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/m² (SDS:4.62, WHO)
- BP: 130/100 mmHg

Physiological anamnesis

- Parental: 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;

Medical history

2 years. BMI 36.4 Kg/m² Normal endocrine and genetic screenings (Prader-Willi syndrome excluded)

7 years. 1st genetic evaluation: no syndromic disorder

14 years. - Impaired glucose tolerance — medroxyprogesterone acetate
- Hyperinsulinemia
- Liver steatosis

6 years. BMI 33.4 Kg/m² MI
- Height for age, 5
- Neck and axillary acanthosis nigricans

10 years. Genetic evaluation at our pediatric outpatient clinic: next generation sequencing (NGS)

This is the first report of a novel homozygous c.1603+3A>T variant in a child with severe obesity.

The proband and her sister have been enrolled in a clinical trial 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

REFERENCES