Long-term outcomes of bariatric surgery in patients with bi-allelic mutations in the *POMC*, *LEPR*, and *MC4R* genes

Poitou C, et al. *Surg Obes Relat Dis*. 2021;17:1449–1456.

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Study at a glance

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Aim:

To examine bariatric surgery as a therapeutic option for patients with monogenic obesity by analysing the postoperative weight course and occurrences of postoperative complications.

Patient population:

Patients with monogenic forms of obesity with bi-allelic variants in *LEPR*, *POMC*, and *MC4R* who had undergone bariatric surgery at one of three major academic specialised medical centres.

Conclusions/interpretation:

The indication for bariatric surgery in patients with monogenic obesity based on biallelic gene mutations and its benefit/risk balance has to be evaluated very cautiously by specialised centres. Furthermore, to avoid an unsuccessful operation, preoperative genetic testing of patients with a history of early-onset obesity might be essential.

LEPR, leptin receptor; MC4R, melanocortin-4 receptor; POMC, proopiomelanocortin.
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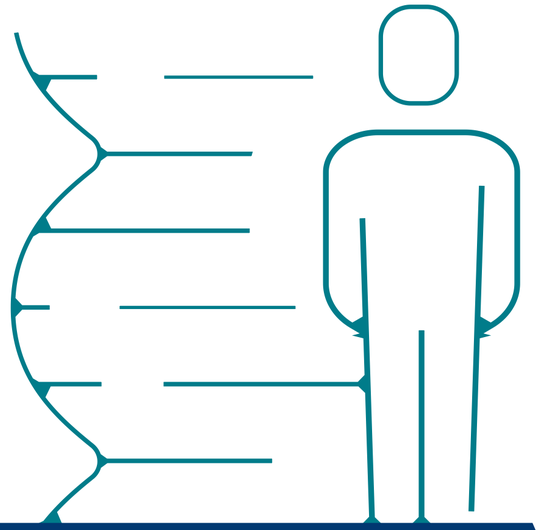
Background

- Among patients with obesity, there is a category of individuals with severe monogenic obesity, which is a rare condition
- The majority of mutations leading to monogenic obesity are identified in genes part of the leptin/melanocortin signalling cascade



Leptin secreted from adipose tissue › **Activates LEPR in the hypothalamus** › **Activation of POMC-expressing neurones** › **Secretion of a–/b–melanocyte stimulating hormone** › **Activation of MC4R** › **Satiety and altered energy expenditure**

- Genetic variants of genes in each step of this highly conserved pathway lead to hyperphagia and severe early-onset obesity
- Individuals with a bi-allelic POMC, MC4R, or LEPR deficiency are ultra-rare, and less than 100 patients for each genetic cause have been described in the literature to date
- Heterozygous variant carriers are much more common, and it has been estimated than 1.7% of individuals with severe obesity are carriers of a functional relevant heterozygous *MC4R* variant

Rationale for discussing bariatric surgery in patients with a genetic defect within the leptin-melanocortin pathway:

- Hyperphagia is a common feature in these patients
- The severity of hyperphagia leads to a severe burden on the affected patients and their families
- In most cases conservative treatment options (increased exercise, reduced caloric intake, and eating behaviour therapies) are not successful to stabilise body weight
- In some cases, caregivers restrict food access with significant effort (e.g., lock the kitchen) because of food-seeking behaviour

Even in adolescents without a monogenic cause for obesity, data about long-term outcomes and safety of bariatric surgery are limited

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Study design

A retrospective clinical evaluation of patients with bi-allelic monogenic obesity who underwent bariatric surgery

Inclusion criteria:

- Patients with monogenic obesity based on functional relevant bi-allelic mutations in 1 of the genes *LEPR*, *POMC*, and *MC4R*, who underwent bariatric surgery in the past
- Written informed consent for the retrospective data analysis

Exclusion criteria:

- Subjects who were legally detained in an official institution
- Subjects missing written informed consent by the patient or a responsible caregiver

- Patients were recruited at two reference centres for genetic obesity in Paris and one reference centre in Berlin and were not identified based on a certain registry
- The data for this retrospective evaluation were collected from clinic charts

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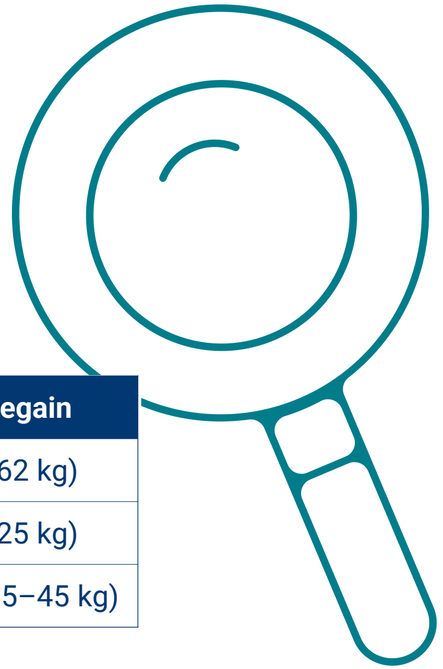
Results

Post surgery weight course was dependent on operation type



Type of surgery	Median weight reduction	Median weight regain
Gastric banding (n=3)	-52.1% EWL (IQR, -60.7 to -51.1% EWL)	42.0 kg (IQR, 0–62 kg)
Sleeve gastrectomy (n=3)	-28.9 % EWL (IQR, -66.4 to -0.6% EWL)	10.0 kg (IQR, 0–25 kg)
Gastric bypass (n=5)	-37.8% EWL (IQR, -52.6 to -29.4% EWL)	24.1 kg (IQR, 19.5–45 kg)

- After individual weight loss and weight regain and, in some cases, multiple operations, the current surgical outcome is a median reduction of body weight of -15.0 kg (IQR, -33.8 to -2.9 kg; -24.2% EWL [IQR, -37.6 to -5.4% EWL])
- Therefore, after surgery all patients were still suffering from morbid obesity, with a median BMI of 44.3 kg/m^2 (IQR, 40.7–58.3 kg/m^2)

Post surgery weight course dependent on genetic variant

Genetic variant	Median weight reduction	Median weight regain	Median final body weight reduction	Median BMI after surgery
LEPR (number of surgeries: 6)	-41.0 kg (IQR, -49.4 to -29.0 kg) and -49.3% EWL (IQR, -52.7 to -28.1% EWL)	25.0 kg (IQR, 16.5–52 kg)	-10.0 kg (IQR, -30.2 to -0.5 kg; -22.8% EWL [IQR, -33.6 to -0.9% EWL])	44.3 kg/m^2 [IQR: 42.3–62.4 kg/m^2]
POMC (number of surgeries: 4)	-35.8 kg (IQR, -88.5 to -5.1 kg) and -35.5% EWL (IQR, -52.7 to -8.8% EWL)	24.1 kg (IQR, 16–65 kg)	-33.7 kg (IQR, -65.9 to -1.5 kg; -21.8% EWL [IQR: -40.3 to -3.2% EWL])	49.6 kg/m^2 [IQR: 40–59.2 kg/m^2]
MC4R (n=1)	-45.0 kg (-66.4% EWL)	25.0 kg	-20.0 kg (-29.5% EWL)	41.5 kg/m^2

EWL, excess weight loss; IQR, interquartile range; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; POMC, proopiomelanocortin.

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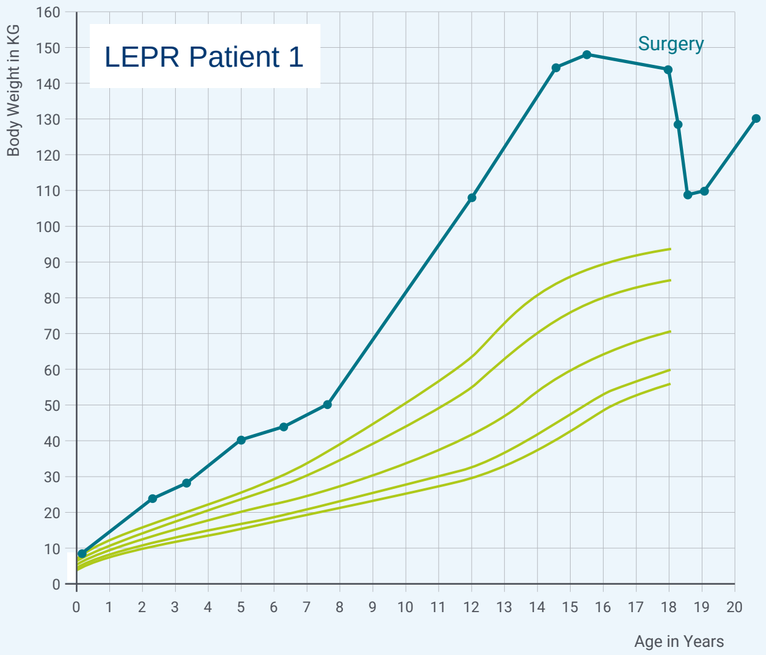
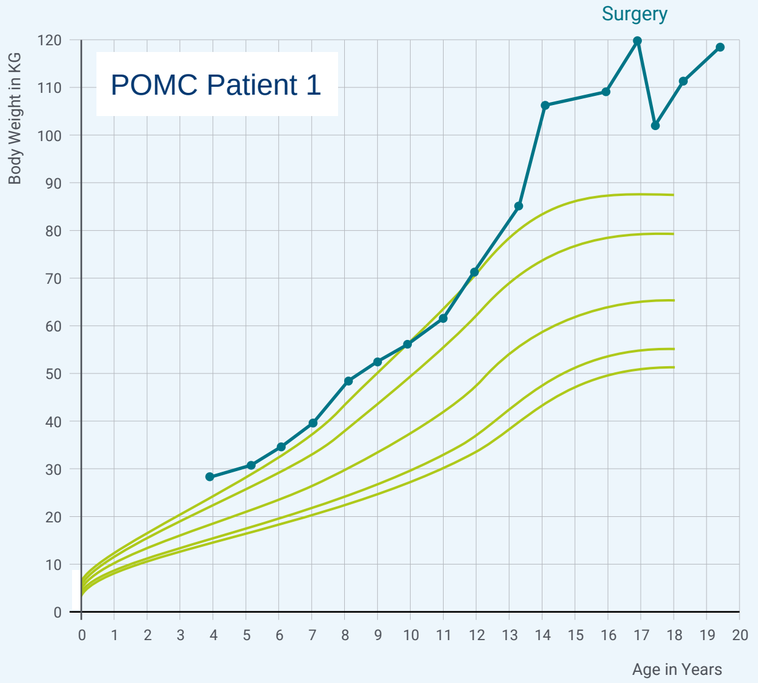
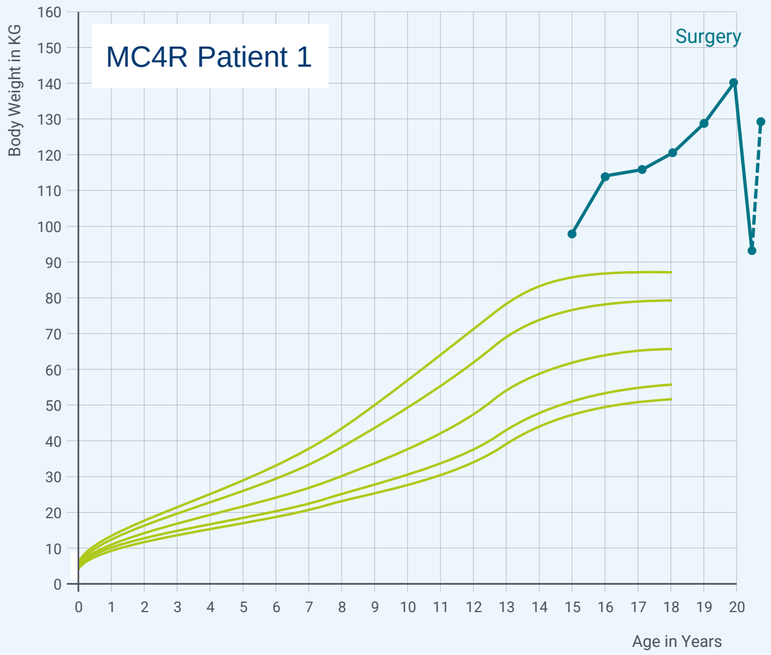
Weight course of patients with monogenic obesity before and after surgery

Initial bariatric surgery was performed at a median age of 19







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Discussion

- Bariatric surgery is a major therapeutic option for patients with severe obesity
- Considerable variability in the individual weight loss response to bariatric surgery has been reported, and clinical and genetic factors have been assumed to have a strong influence on weight loss outcomes after bariatric surgery
- A genetic predisposition might be a determinant in some cases, especially if the genetic variant is leading to uncontrolled hyperphagia
- Treating patients with genetic defects within the leptin/melanocortin pathway using conservative strategies is challenging, so alternative treatment options like bariatric surgery should be discussed
- In patients with a monogenic cause for obesity, the situation is complex, as the major driver of weight gain, hyperphagia, is not targeted by the intervention

- This case series is pointing towards a limited benefit of bariatric surgery for patients with a genetic defect in the leptin-melanocortin pathway
  - At least some patients in the present study stabilised their body weight
  - Nearly all patients in this study lost weight despite weight regain
  - However, all patients finally remained obese
- Observed postoperative complications included:
  - An abdominal wall hernia and chronic infection of the abdominal wall (*POMC* patient 2)
  - Psychological problems, like depression (LEPR patient 3, POMC patient 1, POMC patient 2) or binge-eating disorder (POMC patient 2)
  - Recurrent iron, vitamin D, and B6 deficiencies, which made supplementation therapy necessary (POMC patient 1, POMC patient 2)

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Summary

- This was a retrospective clinical evaluation of patients with bi-allelic monogenic obesity who underwent bariatric surgery (N=8)
- All patients initially experienced weight loss after each bariatric surgery, which was followed by substantial weight regain

Conclusions

- Currently, in most cases patients are not systematically tested for any genetic defect before bariatric surgery
- Given the experience in the reported cases, it is of importance to rule out potential genetic defects causing hyperphagia before a bariatric operation, especially in those with a history of hyperphagia and early-onset obesity
- This retrospective clinical evaluation demonstrated that weight reductions after bariatric surgery in patients with monogenic obesity due to bi-allelic mutations in the leptin-melanocortin signalling pathway may be only moderate, most likely due to the severe and persistent hyperphagia that is the hallmark of these diseases
- The authors therefore advise that genetic testing should be part of the preoperative procedures before bariatric surgery takes place, at least in patients with severe early-onset obesity
  - Although this will incur additional costs, it will prevent harm for the affected patients

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