

# Genetic regulators of energy balance

## Abstract

**Objective:** Polymorphic variations in humans are supposed to be responsible for inter individual differences in susceptibility to multifactorial disorders like obesity. Genetic variants of the melanocortin-4 receptor gene (MC4R), agouti related protein (AGRP) and proopiomelanocortin (POMC) are reported to be associated with obesity. Therefore we tried to see the association of these genes with obesity in north Indian population.

**Methods:** The genotyping was done with Taq man probes and statistical was performed by SPSS software version 19.

**Results:** The CC (homozygous) genotype of MC4R rs17782313, ( $p=0.02$ ; OR=1.7) and CT (heterozygous) genotype of POMC rs1042571, ( $p=0.01$ ; OR=1.6) SNPs were significantly associated with obese individuals ( $BMI \geq 30 \text{ kg/m}^2$ ). However, no association of AGRP rs34123523 ( $p=0.23$ ; OR=1.2) was seen with  $BMI \geq 30 \text{ kg/m}^2$ .

**Keywords:** obesity, genetic variants

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## Introduction

Obesity has received considerable attention as a major health hazard, which is a complex disorder resulting from the interactions of a wide variety of genetic and environmental factors. Overweight and obesity are associated with premature death through increased risk of many chronic diseases including type 2 diabetes (T2D), cardiovascular disease and cancer.<sup>1</sup> In addition, obesity also increases adverse cardiac events indirectly mediated through dyslipidemia, hypertension, glucose intolerance and sleep disorders. It has been hypothesized that polymorphic variations in humans may be responsible for inter-individual differences in susceptibility to multifactorial disorder like obesity. The studies that looked for genes that predispose to common obesity were based on candidate genes, where the focus was on genes with a suspected role in the regulation of metabolism and food intake. The recent emergence of the genome-wide association studies (GWAS) has led to further breakthroughs in gene identification and now nine loci are recognized to be involved in Mendelian forms of obesity along with 58 loci contributing to polygenic obesity. In the present study, we have attempted to investigate in Northern India, the association of few recent loci identified in GWAS and candidate gene studies, with risk of BMI linked obesity and obesity linked comorbidities like Type 2 Diabetes and CardioVascular Disease. Further, we also aimed to explore high order gene-gene interactions using multidimensional statistical approaches to evaluate risk of obesity. Obesity and the associated risks are rising global health burden. Numerous variations in genes may contribute to the pathogenesis of obesity. The physiological pathways related to appetite are complex and involve the mixing of short-term satiety signals from the gut to the brain along with longer-term homeostatic systems which grip the integrated signaling of POMC, AGRP, and MC4R systems and risk an individual to obesity.<sup>2</sup> Agouti related protein (AGRP) is an evolutionary conserved gene mainly located in arcuate neurons that co-express neuropeptide Y (NPY) and is also a strong negotiator of regulation of energy balance.<sup>3</sup>

Melanocortin signaling in the hypothalamus plays a vital role in the control of energy homeostasis. These peptides signal to downstream target neurons in the lateral hypothalamus that express the melanocortin receptor MC4R with consequential decrease in food intake and increase in energy expenditure.<sup>4</sup> Rare mutations in the POMC (proopiomelanocortin) gene (Cytogenetic Location: 2p23.3)

cause early-onset obesity in humans though the influence of common polymorphisms in POMC on obesity phenotypes in less extreme individuals is indistinct.<sup>5</sup> In this study relation of MC4R (rs17782313, rs17700633), AGRP (rs34123523) and POMC (rs1042571) and their association with obesity ( $BMI \geq 30 \text{ kg/m}^2$ ) in North Indian population was observed. The analysis revealed that the CC (homozygous) genotype of MC4R rs17782313, ( $p=0.02$ ; OR=1.7) and CT (heterozygous) genotype of POMC rs1042571, ( $p=0.01$ ; OR=1.6) SNPs were significantly associated with obese individuals ( $BMI \geq 30 \text{ kg/m}^2$ ). However, no association of AGRP rs34123523 ( $p=0.23$ ; OR=1.2) was seen with  $BMI \geq 30 \text{ kg/m}^2$ .<sup>6</sup> The association of the SNP MC4R rs17782313 with obesity has previously been investigated in "European-American" children and studies have reported significant associations.<sup>7</sup> The SNP was also found significantly associated with obesity in adult Chinese,<sup>8</sup> central obesity in Chinese children,<sup>9</sup> Danish,<sup>10</sup> "African" and "European-American" populations.<sup>11</sup> MC4R and POMC variants have influence on obesity and contribute to the variance in body mass index (BMI) in Europeans and East Asians.<sup>12</sup> Studies in two ethnic specific polymorphisms suggest that slight differences in food preference in carriers of the rare AGRP alleles (T/T and Ala67Thr in blacks and whites, respectively) could over time result in lower adiposity.<sup>13</sup> In this study of POMC rs1042571 CT heterozygote and  $BMI \geq 30 \text{ kg/m}^2$  was significantly associated ( $p=0.01$ ; OR=1.6) with higher  $BMI \geq 30 \text{ kg/m}^2$  and results are in agreement with those reported by Krude H et al.<sup>5</sup> In view of the fact that obesity is caused by perturbations of the balance among food intake and energy expenditure, all along with social-environmental factors, which are regulated by a complex physiological system that requires the incorporation of several peripheral signals and central coordination in the brain, the outcome of the study implies that polymorphisms in MC4R, and POMC have a function in the regulation of food intake, energy expenditure and preference for specific food items which may result in obesity. North Indian population is presented in this report for the first time suggesting that naturally occurring mutations in MC4R, AGRP and POMC can make an individual to be at risk of obesity. The results of the study may significantly add to our knowledge and understanding of role of genetic factors in progression of obesity.

## Acknowledgements

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## Conflict of interest

Author declares that there is no conflict of interest.

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