Research Advances on the Relationship Between the Fat Mass and Obesity-Associated Gene and Obesity: Postprint

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Abstract

The fat mass and obesity-associated (FTO) gene is a recently identified gene associated with obesity. Genome-wide association studies have revealed numerous single nucleotide polymorphism (SNP) loci within the FTO gene that are strongly associated with the development of obesity. This review summarizes the discovery, structure, and tissue expression characteristics of the FTO gene, the relationship between FTO gene SNPs and obesity, and how the FTO gene influences obesity development by regulating food intake, aiming to provide a reference for investigating the mechanisms of obesity in animals.

Full Text

Research Advances in the Relationship Between the Fat Mass and Obesity-Associated (FTO) Gene and Obesity

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Abstract: The fat mass and obesity-associated (FTO) gene is a recently discovered gene linked to obesity. Genome-wide association studies have identified numerous single nucleotide polymorphism (SNP) sites within the FTO gene that are closely associated with obesity development. This review summarizes

the discovery, structure, and tissue expression characteristics of the FTO gene, examines the relationship between FTO gene SNP sites and obesity, and discusses how the FTO gene influences obesity by regulating food intake, providing a valuable reference for investigating obesity mechanisms in animals.

Keywords: FTO gene; SNP sites; obesity

Introduction

Obesity is a chronic metabolic disease that severely impacts animal health and carcass quality, resulting from the combined effects of genetic and environmental factors. While environmental changes promote obesity development, genetic factors play a crucial role in determining individual susceptibility to obesity. Genetic research has progressed through two distinct phases: the candidate gene approach and genome-wide association studies (GWAS). The candidate gene method selects potential genes based on existing physiological and biochemical knowledge, identifies disease-associated SNPs within these genes, and validates them across different populations. In contrast, GWAS scans the entire human genome to identify sequence variations (SNPs) and screens for disease-associated variants, which are then validated across populations. The first GWAS on human age-related macular degeneration was reported by Klein et al. in 2005, followed by studies on obesity, type 2 diabetes, and other complex diseases. Large-scale GWAS analyses in recent years have advanced obesity research to new heights, with the FTO gene emerging as the first reliable candidate gene associated with obesity in the general population.

1. Discovery of the FTO Gene

In 1994, Van der Hoeven et al. generated a transgenic mouse model with fused toes mutation. Homozygous embryos died mid-gestation with severe craniofacial malformations, central nervous system defects, polydactyly, and growth retardation, while heterozygotes exhibited characteristic forelimb syndactyly and thymic hyperplasia. A 1.6 Mb deletion on chromosome 8 was identified in these mice, which was later found to contain three functionally unknown genes (FTS, FTM, FTO) and three Iroquois family genes (IRX3, IRX5, IRX6). Peters et al. subsequently identified FTO as a novel gene through positional cloning of wild-type mouse genomic sequences. Similar phenotypes were observed in humans, including unequal breast size, skeletal malformations, mental retardation, and obesity. In 2007, Frayling et al. discovered the association between FTO gene SNP sites and obesity, establishing FTO as a fat mass and obesity-associated gene and sparking intense research interest.

2.1. Gene Structure

Genomic studies reveal that the FTO gene exists in vertebrates and several marine algae but is absent in bacteria, fungi, protozoa, invertebrates, and most plants. The FTO sequence shows strong conservation across species, with a

conserved intron-exon distribution pattern among vertebrates. In humans, FTO is located on the long arm of chromosome 16, spanning approximately 400 kb and comprising 9 exons and 8 introns. The RPGRIP1L gene (associated with Meckel diverticulum syndrome) lies approximately 3.4 kb upstream, while the Iroquois gene family (IRX3, IRX5, IRX6) resides downstream. The first intron contains a CUTL1 transcription factor binding site (also known as CDP, Cut, or Cux, a homeobox transcription factor involved in cell growth, differentiation, development, and transcriptional regulation of numerous genes). This binding site includes the obesity-associated SNP rs8050136, along with other SNPs such as rs1121980 and rs17817449 [Figure 1: see original paper].

2.2. Protein Structure

The FTO protein belongs to the Fe^{2+}- and α-ketoglutarate (α-KG)-dependent dioxygenase superfamily, which catalyzes hydroxylation and demethylation of proteins, nucleotides, lipids, and small molecules. This family includes over 80 enzymes such as E. coli alkane hydroxylase (AlkB), mammalian AlkB homologs (ABH), collagen prolyl 3-hydroxylases (C-P3H), and phytanoyl-CoA α-hydroxylase (PAHX). Within this superfamily, FTO shows the greatest similarity to AlkB and ABH. Sequence alignments demonstrate high conservation of FTO across species, with four specific folds associated with demethylase activity showing particularly strong conservation from algae to mammals. Crystallographic studies reveal that human FTO protein consists primarily of N-terminal and C-terminal domains. To date, advanced structural studies of FTO protein have only been conducted in humans, with no reports in other species [Figure 2: see original paper].

3. Tissue Expression of the FTO Gene

Current research on FTO tissue-specific expression remains limited, focusing primarily on humans and pigs, with no reports in fish, amphibians, or other vertebrates.

Frayling et al. used real-time quantitative PCR to examine FTO expression in fetal and adult human tissues. In fetuses, FTO was detected in brain, kidney, liver, and pancreas, with highest expression in brain and lowest in pancreas, while in adults, expression was observed in brain, skeletal muscle, pancreatic islets, kidney, pancreas, adipose tissue, and liver, again with highest expression in brain and lowest in liver. In mice and rats, FTO expression was detected in brain, adipose tissue, muscle, heart, and liver, with brain showing the highest expression levels. In situ hybridization revealed widespread FTO expression in hypothalamic nuclei controlling energy balance, including the arcuate nucleus (ARC), paraventricular nucleus (PVN), dorsomedial nucleus (DMN), and ventromedial nucleus (VMN), suggesting an important role in energy balance regulation.

Madsen et al. examined FTO expression in various pig tissues, finding expres-

sion in 18 tissues including cerebellum, hippocampus, adipose tissue, muscle, and heart. FTO expression in brain was 7–12 times higher than in peripheral tissues, with cerebellar expression significantly exceeding that in hippocampus and cerebral cortex. Fu et al. analyzed FTO expression in five peripheral tissues of Suzhong pigs, revealing highest expression in backfat and heart, moderate expression in lung and liver, and lowest expression in longissimus dorsi muscle, suggesting a relationship between FTO expression and fat deposition in subcutaneous fat, heart, and muscle tissues.

4.1. Correlation with Obesity

The FTO gene contains multiple SNP sites that have been associated with obesity in diverse populations through GWAS analysis, though specific SNPs vary by geographic region. Dina et al. identified SNP rs1121980 in the first intron as significantly associated with obesity in French populations. In a study of 732 Spanish individuals, the AA homozygote frequency for rs9939609 was significantly higher in obese individuals, with AA carriers showing larger waist circumference than AT or TT carriers, indicating that the A allele increases obesity risk in Spanish populations. This positive correlation between the rs9939609 A allele and obesity was confirmed in Australian and Brazilian children, where increased A allele dosage was accompanied by elevated body mass index (BMI). Korean studies demonstrated that rs1421085 C and rs17817449 G alleles increased obesity risk. In Japanese populations, 15 FTO SNPs were associated with obesity among 927 obese and 1,527 non-obese individuals, with rs1558902 showing the strongest association. Quebec studies found that rs17817449 and rs1421085 correlated with obesity phenotypes, particularly rs17817449, which showed significant associations with BMI, body weight, and waist circumference. Grant et al. reported associations between two FTO variants (rs8050136 and rs3751812) and childhood obesity in African and Caucasian children. Collectively, these studies have identified numerous obesity-associated FTO SNPs, including rs1121980, rs9939609, rs1421085, rs17817449, rs1558902, rs8050136, and rs3751812.

4.2. Influencing Obesity Through Regulation of Food Intake

Current evidence indicates that FTO gene SNPs influence obesity primarily by increasing food intake rather than decreasing energy expenditure. Speakman et al. analyzed 150 white Scottish individuals and found no significant correlation between FTO genotype and basal metabolic rate, but a significant association with food intake. Similarly, a study of 380 Germans showed that SNP rs8050136 did not affect energy expenditure but was significantly associated with food intake, suggesting that rs8050136 promotes weight gain through increased consumption rather than altered energy expenditure. Cecil et al. examined 97 Scottish children and found that FTO variants contribute to obesity by regulating food intake rather than energy expenditure. Wardle et al. investigated

the relationship between rs9939609 and eating behaviors in 3,337 children using dietary behavior questionnaires, revealing that AA homozygotes showed significantly reduced satiety responsiveness, indicating that this SNP increases food intake by diminishing satiety signals. Karra et al. confirmed that rs9939609 influences appetite and food intake. These findings collectively demonstrate that FTO gene variants affect obesity by increasing food intake, likely through modulation of appetite peptide expression levels.

4.3. Regulating Food Intake by Influencing Appetite Peptide Expression

The body produces numerous peptides that regulate food intake, including appetite-stimulating neuropeptide Y (NPY), ghrelin, and agouti-related protein (AgRP), as well as appetite-suppressing cholecystokinin (CCK), leptin, and proopiomelanocortin (POMC). Emerging evidence suggests that FTO gene variants influence the expression levels of ghrelin, leptin, and other metabolic regulators to modulate energy metabolism.

4.3.1. Influencing Ghrelin Expression Levels

Ghrelin is a gastric peptide that enhances appetite, promotes food intake, and regulates energy balance. Studies demonstrate that FTO SNPs affect ghrelin expression and consequently modulate feeding behavior. Karra et al. examined plasma ghrelin levels in 359 Europeans at various time points after meals, finding that individuals with the rs9939609 TT genotype showed significantly greater postprandial reductions in ghrelin levels compared to A allele carriers, indicating that the A allele is associated with impaired postprandial ghrelin suppression. Functional MRI revealed enhanced postprandial activity in brain appetite control regions among rs9939609 A carriers, similar to the effects observed following ghrelin injection, suggesting that the A allele reduces post-meal satiety and increases food intake. Conversely, Benedict et al. found that the rs17817499 C allele was positively correlated with plasma ghrelin levels in 985 elderly individuals. These results collectively demonstrate that FTO SNPs correlate with ghrelin expression levels, thereby influencing food intake and energy balance.

4.3.2. Influencing Leptin Expression Levels

Leptin is an adipose tissue-derived hormone that reduces food intake and inhibits adipocyte synthesis to promote weight loss. Some studies report that plasma leptin levels are negatively correlated with FTO SNP dosage and expression. Qi et al. found that the rs9939609 A allele reduced blood leptin levels, while Speakman et al. reported plasma leptin concentrations of 19.49 ng/mL in TT carriers, 17.55 ng/mL in AT carriers, and 13.59 ng/mL in AA carriers, confirming that the A allele reduces plasma leptin content. After 16 hours of fasting, leptin reduction levels were positively correlated with rs17817449 copy number

in 985 elderly individuals, indicating that more FTO gene copies corresponded to greater leptin decreases.

However, conflicting evidence suggests positive correlations between plasma leptin levels and FTO SNP dosage. Do et al. found that rs17817449 was significantly positively associated with blood leptin levels in 908 volunteers, while European adolescent studies also reported higher plasma leptin in rs9939609 A carriers compared to non-carriers. Arrizabalaga et al. similarly confirmed elevated plasma leptin in rs9939609 A carriers. Despite these contradictory findings, all studies demonstrate that FTO SNP dosage influences plasma leptin content and expression, which is intimately linked to energy balance, though the precise relationship remains unclear.

In summary, FTO gene SNPs influence obesity by affecting appetite peptide expression, particularly ghrelin and leptin. However, the feeding regulation mechanism is highly complex, involving numerous factors, and the relationships between FTO and other appetite-regulating factors require further investigation.

Conclusion

The FTO gene is associated with fat metabolism and obesity, being widely distributed across animal tissues with particularly high expression in brain tissue, especially in the appetite-controlling hypothalamus. The gene contains numerous SNP sites, including rs9939609, rs1421085, and rs17817449, which increase food intake by influencing appetite peptide expression and consequently lead to obesity. With rising global obesity rates becoming a major public health concern and excessive fat deposition commonly observed in livestock such as pigs, chickens, and fish—severely affecting carcass quality and product processing—investigating the molecular regulatory mechanisms of FTO in animals can provide reliable theoretical foundations for preventing and treating human obesity while offering scientific support for animal genetic breeding and improvement programs.

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Note: Figure translations are in progress. See original paper for figures.