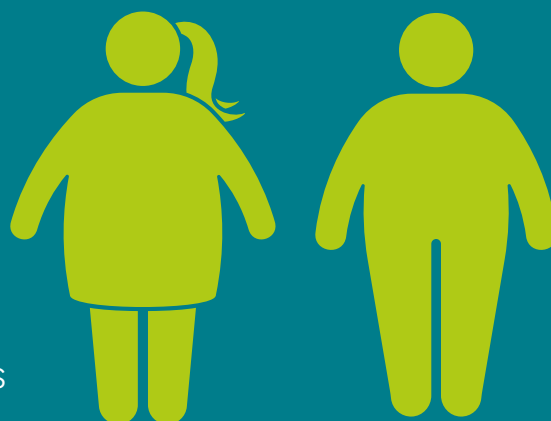


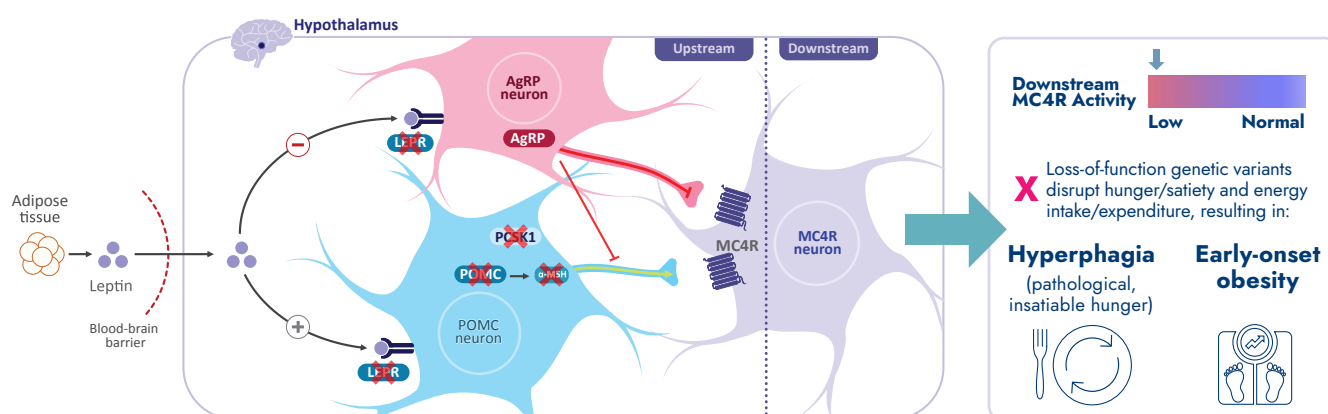
Leptin receptor deficiency and proopiomelanocortin deficiency

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 pathway¹⁻³



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

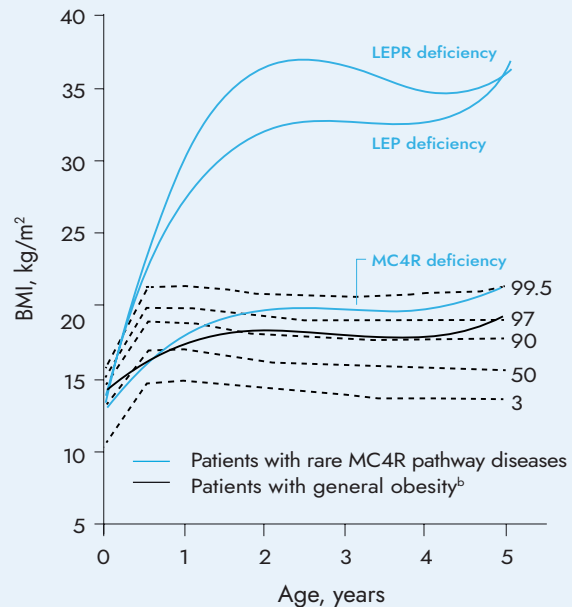
Primary cardinal symptoms of LEPR and POMC deficiency

Hyperphagia⁴

Characteristics and behaviours include:

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

Early-onset obesity^{5,6,a}

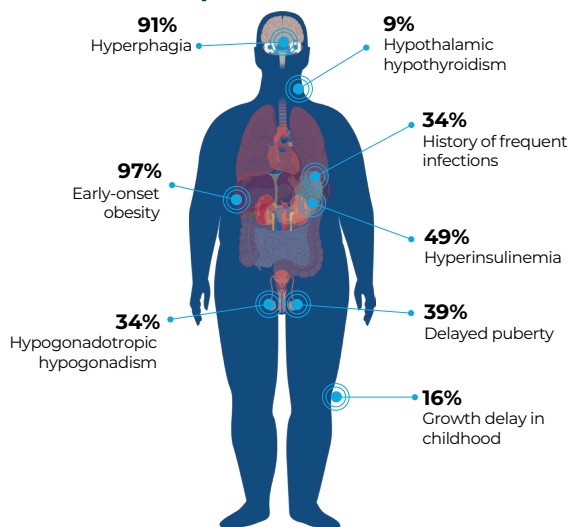


a) Presence of obesity before age 5, and BMI $\geq$ 95th percentile for age and sex.

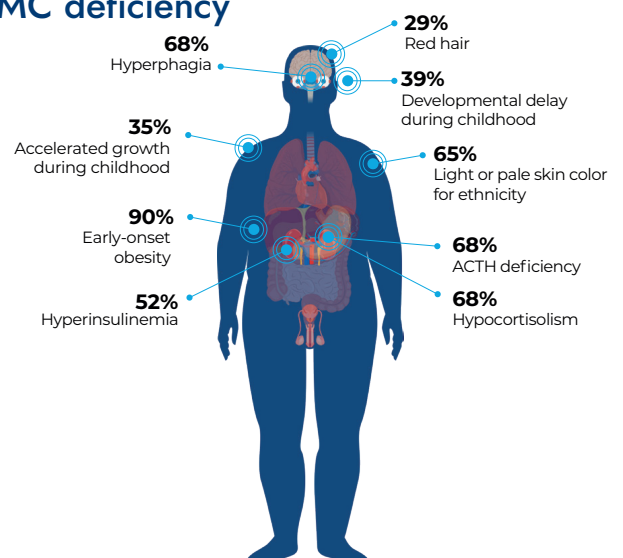
b) Following inclusion criteria for the control group were defined: BMI at the ages 14, 15, or 16 years >30 kg/m², early childhood data on BMI available (at least two values between 0 – 5 years) and exclusion of a mutation in the leptin, leptin receptor, and MC4R gene.

Clinical characteristics of LEPR and POMC deficiency^{7,c}

LEPR deficiency



POMC deficiency



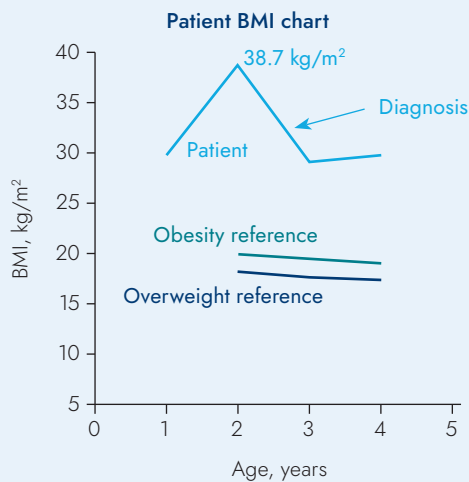
c) Percentages calculated as the number of cases with the characteristic divided by the total number of cases.

Prevalence:

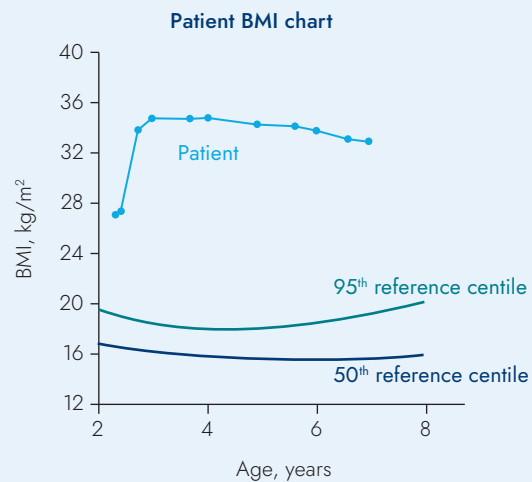
LEPR: 1.34 per million people⁸

POMC/PCSK1: fewer than 50 cases described worldwide for both indications⁹

Example BMI chart: LEPR deficiency¹⁰



Example BMI chart: POMC deficiency¹¹



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 obesity
- Family history of obesity
- Features of syndromic disease
- 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 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

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AT-NP-2200029 04/2025