Genetics of obesity: an overview of current approaches and advancement

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INTRODUCTION

Obesity is a multifactorial condition often associated with an excess of body fat. Nowadays obesity has emerged as second-most important leading cause of death yet, preventable as well as major public health issue. According to the National Center for Health Statistics reports, 61% of adult population in the United States are overweight (body-mass index 25–29.9) and 26% are obese (body-mass index 30); in fact it is no more a health hazard issue only in Western society, but it has also grown up throughout the world by >75% since 1980 (CDC; Cuming and Schwartz, 2003). Although Bangladesh suffers from under nutrition and underweight but there is steady rise of overweight and obesity (Shafique et al., 2007; Balarajan and Villamor, 2009). Obesity became common issue and public health problem in many countries of Asia (Pomerleau et al., 1999; Mohamad et al., 1996; Ismail et al., 2002). Commonly BMI is used for measuring obesity in clinical and research settings, however, alternative anthropometric measures such as waist circumference (WC), and waist-hip-ratio (WHR) that indicates abdominal adiposity have been suggested to be the most accurate determinants and predictors of cardiovascular diseases (CVD) and type 2 diabetes (Wei et al., 1997; Stevens et al., 2001; Janssen et al., 2004; Sailaja and Bhatnagar, 2010) This is based on the background that increased visceral adipose tissue is associated with decreased glucose tolerance, reduced insulin sensitivity and adverse lipid profiles, leading to risk factors for type 2 diabetes and CVD. Several studies also suggest the strong correlation between BMI with WC, and health risk indicator instead of using BMI alone (Chan et al., 1994; Arden et al., 2003; Janssen et al., 2002; Bigaard et al., 2003; Huxley et al., 2010). In support of this (Table 1), the National Institute of Health (NIH) guidelines indicate that the risk of acquiring CVD and type 2 diabetes increases in a graded fashion when moving from normal-weight through obese BMI categories, and that within each BMI category

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men and women with high WC values are at a greater health risk than are those with normal WC values (NIH 1998). The World Health Organization has announced obesity as a global epidemic (Cuming and Schwartz, 2003; WHO). Moreover, obesity predisposes to, or exacerbates, many clinical conditions such as hypertension, type-II diabetes, hyperlipidaemia, gout, gallbladder disease, osteoporosis, cancer and infertility (Digirolamo et al., 2000; Helali et al., 2013). It has been suggested that the obesity epidemic has a strong causal relation with our obesigenic lifestyle, mainly excessive caloric intake and less physical activity as well as increased reliance on mechanized inventing (Shuldiner and Munir, 2003). Furthermore, it has also been demonstrated that genetic factors play a dominant role in person susceptibility to obesity rather than the environmental cause and till date more than 200 candidate genes have been explored by gene mapping studies which have potential influence on developing obesity (Speakman, 2007). Hence, obesity results from gene-environment interaction and the individual’s genetic tendency to become obese can be evident from the exposure to the modern environment (Speakman, 2007). Herein, the recent evidence of genes linked or related to obesity phenotypes has been reviewed.

**Table 1:** Combined recommendations of body mass index and waist circumference cut-off points made for overweight or obesity classifications, and association with disease risk (NIH 1998).

<table>
<thead>
<tr>
<th>Body category</th>
<th>Body Mass Index</th>
<th>Obesity Class</th>
<th>Disease risk (relative to normal weight and waist circumference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td></td>
<td>Men &lt;102 cm Women &lt;88 cm</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5–24.9</td>
<td></td>
<td>Increased High</td>
</tr>
<tr>
<td>Over weight</td>
<td>25.0–29.9</td>
<td>I</td>
<td>Men &gt;102 cm Women &gt;88 cm</td>
</tr>
<tr>
<td>Obesity</td>
<td>30.0–34.9</td>
<td>II</td>
<td>Very High</td>
</tr>
<tr>
<td>Extreme obesity</td>
<td>&gt;35.0</td>
<td>III</td>
<td>Extremely High</td>
</tr>
</tbody>
</table>

**GENETICS OF OBESITY**

The common polygenic obesity in humans

Despite, the strong association of genetic component to human obesity, specific Mendelian mode of inheritance yet is not detected; suggestive of multiple genes’ involvement in obesity (Shuldiner and Munir, 2003). Again, modern genetics researches offer two types of analytical approaches such as, genome wide (Chial and Craig, 2008; Chen et al., 2008; Emilson et al., 2008) and candidate gene analysis (Shuldiner and Munir, 2003; Clément et al., 1996). In genome-wide approaches quantitative trait loci (QTL) are identified which in turns help to identify the regions of chromosome which are known to encode the genes associated with the Mendelian syndromes that possess obesity as one of the feature (Chagnon et al., 2000). Afterwards, positional cloning can be done on the basis of information of human genome database; till date obesity prone genes in various chromosomal regions have been detected namely chromosome 10p, 11q24, 11q24, 16p, 18q21, 20q13, and Xq24 by attaining the genome-wide scan in different populations such as Caucasians, African Americans, Mexican Americans and Pima Indians (Bouchard and Perusse, 1993). In candidate gene approaches, genes those are potentially related to the pathophysiology of obesity are investigated and by comparing the DNA sequences of these genes between obese and non-obese may help to discover the gene variants responsible for obesity vulnerability as well as linkage results of obesity and body fat phenotypes with candidate genes (Chagnon et al., 2000). Two notable examples of candidate gene variants that might have some role in obesity susceptibility, include Trp64Arg β3 adrenoceptor (Walston et al., 1995; Widen et al., 1995; Clement et al., 1995) and Pro12Ala peroxisome proliferator activated Receptor-γ2 (PPAR-γ2) (Yen et al., 1997; Beamer et al., 1998). Recently 22 genes which have five or more positive associations of variants with obesity phenotypes have been explored (Table 2) and it mainly includes members of the leptin–melanocortin pathway, pro-inflammatory cytokines and uncoupling protein (Walley et al., 2006). Meanwhile, it has been concluded by a majority of the study that most of them have a comparatively minor influence on obesity phenotype.

**Monogenic obesity: Single – Gene- Mutation Rodent model**

Animal models of obesity have been studied extensively in an effort to elucidate the mechanisms underlying human obesity, and currently there are several hundred genes that have evidenced the heritability of body weight (Rankinen et al., 2006). Some of the popular genes implicated include leptin (LEP), leptin receptor (LEPR), agouti-related peptide (AgRP), tubby gene, POMC gene (Rankinen et al., 2006; Brockmann and Bevova 2002). Spontaneous mutations in these genes has been detected being responsible for obesity in mouse models and by cloning the corresponding genes both in rodent and humans, their possible functions and pathways of body weight regulation has been identified (Inui 2000). Furthermore, the cognition of this pathway combined with modern genetic methods provides the new insights and paved a way of unraveling the complex nature of human obesity.

**Leptin (LEP) Gene**

The role of leptin in obesity was first explored in studies on severely obese ob/ob mice, which has a mutation in the gene encoding the leptin, which is a hormone secreted by adipose tissue and directly proportional to fat mass; leptin has significant impact on appetite and energy expenditure (Considine et al., 1996; Maffei et al., 1996; Farooqi et al., 2005; Farooqi et al., 2006; Farooqi et al., 2007).

Leptin is highly similar among species and there are 83%-84% similarity reported between rodents and humans (O’Rahilly and Farooqi, 2006; Chagnon et al., 1999). Treatment of ob/ob mouse with the recombinant leptin reduces the appetite as well as their body weight and corrects all their phenotypic abnormalities (Montague et al., 1997; Kalra and Kalra, 2002; Iwaniec et al., 2007). Similarly, after screening of thousands of obese individuals, mutations have been detected at three different families. Two cousins who were both normal weights at birth and afterwards suddenly gained weight and became obese were reported due to lack of circulating OB protein in their blood like OB protein deficient mice (Camfield and Smith, 2000). The causal
relation of obesity and ob gene mutation was also found in three members of another family of turkey (Camfield and Smith, 2000; David et al., 2002). But, other attempts of finding associations between LEP mutation and human obesity have failed and it was suggested that obesity is more related to congenital deficiency in leptin production rather than leptin mutation (Montague et al., 1997; Yang and Barouch, 2007). Besides this, a number of studies demonstrated that leptin deficiency leads to increase insulin resistance with age and thus causes obesity (Montague et al., 1997; Martin et al., 2008).

Another hypothesis established that, an absolute deficit of leptin does not underlie most cases of obesity. Instead, most obese individuals exhibit elevated circulating leptin levels (leptin resistance), which increase proportionally with their adipose mass (Considine et al., 1996; Maffei et al., 1996; Farooqi, 2005). A number of mechanisms have been proposed to explain leptin resistance, and these include the failure of circulating leptin to reach its target receptor within the brain, decreased expression of the leptin receptor within hypothalamic neurons, perturbations in developmental programming, etc (Björbaek and Kahn, 2004; Flier 2004; Remacle et al., 2004).

Another mechanism that has received attention is the attenuation of the intracellular leptin signaling cascade (Björbaek et al., 1998). The action of various cytokine receptors is negatively regulated by an intracellular protein, the suppressor of cytokine signaling-3 (Socs-3) (Starr et al., 1997). Leptin is structurally related to cytokines and acts via a receptor that belongs to the cytokine receptor family. It is, therefore believed that Socs-3 limits leptin signalling, and mediates leptin resistance (Kievit et al., 2006).

**The Leptin-Receptor (LEPR) Gene**

The rodent leptin-receptor Lepr gene encodes a protein of 1164 amino acids with a 22 amino acid secretory signal sequence, a predicted transmembrane domain and a cytoplasmic domain with variable length and constituent. In human Lepr is named LEPR and structure is very similar to those of rodents, with a similarity of 78% and 71% for extra and intracellular domains (Bouchard, 1995).

After deleting the signalling form of the leptin receptor in db/db mice were associated with unresponsiveness to endogenous or exogenous leptin and the result was the earlier development of hyperglycaemia (O’Rahilly and Farooqi, 2006; Zhang et al., 1994). Similarly, a splice mutation in the leptin receptor that produced truncated receptor lacking both transmembrane and intracellular portion of the receptor has been reported in a consanguineous family of Kabilian origin (O’Rahilly and Farooqi, 2006). Obese individuals were shown to be homozygotes for the mutation that produced an early-onset morbid obesity with hyperphagia and hypogonadotropic hypogonadism which is suggestive of the direct role of LEPR in the control of adiposity and human body composition and also a good manifest of DNA sequence variation in the LEPR directly contribute to the human obesity (Farooqi et al., 2007; Clement et al., 1998).

**The Agouti Signalling-Protein (ASIP) Gene/Agouti-related peptide (AgRP)**

Mutations in the agouti- signalling protein which acts through the melanocortin receptors to modulate eating behaviour are found to be associated with mouse obesity; the mouse AgRP gene is very similar to an ASIP gene in human. In humans the effect varies according to age, with loss of AgRP leading to a severe life threatening hypophagia in adults while in newborn babies it results in mild food suppression and body weight loss (Flier, 2006). But there have so far been no linkage and mutation studies of AgRP gene responsible for human obesity have been reported (Shuldiner and Munir, 2003; Chagnon et al., 2000).

**POMC (Pro-opiomelanocortin) gene Deficiency**

It is the first-order neuronal targets of leptin action in the brain which is anorectic (reducing food intake). Again, it has been reported that 40% of POMC neurons in the arcuate nucleus is responsible for the expression of the mRNA that is required for the long form of the leptin receptor and leptin is also associated with POMC expression (O’Rahilly and Farooqi 2006). The pro hormone processing enzyme, pro-hormone convertase 1 or PC-1 is required for post- translational processing of POMC for yielding biologic peptide.

However, a mutation in the gene for PC-1 was found to be related to obesity (Changnon et al., 2000). Besides this, hyperphagia and early onset obesity accompanied by adrenal insufficiency and red hair pigmentation have been reported due to direct homozygous or heterozygous mutations in POMC (Krude et al., 1998).

**Prohormone Convertase 1 Deficiency**

In addition to the relation of PC-1 to POMC, PC 1 is also responsible for the cleavage of number of peptide such as GLP1, in the hypothalamus and GLP -1 is related to feeding behaviour. It has been demonstrated that early onset obesity which results from severe small-intestinal absorptive dysfunction as well as impaired pro-hormone processing and hypocortisolaemia is related to the maturation failure of pro-peptide that express PCI throughout the gut (O’Rahilly and Farooqi, 2006).

**The Tubby (TUB) gene**

In tub mouse it has been found that there is a positive correlation between let onset obesity and also moderate type of obesity with tubby gene mutation (mutation in insulin signaling protein). However, no mutation in human equivalent to the gene has reported yet (Changnon et al., 2000).

**MC4R mutations**

Although currently no known MC4R obesity-causing mutation in animal models, in humans, MC4R defects are the most common causes of monogenic obesity with more than100 mutations described in different ethnic groups and the most of the mutations are transmitted in an autosomal dominant manner (Krude et al., 1998; Yeo et al., 1998; Kobayashi et al., 2002;
Mergen et al., 2001; Vaisee et al., 1998). Clinical heterogeneity and sometimes incomplete disease penetrance are the characterized features of these mutations.

**PHARMACOLOGICAL INTERVENTIONS**

Obesity potentially increases the risk of cardiovascular diseases, type II diabetes, dyslipidemia, arthritis, and some type of cancers and also reduces both quality of life and average life expectancy (Haslam and James, 2005). The effective treatment of obesity will reduce the load of disease as personally and also for the community (Hainer et al., 2008). Anti-obesity drugs have abuse potential also (Kroll, 2013). Researchers found at Columbia University College New York that ‘anti-obesity drug that turns off the single blood test the health professionals will be able to diagnose tools and hopefully within the next few years these genes through the genome wide approaches or candidate gene approaches can provide powerful tool for identifying the genetics of obesity and obesity genetic system; possibly the more severe individuals carry the higher efficacy and drugs usually need for these patients like antihypertensive, anti-diabetics, and cardio-tionics (Al-Suwailem et al., 2006). Therefore in current context low-calorie diet and low-calorie diet in combination with orlistat shows higher efficacy cost-effectiveness (van Baal et al., 2008). Researchers expect that in near future more effective and well tolerated drug will be developed soon with ‘a better understanding of the multiple mechanisms and complex physiological systems is targeting appetite’. It is estimated medical cost of obesity is more 150 billion per year in USA (Finkelstein et al., 2009). Henceforth, scholars and patients also expect that beside scientific and regulatory issues researches will also consider patients’ financial burden as obesity is not only a trouble of rich country but also of the developing countries. There are also need appropriate policies for social intervention as a means of managing obesity because obese patients often return to toxic environments and behaviours’ (Kang and Park, 2012).

**CONCLUSION**

The substantial advances have been achieved in the last few years through the cloning of the genes those are responsible for the obesity and comorbidities in the single-gene rodent models of obesity. It can be assumed that several genes have the potential for human obesity and obesity genotype to cause obesity in humans. It seems likely that the obesity genotype is a complicated multi-genic system; possibly the more severe individuals carry the mutation at multiple loci and less severe cases may carry only one mutated genes. However, clarification of obesity susceptibility genes through the genome wide approaches or candidate gene approaches can provide powerful tool for identifying the genetics beneath the obesity. Eventually, the new insight for the pathogenesis of obesity then contribute to the new medicines and diagnostic tools and hopefully within the next few years these innovations will be applied to the clinical field; for instance with the single blood test the health professionals will be able to
demonstrate the individual’s genetic burden to obesity genes as well as genetic elements associated with co-morbid risks. In conclusion, there is an emergent call for effective research for the development of effective and safe treatment modalities to combat global threat of obesity and related issues for developed and developing countries.

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