

Carbohydrate Intake and Physical Activity Levels Modify the Association between FTO Gene Variants and Obesity and Type 2 Diabetes: First Nutrigenetics Study in an Asian Indian Population

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Abstract : Gene-lifestyle interaction studies have been carried out in various populations. However, to date there are no studies in an Asian Indian population. Hence, we examined whether lifestyle factors such as diet and physical activity modify the association between fat mass and obesity-associated (FTO) gene variants and obesity and type 2 diabetes (T2D) in an Asian Indian population. We studied 734 unrelated T2D and 884 normal glucose-tolerant (NGT) participants randomly selected from the Chennai Urban Rural Epidemiology Study (CURES) in Southern India. Obesity was defined according to the World Health Organization Asia Pacific Guidelines (non-obese, BMI < 25 kg/m²; obese, BMI ≥ 25 kg/m²). Six single nucleotide polymorphisms (SNPs) in the FTO gene (rs9940128, rs7193144, rs8050136, rs918031, rs1588413 and rs11076023) identified from recent genome-wide association studies for T2D were genotyped by polymerase chain reaction-restriction fragment length polymorphism and direct sequencing. Dietary assessment was carried out using a validated food frequency questionnaire and physical activity was based upon the self-report. Interaction analyses were performed by including the interaction terms in the model. A joint likelihood ratio test of the main SNP effects and the SNP-diet/physical activity interaction effects was used in the linear regression analyses to maximize statistical power. Statistical analyses were performed using STATA version 13. There was a significant interaction between FTO SNP rs8050136 and carbohydrate energy percentage (Pinteraction=0.04) on obesity, where the 'A' allele carriers of the SNP rs8050136 had 2.46 times higher risk of obesity than those with 'CC' genotype (P=3.0x10⁻⁵) among individuals in the highest tertile of carbohydrate energy percentage. Furthermore, among those who had lower levels of physical activity, the 'A' allele carriers of the SNP rs8050136 had 1.89 times higher risk of obesity than those with 'CC' genotype (P=4.0x10⁻⁵). We also found a borderline interaction between SNP rs11076023 and carbohydrate energy percentage (Pinteraction=0.08) on T2D, where the 'A' allele carriers in the highest tertile of carbohydrate energy percentage, had 1.57 times higher risk of T2D than those with 'TT' genotype (P=0.002). There was also a significant interaction between SNP rs11076023 and physical activity (Pinteraction=0.03) on T2D. No further significant interactions between SNPs and macronutrient intake or physical activity on obesity and T2D were observed. In conclusion, this is the first study to provide evidence for a gene-diet and gene-physical activity interaction on obesity and T2D in an Asian Indian population. These findings suggest that the association between FTO gene variants and obesity and T2D is influenced by carbohydrate intake and physical activity levels. Greater understanding of how FTO gene influences obesity and T2D through dietary and exercise interventions will advance the development of behavioral intervention and personalised lifestyle strategies predicted to reduce the development of metabolic diseases in 'A' allele carriers of both SNPs in this Asian Indian population.

Keywords : dietary intake, FTO, obesity, physical activity, type 2 diabetes, Asian Indian.

Conference Title : ICBNPA 2015 : International Conference on Behavioral Nutrition and Physical Activity

Conference Location : Sydney, Australia

Conference Dates : December 10-11, 2015