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

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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 heterogeneous 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, MRAF2, 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 (ORs=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. ADENYLYL CYCLASE 3).
  - LEPR (MIM* 161460. LEPTIN). LEPR (MIM* 61007. 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).
  - MRAF2 (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: SRCT).
  - PCSK1 (MIM* 162150. PROTEIN CONVERTASE, SUBTILISIN/KEXIN-TYPE, 1).
  - POMC (MIM* 176830. PROOPiomelanocortin).
  - SH2B1 (MIM* 609837. 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).

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.

Table 1: Comparison of hetRSVs frequency in 1066 OB and 81 controls

<table>
<thead>
<tr>
<th>Gene</th>
<th>OB (n)</th>
<th>Controls (n)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADCY3</td>
<td>119</td>
<td>52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CPE</td>
<td>70</td>
<td>41</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LEPR</td>
<td>85</td>
<td>46</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MC3R</td>
<td>104</td>
<td>65</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MC4R</td>
<td>104</td>
<td>65</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NCOA1</td>
<td>40</td>
<td>25</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table legend: Abbreviations: OB: Obesity group.