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RESEARCH ARTICLE

ASSOCIATIONAL STUDY OF FTO GENE POLYMORPHISM WITH OBESITY IN VINDHYAN REGION

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ABSTRACT

Recent studies reported that the occurrence of obesity is determined by both environmental and genetic factor. This study was carried out to investigate whether the *FTO* gene is associated with obesity and related disorders in the populations of Vindhyan region. In general, the genomic DNA extracted from peripheral blood of healthy individuals and diseased individuals was subjected to PCR for polymorphism screening. The results were in normal subjects as mean of weights were 76.oo Kg, in overweight subject's weight was calculated 90.4 Kg. In obese subjects mean weight was calculated 105.1 Kg. The mean height was measured 172.2 m, 173.1 m and 172.4 m in Normal weight, overweight and obese subjects respectively. The mean BMI in all three groups were 20.9, 25.3 and 28.4 for Normal weight, overweight and obese subjects respectively. Determination of FTO genotype in all three groups was performed by allele specific PCR reaction. The genotype scored in Normal weight subjects was TT = 40, TA = 46 and AA = 14. In the Overweight subjects it was 37, 45 and 17 for TT, TA and AA respectively. In the obese subjects it is scored 30 for TT, 54 for TA and 17 for AA genotype.

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INTRODUCTION

Adverse changes in lifestyle over the past fifty years have led to what is now termed an "obesogenic" environment, i.e. reduced physical activity and easy access and consumption of energy-dense food. Trends in energy consumption are difficult to establish because of a variety of measurement issues. People under-report their energy intake, and higher BMI is associated with a greater degree of under-reporting (Heitmann and Lissner, 1995). However, it is likely that increased energy intake has had a major impact on the development of obesity. In the Indian population, the increase in caloric intake over the past 20 years is approximately 200 kcal/day. A very recent report shows that for the US population to return to the mean weights of the 1970s, the increased daily energy intake of 350 kcal for children and 500 kcal for adults would need to be reversed.Cultural changes have caused dramatic reduction in total daily physical activity. Most occupations no longer involve physical activity, and we rarely need to be physically active for transportation. Moreover, the development of television, computers, the internet, and video games has filled leisure time with sedentary pursuits. Recent studies also suggest that short sleep duration may be associated with the development of obesity from childhood to adulthood.From a genetic standpoint, humans living today are Stone Age hunter gatherers displaced through time to a world that differs from that for which our genetic constitution was selected. Genes, that might have provided a survival advantage before may today predispose to obesity (Li and Loos, 2008). Secondly, not everyone developes obesity in the present-day obesogenic environment, which highlights the multifactorial nature of the polygenic condition. Family and twin studies suggest that genetic factors contribute 40-70% to the inter-individual variation in common obesity (Allison *et al*., 1996; Maes *et al*., 1997; Nelson *et al*., 2000). Despite a relatively high heritability, progress in identification of the genetic variants influencing predisposition to common form of obesity has been slow. Initial reports of promising associations between obesity and common variants in genes *GAD2*, *ENPP1* and *INSIG2* had been reported, but the findings were not successfully replicated. However, latest advancements in gene finding technology have led to rapid progress in understanding the genetic basisof common diseases. Genome-wide association (GWA) approaches cover the whole genome and have a great power to detect minor gene effects. The first three high-density GWAs for obesity related traits took place in 2007. Each confirmed the fat mass and obesity associated gene (*FTO*) as the first gene incontrovertibly associated with common obesity and related traits,also in children.Obesity can be characterised by adipocyte hypertrophy (increased size) and hyperplasia (increased number) (Faust *et al*., 1978). Based on very recent data, obese subjects are characterised by a higher total adipocyte number than lean individuals. This number is set during childhood and

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adolescence and stays approximately constant in adulthood. Approximately 10% of the total fat cell pool is renewed by ongoing adipogenesis and adipocyte death annually at all adult ages and levels of BMI (Spalding *et al*., 2008). Until a few decades ago, adipose tissue was regarded mainly as an inert reservoir storing triglycerides. Currently, it is considered a complex, highly active metabolic and endocrine organ (Juge-Aubry *et al*., 2005; MacDougald and Burant, 2007). Adipose tissue produces a large variety of proteins (termed adipokines) regulating systemic processes, including food intake and nutrient metabolism, insulin sensitivity, stress responses, reproduction, bone growth and inflammation. Obesity induced changes in adipose tissue metabolism and the development of metabolic disturbances are illustrated in Figure 1. The number of adipokines has expanded rapidly since the first characterized adipokine, the satiety factor leptin, in 1994 (Zhang *et al*., 1994). The first pioneering observations underscoring the role of adipose tissue as a major site of production for pro-inflammatory molecules was conducted in 1993 by Hotamisligil *et al*. (1993) who showed that white adipose tissue synthesizes tumor necrosis factor α (TNF-α). More recently, the expression and secretion of a substantial number of factors linked to inflammation have been identified including members of the cytokine family (interleukins), proteins secreted in the acute phase of inflammation and chemokines that seem to play a role in the obesity-associated infiltration of macrophages into adipose tissue (Cancello and Clement, 2006; Sethi and Vidal-Puig, 2007; Luster, 1998; Weisberg *et al*., 2003).

An important aspect of adipose tissue endocrinology is the recognition that besides adipocytes, adipose tissue contains pre-adipocytes, macrophages, endothelial cells, fibroblasts, and leukocytes (Fain *et al*., 2004). This diverse composition renders adipose tissue an important mediator of inflammation and whole body metabolism. Adding to the complexity, the different fat depots (visceral and subcutaneous) are considerably heterogeneous in terms of adipokine secretion and expression patterns (Kershaw and Flier, 2004; Berndt *et al*., 2005; Montague *et al*., 1998; Tchkonia *et al*., 2006). Some studies suggest that macrophage infiltration is for clearance of dead adipocytes in the adipose tissue (Cinti *et al*., 2005; Strissel *et al*., 2007). Furthermore, macrophage infiltration might be involved in the stimulation of angiogenesis during expansion of adipose tissue (Samta Shukla and Shrikant Kol, 2017). A potential basis for the initiation of inflammation in obesity is also endoplasmic reticulum (ER) stress (Rishabh Dev Saket *et al*., 2015). Obesity may cause ER stress in adipose tissue due to excess lipid accumulation and disturbed energy metabolism. ER stress activates a stress response signaling network termed the unfolded protein response (UPR) that drives protective but also apoptotic and inflammatory signaling cascades. A central mediator of inflammatory and stress responses is the nuclear factor (NF)-κB family of transcription factors (Pang *et al*., 2008). Another mechanism that could link obesity to altered production of adipokines is hypoxia present in adipose tissue (Ozcan *et al*., 2004; Li and Verma, 2002; Trayhurn and Wood, 2004; Hosogai *et al*., 2007; Trayhur *et al*., 2008). In our present investigation we are investigating relationship between obesity and FTO genotype.

MATERIALS AND METHODS

The present study has been under taken to analyze the influence of genetic polymorphism in FTO gene associated with obesity and to find its involvement in obesity. One hundred obese and one hundred slim peoples were recruited as subject in the present study. Criteria for the subject selection were based on a questionnaire covering medical, pathological, and histopathological record from the Out Patient Department (OPD) of Medicine, S.S.M.C. Rewa (M.P.). The Height and Weight were measured in light clothes and without shoes. Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured in standing position midway between iliac crest and lower costal margin and hip circumference was measured at its maximum waist to hip ratio (WHR) was calculated using waist and hip circumferences. Systolic and diastolic blood pressures were measured twice in the right arm in sitting position after resting for at least 5 minute using a standard sphygmomanometer and the average of the two reading was used.

In general, the genomic DNA extracted from peripheral blood of healthy individuals and diseased individuals was subjected to PCR followed by restriction digestion and electrophoresis to genotype both the groups for relevant gene of interest. Statistical analysis was done by comparing the distribution of genotype frequencies and allele frequencies for all polymorphisms in all groups of study subjects. The proportions of different genotypes for a gene in a population are known as genotype frequencies.

RESULTS

The genotype frequencies of each study group were tested to be in accordance with hardy – Weinberg equilibrium using chi square test for independence. All the calculated values were compared with tabulated values and found that all the frequencies were in Hardy – Weinberg equilibrium. For the study subjects' weight, Length and BMI was measured as clinical parameters. In normal weight subjects mean of weight was 76.oo Kg, in overweight subject's weight was calculated 90.4 Kg. In obese subjects mean weight was calculated 105.1 Kg. The mean height was measured 172.2 m, 173.1 m and 172.4 m in Normal weight, overweight and Obese subjects respectively. The mean BMI in all three groups were 20.9, 25.3 and 28.4 for Normal weight, Overweight and obese subjects respectively.Determination of FTO genotype in all three groups was performed by allele specific PCR reaction. The genotype scored in Normal weight subjects was TT = 40, TA = 46 and AA = 14. In the Overweight subjects it was 37, 45 and 17 for TT, TA and AA respectively. In the Obese subjects it is scored 30 for TT, 54 for TA and 17 for AA genotype (Table-1).

DISCUSSION

Peoples are heavily relying on high energy diet but average physical activity decreases by the new advancement of science. Physical inactivity and intake of high energy diet may be one important reason for the obesity disorder but one cannot ignore the role of genetic factors and ethnicity in the obesity.Recent finding suggests that there are some metabolism related gene polymorphism are play important role in obesity progression, especially FTO. *FTO* gene expression profiles from human fetal and adult samples show that it is ubiquitously expressed in central and peripheral tissues and organs. The highest relative levels have been found in the brain, particularly in the hypothalamus and cortex area. Similarly, studies in animals

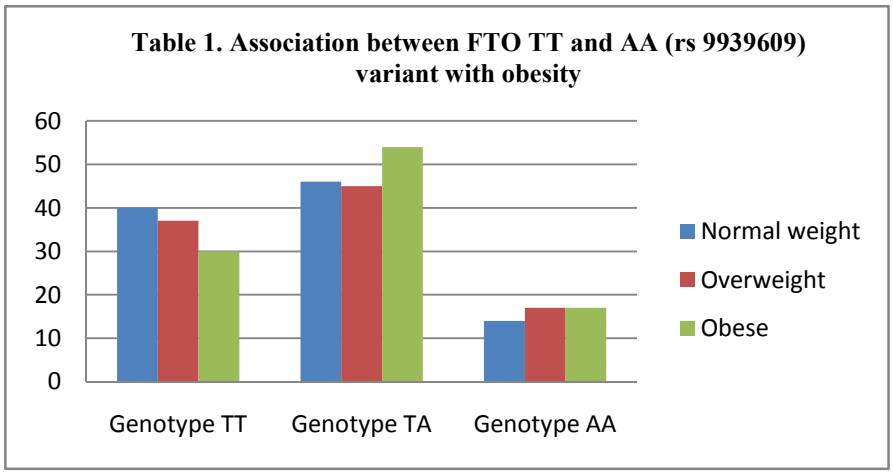
Table 1. Association between FTO TT and AA (rs 9939609) variant with obesity

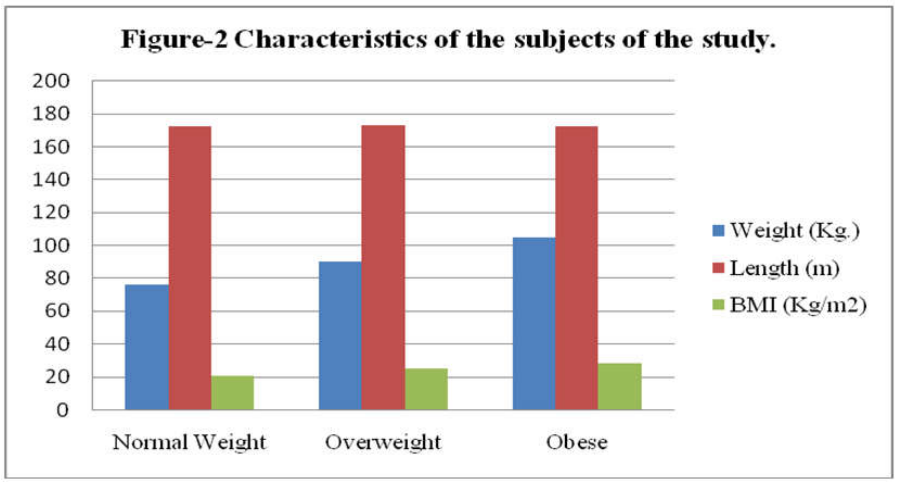
Group	Genotype TT	Genotype TA	Genotype AA	p Value
Normal weight	40	46	14	--
Overweight	37	45	17	0.242
Obese	30	54	17	0.203

Table 2. Characteristics of the subjects of the study

Clinical Parameters	All	Normal Weight	Overweight	Obese
Weight (Kg.)	70.8 ±20.0	76.00 ± 18	90.4 ± 22	105.1 ± 25
Length (m)	165.2 ± 6.8	172.2 ± 8.00	173.1 ± 8	172.4 ± 8.1
BMI (Kg/m^2)	23.2 ± 2.8	20.9 ± 2.1	25.3 ± 2.9	28.4 ± 2.4

Note:- Values are the geometric means ± SD





have indicated that *FTO* mRNA expression is found to be abundant in the brain, suggesting a central neuronal role for *FTO*. However, evidence for a peripheral role for *FTO* has also been found in obesity, adipose tissue represents primary candidate to study the *FTO* geneexpression and functional relevance. Studies that have compared the *FTO* expression between the lean and obese individuals have mainly shown greater expression levels for obese than for normal weight subjects. And the heritability of *FTO* expression in adipose tissue and skeletal muscle has been found to be low. The results on site-specific differences in *FTO* mRNA levels between subcutaneous and visceral adipose tissue are discordant. Differences between the depots can be due to number of factors differentiating these two depots, such as altered adipokine expression and lipolysis. *FTO* expression in the two depots correlates only modestly, which may suggest that expression is controlled locally. According to researchers *FTO* mRNA in subcutaneous adipose tissue is largely derived from fat cells, rather than from the other cell types populating adipose tissue. It is also demonstrated in preadipocytes that *FTO* mRNA expression is induced at an early stage in the differentiation process and thereafter expression decreased during adipogenesis. Klöting *et al*. found a negative correlation between *FTO* gene expression and BMI and body fat percentage. This may suggest that *FTO* expression is down-regulated in response to fat accumulation. This observation raises question whether the suppression of *FTO* expression aids the transformation of pre-adipocytes to fat laden mature adipocytes. On the other hand, it has been reported that the expression of *FTO* was moderately increased in adipocytes compared with preadipocytes and was substantially reduced in white adipose tissues of obese, diabetic *db/db* mice, indicating that it may play a role in adipocyte function, but not in adipogenesis.Recent findings suggest that *FTO* expression in human adipose tissue may play a role in the development of inflammation. We find that the FTO is a important gene to measure obesity and other obesity related complications.

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