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 \([0.52 \text{ kg/m}^2 (95\% \text{ CI 0.15-0.89); P = 0.006}\) and the UK Asian Diabetes Study/Diabetes Genetics in Pakistan (UKADS/DGP) study \([0.42 \text{ kg/m}^2 (95\% \text{ CI 0.16-0.68); P = 0.002}\), and combined meta-analysis of these two studies \([0.45 \text{ kg/m}^2 (95\% \text{ CI 0.24-0.67); P = 0.001}\) 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.
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\(^2\). 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.

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