FTO genotype and weight gain in obese and normal weight adults from a Norwegian population based cohort (the HUNT study).

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Abstract

The fat mass and obesity associated gene (FTO) is associated with bodyweight and obesity. The aim of this study was to investigate if FTO genotype affects weight gain in adulthood. We investigated the weight development over a period of 11 years in a case-control study, consisting of 1,632 cases (BMI≥35 kg/m (2)) and 3,379 normal weight controls (BMI 20-24.9 kg/m (2)) from a Norwegian population based cohort, the HUNT study. Subjects were aged 20-80 at baseline, 25% men and 75% women. FTO genotype was assessed by genotyping of the SNP rs1421085. A strong association between FTO and obesity was found, consistent with an additive gene effect. Cases had an average weight gain of 11.1 kg, whereas controls had an average weight gain of 1.4 kg. Genotype was neither associated with weight gain in obese, nor controls. Cases had an average weight gain of 10.7 kg for individuals with zero risk alleles, 11.3 for one risk allele and 11.1 kg for two risk alleles. Controls had an average weight gain of 1.4 kg, 1.4 and 1.3 for the respective genotypes. In conclusion, FTO was associated with obesity, but not with weight gain in adults during 11 years of follow-up.

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Abstract

Single nucleotide polymorphisms (SNPs) in the fat mass and obesity associated (FTO) gene are associated with body mass index (BMI) in populations of European descent. The FTO rs9939609 variant, first detected in a genome-wide association study of diabetes, conferred an increased disease risk that was abolished after adjustment for BMI, suggesting that the association may be due to variation in adiposity. The relationship between diabetes, four previously identified FTO polymorphisms that span a 19.6-kb genomic region, and obesity was therefore evaluated in the biracial population-based Atherosclerosis Risk in Communities Study with the goal of further refining the association by comparing results between the two ethnic groups. The prevalence of diabetes and obesity (BMI > or = 30 kg/m(2)) was established at baseline, and diabetes was determined by either self-report, a fasting glucose level > or = 126 mg/dL, or non-fasting glucose > or = 200 mg/dL. There were 1,004 diabetes cases and 10,038 non-cases in whites, and 670 cases and 2,780 non-cases in African-Americans. Differences in mean BMI were assessed by a general linear model, and multivariable logistic regression was used to predict the risk of diabetes and obesity. For white participants, the FTO rs9939609 A allele was associated with an increased risk of diabetes (odds ratio (OR) = 1.19, $p<0.001$) and obesity (OR = 1.22, $p<0.001$) under an additive genetic model that was similar for all of the SNPs analyzed. In African-Americans, only the rs1421085 C allele was a determinant of obesity risk (OR = 1.17, $p = 0.05$), but was found to be protective against diabetes (OR = 0.79, $p = 0.03$). Adjustment for BMI did not eliminate any of the observed associations with diabetes. Significant statistical interaction between race and the FTO variants suggests that the effect on diabetes susceptibility may be context dependent.

chr16:53800954 (rs1421085)

The analyses of genome-wide association data from 1,380 Europeans with early-onset and morbid adult obesity and 1,416 age-matched normal-weight controls found a strong association of this variant in the first intron of FTO for risk of pooled childhood and adult severe obesity.

Abstract

Obesity is a serious international health problem that increases the risk of several common diseases. The genetic factors predisposing to obesity are poorly understood. A genome-wide search for type 2 diabetes-susceptibility genes identified a common variant in the FTO (fat mass and obesity associated) gene that predisposes to diabetes through an effect on body mass index (BMI). An additive association of the variant with BMI was replicated in 13 cohorts with 38,759 participants. The 16% of adults who are homozygous for the risk allele weighed about 3 kilograms more and had 1.67-fold increased odds of obesity when compared with those not inheriting a risk allele. This association was observed from age 7 years upward and reflects a specific increase in fat mass. Rs9939609

[FTO gene and his role in genetic determination of obesity].

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Abstract

Obesity is a risk factor for development of cardiovascular disease, type 2 diabetes and some cancers. Substantial proportions of obese people die from diseases caused by complications of overweight. The incidence of obesity in different populations exceeds 15%. The emergence of obesity is influenced by external factors (especially excessive energy intake and reduced physical activity). Body Mass Index (BMI) is also influenced by genetic factors, estimates of the degree of inheritance of obesity, according to the type of study range from 30 to 70%. Newly detected genetic risk factor for body weight is the FTO gene ("fat mass and obesity associated"). Variants in the first (and in some populations also in the third) intron of this gene are associated with BMI values and the presence of one risk allele is associated with an increase of body weight by about 1.5-2 kg. Studies on the possible causality (impact on energy intake, basal metabolism, physical activity) did not show consistent results. Variants in the first intron are also associated with higher risk of type 2 diabetes, polycystic ovary syndrome, and cardiovascular disease and seem to play a role in the determination of certain types of cancer and are associated with higher mortality. The exact mechanism of the effect of FTO on BMI determination is not yet known, however, the FTO exhibit a DNA demethylase activity and its role is designed as a transcription coactivator.

Risk of type 2 diabetes and obesity is differentially associated with variation in FTO in whites and African-Americans in the ARIC study.

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Abstract

Single nucleotide polymorphisms (SNPs) in the fat mass and obesity associated (FTO) gene are associated with body mass index (BMI) in populations of European descent. The FTO rs9939609 variant, first detected in a genome-wide association study of diabetes, conferred an increased disease risk that was abolished after adjustment for BMI, suggesting that the association may be due to variation in adiposity. The relationship between diabetes, four previously identified FTO polymorphisms that span a 19.6-kb genomic region, and obesity was therefore evaluated in the biracial population-based Atherosclerosis Risk in Communities Study with the goal of further refining the association by comparing results between the two ethnic groups. The prevalence of diabetes and obesity (BMI > or = 30 kg/m(2)) was established at baseline, and diabetes was determined by either self-report, a fasting glucose level > or = 126 mg/dL, or non-fasting glucose > or = 200 mg/dL. There were 1,004 diabetes cases and 10,038 non-cases in whites, and 670 cases and 2,780 non-cases in African-Americans. Differences in mean BMI were assessed by a general linear model, and multivariable logistic regression was used to predict the risk of diabetes and obesity. For white participants, the FTO rs9939609 A allele was associated with an increased risk of diabetes (odds ratio (OR) = 1.19, p<0.001) and obesity (OR = 1.22, p<0.001) under an additive genetic model that was similar for all of the SNPs analyzed. In African-Americans, only the rs1421085 C allele was a determinant of obesity risk (OR = 1.17, p = 0.05), but was found to be protective against diabetes (OR = 0.79, p = 0.03). Adjustment for BMI did not eliminate any of the observed associations with diabetes. Significant statistical interaction between race and the FTO variants suggests that the effect on diabetes susceptibility may be context dependent.

ADRB2 Arg16Gly (R16E) and Gln27Glu (Q27E) Polymorphisms

The beta-2 adrenergic receptor (ADRB2) gene product ADRB2 protein is expressed in fat cells. This receptor protein is involved in the mobilization of fat from the fat cells for energy in response to hormones called catecholamines (adrenaline, noradrenaline and dopamine). Several polymorphisms of this gene that result in amino acid changes have been identified.

The two main well-characterized polymorphisms Arg16Gly and Gln27Glu are the most common in Caucasians. Laboratory studies indicate that these polymorphisms affect the overall expression (production) of the receptor (22). The recent obesity gene map (18) shows association between variants in the ADRB2 gene and obesity, with most of the positive findings involving the Arg16Gly or Gln27Glu polymorphisms. Multiple studies show association between Glu27 and Gly16 alleles carriers and abdominal (23, 24) and central obesity (25). A long-term clinical study showed that weight gain from childhood to adulthood (26) and weight gain during adulthood (27, 28) are higher in individuals who carry the Gly16 allele. A clinical study involving women with high carbohydrate diet reported that women with 27Gln/Glu genetic makeup had increased risk of obesity, while no association of obesity was observed in 27Gln/Gln women (29).

27Gln/Gln was found to be a risk genetic profile in studies involving overfeeding of identical twins where higher weight gain and subcutaneous fat were observed compared to those with the Glu27 allele (30). A study of overweight Japanese men enrolled in a 24-month weight loss program (1,600 kcal/day and aerobic exercise one hour daily) showed that men with the Gly16 allele were more resistant to weight loss and more likely to regain body weight after 6 months (27). Women who were more active during their leisure time and were carriers of the Glu27 allele had higher BMI compared to similarly-active carriers, suggesting that these women may be more resistant to losing weight (31). Results from intervention studies (exercise or diet) involving the Arg16Gly polymorphism indicate Gly16 allele is the high-risk allele, especially in studies involving exercise and endurance training. Long-term studies suggest that the Gly16 allele is associated with greater weight gain over time. Results from association studies suggest that the Glu27 allele is associated with an increased risk of obesity, abdominal obesity and obesity when adhering to a high carbohydrate diet.

Several years ago, a team led by Dolores Corella and Jose Ordovas discovered that the rs5082 variant in the APOA2 gene is associated with obesity as well as general food measures like total calorie and protein intake. In a new study published last month in the Archives of Internal Medicine, Corella and Ordovas replicated the association with obesity in three independent populations and determined that the association depends specifically on the amount of saturated fat in the diet. More than 3400 individuals across three population groups – 2532 people of European ancestry and 930 Hispanics from Puerto Rico – participated in the study, providing data on dietary intake, physical activity, body mass index (BMI) and other variables.

In the two European populations, individuals with two copies of the C version of rs5082 had significantly higher calorie intake than individuals with at least one copy of the T version – a finding that echoed their previous work. When Corella and her colleagues looked at BMI, however, they found that rs5082 was significantly associated with higher BMI, but only in individuals who consumed high amounts of saturated fat, irrespective of total calorie intake.

In all three populations, there was no association between rs5082 genotype and BMI in individuals who consumed diets low in saturated fat. Furthermore, there was no significant difference in BMI for individuals who had low intake and individuals who had high intake if they had at least one copy of the T version. But people with the CC genotype who consumed diets high in saturated fat had significantly higher BMI than people with either the TC or TT genotype who also consumed high saturated fat diets. After combining data from the three groups, Corella's team determined that individuals with the CC genotype who had high saturated fat intake also had about 1.8 times higher odds of obesity than individuals with the T version who consumed similar amounts of saturated fat, total calorie intake being equal.

Although earlier research in animals has implicated APOA2 in obesity, its role in human health has been controversial. In this study, Corella and her team show that saturated fat intake can interact with a genetic variant in APOA2 to increase obesity risk. In fact, the variant makes more of a difference the more saturated fat one consumes. While minimizing saturated fat intake continues to be common sense, in a society characterized by rich diets and increasingly sedentary lifestyles, discoveries like this drive home the fact that genetics and environment together form an intricately interwoven picture of our health.