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.

ADRB2 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).

This SNP was shown as the strongest associated in the original work by Dina et al [PMID 17496892]. Moreover, it is located in a conserved region.

Within the FTO gene, many SNPs appear to be co-inherited. The SNP showing the strongest association with body weight (i.e. body mass index, BMI) is not **rs1421085**, although this SNP is one of co-inherited SNPs in the FTO gene region. For more information, refer to the FTO gene or the most studied of FTO SNPs, rs9930506. [PMID 17658951]

However, in one study of 583 extremely obese women with several FTO SNPs, the strongest association was with **rs1421085** ($p=3.04x10^{-10}$, OR = 1.75, CI: 1.47-2.08).[PMID 18218107]

[PMID 18719664] This SNP is also associated with adult obesity in Mexicans.

[PMID 19153581] rs17782313(C) more snacking, however **rs1421085**(C) did not influence eating behavior

[PMID 18551112] **rs1421085**(C) and rs17817449(G) significantly associated with increased BMI. Our results suggest that FTO may be one of the worldwide obesity-risk genes.

Neighbor	rs9940128
Distance	200

GWAS snp	
PMID	[PMID 19151714]
Trait	Obesity
Title	Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations
Risk Allele	C
P-val	1E-28
Odds Ratio	1.39 [1.27-1.51]

[PMID 19322589] Analysis of FTO gene variants with measures of obesity and glucose homeostasis in the IRAS Family Study.

rs9939609 were associated with BMI and WAIST (P values of 0.011 and 0.034), and associated or trending towards association with SAT (P values of 0.038 and 0.058). These results confirm that FTO variants are associated with adiposity measures, predisposing individuals to obesity by increasing overall fat mass in Hispanic Americans and to a lesser degree in African Americans.

OMIM	612460
Desc	BODY MASS INDEX QUANTITATIVE TRAIT LOCUS 14; BMIQ14
Variant	
Related	also

[PMID 19818665] Apolipoprotein E genotype is associated with serum C-reactive protein but not abdominal aortic aneurysm

PharmGKB	PA162565809
Name	
Annotation	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.
Gene	FTO
Featue	
Evidence	PubMed ID:19174833
Drugs	
Diseases	Obesity

Curation Level Curated

[PMID 20502638] Risk of Type 2 Diabetes and Obesity Is Differentially Associated with Variation in FTO in Whites and African-Americans in the ARIC Study

PharmGKB	PA161660932
Name	
Annotation	The variant is significantly associated with several obesity-related phenotypes.
Gene	FTO
Featue	
Evidence	PubMed ID:18316358
Drugs	
Diseases	Obesity
Curation Level	Curated
PharmGKB	PA164740067
Name	
Annotation	GWAS results: Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations. (Initial Sample Size: 695 obese adults, 685 obese children, 731 lean adults, 685 lean children; Replication Sample Size: 1,171 obese adults, 896 obese children, 1,114 lean adults, 1,297 lean children, 4,417 adults, 5,291 children); (Region: 16q12.2; Reported Gene(s): FTO; Risk Allele: rs1421085-C); (p-value= 1E-28).This variant is associated with Obesity.
Gene	FTO
Featue	
Evidence	PubMed ID:19151714; Web Resource:http://www.genome.gov/gwastudies/
Drugs	
Diseases	Obesity
Curation Level	Non-Curated

[PMID 21248310] Examining Overweight and Obesity as Risk Factors for Common Mental Disorders Using Fat Mass and Obesity-Associated (FTO) Genotype-Instrumented Analysis: The Whitehall II Study, 1985-2004

[PMID 21796137] Association of variations in the FTO, SCG3 and MTMR9 genes with metabolic syndrome in a Japanese population

Categories: Is a snp | In dbSNP | Has genotype | SNPs on chromosome 16 | Has population | Has a neighbor | Uses omim | On chip Affy GenomeWide 6 | On chip Illumina Human 1M | On chip 23andMe v2 | On chip 23andMe v3 | On chip HumanOmni1Quad

The effect of PCSK1 variants on waist, waist-hip ratio and glucose metabolism is modified by sex and glucose tolerance status.

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Source

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Abstract

BACKGROUND:

We aimed to evaluate the effects of the G-allele of rs6232 and the C-allele of rs6235 within PCSK1 on measures of body fat and glucose homeostasis in Danish individuals and to assess interactions of genotypes with age, sex and glucose tolerance status. Data were included in meta-analyses of additional Europeans.

METHODOLOGY/PRINCIPAL FINDINGS:

Rs6232 and rs6235 were genotyped in 6,164 Danes from the Inter99 study of middle-aged people. Results from these analyses were combined with previously published studies in meta-analyses of a total of 27,786 individuals. The impact of the variants was also investigated in a subset of 62 glucose-tolerant men during a meal challenge including measures of serum incretins. In men we found an effect on body composition in sex-stratified analyses where the rs6235 C-allele conferred an increased waist circumference of 0.8 cm per allele (0.2-1.5, p=0.008) and increased waist-to-hip ratio of 0.004 (0.0005-0.008, p=0.027). In the meta-analyses where men and women were combined, the rs6232 G-allele associated with increased waist-to-hip ratio (p=0.02) and the rs6235 C-allele associated with increased waist circumference (p=0.01). Furthermore, the rs6235 C-allele was associated nominally with a 0.6% (0.1-1%, p=0.01) reduction in fasting glucose, it interacted with glucose tolerance status for traits related to glucose metabolism and analysis among individuals having abnormal glucose tolerance revealed a 5% (-0.7-9%, p=0.02) elevated level of acute insulin response for this variant. Finally, we found that the rs6232 G-allele associated with higher levels of GLP-1, GLP-2 and glucagon and that the rs6235 C-allele associated with higher levels of GIP and glucagon during a meal-test.

CONCLUSIONS/SIGNIFICANCE:

PCSK1 rs6232 G-allele and rs6235 C-allele have an effect on body composition which may be modified by sex, whereas the effect of rs6235 C-allele on fasting and stimulated circulating plasma glucose and hormone levels may be influenced by glucose tolerance status.

Common nonsynonymous variants in PCSK1 *confer risk of obesity*

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Abstract

Mutations in *PCSK1* cause monogenic obesity. To assess the contribution of *PCSK1* to polygenic obesity risk, we genotyped tag SNPs in a total of 13,659 individuals of European ancestry from eight independent case-control or family-based cohorts. The nonsynonymous variants rs6232, encoding N221D, and rs6234-rs6235, encoding the Q665E-S690T pair, were consistently associated with obesity in adults and children ($P = 7.27 \times 10^{-8}$ and $P = 2.31 \times 10^{-12}$, respectively). Functional analysis showed a significant impairment of the N221D-mutant PC1/3 protein catalytic activity.

In 1998, it was reported that MC4R mutations were associated with inherited human obesity. They were found in heterozygotes, suggesting an autosomal dominant inheritance pattern. However, based on other research and observations, these mutations seem to have an incomplete penetrance and some degree of codominance. It has a prevalence of 1-2.5% in people with BMIs of greater than 30, making it the most commonly known genetic defect predisposing people to obesity

A mutation (rs1815739; R577X) has been identified in the ACTN3 gene which results in a deficiency of alpha-actinin 3 in a significant proportion of the population.[3] Based on ethnicity the deficiency is found in 20-50% of people. Generally, Africans have the lowest incidence of the mutation whilst Asians have the highest. Scientists believe that variations in this gene evolved to accommodate the energy expenditure requirements of people in various parts of the world.

Studies have linked the fiber twitch type with ACTN3, i.e. fast twitch fiber abundant individuals carry the non-mutant gene version. Also, studies in elite athletes have shown that the ACTN3 gene may influence athletic performance. Whilst the non-mutant version of the gene is associated with sprint performance, the mutant version is associated with endurance.[4][5][6][7][8]

[edit] Interactions

Mitochondrial DNA and ACTN3 genotypes in Finnish elite endurance and sprint athletes.

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Source

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Abstract

Differences in ACTN3 (alpha-actinin 3) genotypes have been reported among endurance and power athletes. Elite athletic performance in endurance sports should also depend on mitochondrial oxidative phosphorylation (OXPHOS) that produces ATP for muscle metabolism. We determined mitochondrial DNA (mtDNA) and ACTN3 genotypes in Finnish elite endurance (n = 52) and sprint (n = 89) athletes, and found that the frequencies of mtDNA haplogroups differed significantly between the two groups. Most notably, none of the endurance athletes belonged to haplogroup K or subhaplogroup J2, both of which have previously been associated with longevity. The frequency of ACTN3 XX genotype was higher and that of RR was lower among Finnish endurance athletes, and, in addition, none of the top Finnish sprinters had the XX genotype. Lack of mtDNA haplogroup K and subhaplogroup J2 among elite endurance athletes suggests that these haplogroups are 'uncoupling genomes'. Such genomes should not be beneficial to endurance-type athletic performance but should be beneficial to longevity, since uncoupling of OXPHOS reduces the production of ATP, reduces the release of reactive oxygen species and generates heat.

Abstract

There is increasing evidence for strong genetic influences on athletic performance and for an evolutionary “trade-off” between performance traits for speed and endurance activities. We have recently demonstrated that the skeletal-muscle actin-binding protein α-actinin-3 is absent in 18% of healthy white individuals because of homozygosity for a common stop-codon polymorphism in the *ACTN3* gene, R577X. α-Actinin-3 is specifically expressed in fast-twitch myofibers responsible for generating force at high velocity. The absence of a disease phenotype secondary to α-actinin-3 deficiency is likely due to compensation by the homologous protein, α-actinin-2. However, the high degree of evolutionary conservation of *ACTN3* suggests function(s) independent of *ACTN2*. Here, we demonstrate highly significant associations between *ACTN3* genotype and athletic performance. Both male and female elite sprint athletes have significantly higher frequencies of the 577R allele than do controls. This suggests that the presence of α-actinin-3 has a beneficial effect on the function of skeletal muscle in generating forceful contractions at high velocity, and provides an

evolutionary advantage because of increased sprint performance. There is also a genotype effect in female sprint and endurance athletes, with higher than expected numbers of 577RX heterozygotes among sprint athletes and lower than expected numbers among endurance athletes. The lack of a similar effect in males suggests that the *ACTN3* genotype affects athletic performance differently in males and females. The differential effects in sprint and endurance athletes suggests that the R577X polymorphism may have been maintained in the human population by balancing natural selection.

Genome-wide association studies (GWAS) have successfully contributed to the detection of genetic variants involved in body-weight regulation. We jointly analysed two GWAS for early-onset extreme obesity in 2,258 individuals of European origin and followed-up the findings in 3,141 individuals. Evidence for association of markers in two new genetic loci was shown (*SDCCAG8* on chromosome 1q43–q44 and between *TNKS/MSRA* on chromosome 8p23.1). We also re-identified variants in or near *FTO*, *MC4R*, and *TMEM18* to be associated with extreme obesity. In addition, we assessed the effect of the markers in 31,182 obese, lean, normal weight, and unselected individuals from population-based samples and showed that the variants near *FTO, MC4R, TMEM18*, and *SDCCAG8* were consistently associated with obesity. For variants of *TNKS/MSRA*, the obesity association was limited to children and adolescents. In summary, we detected two new obesity loci and confirmed that the currently known major common variants related to obesity overlap to a substantial degree between children and adults.

Abstract
Background: TMEM18 is a hypothalamic gene that has recently been linked to obesity and BMI in genome wide association studies. However, the functional properties of TMEM18 are obscure.
Methods: The evolutionary history of TMEM18 was inferred using phylogenetic and bioinformatic methods. The gene's expression profile was investigated with real-time PCR in a panel of rat and mouse tissues and with immunohistochemistry in the mouse brain. Also, gene expression changes were analyzed in three feeding-related mouse models: food deprivation, reward and diet-induced increase in body weight. Finally, we genotyped 502 severely obese and 527 healthy Swedish children for two SNPs near TMEM18 (rs6548238 and rs756131).
Results: TMEM18 was found to be remarkably conserved and present in species that diverged from the human lineage over 1500 million years ago. The TMEM18 gene was widely expressed and detected in the majority of cells in all major brain regions, but was more abundant in neurons than other cell types. We found no significant changes in the hypothalamic and brainstem expression in the feeding-related mouse models. There was a strong association for two SNPs (rs6548238 and rs756131) of the TMEM18 locus with an increased risk for obesity ($p = 0.001$ and $p = 0.002$).
Conclusion: We conclude that TMEM18 is involved in both adult and childhood obesity. It is one of the most conserved human obesity genes and it is found in the majority of all brain sites, including the hypothalamus and the brain stem, but it is not regulated in these regions in classical energy homeostatic models.

Conclusions
In conclusion, we show that common variations nearby the TMEM18 gene are associated not only to adult obesity but also obesity in severely obese children in a similar magnitude as FTO, the first gene associated with the common form of obesity. TMEM18 has a remarkably long evolutionary history that spans at least 1500 MY, longer than most other genes implicated in body weight regulation that we are aware of. The gene is widely distributed in the brain, found in the majority of all cells in the brain with slight, yet significant, enrichment in neurons compared to non-neurons.