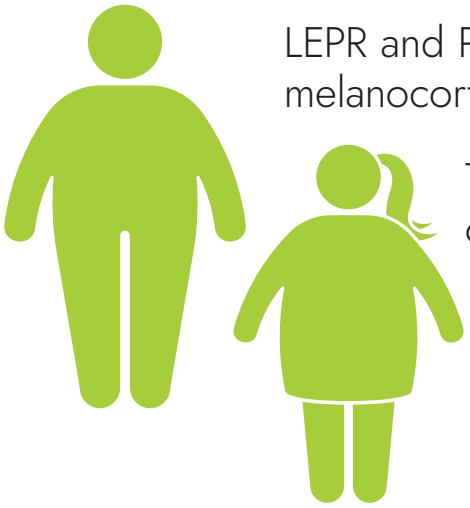
Leptin receptor (LEPR) deficiency and proopiomelanocortin (POMC) deficiency

What are LEPR and POMC deficiency?



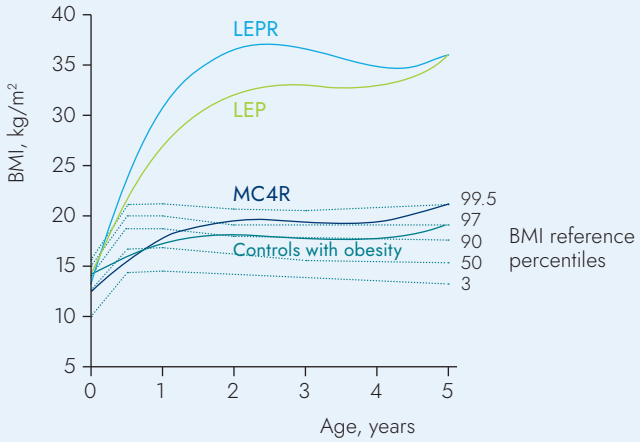
LEPR and POMC deficiency are genetically identifiable rare melanocortin-4 receptor (MC4R) pathway diseases.

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

Primary clinical features of LEPR and POMC deficiency[2,3]

Early-onset obesity

BMI in young children with LEPR, LEP or MC4R variants exceeds that in controls with obesity[a]



Hyperphagia

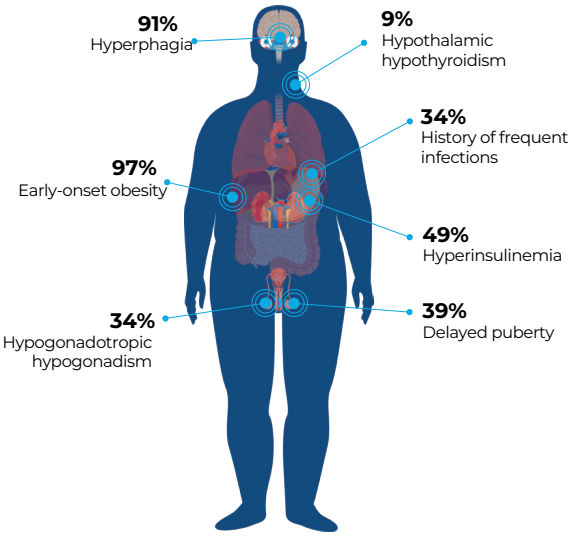
Clinical characteristics of hyperphagia[2]

- **Heightened and prolonged hunger**
- **Severe preoccupation with food** (hyperphagic drive)
- **Longer time to reach satiety**
- **Food-seeking behaviors** (night eating, stealing food, foraging for food in trash)
- **Shorter duration of satiety**
- **Distress and inappropriate behavioral response if denied food**

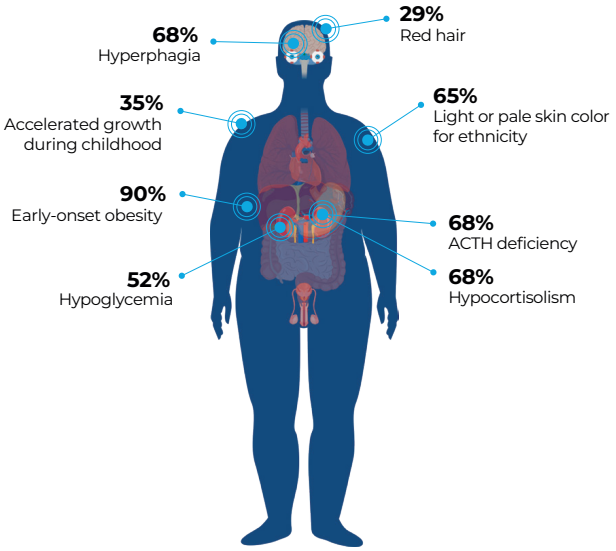
[a] Controls with obesity have a BMI >30 kg/m² by age 14-16 years and do not have a variant in LEPR, LEP, or MC4R. Figure adapted from Kohlsdorf et al. Int J Obes (Lond). 2018;42:1602-1609.

Clinical Characteristics of LEPR and POMC deficiency[8,a]

LEPR deficiency



POMC deficiency



[a] Percentages calculated as the number of cases with the characteristic divided by the total number of cases.

Prevalence:

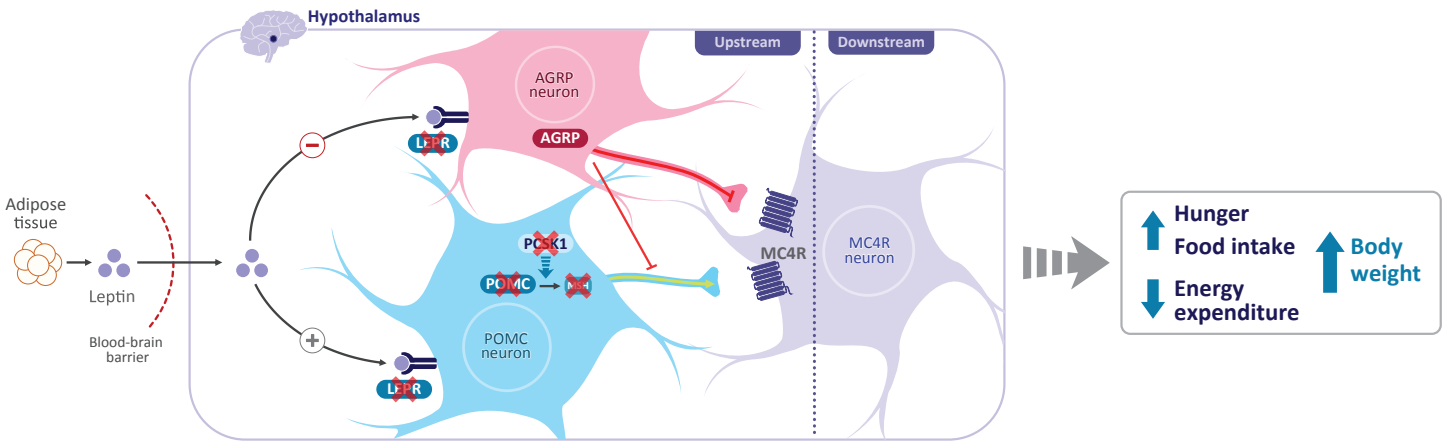
LEPR: 1.34 per million people[7]

POMC/PCSK1: fewer than 50 cases described worldwide for both indications[1]

True prevalence of rare genetic diseases of obesity is unknown because genetic testing is not often done in individuals with obesity[2,7]

Rare genetic variants within the MC4R pathway — a key pathway responsible for regulating hunger — may result in impaired neuronal signaling, leading to rare MC4R pathway diseases such as LEPR deficiency and POMC deficiency[9,10]

Impaired MC4R pathway



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.

How are LEPR and POMC deficiency diagnosed?[11]

Diagnosis of LEPR and POMC deficiency may be suspected on the basis of clinical manifestations and is confirmed by genetic testing

Paediatric patients

Genetic testing is recommended in peadiatric patients with:[11,12]

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

Adult patients

Characteristics discussed in case reports and studies of patients diagnosed in adulthood include:[11,13-16]

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

Clinical characteristics can vary on an individual basis and between gene variants.[12,15,16]

It's therefore important to:[13,18]

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

Obesity in LEPR and POMC deficiency

- Obesity can begin in childhood and can increase in severity with age[1,14]
- Obesity may have a detrimental impact on long-term health, due to its association with increased morbidity, social stigma, and reduced quality of life[19]
- Hyperphagia may contribute to obesity in patients with LEPR and POMC deficiency[1,20]
- Hyperphagia is generally characterized by the following:[3]

Insatiable hunger

Heightened and prolonged hunger

Longer time to reach satiation

Shorter duration of satiety

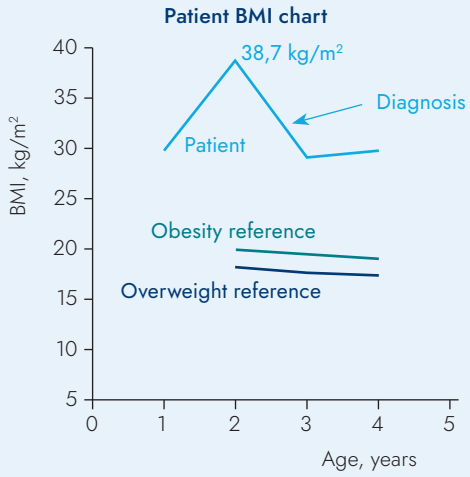
Excessive drive to eat

Severe preoccupation with food

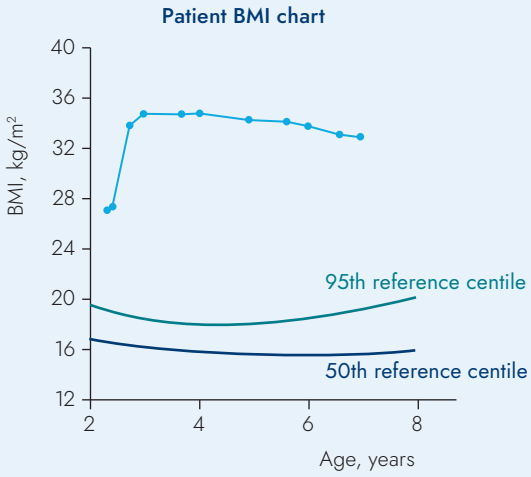
Persistent food-seeking behaviors (eg, stealing food, night eating, eating food from the trash)

Distress and functional impairment due to denial of food

Example BMI chart: LEPR deficiency[11]



Example BMI chart: POMC deficiency[21]



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