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Review

Association of FTO gene (rs9939609) with obesity and type-2 diabetes mellitus: Review from current studies

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Abstract

Obesity and type-2 diabetes mellitus (T2DM) have become a common and increasingly growing chronic non-communicable disease worldwide with potentially devastating complications and the FTO gene (rs9939609) are found to be associated with obesity and T2DM in several studies. So, the present review is aimed to investigate the current understanding of the effect of the FTO gene (rs9939609) on obesity and T2DM. PubMed, Medline, Google Scholar, Cochrane library, and several other databases were searched up from 2000 to 2019 to identify and select relevant studies. Research conducted using humans are only considered as eligible. Among the 17 prospective cohort studies, two have found no significant association between the FTO gene and type-2 diabetes (T2D), four studies revealed an association of the FTO gene with obesity and T2D and 11 studies identified a positive association of the FTO gene with obesity. The current study confirmed the significant association of the FTO gene with the risk of obesity and T2DM. Further studies should be conducted to identify the causal variant and the underlying mechanisms of the identified association.

Keywords: FTO gene, obesity, type-2 diabetes mellitus, BMI, lifestyles.

Introduction

Obesity is one of the common non-communicable diseases that results from high energy intake and low energy expenditure, producing an excessive fat depot accumulation in fatty tissue. Evidence from several studies states that human obesity is caused by a multifactorial disorders such as genes and lifestyle factors, including physical activity and diet are important factors (1). A recent genome-wide search for susceptibility genes for type 2 diabetes mellitus (T2DM) revealed a novel gene with an unknown function that contributes significantly to common obesity when Frayling et al. (and the Welcome Trust Case Control Consortium, WTCCC) discovered a cluster of SNPs in the FTO gene that are highly associated with obesity (2).

FTO gene which is involved in the regulation of food intake and energy expenditure is highly expressed in the hypothalamus region of the brain (3). In mice, it was identified as fused toe (Ft) and it was mapped on the chromosome. Animals that are heterozygous showed fused toes on their limbs and thymic hyperplasia, while homozygous mice exhibited a lethal malformation of

the developing brain. Although FTO mRNA was expressed in different human tissues, such as adipose tissue and beta cells, the highest levels of FTO gene expression were found in the brain, specifically in the hypothalamus, pituitary, and adrenal glands (4).

They replicated the associations (rs9939609) with obesity in a total of 38,759 individuals. Strong associations of single-nucleotide polymorphisms (SNPs) (rs1421085 and rs17817449) of the FTO gene with childhood and severe adult obesity are also found (5). Two other genome-wide association studies also independently reported the associations of nearby FTO genetic variants (rs9930506, rs8050136, rs7193144, rs1121980, and rs9939973) with obesity and obesity-related traits in European and Hispanic populations (6). The diabetes associations with both rs9939609 and rs8050136 appeared to be largely mediated through their high associations with BMI (body mass index) (7). There is evidence to suggest ethnic differences for the associations of FTO variants and obesity and/or diabetes, but very few data are available from a well-characterized multiethnic cohort of US populations, especially American minority groups (8, 9).

FTO polymorphisms associated with T2D (type-2 diabetes) or BMI are in tight linkage disequilibrium (HapMap release 23, March 2008), including rs9939609, rs1121980, rs17817449, rs3751812, and rs1421085. Therefore, we investigated the association between the FTO rs9939609 polymorphism and the risk of obesity and T2D as well as clinical and biochemical phenotypes in the French Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) population study (10).

In the multifactorial pathogenesis of T2DM, it is crucial to use an approach to analyze the association of the FTO gene with T2DM, taking into account the influence of the socio-economic status, lifestyle factors, and obesity-related measurements. Therefore, the purpose of the study was to evaluate the association of FTO-rs9939609 polymorphism with T2D and obesity from current studies.

Methods

Search strategy

This review is mainly accumulated the current published data or information. Several databases and search engines including PubMed, Medline, Google Scholar, Cochrane library etc. were searched for literature from 2000 to 2019. Reference lists of the studies that were included in the analysis were also searched as well. For an appropriate searching keyword like FTO gene, rs9939609, obesity, obese, BMI, T2DM, diabetes, blood sugar, etc. were used. Searches were limited to articles published in the English language.

Study selection

Any cross-sectional, case-control, cohort, and experimental study on humans providing sufficient information on the effect FTO gene on obesity and T2DM was considered eligible for review. Articles published before 2000, reviews and not assessing the effect of the FTO gene (rs9939609) on T2D and obesity were excluded.

Results

In the current review, seventeen prospective cohort studies were explored that identified the effect of the FTO gene on obesity and T2DM (Table 1). Among the seventeen prospective cohort studies, two have found no significant association between the FTO gene and T2D, four studies revealed an association of the FTO gene with obesity and T2D and eleven studies identified a positive association of the FTO gene with obesity.

Discussion

In this review, there lies an incongruity in the prospective cohort studies while exploring

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Table 1: Effects of FTO gene on obesity and type-2 diabetes mellitus.

S. No.	Author, year	Origin	Ethnicity	Sample size case (n)/ control (n)	Geno-typing method	Matching criteria	M/F case/ control	Age (Mean±SD) case/ control	Genotype		
									TT	AT	AA
1	Peeters A. et al. 2007 (2)	Belgium	Caucasian	1099/268	TaqMan genotyping	Age			316/94	553/133	230/41
2	Jai Prakash et al. 2015 (3)	India	Asian	309/333	PCR-RFLP	Age-Sex	153/194 156/139	36.8±2.4 35.4±2.2	97/128	138/148	74/57
3	Zabena C. et al. 2009 (4)	Spain	Caucasian	75/180	RT-PCR	Age-Sex	29/45 46/135		19/78	34/81	22/21
4	Binh T. et al. 2012 (11)	Vietnam		98/251	ASP PCR-RFLP	Age-Sex	44/90 54/161	54.3±6.7 53.0±5.8	54/164	38/83	6/4
5	Jacobbson et al. 2008 (12)	Sweden	Caucasian	450/512	TaqMan genotyping	Age-Sex	218/244 232/268	12.6±3.3 17.1±0.8	133/174	206/244	111/92
6	Kikuko Hotta et al. 2008 (13)	Japan	Asian	927/1527	TaqMan genotyping	Age-Sex	419/658 508/842	49.1±14.2 48.2±16.5	51/56	334/443	534/1504
7	Price A. et al. 2008 (14)	USA	Caucasian	583/544	Applied biosystemTaqMan 7300	Age		41.05±9.42 42.63±8.75	152/207	242/257	133/56
8	Muller T. et al. 2008 (15)	Germany	Caucasian	519/178	ARMS-PCR	Age-Sex	249/270 70/108	10.71±3.10 24.58±2.56	140/56	238/86	141/36
9	Chang Yi et al. 2008 (16)	China	Asian	638/1610	FASTSNP	Age-Sex	219/822 419/788	37.0±0.56 61.08±0.33	18/20	167/347	425/1158
10	Song Y. et al. 2008 (17)	WHO	White Black Hispanic Asian	936/935 365/749 139/276 77/163	ABI TaqMan system	Age-Sex	1517/2123		324/358 112/239 75/137 50/114	433/412 161/351 54/108 23/43	179/165 91/159 11/31 4/6
11	Shabana et al. 2015 (18)	Pakistan	Asian	346/285	Tetra-ARMS-PCR	Age-Sex		40.63±15.19 39.78±11.53	183/165	123/106	40/14
12	Magdalena Muc et al. 2015 (19)	Portugal	Caucasian	116/434	TaqMan assay	Age-Sex			40/171	51/204	25/59

S. No.	Author, year	Origin	Ethnicity	Sample size case (n)/control (n)	Geno-typing method	Matching criteria	M/F case/ control	Age (Mean±SD) case/control	Genotype TT	AT	AA
13	Ahmad Al-Serri et al. 2018 (20)	Kuwait	Kuwati	214/674	RT-PCR	Age-Sex	257/417 72/142	45.5±17.6 29.3±15.5	187/71	325/101	162/42
14	Bo Xi et al. 2010 (21)	China	Asian	1229/2274	RT-PCR	Age-Sex	786/995 443/1279	11.8±2.9 12.7±3.1	915/1803	288/436	26/35
15	Patrizia Zavattari et al. 2011 (22)	Italy	Caucasian	912/543	Applied biosystemsTaqMan 7000 system	Age-Sex	426/250 486/293	10.5±3.3 34.2±7.7	197/183	430/254	285/106
16	Min Yang et al. 2014 (23)	China	Asian	1400/2600	TaqMan-based SNP allelic genotyping assay (Applied Biosystems)	Age-Sex	928/1699 420/877	11.0±2.6 17.0±2.3	951/2031	356/519	41/26
17	Camilla H. Andreasen et al. 2008 (24)	Denmark	Caucasian	3856/4861	TaqMan genotyping	Age-Sex	2286/2259 1567/2602		1210/1676	1907/2391	739/794

PCR-RELP, Polymerase Chain Reaction Restriction Fragment Lenth Polymorphism; RT-PCR, Real Time Polymerase Chain Reaction; ARMS-PCR, Amplification Refractory Mutation System-PCR; FASTSNP, Function Analysis and Selection Tool for Single Nucleotide Polymorphism; ABI TaqMan system, Applied Biosystem TaqMan system.

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the relationship of the FTO gene between obesity and diabetes. Several studies found a positive association of increased obesity and T2DM with the FTO gene, but others showed no association with T2DM.

Many genes have been studied to be associated with obesity, which one of the most important of these genes is the FTO gene (25). FTO association with obesity was confirmed through the presence of single nucleotide polymorphisms (SNPs) (26).

Some studies have shown a positive relationship between FTO gene expression levels with BMI (27). However, one study indicated that there is an inverse relationship between obesity and FTO gene expression in visceral adipose tissue in humans (28). It's suggested that the FTO gene has a role in body fat metabolism. Those who carry the FTO obesity-associated risk allele had less lipolysis in adipocytes, indicating a possible role for the FTO gene in the metabolism of adipose tissue (29). In another study that FTO gene expression was suppressed in mice, weight loss, and decreased ratio of white adipose tissue (WAT) to brown adipose tissue (BAT) was reported. This means that FTO may be involved in turning the WAT into BAT. Moreover, energy intake and energy expenditure significantly increased in these mice (30). In general, most studies have shown that FTO gene expression and FTO polymorphism are related to body weight and composition (31).

Childhood obesity is also increasing rapidly worldwide and is a cause of considerable concern (32). To determine the age at which the association of FTO SNP rs9939609 with BMI first becomes evident, we analyzed two large birth cohorts for which suitable measures were available from birth to early adolescence (26).

The National Nutrition Survey of Japan reported that the prevalence of subjects with a BMI of 30 kg/m2 is only 2.3% in men and 3.4% in women aged 20 years and older (33), and the mean BMI was approximately 23 kg/m2 for ages 15–84 years (34). Inconsistency in the results of effects of variations in the FTO gene on BMI between Japanese and Europeans may be due to the relatively small mean and variance of BMI in the former than the latter (13).

Conclusion

Obesity and T2DM is not a disease of affluence now but has become a burden for the whole society of the world. Numerous studies along with the World Health Organization (WHO) have reported the devastating health outcome of T2DM and obesity together with a serious economic crisis.

In the present review, an attempt has been made to provide comprehensive detail of the association of the FTO gene with obesity and T2DM risk. Therefore, to get a better understanding of this area of knowledge, further investigation is necessary to generate uncontroversial evidence.

Conflict of interest:

None.

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