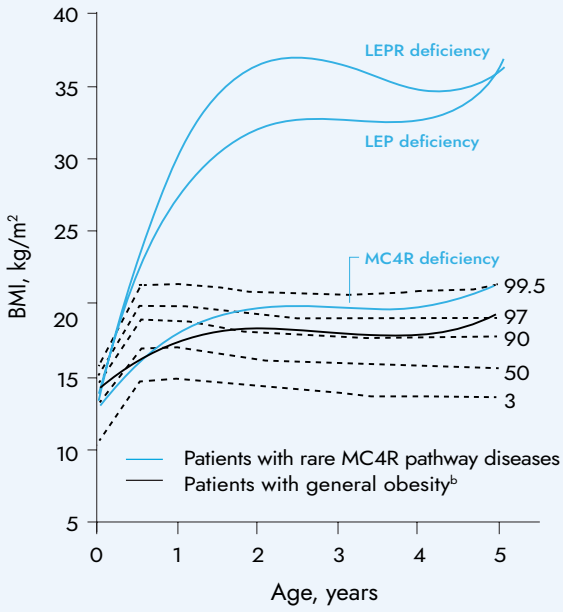
Primary cardinal symptoms of LEPR and POMC deficiency

Hyperphagia[4]

Characteristics and behaviours include:

- **Heightened and prolonged hunger**
- **Longer time to reach satiety**
- **Shorter duration of satiety**
- **Severe preoccupation with food** (hyperphagic drive)
- **Food-seeking behaviours** (sneaking and stealing food)
- **Distress and inappropriate behavioural response if denied food**

Early-onset, severe obesity[5,6,a]



a) Defined as having a BMI ≥120% of the 95th percentile and onset before the age of 5.
b) Patients with general obesity have a BMI >30 kg/m² by age 14-16 years and do not have a variant in *LEPR, LEP,* or *MC4R.*
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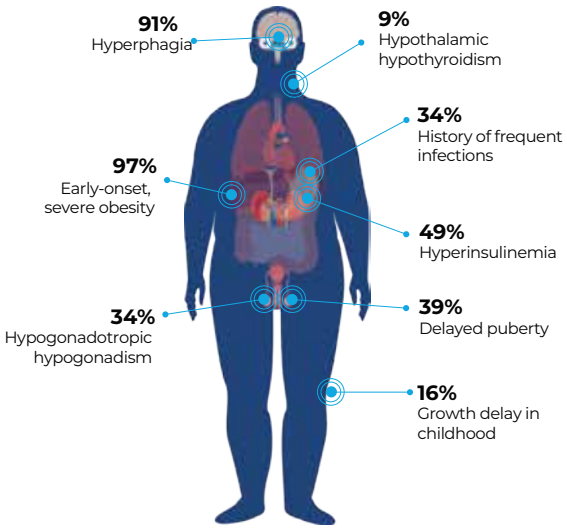
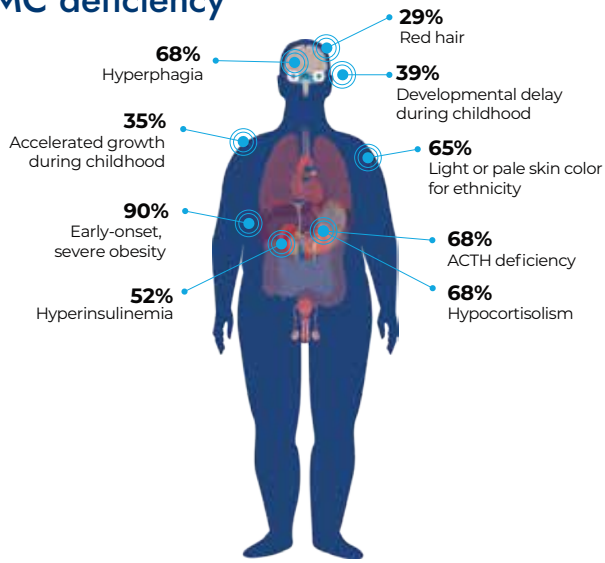
Clinical characteristics of LEPR and POMC deficiency[7,c]

LEPR deficiency



POMC deficiency



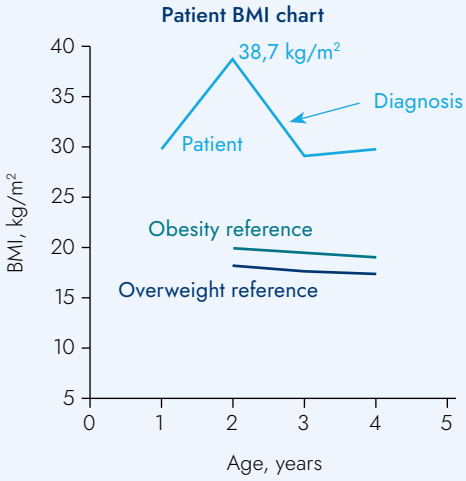
c) Percentages calculated as the number of cases with the characteristic divided by the total number of cases.

Prevalence:

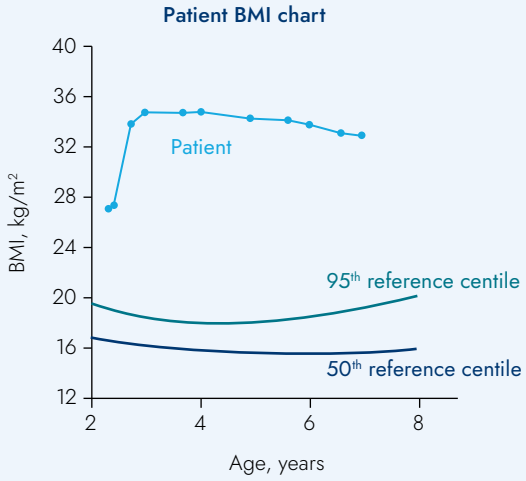
LEPR: 1.34 per million people[8]

POMC/PCSK1: fewer than 50 cases described worldwide for both indications[9]

Example BMI chart: LEPR deficiency[10]



Example BMI chart: POMC deficiency[11]



How are LEPR and POMC deficiency diagnosed?

Diagnosis of LEPR and POMC deficiency may be suspected on the basis of clinical manifestations and is confirmed by genetic testing.[10,12]

Paediatric patients

Genetic testing is recommended in paediatric patients with:[4,10,12]

- Early-onset, severe obesity
- Family history of severe obesity
- Features of syndromic obesity
- History of food-seeking behaviours
- Hyperphagia
- Neurodevelopmental abnormalities

Adult patients

Characteristics of patients diagnosed in adulthood include:[12-14]

- Endocrine abnormalities
- History of early-onset, severe obesity
- Hyperphagia from early age
- Resistant to obesity management approaches
- Red hair

Clinical characteristics can vary on an individual basis and between gene variants. It's therefore important to:[10,12,13]

- Take a detailed clinical history
- Record family history, if available
- Monitor resistance to traditional obesity management strategies

References: 1. Huvenne H, et al. *Obes Facts*. 2016;9(3):158–173. 2. Yazdi FT, et al. *Peer J*. 2015;3:e856. 3. Loos RJF and Yeo GSH. *Nat Rev Gens*. 2022;23:120–13. 4. Heymsfield BS, et al. *Obesity (Silver Spring)*. 2014;22(suppl 1):S1–S17. 5. Kohlsdorf K, et al. *Int J Obes*. 2018;42:1602–1609. 6. Hampl SE, et al. Pediatrics. 2023;151(2):e2022060640. 7. Argente J, et al. Poster presented at: 21st European Congress of Endocrinology; May 18–21, 2019; Lyon, France. 8. Kleinendorst L, et al. *Eur J Endocrinol*. 2020;182(1):47–56. 9. Malhotra S, et al. *J Pediatr Genet*. 2021;10:194–204. 10. Kleinendorst L, et al. *BMJ Case Rep*. 2017. 11. Hilado MA and Randhawa SR, *J Pediatr Endocrinol Metab*. 2018.31(7): 815–819. 12. Styne DM, et al. *J Clin Endocrinol Metab*. 2017;102(3):709–757. 13. Zorn S, et al. *Mol Cell Pediatr*. 2020;7(15). 14. Gregoric N, et al. *Front Endocrinol (Lausanne)*. 2021;12:689387.

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