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Commentary

Is fat mass & obesity-associated (*FTO*) gene master regulator of obesity ?

Obesity is a major health problem worldwide and is associated with a risk of many chronic diseases like type 2 diabetes, cardiovascular disease and cancer[1]. The aetiology of obesity is multi-factorial and any combination of environmental and lifestyle factors may possibly interact with multiple genetic variants to result in obesity[2]. In such multifactorial disorders, genome-wide association study (GWAS) is used to discover genetic variants associated with diseases. In 2007, using GWAS, a UK research team led by Dr Andrew Hattersley of Peninsula Medical School in Exeter discovered a gene variant that showed strong link with body mass index (BMI)[3]. The gene harbouring the variant was named as fat mass and obesity-associated (FTO). Further studies on 13 cohorts of 38,759 Britons, Finns and Italians also showed similar link between the *FTO* variant and body weight. Subsequently, several other genetic variants of *FTO* such as rs9939609[4], rs9930506[5], rs1421085, rs17817449, and rs1121980[6] have also been shown to confer very significant risk for obesity.

In subsequent years, studies in different cohorts such as control of blood pressure and risk attenuation (COBRA) study [0.52 kg/m^2 (95% CI 0.15-0.89); P = 0.006] and the UK Asian Diabetes Study/Diabetes Genetics in Pakistan (UKADS/DGP) study[7] [0.42 kg/m^2 (95% CI 0.16-0.68); P = 0.002], and combined meta-analysis of these two studies [0.45 kg/m^2 (95% CI 0.24-0.67); P = 0.001] have shown increase in BMI with rising numbers of risk-alleles of FTO[7]. A replication study in Singaporean Chinese, Malay and Asian-Indian populations have also confirmed the effect of *FTO* genetic variants and obesity risk[8]. Replication studies of *FTO* rs9939609 carried out in Polish population showed that the AA genotype of rs9939609 was associated with higher BMI in children and adults[9,10]. It has been shown that the risk alleles of several *FTO* genetic variants within 47 kb linkage disequilibrium (LD) block on sections of intron 1 and exon 2 of *FTO* gene are associated with obesity[4-6].

In the current issue, Wrzosek *et al*[11] investigated the association between *FTO* linked single nucleotide polymorphism (SNP, rs9930506) with obesity risk in Polish population. Their study group consisted of 442 adults, aged 33.9 ±12.7 yr with mean BMI 27.2 ± 5.4 kg/m^2. They found that variant G-allele of rs9930506 was associated with higher BMI and a 1.5 kg/m^2 increase in BMI per G-allele was also noticed. The results of this individual association study in context to obesity and *FTO* rs9930506 association indicated that parts of the Polish population are carriers of this genetic variant which may significantly increase the risk of developing obesity in their population. However, the study evaluated the association of single SNP with BMI but its association with other obesity-linked anthropometric and biochemical parameters could also have been evaluated.

In humans, *FTO* is expressed in the cell nucleus of every tissue[6]. The gene is highly expressed in hypothalamus and its arcuate, paraventricular, dorsomedial and ventromedial nuclei[12] controlling energy homeostasis and eating behaviour[3]. Studies in mouse models have shown that non-coding *FTO* regions act as long range enhancers contributing to obesity-linked phenotypes[13-15]. However, there is no evidence that such enhancers are connected with regulation of *FTO* expression[16-18].

Recently, it has been revealed that *FTO* and obesity association might be due to linkage disequilibrium between *FTO* intronic variations and other genes. Smemo and colleagues[19] have shown that variants within *FTO* act as long-range target on *IRX3* gene located approximately 500kb downstream.

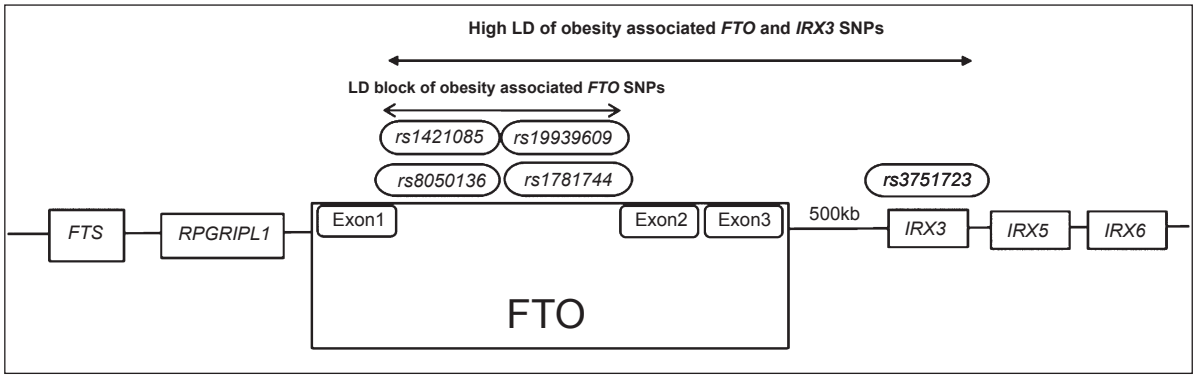

Figure. Genomic organization of *FTO* region in high linkage disequilibrium (LD) to its neighbouring genes. The FTO variants rs1421085, rs9939609, rs8050136 and rs1781744 are reported to act as long range enhancers for *IRX3* gene, believed to be master regulator of obesity. The enhancers located in *FTO* are also believed to influence the expression of other cis-located neighbouring genes such as *IRX5*, *IRX6*, *RPGRIPL1* and *FTS* which may also contribute to obesity phenotype. SNP, single nucleotide polymorphism.

Our unpublished results also support that genetic variants of *FTO* rs8050136, rs1421085, rs9939609, rs17817449 and *IRX3* rs3751723 are in high linkage disequilibrium (LD) and their interactions significantly contribute towards obesity risk in north Indian population[20]. Thus, the association between *FTO* and obesity appears to be due to its influence on expression of *IRX3* (Figure). Genetic studies indicated *FTO* as an important gene for obesity risk in various populations but the recent developments suggest that obesity-associated *FTO* SNPs have long-range interactions with *IRX3*. Therefore, the exact contribution of *FTO* in obesity risk is still debatable. In addition, it would be of interest to identify various genes and molecules regulated by *FTO-IRX3* for the development of novel therapies against obesity and diabetes.

Balraj Mittal[*#], Apurva Srivastava[*†] & Neena Srivastava[†]
[*]Department of Genetics,
Sanjay Gandhi Post Graduate Institute of Medical Sciences &
[†]Department of Physiology,
King George's Medical University,
Lucknow 226 024, Uttar Pradesh, India
[#]*For correspondence*:
bml_pgi@yahoo.com

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