Review Article

The effects of fat mass and obesity-associated gene variants on the body mass index among ethnic groups and in children and adults

Keiko Shinozaki, Masayuki Okuda

Department of Environmental Safety, Graduate School of Science and Engineering, Yamaguchi University, Japan

ABSTRACT

Genome-wide association analyses have revealed common gene variations related to obesity. Variants of the fat mass and obesity-associated (*FTO*) gene among more than 40 genes studied were most closely associated with obesity, but the association varies among ethnicities. Moreover, the effect is significant in people of European descent as well as Asians, but less significant among people of African descent. Although the variants were also associated with type 2 diabetes and glucose homeostasis, the associations were attenuated or abolished after adjusting for adiposity. The present review considers our current understanding of the effects of the *FTO* variants in different ethnic groups and in adults and children.

Key words: Body mass index, child, diabetes, ethnicity, fat mass and obesity-associated gene, glucose homeostasis

Introduction

The prevalence of obesity is increasing worldwide.[1] Obesity is a major cause of common pathologies, such as type 2 diabetes and cardiovascular disease.[2] Recent advances in genomics technology have uncovered candidates for more than 40 genes associated with obesity, including fat mass and obesity-associated (*FTO*), transmembrane protein 18 (TMEM18), MCR, glucosamine-6-phosphate deaminase 2 (GNPDA2), brain-derived neurotrophic factor (BDNF), neuronal growth regulator 1 (NEGR1), SH2B adaptor protein 1 (SH2B1), ets variant gene 5 (ETV5), mitochondrial carrier 2 (MTCH2), and potassium channel tetramerisation domain containing 15 (KCTD15),[3] of which *FTO* is the most closely related to obesity in the general population.[3,4]

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.105576

The Function of Fat Mass and Obesity Associated Gene Variants

We searched PubMed up to August 2012 for studies concerning the association between *FTO* and obesity or glucose homeostasis. Key words "glucose OR insulin OR homeostasis model assessment-insulin resistance (HOMA-IR) OR diabetes," and "adult OR children OR childhood OR puberty", were combined with FTO or other obesity and age-related terms as follows: "FTO" and "body mass index (BMI) OR adiposity"

FTO gene initially reported in 2007 was found to be associated with type 2 diabetes and obesity in human populations.[5,6] Since then, the associations with obesity have been shown by many studies in different ethnic groups. Human *FTO* is the homolog of the mouse fusion toe (*FTO*) gene, which was identified in 1999 before its effect on adiposity of humans was discovered.[7,8] *FTO* comprises 9 exons that span >400 kb on human chromosome 16.[9]

A causal variant in the *FTO* remains to be discovered; however, the highly studied single nucleotide polymorphism (SNP) is the rs9939609 allele, which is positioned in the first

Corresponding Author: Dr. Masayuki Okuda, Department of Environmental Safety, Graduate School of Science and Engineering, Yamaguchi University, 1-1-1 Minami-Kogushi, Ube 755-8505, Japan. E-mail: okuda@yamaguchi-u.ac.jp

intron of the gene, a region of strong sequence conservation across species. The gene encodes a 2-oxalutarate-dependent nucleic acid demethylase as established by amino acid sequence comparisons of *FTO* encoded by (human and mouse genomes;[10,11]); however, the mechanism responsible for its influence on the development of obesity remains to be explained. *FTO* messenger RNA (mRNA), which is widely expressed in many tissues, is the most highly expressed in the brain, in particular, in the hypothalamus–a region that plays a key role in the control of energy homeostasis.[7,8] A recent animal study showed that adipose tissue and lean body mass in Fto-deficient mice are significantly reduced, resulting from an increase in energy expenditure and systemic sympathetic activation despite decreased spontaneous locomotor activity and relative hyperphagia.[12]

Glucose metabolism in Fto-deficient mice remains unaltered with mild improvement in insulin sensitivity because of leanness and increased plasma adiponectin concentrations.[12] Grunnet *et al.*[13] studied Danish twins to determine the levels of expression of *FTO* in the skeletal muscle and its peripheral role in glucose metabolism; however, the heritability of *FTO* expression in adipose tissue and skeletal muscle was not influenced by the *FTO* genotypes. In addition, *FTO* expression in the adipose tissue and skeletal muscle did not affect glucose tolerance or HOMA, IR.

A study in Europe has shown that the levels of expression of *FTO* mRNA in adipose tissues did not differ between genotypes,[14] and an analysis of biopsy specimens from subcutaneous adipose tissue in Scandinavian showed that basal lipolysis was elevated in the homozygous carriers of the wild-type allele compared with that in the carriers of the susceptibility allele.[15]

The Effects of Fat Mass and Obesity Associated Gene Alleles on Adiposity in Adult

Cross-sectional studies of people of European ancestry by Frayling *et al.* resulted in the discovery of the association between *FTO* and body mass index (BMI) [Table 1].[5] This study of seven general populations revealed that BMI values varied by 0.59-0.95 kg/m^2 between two homozygous groups, and the odds ratios of a risk allele were 1.31 (1.23-1.39) for obesity and 1.18 (1.13-1.24) for overweight or obesity. Subsequent studies of general populations uncovered a significant association between the gene and BMI, but the range of the effect sizes is wide in cross-sectional and case-control studies.[6,16-20] Hertel *et al.* analyzed three Norwegian studies and found that the allelic effect was approximately 0.28 kg/m^2.[21] Speliotes *et al.* reviewed and re-analyzed the data for 249,796 individuals of European ancestry acquired in 46 studies. The effect size per allele (rs1558902) for BMI was 0.39 kg/m^2, which explains 0.34% of the variance.[3] The effect size of the susceptible allele in populations of European ancestry is consistent as revealed by meta-analyses.[3,21] However, the

Table 1: Summary of studies on fat mass- and obesity-associated gene polymorphisms in adult populations differing in national origin

Subjects	Number of subjects	Age, years	Gender, male (%)	Difference in BMI, kg/m^2 (minor homozygotes – major homozygotes)	Obesity risk (odds ratio)	Reference number
Caucasians	10,903	55.2±5.7	50	/	1.22	[16]
African Americans	3,382	54.2±5.7	37	/	1.17[a]	[16]
East Asians	obese: 638 control: 1,610	obese: 37.00±0.56 control: 61.08±0.33	34	/	1.43	[27]
East Asians	1,957	/	/	/	1.39	[33]
South Asians	4,411	40s–50s	52	/	1.17 (including overweight)	[30]
Caucasians	14,409	28–74	42–100	0.59–0.95	1.31	[5]
South East Asians	1,886	48.4±6.1	0 (only women)	0.8	1.30 (including overweight)	[29]
Caucasians	1,276	30s–50s	45	0.9	/	[19]
Caucasians	1,471	14–102	/	1.5[b]	/	[6]
Caucasians	1,466	30s	66	2.4[c]	/	[18]
Caucasians	5,722	30s–40s	50	1.1	/	[20]
Caucasians	359	30s–40s	/	3.4[d]	/	[17]
Hispanic Americans	1,268	42.8±14.6	41.2	2.0	/	[39]
Hispanic Americans	824	14–102	/	1.3[e]	/	[6]
East and South Asians	6,700	20s–60s	45.6–48.1	0.10-0.89	/	[31]
East Asians	1,733	35.38	31	0.97[f]	/	[25]
East Asians	1,064	45.5±9.5	60	1.0[g]	/	[28]

Effects of rs9939609 are shown, except when other single nucleotide polymorphisms are indicated, /: not shown, [a]rs1421085, [b]rs9930506, [c]rs8050136, [d]rs17817449, [e]rs9930506, [f]rs1421085 and rs17817449, [g]rs8050136, BMI: Body mass index, SNP: Single nucleotide polymorphism

association between the variant of the gene and BMI are inconsistent in findings for other ethnicities such as Asians and African Americans.

Studies on Asian subjects did not initially support a role for *FTO* in adiposity.[22-24] Two studies examined general populations (3,210 Chinese Han and 1,488 Japanese), and another analyzed the subjects using a case-control design (1,514 Japanese). Subsequent studies on East and South Asian populations revealed a significant association between the variants in *FTO* intron 1 and BMI.[25-31] More recent meta-analyses of people of Asian descent are available.[32-34] Xi *et al.* reported that a minor allele is significantly associated with obesity with odds ratios ranging from 1.25 to 1.28,[32] and Liu *et al.* reported odds ratios ranging from 1.39 to 1.45.[33] Li *et al.* reanalyzed the combined data (71,273 individuals) from 24 East to South Asian populations and concluded that the allelic odds ratios were 1.25 (1.19-1.31) for obesity (BMI ≥28 kg/m^2) and 1.13 for overweight (BMI ≥24 kg/m^2).[35]

The results of Asian studies were comparable with those acquired from studies of people of European descent with the following two exceptions which are as follows:[1] the definition of obesity (a lower BMI cutoff point for Asians)[36] and[2] reduced minor allelic frequency (0.12-0.23).[35] For individuals of African ancestry, four studies failed to detect an association between the variants and BMI[6,16,37,38] (whereas positive associations were established in three studies.[39-41] Although a meta-analysis reported that the minor allele frequency in the individuals of African ancestry was similar to that of Caucasians (>0.4), the linkage disequilibrium pattern differed between Africans and others.[34] These findings of the difference between Europeans and African Americans might reflect the difference in the phenotype of adiposity. Moreover, factors such as dietary habits and physical activity might also mediate these effects. In Oceanians, there are few reports about the association between *FTO* gene polymorphisms and adiposity; however, the variant (rs9939609 and other 1188 SNPs) is not significantly associated with this phenotype.[42,43]

The studies described above provide evidence that common variants of *FTO* are associated with obesity in most ethnic populations worldwide, but the effect of the variant of *FTO* on adiposity in adult varies.[34]

The Effects of Fat Mass and Obesity-Associated Gene Alleles on Glucose Homeostasis in Adults

Numerous studies have been conducted to detect common allelic variants responsible for obesity and to identify candidate genes for type 2 diabetes. Large population studies as well as meta-analyses of Europeans and Asians reveal that the variants related to obesity are also associated with type 2 diabetes, although the effect diminished after adjusting for BMI.[3,5,33,35] There are some studies showing that fasting glucose or insulin levels are significantly higher[17,39,44,45] or lower[18] among individuals possessing the risk alleles than for those who do not. However, the effect of *FTO* on glucose homeostasis in these reports is not evident after correction for BMI.

Studies on Danish people have reported that, although the levels of fasting glucose and insulin were not different among the genotypes of rs9939609, dynamic indices of insulin sensitivity decreased and the indices of β-cell function increased among the homozygous carriers of the minor A-allele of rs9939609.[20,46] The sample size of these studies is relatively small[20,46] when compared with those of others.[5] A 12-year longitudinal study on the general population of Hong Kong found that persistent metabolic syndrome was associated with a combination of three SNPs (*FTO*, *GNPDA2,* and *MC4R*), but the effect is abolished on adjustment for BMI or the level of fasting insulin, suggesting that the effect is likely to be mediated through adiposity.[47] The association of *FTO* variants with the response and sensitivity to insulin did not reach a significant level in Europeans.[19]

The association with type 2 diabetes in large studies was attenuated with the adjustment for BMI, which was a surrogate marker for adiposity, such as visceral fat, and was influenced by height, bone mass, and lean mass. Variants of *FTO* were considered to be associated with the development of diabetes mediated by obesity.[48]

The Effects of Fat Mass and Obesity Associated Gene Alleles on Adiposity in Children

The minor allele of *FTO* has an impact on the body composition and the risk for development of overweight and obesity in childhood as well as through adolescence. Cross-sectional and case-control studies on European children and adolescents determined that the odds ratios were between 1.20 and 2.14 [Table 2].[5] The association of *FTO* variants with BMI has been shown by other studies on people of European ancestry.[49,50]

The association with BMI or obesity was found to be significant in Asian populations. In Chinese aged 8-18 years, the odds ratios of carriers of the minor allele were determined to range from 1.29 to 1.79 for obesity

Table 2: Summary of studies of fat mass- and obesity-associated gene polymorphisms in children and adolescents

Subjects	Number of subjects	Age, years	Gender, male (%)	Difference in BMI, kg/m² (minor homozygotes – major homozygotes)	Obesity risk (odds ratio)	Reference number
Caucasians	3,940–5,258	7–14	47–49	/	1.20 at 7 years 1.24 at 8 years 1.39 at 9 years 1.36 at 10 years 1.35 at 11 years 2.14 at 14 years	[5]
Caucasians	381	7	100 (only men)	/	1.26	[61]
Caucasians	519	10.71±3.10	48	/	1.54	[49]
Caucasians	Obese: 418 Control: 2,270	2–18	/	/	1.266[a], 1.267[b]	[54]
Caucasians	Obese: 199 Control: 634	14.01±3.24	54	/	1.97	[50]
African Americans	Obese: 578 Control: 1,424	2–18	/	/	1.313[c]	[54]
East Asians	Overweight: 133 Control: 133	10–13	46.6, 60.2	/	2.22[d] 2.20[e]	[53]
Caucasians	658	3–17	47	1.52	/	[56]
Caucasians	640: 7 months, 196: 5–15 years	7 month–15	/	1.0 at 15 years	1.67 at 7-15 years	[58]
East Asians	3,503	6–18	50	1.3	1.29	[52]
East Asians	670	8–11	50	0.9[f]	1.79	[51]
Caucasians	Obese: 450 Control: 512	obese: 12.6±3.3 healthy: 17.1±0.8	48	1.6 (all subjects) 1.6 (all obese)	/	[60]
Caucasians	225	0–2 weeks	48	0.2 kg (body weight) at 2 weeks	/	[57]
Caucasians	2,466	2–53	50	0.5 at 11 years 0.7 at 15 year	/	[62]

Effects of rs9939609 are shown, except when other single nucleotide polymorphisms are indicated, /: not shown, [a]rs8050136, [b]rs3751812, [c]rs3751812, [d]rs3751812, [e]rs1558902, [f]Difference in BMI, kg/m² (minor homozygotes – major homozygotes/hetero type), BMI: Body mass index, SNP: Single nucleotide polymorphism

and overweight and obesity after adjustment for age and gender.[51,52] A study on the children living in Shanghai, China, revealed a strong association with BMI in school children; the percentages of the explained variance were 0.54% for all subjects and 1.94% for girls.[4] A nested case-control study conducted in Japan also determined that the odds ratio per allele was 2.2; cases were overweight or obese.[53] However, one report among African American showed a significant association with obesity (one out of 13 SNPs),[54] but the other did not show a significant association among people of African ancestry.[54,55]

We noted an interesting difference in BMI among the *FTO* genotypes. Thus, the timing of the appearance of the effect of *FTO* on BMI in childhood was different in the reported studies. The variant in *FTO* did not influence the birth weight of Fins[5] or European Americans.[56] The birth weight was not different among the genotypes in a Spanish study, but the statistical differences in weight and the change of weight were evident at the age of 2 weeks (the difference was 0.2 kg).[57] Most studies have shown that the effect of the gene variant appears between 3 and 7 years.[58,59] A German birth cohort followed from birth to the age of 6 years revealed that the association between the *FTO* genotype and BMI evolved gradually, became descriptively detectable from the age of 3 years, and became significant from the age of 4 years after adjusting for gender and maternal smoking during pregnancy.[59] A Finish cohort followed from the age of 7 months to 15 years did not show a difference between carriers of minor A-allele of rs9939609 (AT and AA genotypes) and non-carriers (TT genotype) until the age of 6 years, but the effect of the gene variant appeared at 7 years and older.[58] A gender difference was seen in Swedish children.[60]

It is possible that the effect of the minor *FTO* allele on BMI possibly appears by 7 years; however, the significance of gender differences during childhood is unclear at present because supporting evidence is limited.[59]

There are few studies, to our knowledge, about the effect of the *FTO* variant (rs9939609) in adolescence that might link its effects between children and adults.

For example, the odds ratio for obesity was 2.14 in Finnish children, which was lower than that in Finnish adults aged 31 years.[5] The difference in the effects of the gene variant between children and adults indicates the change in the effects with age. Non-Hispanic white children possessing the homozygous minor allele gained more weight than other genotypes (rs9939609) from the age of 8 to 17 years.[55]

A 50-year-longitudinal study among Danish found that homozygotes of the minor allele were associated with weight gain from birth to the age of 7 years but not with further weight gain during childhood and adolescence.[61] After the age of 20 years, weight gain was apparent in the homozygotes. In a British longitudinal study of subjects followed for >50 years, the minor allele was positively associated with BMI from ages 13 to 36 years.[62] The association between the gene variant and the BMI standard deviation score strengthened between 2 and 20 years and reached a peak at 20 years of age. Thereafter, the association with BMI weakened from 2 to 53 years of age. A similar pattern was observed for weight, but not for height. The results of these longitudinal studies show weight gain due to the presence of the gene variant from childhood through adolescence in individuals of European ancestry.

To our knowledge, there are few studies concerning the longitudinal effects of the gene variant for other ethnicities. Ethnic differences in adiposity is already present in adolescents of Asian ancestry; thus, the trunk fat/peripheral fat ratio is higher in Asians than for other ethnicities.[63] In Japanese children aged 10-11 to 13-14 years, the association between the genotype and the change of BMI during 3 years was not significant; however, the sample size of this study was small.[53] Wang *et al.* suggested that the variant might exert greater influence during puberty.[4]

Asians are at an elevated risk for diabetes and cardiovascular disease at lower BMI,[64-66] and lower cutoff values for BMI were used in this study to assess adult obesity.[36] The pattern of BMI or weight change through adolescence due to the effect of the *FTO* variant in individuals of Asian ancestry might differ from that in Europeans. A larger longitudinal study is required to definitively elucidate the pattern in Asian and other populations.

The Effect of Fat Mass and Obesity-Associated on Glucose Homeostasis During Childhood

Only a limited number of reports describe the association between fasting glucose and intron 1 of *FTO*. Only small sample sizes were analyzed, and the subjects of several studies were obese, potentially biasing the outcomes.

A Dutch study showed that the minor allele was associated with fasting glucose levels and overweight.[67] After adjustment for age, pubertal stage, and adiposity, the association did not change and remained significant (coefficients of glucose z score per allele were 0.10 before and after adjustment for BMI, percentage body fat, and waist circumference).

The association with glucose homeostasis was inconsistent between genders in two studies involving obese subjects. Obese Swedish patients with the homozygous minor allele exhibited significantly higher glucose levels than those with the homozygous major allele (difference between homozygotes was 0.2 mmol/L), with adjustment for age and BMI. When stratified for gender, the effect of the variant was significant in obese girls but not in obese boys.[60] In contrast, insulin sensitivity differed among the genotypes, and this association was evident only in boys.

In Chilean children aged 6-11 years, fasting insulin levels and a HOMA as an index of IR were significantly higher in obese girl carriers of the minor allele compared with non-carriers. Further adjustment for BMI and age did not alter the result, but the level of significance was reduced.[68] In contrast, the association was not observed among normal weight girls or the normal weight or obese boys.

Other studies do not show significant associations between the *FTO* variant and the levels of plasma or serum glucose. In overweight and obese German and Italian children, a fasting glucose level was not associated with the gene variant.[49,69] Studies of Chinese and Japanese, in which the subjects were between 6 and 18 years of age, did not detect an association with plasma glucose levels[51-53] or an association with fasting insulin levels and insulin resistance.[51]

Although a significant association with glucose homeostasis was observed in children, the effect size was small. A Swedish study discovered another candidate variant (c. 896 + 233A > G) in intron 4 of *FTO*, which is not in linkage disequilibrium with the variants in intron 1.[70] Obese individuals carrying the homozygous minor allele exhibited an approximately 30% increase in fasting serum insulin levels and degree of insulin resistance. The associations remained significant after correction for BMI, but the result was not replicated in other populations.

Conclusion

Among common allelic variants that are candidate etiological factors for obesity and diabetes, those present in intron 1 of *FTO* are most relevant to obesity, but the effect size is small and the variance of BMI is explained at a maximum of 0.5%.[3,4,71] The outcome of our present review leads us to conclude that the effect of *FTO* gene on adiposity is significant in people of European descent as well as Asians but less significant among those of African

descent. However, in Asian children, the association is either the same as in European children or stronger.

The association between *FTO* polymorphism and glucose homeostasis has not been established for adults and children**.** However, numerous studies have concluded that *FTO* polymorphism influences glucose homeostasis in obese adults. In children, some studies showed that a minor allele was associated with the level of glucose and insulin and insulin sensitivity. In contrast to adults, a correlation in children is revealed after adjustment for adiposity. The direct effect of the *FTO* genotype on the levels of insulin and glucose might possibly be detected from childhood. However, these traits could be abolished depending on diverse environmental factors that vary from childhood to adulthood.

We believe that the interactions between genotype and the environment must be explained, because health-related behavior such as physical activity, diet, and sleep are known to modify the effect of the *FTO* variant.[20,52,72-76] Moreover, ethnic variations in the effect of the gene variant are evident; therefore, longitudinal studies from childhood to adulthood by using large populations of subjects are required to better understand the influence of *FTO*.

References

1. World Health Organization. World Health Organization Fact Sheet: obesity and Overweight. Geneva: WHO; 2006. Available from: http://www.who.int/mediacentre/factsheets/fs311/en/index.html. [Last accessed on 2012 Oct 18].
2. World Health Organization. Obesity: Preventing and managing the global epidemic. Report of a WHO Consultation. Geneva: WHO; 2000.
3. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, *et al*. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet 2010;42:937-48.
4. Wang J, Mei H, Chen W, Jiang Y, Sun W, Li F, *et al*. Study of eight GWAS-identified common variants for association with obesity-related indices in Chinese children at puberty. Int J Obes (Lond) 2012;36:542-7.
5. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, *et al*. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 2007;316:889-94.
6. Scuteri A, Sanna S, Chen WM, Uda M, Albai G, Strait J, *et al*. Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. PLoS Genet 2007;3:e115.
7. Fischer J, Emmerling C, Ruther U. On the history of Fto. Obes Facts 2008;1:43-4.
8. Peters T, Ausmeier K, Rüther U. Cloning of Fatso (Fto), a novel gene deleted by the Fused toes (Ft) mouse mutation. Mamm Genome 1999;10:983-6.
9. Boissel S, Reish O, Proulx K, Kawagoe-Takaki H, Sedgwick B, Yeo GS, *et al*. Loss-of-function mutation in the dioxygenase-encoding FTO gene causes severe growth retardation and multiple malformations. Am J Hum Genet 2009;85:106-11.
10. Gerken T, Girard CA, Tung YC, Webby CJ, Saudek V, Hewitson KS, *et al*. The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. Science 2007;318:1469-72.
11. Fredriksson R, Hägglund M, Olszewski PK, Stephansson O, Jacobsson JA, Olszewska AM, *et al*. The obesity gene, FTO, is of ancient origin, up-regulated during food deprivation and expressed in neurons of feeding-related nuclei of the brain. Endocrinology 2008;149:2062-71.
12. Fischer J, Koch L, Emmerling C, Vierkotten J, Peters T, Brüning JC, *et al*. Inactivation of the Fto gene protects from obesity. Nature 2009;458:894-8.
13. Grunnet LG, Nilsson E, Ling C, Hansen T, Pedersen O, Groop L, *et al*. Regulation and function of FTO mRNA expression in human skeletal muscle and subcutaneous adipose tissue. Diabetes 2009;58:2402-8.
14. Klöting N, Schleinitz D, Ruschke K, Berndt J, Fasshauer M, Tönjes A, *et al*. Inverse relationship between obesity and FTO gene expression in visceral adipose tissue in humans. Diabetologia 2008;51: 641-7.
15. Wåhlén K, Sjölin E, Hoffstedt J. The common rs9939609 gene variant of the fat mass- and obesity-associated gene FTO is related to fat cell lipolysis. J Lipid Res 2008;49:607-11.
16. Bressler J, Kao WH, Pankow JS, Boerwinkle E. Risk of type 2 diabetes and obesity is differentially associated with variation in FTO in whites and African-Americans in the ARIC study. PLoS One 2010;5:e10521.
17. Do R, Bailey SD, Desbiens K, Belisle A, Montpetit A, Bouchard C, *et al*. Genetic variants of FTO influence adiposity, insulin sensitivity, leptin levels, and resting metabolic rate in the Quebec Family Study. Diabetes 2008;57:1147-50.
18. Haupt A, Thamer C, Machann J, Kirchhoff K, Stefan N, Tschritter O, *et al*. Impact of variation in the FTO gene on whole body fat distribution, ectopic fat, and weight loss. Obesity 2008;16:1969-72.
19. Pascoe L, Tura A, Patel SK, Ibrahim IM, Ferrannini E, Zeggini E, *et al*. Common variants of the novel type 2 diabetes genes CDKAL1 and HHEX/IDE are associated with decreased pancreatic beta-cell function. Diabetes 2007;56:3101-4.
20. Andreasen CH, Stender-Petersen KL, Mogensen MS, Torekov SS, Wegner L, Andersen G, *et al*. Low physical activity accentuates the effect of the FTO rs9939609 polymorphism on body fat accumulation. Diabetes 2008;57:95-101.
21. Hertel JK, Johansson S, Sonestedt E, Jonsson A, Lie RT, Platou CG, *et al*. FTO, type 2 diabetes, and weight gain throughout adult life: A meta-analysis of 41,504 subjects from the Scandinavian HUNT, MDC, and MPP studies. Diabetes 2011;60:1637-44.
22. Horikoshi M, Hara K, Ito C, Shojima N, Nagai R, Ueki K, *et al*. Variations in the HHEX gene are associated with increased risk of type 2 diabetes in the Japanese population. Diabetologia 2007;50:2461-6.
23. Li H, Wu Y, Loos RJ, Hu FB, Liu Y, Wang J, *et al*. Variants in the fat mass- and obesity-associated (FTO) gene are not associated with obesity in a Chinese Han population. Diabetes 2008;57:264-8.
24. Shimaoka I, Kamide K, Ohishi M, Katsuya T, Akasaka H, Saitoh S, *et al*. Association of gene polymorphism of the fat-mass and obesity-associated gene with insulin resistance in Japanese. Hypertens Res 2010;33:214-8.
25. Cha SW, Choi SM, Kim KS, Park BL, Kim JR, Kim JY, *et al*. Replication of genetic effects of FTO polymorphisms on BMI in a Korean population. Obesity 2008;16:2187-9.
26. Ng MC, Park KS, Oh B, Tam CH, Cho YM, Shin HD, *et al*. Implication of genetic variants near TCF7 L2, SLC30A8, HHEX, CDKAL1,

CDKN2A/B, IGF2BP2, and FTO in type 2 diabetes and obesity in 6,719 Asians. Diabetes 2008;57:2226-33.
27. Chang YC, Liu PH, Lee WJ, Chang TJ, Jiang YD, Li HY, *et al*. Common variation in the fat mass and obesity-associated (FTO) gene confers risk of obesity and modulates BMI in the Chinese population. Diabetes 2008;57:2245-52.
28. Omori S, Tanaka Y, Takahashi A, Hirose H, Kashiwagi A, Kaku K, *et al*. Association of CDKAL1, IGF2BP2, CDKN2A/B, HHEX, SLC30A8, and KCNJ11 with susceptibility to type 2 diabetes in a Japanese population. Diabetes 2008;57:791-5.
29. Marvelle AF, Lange LA, Qin L, Adair LS, Mohlke KL. Association of FTO with obesity-related traits in the Cebu Longitudinal Health and Nutrition Survey (CLHNS) Cohort. Diabetes 2008;57: 1987-91.
30. Rees SD, Islam M, Hydrie MZ, Chaudhary B, Bellary S, Hashmi S, *et al*. An FTO variant is associated with Type 2 diabetes in South Asian populations after accounting for body mass index and waist circumference. Diabet Med 2011;28:673-80.
31. Tan JT, Dorajoo R, Seielstad M, Sim XL, Ong RT, Chia KS, *et al*. FTO variants are associated with obesity in the Chinese and Malay populations in Singapore. Diabetes 2008;57:2851-7.
32. Xi B, Mi J. FTO polymorphisms are associated with obesity but not with diabetes in East Asian population: A meta-analysis. Biomed Environ Sci 2009;22:449-57.
33. Liu Y, Liu Z, Song Y, Zhou D, Zhang D, Zhao T, *et al*. Meta-analysis added power to identify variants in FTO associated with type 2 diabetes and obesity in the Asian population. Obesity 2010;18:1619-24.
34. Peng S, Zhu Y, Xu F, Ren X, Li X, Lai M. FTO gene polymorphisms and obesity risk: A meta-analysis. BMC Med 2011;9:71.
35. Li H, Kilpeläinen TO, Liu C, Zhu J, Liu Y, Hu C, *et al*. Association of genetic variation in FTO with risk of obesity and type 2 diabetes with data from 96,551 East and South Asians. Diabetologia 2012;55:981-95.
36. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157-63.
37. Hennig BJ, Fulford AJ, Sirugo G, Rayco-Solon P, Hattersley AT, Frayling TM, *et al*. FTO gene variation and measures of body mass in an African population. BMC Med Genet 2009;10:21.
38. Song Y, You NC, Hsu YH, Howard BV, Langer RD, Manson JE, *et al*. FTO polymorphisms are associated with obesity but not diabetes risk in postmenopausal women. Obesity 2008;16:2472-80.
39. Wing MR, Ziegler J, Langefeld CD, Ng MC, Haffner SM, Norris JM, *et al*. Analysis of FTO gene variants with measures of obesity and glucose homeostasis in the IRAS Family Study. Hum Genet 2009;125:615-26.
40. Hassanein MT, Lyon HN, Nguyen TT, Akylbekova EL, Waters K, Lettre G, *et al*. Fine mapping of the association with obesity at the FTO locus in African-derived populations. Hum Mol Genet 2010;19:2907-16.
41. Adeyemo A, Chen G, Zhou J, Shriner D, Doumatey A, Huang H, *et al*. FTO genetic variation and association with obesity in West Africans and African Americans. Diabetes 2010;59:1549-54.
42. Ohashi J, Naka I, Kimura R, Natsuhara K, Yamauchi T, Furusawa T, *et al*. FTO polymorphisms in oceanic populations. J Hum Genet 2007;52:1031-5.
43. Karns R, Viali S, Tuitele J, Sun G, Cheng H, Weeks DE, *et al*. Common variants in FTO are not significantly associated with obesity-related phenotypes among Samoans of Polynesia. Ann Hum Genet 2012;76:17-24.
44. Freathy RM, Timpson NJ, Lawlor DA, Pouta A, Ben-Shlomo Y, Ruokonen A, *et al*. Common variation in the FTO gene alters diabetes-related metabolic traits to the extent expected given its effect on BMI. Diabetes 2008;57:1419-26.
45. Karasawa S, Daimon M, Sasaki S, Toriyama S, Oizumi T, Susa S, *et al*. Association of the common fat mass and obesity associated (FTO) gene polymorphism with obesity in a Japanese population. Endocr J 2010;57:293-301.
46. Kring SI, Holst C, Zimmermann E, Jess T, Berentzen T, Toubro S, *et al*. FTO gene associated fatness in relation to body fat distribution and metabolic traits throughout a broad range of fatness. PLoS One 2008;3:e2958.
47. Cheung CY, Tso AW, Cheung BM, Xu A, Ong KL, Law LS, *et al*. Genetic variants associated with persistent central obesity and the metabolic syndrome in a 12-year longitudinal study. Eur J Endocrinol 2011;164:381-8.
48. McCarthy MI. Genomics, type 2 diabetes, and obesity. N Engl J Med 2010;363:2339-50.
49. Müller TD, Hinney A, Scherag A, Nguyen TT, Schreiner F, Schäfer H, *et al*. Fat mass and obesity associated gene (FTO): No significant association of variant rs9939609 with weight loss in a lifestyle intervention and lipid metabolism markers in German obese children and adolescents. BMC Med Genet 2008;9:85.
50. Luczynski W, Zalewski G, Bossowski A. The association of the FTO rs9939609 polymorphism with obesity and metabolic risk factors for cardiovascular diseases in Polish children. J Physiol Pharmacol 2012;63:241-8.
51. Fang H, Li Y, Du S, Hu X, Zhang Q, Liu A, *et al*. Variant rs9939609 in the FTO gene is associated with body mass index among Chinese children. BMC Med Genet 2010;11:136.
52. Xi B, Shen Y, Zhang M, Liu X, Zhao X, Wu L, *et al*. The common rs9939609 variant of the fat mass and obesity-associated gene is associated with obesity risk in children and adolescents of Beijing, China. BMC Med Genet 2010;11:107.
53. Okuda M, Hinoda Y, Okayama N, Suehiro Y, Shirabe K, Sasaki S, *et al*. Association between the FTO gene and overweight in Japanese children and adolescents. Pediatr Diabetes 2011;12:494-500.
54. Grant SF, Li M, Bradfield JP, Kim CE, Annaiah K, Santa E, *et al*. Association analysis of the FTO gene with obesity in children of Caucasian and African ancestry reveals a common tagging SNP. PLoS One 2008;3:e1746.
55. Hallman DM, Friedel VC, Eissa MA, Boerwinkle E, Huber JC Jr, Harrist RB, *et al*. The association of variants in the FTO gene with longitudinal body mass index profiles in non-Hispanic white children and adolescents. Int J Obes (Lond) 2012;36:61-8.
56. Mei H, Chen W, Srinivasan SR, Jiang F, Schork N, Murray S, *et al*. FTO influences on longitudinal BMI over childhood and adulthood and modulation on relationship between birth weight and longitudinal BMI. Hum Genet 2010;128:589-96.
57. López-Bermejo A, Petry CJ, Díaz M, Sebastiani G, de Zegher F, Dunger DB, *et al*. The association between the FTO gene and fat mass in humans develops by the postnatal age of two weeks. J Clin Endocrinol Metab 2008;93:1501-5.
58. Hakanen M, Raitakari OT, Lehtimäki T, Peltonen N, Pahkala K, Sillanmäki L, *et al*. FTO genotype is associated with body mass index after the age of seven years but not with energy intake or leisure-time physical activity. J Clin Endocrinol Metab 2009;94:1281-7.
59. Rzehak P, Scherag A, Grallert H, Sausenthaler S, Koletzko S, Bauer CP, *et al*. Associations between BMI and the FTO gene are age dependent: Results from the GINI and LISA birth cohort studies up to age 6 years. Obes Facts 2010;3:173-80.

60. Jacobsson JA, Danielsson P, Svensson V, Klovins J, Gyllensten U, Marcus C, *et al*. Major gender difference in association of FTO gene variant among severely obese children with obesity and obesity related phenotypes. Biochem Biophys Res Commun 2008;368:476-82.
61. Jess T, Zimmermann E, Kring SI, Berentzen T, Holst C, Toubro S, *et al*. Impact on weight dynamics and general growth of the common FTO rs9939609: A longitudinal Danish cohort study. Int J Obes (Lond) 2008;32:1388-94.
62. Hardy R, Wills AK, Wong A, Elks CE, Wareham NJ, Loos RJ, *et al*. Life course variations in the associations between FTO and MC4R gene variants and body size. Hum Mol Genet 2010;19:545-52.
63. Morimoto Y, Maskarinec G, Conroy SM, Lim U, Shepherd J, Novotny R. Asian ethnicity is associated with a higher trunk/peripheral fat ratio in women and adolescent girls. J Epidemiol 2012;22: 130-5.
64. Huxley R, James WP, Barzi F, Patel JV, Lear SA, Suriyawongpaisal P, *et al*. Ethnic comparisons of the cross-sectional relationships between measures of body size with diabetes and hypertension. Obes Rev 2008;9:53-61.
65. Stommel M, Schoenborn CA. Variations in BMI and prevalence of health risks in diverse racial and ethnic populations. Obesity 2010;18:1821-6.
66. Maskarinec G, Grandinetti A, Matsuura G, Sharma S, Mau M, Henderson BE, *et al*. Diabetes prevalence and body mass index differ by ethnicity: The Multiethnic Cohort. Ethn Dis 2009;19:49-55.
67. Liem ET, Vonk JM, Sauer PJ, van der Steege G, Oosterom E, Stolk RP, *et al*. Influence of common variants near INSIG2, in FTO, and near MC4R genes on overweight and the metabolic profile in adolescence: The TRAILS (TRacking Adolescents' Individual Lives Survey) Study. Am J Clin Nutr 2010;91:321-8.
68. Riffo B, Asenjo S, Sáez K, Aguayo C, Muñoz I, Bustos P, *et al*. FTO gene is related to obesity in Chilean Amerindian children and impairs HOMA-IR in prepubertal girls. Pediatr Diabetes 2012.
69. Zavattari P, Loche A, Pilia S, Ibba A, Moi L, Guzzetti C, *et al*. rs9939609 in the FTO gene is associated with obesity but not with several biochemical parameters in Sardinian obese children. Ann Hum Genet 2011;75:648-54.
70. Jacobsson JA, Klovins J, Kapa I, Danielsson P, Svensson V, Ridderstråle M, *et al*. Novel genetic variant in FTO influences insulin levels and insulin resistance in severely obese children and adolescents. Int J Obes (Lond) 2008;32:1730-5.
71. Dorajoo R, Blakemore AI, Sim X, Ong RT, Ng DP, Seielstad M, *et al*. Replication of 13 obesity loci among Singaporean Chinese, Malay and Asian-Indian populations. Int J Obes (Lond) 2012;36: 159-63.
72. Cecil JE, Tavendale R, Watt P, Hetherington MM, Palmer CN. An obesity-associated FTO gene variant and increased energy intake in children. N Engl J Med 2008;359:2558-66.
73. Tanofsky-Kraff M, Han JC, Anandalingam K, Shomaker LB, Columbo KM, Wolkoff LE, *et al*. The FTO gene rs9939609 obesity-risk allele and loss of control over eating. Am J Clin Nutr 2009;90:1483-8.
74. Prats-Puig A, Grau-Cabrera P, Riera-Pérez E, Cortés-Marina R, Fortea E, Soriano-Rodríguez P, *et al*. Variations in the obesity genes FTO, TMEM18 and NRXN3 influence the vulnerability of children to weight gain induced by short sleep duration. Int J Obes (Lond) 2012. [In Press].
75. Lear SA, Deng WQ, Paré G, Sulistyoningrum DC, Loos RJ, Devlin A. Associations of the FTO rs9939609 variant with discrete body fat depots and dietary intake in a multi-ethnic cohort. Genet Res (Camb) 2011;93:419-26.
76. Timpson NJ, Emmett PM, Frayling TM, Rogers I, Hattersley AT, McCarthy MI, *et al*. The fat mass-and obesity-associated locus and dietary intake in children. Am J Clin Nutr 2008;88:971-8.

Cite this article as: Shinozaki K, Okuda M. The effects of fat mass and obesity-associated gene variants on the body mass index among ethnic groups and in children and adults. Indian J Endocr Metab 2012;16:588-95.

Source of Support: Nil, **Conflict of Interest:** None declared