A novel homozygous variant of the leptin receptor (LEPR) gene causing familiar early-onset severe obesity in two siblings

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INTRODUCTION

In Paediatrics, obesity is mostly essential, with predisposing and environmental factors playing a synergic effect. Less than 1% of all cases of paediatric obesity is due to either syndromic or monogenic conditions, with the latter being associated with remarkable diagnostic delay due to the lack of associated dysmorphic features.[1]

The **leptin-melanocortin pathway** is a well-studied pivotal player of body weight regulation and energy homeostasis. Pathogenic mutations of the genes involved in this pathway may result in **early-onset severe obesity (ESO)**.

CASE REPORT

Reason for referral

Longstanding history of extremely **severe** and progressive obesity with very **early-onset**
Referred to our Centre at the age of 16 years

Clinical examination

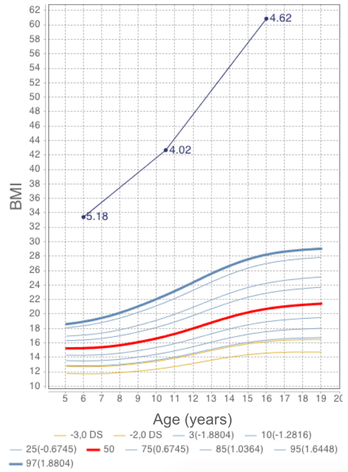
- Weight: 165.7 Kg (SDS: 5.47, WHO)
- Height: 165.0 cm (SDS: 0.37, WHO)
- BMI: 60.86 Kg/m^2 (SDS:4.62, WHO)
- BP: 130/100 mmHg
- Neck and axillary acanthosis nigricans
- Post-pubertal

Family history

- Moroccan origins
- Parents: non-obese first-degree cousins
- Two healthy brothers, with normal BMI
- 8-year-old **sister with ESO**

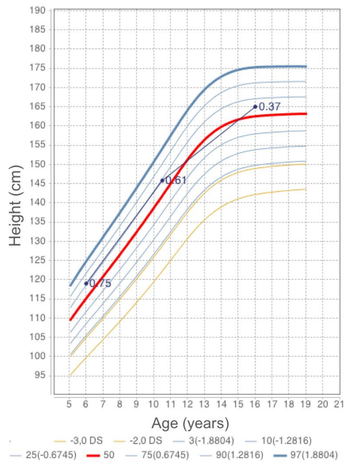
Physiological anamnesis

- Physiological pregnancy and delivery, birth weight: 3000 grams (-1.1 SDS, WHO).
- Progressive weight gain with hyperphagia and rapid onset of severe obesity from the first months of life;
- Regular height velocity in time, without growth deceleration;



Girls Chart - BMI for age, 5-19 years (WHO, 2007)

Age (years)	Weight (kg)	Height (cm)	BMI (kg/m2)	BMI (SDS)
3	35,0	98,0	**36,44**	2,89
6	47,3	119,0	**33,40**	5,18
10,5	90,7	145,8	**42,67**	4,02
16	165,7	165,0	**60,86**	4,62



Girls Chart - Height for age, 5-19 years (WHO, 2007)

Medical history

3 years.
BMI 36,4 Kg/m^2
Normal endocrine and genetic testings (Prader Willi syndrome excluded)

7 years.
1° genetic evaluation: no syndromic disorder

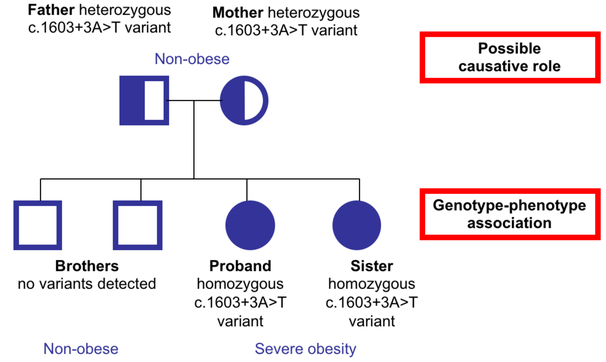
14 years.
- Impaired glucose tolerance → metformin
- Obstructive sleep apnea → nocturnal oxygen therapy
- Liver steatosis

6 years.
BMI 33,4 Kg/m^2
Mild hypertransaminasemia, hypercolesterolemia

16 years.
Genetic evaluation at our pediatric ourpatient clinic: next generation sequencing (NGS)

homozygous c.1603+3A>T variant in leptin receptor (LEPR) gene

Genetic analyses in the proband and her family



The proband and her sister have been enrolled in a **clinical trial** treatment with a **melanocortin-4 receptor (MC4R)-agonist**, a promising weight loss drug for patients presenting with LEPR resistance.

DISCUSSION

Monogenic obesity resulting from mutations in the LEPR gene has been described for the first time two decades ago.[2] **The inheritance pattern and the genotype-phenotype association support the hypothesis of a pathogenic role of the novel c.1603+3A>T variant hereby described.**
Functional analysis may confirm the pathogenicity of c.1603+3A>T variant.

CONCLUSION

Red flags for monogenic obesity

- Early onset of obesity
- Severe obesity (BMI >>> +2 SDS) and hyperphagia
- **consanguineous parents**
- **patchy familiar involvement**

The therapeutic effectiveness of a novel **MC4R-agonist** will be tested in the proband and her sister, as they have been enrolled in a clinical trial for the treatment of patients with ESO due to inactivating LEPR gene mutations.[3,4]

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4. Clément K et al. MC4R agonism promotes durable weight loss in patients with leptin receptor deficiency. Nat Med. 2018;24(5):551–5.