Identification of MC4R Pathway Variants in Individuals With Extreme Obesity

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Summary

On the basis of a literature and computational search, the analyses identify a collection of POMC, PCSK1, and LEPR gene variants predicted to be associated with dysfunction within the melanocortin-4 receptor (MC4R) pathway that may cause a rare genetic disorder of obesity

Sequence data demonstrate that ~0.9% of obese individuals are likely to have a rare genetic disorder of obesity due to a homozygous loss-of-function (LOF) mutation in POMC, PCSK1, or LEPR

The identification of these gene variants defines a patient population in which treatment designed to compensate for low MC4R activity is hypothesized to reduce insatiable hunger and obesity

Background

The hypothalamic MC4R pathway, which is a component of the central melanocortin pathway, regulates energy balance and appetite (Figure 1)1-3

Genetic mutations in components comprising the MC4R pathway may cause early-onset insatiable hunger (hyperphagia) and severe obesity4

Rare genetic disorders of obesity characterized by MC4R pathway dysfunction include LEP, LEPR, POMC, PCSK1, and MC4R genetic deficiencies; Bardet-Biedl syndrome; and Alström syndrome1,5

Because the prevalence of these disorders may be underestimated,4 the relevance of variants in genes within the MC4R pathway remains unknown, and studies are ongoing

Objectives

To generate a compendium of variants within the POMC, PCSK1, and LEPR genes

To identify individuals who have variants in genes within the MC4R pathway and are affected by rare genetic disorders of obesity

Methods

A list of LOF mutations in POMC, PCSK1, and LEPR was compiled from the published literature and supplemented with unpublished computationally predicted deleterious missense mutations (WuXi DeepCode score >0.9)4

On the basis of confidence and likely impact, variants were bucketed into 2 groups:

Group 1: literature-validated variants and variants arising from high-impact mutations (nonsense, frameshift indel, and splice alterations)

Group 2: predicted LOF missense variants expected to have a high functional impact based on the DeepCODE algorithm, and absent or present at <0.1% in the Genome Aggregation Database (gnomAD)

Individuals with severe early-onset obesity and hyperphagia were sequenced for POMC, PCSK1, and LEPR

Participants include 1886 individuals with biobanked DNA samples from 8 clinical obesity centers and 916 participants in the Genetic Obesity Identification genotyping prospective study (GO-ID; NCT02849977)

Table 1. GO-ID Inclusion Criteria for the First Cohort4

<table>
<thead>
<tr>
<th>GO-ID Inclusion Criteria for the First Cohort4</th>
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<tr>
<td>BMI and hyperphagia cohort, &gt;2 years of age</td>
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<tr>
<td>Adult: BMI ≥40 kg/m²</td>
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<tr>
<td>Child: BMI &gt;14 × 95th percentile</td>
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<tr>
<td>Hyperphagia</td>
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<td>Evidence of pediatric onset</td>
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Results

6863 known or suspected LOF variants were identified

315 High-confidence LOF variants in POMC, PCSK1, and LEPR from the published literature and in genetic databases (Group 1)

6548 Computationally predicted deleterious missense variants (419 observed at <0.1% prevalence in gnomAD) (Group 2)

From sequenced biobank and GO-ID first cohort samples

6.2% of individuals with early-onset severe obesity and hyperphagia carried ≥1 LOF allele carried a Group 1 (high-impact and/or published) LOF allele

1.5% carried a Group 2 (computationally defined) LOF allele

4.7% were homozygous for either a Group 1 or Group 2 LOF allele (24 patients [n=2804]; Table 2)

5 individuals carried mutations in 2 of the 3 MC4R pathway genes assessed; previous analyses have demonstrated an association between carrying multiple MC4R pathway mutations and increased body mass index

Table 2. Number of Homozygous LOF Variants Found in the Sequenced Biobank and GO-ID First Cohort Samples From Obese Individuals

<table>
<thead>
<tr>
<th>Sequenced sample study</th>
<th>Group 1 homozygotes</th>
<th>Group 2 homozygotes</th>
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<tbody>
<tr>
<td>GO-ID first cohort, n/N (%)</td>
<td>6/918 (0.65%)</td>
<td>11/918 (1.20%)</td>
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<tr>
<td>Biobank, n/N (%)</td>
<td>6/1886 (0.32%)</td>
<td>1/1886 (0.05%)</td>
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<tr>
<td>Total, n/N (%)</td>
<td>12/2804 (0.43%)</td>
<td>12/2804 (0.43%)</td>
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<tr>
<td>POMC, n</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>PCSK1, n</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>LEPR, n</td>
<td>6</td>
<td>6</td>
</tr>
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</table>

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