Melanocortin 4 Receptor Pathway Dysfunction in Obese Patients: Prevalence Estimates of LEPR, POMC, and PCSK1 Variants

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Introduction

The hypothalamic melanocortin 4 receptor (MC4R) pathway plays a critical role in controlling food intake and energy expenditure through brain–periphery signaling networks. 1 Mutations in several genes within the MC4R pathway lead to autosomal recessive forms of obesity, related to loss-of-function (LoF) effects of various factors.

Results

Identification of LoF Genetic Variants in POMC, PCSK1, and LEPR

• A total of 63 credible LoF variants were identified from the literature.

• An additional 13 nonsense, frame-shift, and splice site variants and 421 computationally predicted LoF missense variants were identified from the gnomAD database (v.3.1), and Mount Sinai Hospital internal data (Table).

• LoF variants were classified into three groups on the basis of the nature of the supporting evidence:
  - Group 1 included LoF variants experimentally validated in the literature or that could be confidently predicted as such based on published protein functional literature.

Methods

• Known LoF variants in the POMC, PCSK1, and LEPR genes were identified through a comprehensive literature search and through analysis of several genetic databases, including HGVDS and ClinVar.

• Computationally predicted LoF variants were identified using the DeepCODE deep learning algorithm (Yang et al. 2017, manuscript in preparation).

• The prevalence of individuals with homozygous or compound heterozygous LoF variants of interest was estimated for each gene.

• The association between any 2 variants was assumed to be negligible, as most heterozygous variants of interest were estimated for each gene.

• Overall, these findings suggest that LoF variants in the MC4R pathway contribute to severe obesity.

Conclusions

• We estimate that ~12,000 individuals in the United States are homozygous or compound heterozygous for LoF variants in POMC, PCSK1, or LEPR.

• This prevalent population requires almost entirely undiagnosed because genetic testing is rarely performed in obese patients.

• Guidelines on pediatric obesity suggest genetic testing in patients with extreme early-onset obesity (<5 years of age), and who have clinical features of genetic obesity syndromes (in particular, extreme hyperphagia) and/or a family history of extreme obesity.

• The overall frequency burden of 3 LoF alleles in at least 1 of the 3 genes tested among 234 individuals with no LoF variants (P = 0.099, Figure 2C).

• To evaluate the significance of variants other than PCSK1 N221D, we compared individuals with N221D plus another variant (n=219) with individuals with N221D alone (n=1,719).

• These results suggest a association between a burden of LoF variants in the MC4R pathway and higher BMI when compared with individuals with no LoF variants.

Disclosures

• The hypotheses set for this postdoc are not being reviewed by the research council. The hypotheses set for this postdoc are not being reviewed by the research council. The hypotheses set for this postdoc are not being reviewed by the research council.

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References


Prevalence of LoF Genetic Variants in POMC, PCSK1, and LEPR in the United States

• Based on an approximate US population of 300 million, the estimated numbers of homozygous and compound heterozygous individuals with no LoF variants were 3,628 individuals for LEPR, 456 individuals for a novel-melanocyte-stimulating hormone (a-MSH)/POMC, and 405 individuals for PCSK1 (Figure 1).

• The total combined prevalence for biallelic LoF variants was predicted to be 12,046 individuals in the United States (Figure 1).

• We have excluded from these analyses a small subset of less rare variants that have been previously evaluated and where the effects of these variants on severe obesity remain unclear. The remaining 36 of the 1,320 LoF variants were classified into the MC4R pathway (1,145,991 variants), and POMC/PCSK1 (454 variants, 80 variants for PCSK1) (Figure 1).

• The association between cumulative allelic burden and BMI was computed from allele frequencies in gnomAD (http://gnomad.ensembl.org), the UK10K (https://www.uk10k.org/), and Mount Sinai Hospital internal data (Figure 1).

• The leptin receptor (LEPR) is a critical role in controlling food intake and energy expenditure through brain–periphery signaling networks. 1 Mutations in several genes within the MC4R pathway lead to autosomal recessive forms of obesity, related to loss-of-function (LoF) effects of various factors.

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Discuss the role of LEPR, POMC, and PCSK1 variants in the pathogenesis of obesity, the potential implications for clinical practice, and the importance of further research in this area. Consider the implications for genetic counseling and the potential for targeted therapies in patients with LoF variants.