# RARE HETEROZYGOUS VARIANTS IN GENES OF THE LEPTIN-MELANOCORTIN SATIETY PATHWAY CONTRIBUTE TO CHILDHOOD OBESITY

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**The authors have nothing to disclose**

## INTRODUCTION

- The central melanocortin signaling pathway is highly involved in the control of energy homeostasis and metabolism, receiving and integrating numerous peripheral metabolic signals, such as leptin or insulin.
- Biallelic mutations in several genes of the leptin-melanocortin pathway have been reported in severe obesity. However, whether and how **heterozygous rare sequence variants** (**hetRSVs**) in genes of this satiety pathway contribute to the development of obesity is poorly explored.

## AIM

- Our aim was to investigate whether **hetRSVs** in 13 genes involved in the leptin-melanocortin pathway contribute to childhood obesity by comparing their prevalence in 1066 children and adolescents with obesity and a country-matched control population.

## PATIENTS AND METHODS

- A transversal study of 1066 children and adolescents (below age 18 years) with obesity (BMI Z-score > 2, **OB**) was carried-out with next generation sequencing (NGS) analysis of *ADCY3, CPE, LEP, LEPR, MC3R, MC4R, MRAP2, NCOA1, PCSK1, POMC, SH2B1, SIM1* and *TBX3* performed.
- The population was made up of 48.6% females / 51.4% males of whom 54.4% were prepubertal children / 45.6% adolescents and 71.7% Caucasians. Mean population age and BMI Z-score were 10.37 ± 3.44 years and +4.38 ± 1.77, respectively.
- Rare (population frequency <0.01) heterozygous variants with a Combined Annotation Dependent Depletion (CADD) score of "deleteriousness" >20 and >25 in each gene were considered and their relative frequency compared with that in a country matched control population (**C**, n=1012).

## RESULTS

- A total of 199 patients of the OB group (18.8%) and 81 controls (8.0%) carried heterozygous RSVs with **CADD > 20** in the 13 selected genes (**OR=2.64**, 95% CI = 2.00-3.47**, p<0.0001**).
- Out of them, 101 patients *vs.* 45 controls harboured **hetRSVs** with **CADD > 25** (9.47% *vs*. 4.44%, **OR = 2.25**, 95% CI = 1.56-3.23, **p<0.0001**).
- **No significant differences** in the prevalence of hetRSVs between groups were observed in:
  - ***ADCY3*** (MIM* 600291. ADENYLATE CYCLASE 3)
  - ***LEP*** (MIM* 164160. LEPTIN) - ***LEPR*** (MIM* 601007. LEPTIN RECEPTOR)
  - ***TBX3*** (MIM* 601621. T-BOX TRANSCRIPTION FACTOR 3)
- In contrast, **OB** showed a significantly **higher prevalence of hetRSVs** with CADD > 20 in:
  - ***CPE*** (MIM* 114855. CARBOXYPEPTIDASE E).
  - ***MRAP2*** (MIM* 615410. MELANOCORTIN 2 RECEPTOR ACCESSORY PROTEIN 2).
  - ***MC3R*** (MIM* 155540. MELANOCORTIN 3 RECEPTOR).
  - ***MC4R*** (MIM* 155541. MELANOCORTIN 4 RECEPTOR).
  - ***NCOA1*** (MIM* 602691. NUCLEAR RECEPTOR COACTIVATOR 1) (*Alternative nomenclature:* ***SRC1***).
  - ***PCSK1*** (MIM* 162150. PROPROTEIN CONVERTASE, SUBTILISIN/KEXIN-TYPE, 1).
  - ***POMC*** (MIM* 176830. PROOPIOMELANOCORTIN).
  - ***SH2B1*** (MIM* 608937. SH2B ADAPTOR PROTEIN 1).
  - ***SIM1*** (MIM* 603128. SIM bHLH TRANSCRIPTION FACTOR 1).
- These intergroup differences were particularly relevant for ***POMC***, ***PCSK1***, ***MC4R*** and ***NCOA1*** (**Table**).

| | Variants (n): OB | | | Variants (n): C | | | Intergroup comparison |
|---|---|---|---|---|---|---|---|
| CADD | > 25 | 20-25 | Total >20 | >25 | 20-25 | Tota l>20 | |
| ***ADCY3*** | 9 | 7 | 16 | 5 | 5 | 10 | N.S. |
| ***CPE*** | 4 | 8 | 12 | 2 | 2 | 4 | p < 0.05 |
| ***LEP*** | 0 | 0 | 0 | 1 | 0 | 1 | N.S. |
| ***LEPR*** | 9 | 4 | 13 | 8 | 5 | 13 | N.S. |
| ***MC3R*** | 6 | 6 | 12 | 5 | 0 | 5 | p < 0.05 |
| ***MC4R*** | 13 | 10 | 23 | 2 | 1 | 3 | **p < 0.01** |
| ***MRAP2*** | 6 | 2 | 8 | 2 | 0 | 2 | p < 0.05 |
| ***NCOA1*** | 14 | 24 | 38 | 6 | 6 | 12 | **p < 0.01** |
| ***PCSK1*** | 5 | 6 | 11 | 0 | 4 | 4 | **p < 0.01** |
| ***POMC*** | 21 | 8 | 29 | 1 | 5 | 6 | **p < 0.01** |
| ***SH2B1*** | 5 | 6 | 11 | 4 | 1 | 5 | p < 0.05 |
| ***SIM1*** | 7 | 8 | 15 | 3 | 4 | 7 | p < 0.05 |
| ***TBX3*** | 2 | 9 | 11 | 6 | 3 | 9 | N.S. |
| **13 genes** | 101 | 98 | 199 | 45 | 36 | 81 | **p < 0.0001** |

Table legend: *Abbreviations:* **C:** Control group; **CADD:** Combined Annotation Dependent Depletion score; **N.S.:** Non significant, **OB**: Obesity group.

## CONCLUSIONS

- **The prevalence of heterozygous variants in leptin-melanocortin pathway genes, particularly in *POMC*, *PCSK1*, *MC4R* and *NCOA1*, in childhood obesity is higher than in general population, so they likely contribute to the early development of obesity in these patients.**

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