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. Obesity is a major cause of common pathologies, such as type 2 diabetes and cardiovascular disease. 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), of which FTO is the most closely related to obesity in the general population.

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. 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. FTO comprises 9 exons that span >400 kb on human chromosome 16.

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
The 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); 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.

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.

Glucose metabolism in Fto-deficient mice remains unaltered with mild improvement in insulin sensitivity because of leanness and increased plasma adiponectin concentrations. Grunnet et al. 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, 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.

**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]. This study of seven general populations revealed that BMI values varied by 0.59-0.95 kg/m² 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. Hertel et al. analyzed three Norwegian studies and found that the allelic effect was approximately 0.28 kg/m². 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/m², which explains 0.34% of the variance. The effect size of the susceptible allele in populations of European ancestry is consistent as revealed by meta-analyses. However, the

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**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/m² (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*                    | [16]             |
| East Asians               | 1,957              | /          | /                | /                                                              | 1.39                     | [33]             |
| East Asians              obese: 638 control: 1,610 | /          | 34               | /                                                              | 1.17 (including overweight) | [30]             |
| South Asians             obese: 37.0±0.56 control: 61.0±0.33 | /          | /                | /                                                              | /                        | [27]             |
| Caucasians                | 14,409             | 28–74      | 42–100           | 0.59–0.95                                                      | 1.31                     | [5]              |
| South East Asians        0 (only women) | 1,886              | 48.4±6.1   | /                | 0.8                                                            | 1.30 (including overweight) | [29]             |
| Caucasians                | 1,276              | 30s–50s    | 45               | 0.9                                                            | /                        | [19]             |
| Caucasians                | 1,471              | 14–102     | /                | 1.5*                                                          | /                        | [6]              |
| Caucasians                | 1,466              | 30s        | 66               | 2.4                                                           | /                        | [18]             |
| Caucasians                | 5,722              | 30s–40s    | 50               | 1.1                                                           | /                        | [20]             |
| Caucasians                | 359                | 30s–40s    | /                | 3.4*                                                          | /                        | [17]             |
| Hispanic Americans        | 1,268              | 42.8±14.6  | 41.2             | 2.0                                                           | /                        | [39]             |
| Hispanic Americans        | 824                | 14–102     | /                | 1.3*                                                          | /                        | [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                                                           | /                        | [25]             |
| East Asians               | 1,064              | 45.5±9.5   | 60               | 1.0                                                           | /                        | [28]             |

Effects of rs9939609 are shown, except when other single nucleotide polymorphisms are indicated. /: not shown, *rs1421085, *rs9930506, *rs8050136, *rs17817449, *rs9930506, *rs1421085 and rs17817449, *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. 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. More recent meta-analyses of people of Asian descent are available. Xi et al. reported that a minor allele is significantly associated with obesity with odds ratios ranging from 1.25 to 1.28, and Liu et al. reported odds ratios ranging from 1.39 to 1.45. 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/m²) and 1.13 for overweight (BMI ≥ 24 kg/m²).

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: the definition of obesity (a lower BMI cutoff point for Asians) and reduced minor allelic frequency (0.12-0.23). For individuals of African ancestry, four studies failed to detect an association between the variants and BMI (whereas positive associations were evident in Europeans). 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.

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.

**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. There are some studies showing that fasting glucose or insulin levels are significantly higher 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. The sample size of these studies is relatively small when compared with those of others. 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, GNPD42, 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. The association of FTO variants with the response and sensitivity to insulin did not reach a significant level in Europeans.

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.

**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. The association of FTO variants with BMI has been shown by other studies on people of European ancestry.

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.
and overweight and obesity after adjustment for age and gender. 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. A nested case-control study conducted in Japan also determined that the odds ratio per allele was 2.2; cases were overweight or obese. However, one report among African American showed a significant association with obesity (one out of 13 SNPs), but the other did not show a significant association among people of African ancestry.

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 or European Americans. 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). Most studies have shown that the effect of the gene variant appears between 3 and 7 years. 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. A Finnish 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. A gender difference was seen in Swedish children.

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.

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. 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.

| 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          | [5]              |
|                    |                    |            |                  |                                                               | 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         |                  |
| Caucasians         | 381                | 7          | 100 (only men)   | /                                                             | 1.26                      | [61]             |
| Caucasians         | 519                | 10.7 ± 3.10| 48               | /                                                             | 1.54                      | [49]             |
| Caucasians         | Obese: 418         | 2–18       | /                |                                                               | 1.266±, 1.267±           | [54]             |
|                    | Control: 2,270     |            |                  |                                                               |                          |                  |
| Caucasians         | Obese: 199         | 14.0 ± 3.24| 54               | /                                                             | 1.97                      | [50]             |
|                    | Control: 634       |            |                  |                                                               |                          |                  |
| African Americans  | Obese: 578         | 2–18       | /                |                                                               | 1.313±                   | [54]             |
|                    | Control: 1,424     |            |                  |                                                               |                          |                  |
| East Asians        | Obese: 133         | 10–13      | 46.6, 60.2       | /                                                             | 2.22± 2.20±              | [53]             |
|                    | Control: 133       |            |                  |                                                               |                          |                  |
| 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               | 0.9f                                                         | 1.79                      | [51]             |
| Caucasians         | Obese: 450         | obese: 12.6 ± 3.3 | 48     | 1.6 (all subjects) 1.6                                        | /                        | [60]             |
|                    | Control: 512       | healthy: 17.1 ± 0.8 | /             | (all obese)                                                  |                          |                  |
| 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, *rs8050136, *rs3751812, *rs3751812, *rs3751812, *rs1558902, 'Difference in BMI, kg/m² (minor homozygotes – major homozygotes/hetero type), BMI: Body mass index, SNP: Single nucleotide polymorphism
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. 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. 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 are already present in adolescents of Asian ancestry; thus, the trunk fat/peripheral fat ratio is higher in Asians than for other ethnicities. 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. Suggested that the variant might exert greater influence during puberty.

Asians are at an elevated risk for diabetes and cardiovascular disease at lower BMI, and lower cutoff values for BMI were used in this study to assess adult obesity. 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. 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. 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. 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. 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 or an association with fasting insulin levels and insulin resistance.

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. 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%. 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.\textsuperscript{[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.

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