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Genetics of obesity: an overview of current approaches and advancement

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ABSTRACT

Elucidation of obesity susceptibility genes through genome wide approaches as well as candidate gene approaches provides great promise in ultimately determining the genetic underpinnings of obesity. The complex nature of human obesity stems from the multiple interaction of several genes that control the physiology of food intake, energy expenditure, development of the body, and behavioural patterns towards food intake, and the environment. According to twin, adoptees and family studies, genetic factors account for 40-70% of the variability observed in human adiposity. Twin studies supported that the heritability of adiposity is higher than other quantitative traits. The heritability of obesity traits has been further evidenced by identification of quantitative trait loci (QTL) and genes through methods such as genome-wide scans (studies conducted on unrelated obese individuals), linkage analyses (conducted in families), and association studies (investigating the correlation between obesity and polymorphisms). The number of contributing genes, however, is still unknown. Although research on the genetic basis of obesity has advanced, the mechanisms underlying the condition are still complex due to its heterogeneity even within families.

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; Cumming 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; Huzxley *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 (Cumming 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).

Body weight category	Body Mass Index	Obesity Class	Disease risk (relative to normal weight and waist circumference)	
			Men < 102 cm Women < 88 cm	Men >102 cm Women >88 cm
Underweight	<18.5			
Normal	18.5–24.9			
Over weight	25.0–29.9		Increased	High
Obesity	30.0–34.9	I	High	Very High
	35.0–39.9	II	Very High	Very high
Extreme obesity	>40.0	III	Extremely High	Extremely High

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 (Bjørbaek and Kahn, 2004; Flier 2004; Remacle *et al.,* 2004).

Another mechanism that has received attention is the attenuation of the intracellular leptin signaling cascade (Bjørbaek *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- signaling 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 Convertage 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 PC1 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;

Table 2: Genes with five or more positive associations of variants with obesity or obesity-related phenotypes (Walley *et al.*, 2006).

Gene symbol	Full name	Chromosomal location	Number of studies	*P*-value
ACE	Angiotensin I-converting enzyme (peptidyl-dipeptidase A) 1	17q24.1	6	0.05–0.0023
ADIPOQ	Adiponectin, C1Q and collagen domain containing	3q27	11	0.05–0.001
ADRB2	Adrenergic, beta-2-, receptor, surface	5q31–q32	20	0.05–0.0001
ADRB3	Adrenergic, beta-3-, receptor	8p12–p11.2	29	0.05–0.001
DRD2	Dopamine receptor D2	11q23.2	5	0.03–0.002
GNB3	Guanine nucleotide binding protein (G protein), beta polypeptide 3	12p13.31	14	0.05–0.001
HTR2C	5-hydroxytryptamine (serotonin) receptor 2C	Xq24	10	0.05–0.0001
IL6	Interleukin 6 (interferon, beta 2)	7p21	6	0.03–0.003
INS	Insulin	11p15.5	7	0.05–0.0002
LDLR	Low density lipoprotein receptor (familial hypercholesterolaemia)	19p13.2	5	0.04–0.001
LEP	Leptin (obesity homologue, mouse)	7q31.3	10	0.05–0.003
LEPR	Leptin receptor	1p31	16	0.04–0.0001
LIPE	Lipase, hormone-sensitive	19q13.2	5	0.05–0.002
MC4R	Melanocortin 4 receptor	18q22	8	0.04–0.002
NR3C1	Nuclear receptor sub-family 3, group C, member 1 (glucocorticoid receptor)	5q31	10	0.05–0.001
PLIN	Perilipin	15q26	5	0.05–0.0008
PPARG	Peroxisome proliferative activated receptor, gamma	3p25	30	0.05–0.001
RETN	Resistin	19p13.2	5	0.048–0.001
TNF	Tumor necrosis factor (TNF superfamily, member 2)	6p21.3	9	0.05–0.004
UCP1	Uncoupling protein 1 (mitochondrial, proton carrier)	4q28–q31	10	0.05–0.001
UCP2	Uncoupling protein 2 (mitochondrial, proton carrier)	11q13.3	11	0.05–0.001
UCP3	Uncoupling protein 3 (mitochondrial, proton carrier)	11q13	12	0.049-0.0005

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 same brain circuits which trigger the marijuana-induced hunger pangs appears to produce sustained weight loss among patients'. This finding probably delayed the approval of the world first blockbuster anti-obesity medicine Rimonabant (News Medical, 2006). Rimonabant is not now considered as safe drug as it is reported to cause increased number of psychiatric diseases in otherwise normal individual (Soyka, 2008). Obesity is a multifactorial chronic medical disorder. Again there is almost no short cut way to treat the condition instantly. Physicians need to educate their patients about obesity and available pharmacological interventions (Wyatt and Hill, 2004). Again it is always no medication is absolutely free from adverse drug reactions. Henceforth, anti-obesity drug is not answer (Wyatt and Hill, 2004). 'Life-threatening safety issues led to the withdrawal of number of antiobesity drugs from the US market, including a multibillion dollar settlement by the manufacturers of these drugs' (Elangbam, 2009). Orlistat is considered as a safe agent for obesity. Hence, National Institute of Health Care Excellence (NICE), UK also suggests orlistat because it's higher efficacy and also cost-effective (Hampp *et al.*, 2008). Orlistat has quite free drug interactions especially with drugs of low therapeutic index or drugs usually need for these patients like antihypertensive, anti-diabetics, and cardio-tonics (Al-Suwailem *et al.*, 2006). Therefore in current context low-calorie diet and low-calorie diet in combination with or listat 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 patents' 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.

REFERENCES

Al-Suwailem K, Al-Tamimi AS, Al-Omar MA, Al-Suhibani MS. Safety and Mechanism of Action of Orlistat (Tetrahydrolipstatin) as the First Local Antiobesity Drug. Journal of Applied Sciences Research 2006; 2(4); 205-208. Available from http://www.faculty.ksu.edu.sa/Alomar/Full%20Text%20Articles/287-RJAS.pdf [Accessed on 17th September 2013]

Ardern CI, Katzmarzyk PT, Janssen I, Ross R. Discrimination of health risk by combined body mass index and waist circumference. Obes Res, 2003;11: 135-42.

Balarajan Y, Villamor E. Nationally Representative Surveys Show Recent Increases in the Prevalence of Overweight and Obesity among Women of Reproductive Age in Bangladesh, Nepal, and India. J Nutr, 2009;139(11):2139-44. doi: 10.3945/jn.109.112029. Available from http://jn.nutrition.org/content/139/11/2139.full.pdf+html [Accessed on 16th September 2013]

Beamer BA, Yen CJ, Andersen RE, Muller D, Elahi D, Cheskin LJ, Andres R, Roth J, Shuldiner AR. Association of the Pro12Ala Variant in the Peroxisome Proliferator-Activated Receptor-γ2 Gene with Obesity in Two Caucasian Populations. Diabetes, 1998; 47:1806-08.

Bigaard J, Tjønneland A, Thomsen BL, Overvad K, Heitmann BL, Sørensen TI. Waist circumference, BMI, smoking, and mortality in middle-aged men and women. Obes Res, 2003; 11: 895–903.

Bjørbaek C, Elmquist JK, Frantz JD, Shoelson SE, Flier JS. Identification of SOCS-3 as a potential mediator of central leptin resistance. Mol Cell, 1998;1(4):619-25.

Bjørbaek C, Kahn BB. Leptin signaling in the central nervous system and the periphery. Recent Prog Horm Res, 2004; 59:305-31.

Bouchard C, Perusse L. Genetics of Obesity. Annu. Rev. Nutr., 1993; 13:337-54.

Bouchard C. The genetics of obesity: from genetic epidemiology to molecular markers. Mol Med Today., 1995; 1(1):45-50.

Brockmann GA, Bevova MR. Using mouse models to dissect the genetics of obesity. Trends Genet, 2002; 18(7):367-76.

Camfield LA, Smith FJ. 2000. Pharmacological treatment of obesity : outcomes and New tools.In: Dean H, Lockwood MD., Thomas C (eds.), Handbook of Experimental Pharmacology, Springer, Germany. pp 177-94.

Centres for Disease Control and Prevention. Available at: http://www.cdc.gov/obesity/data/adult.html [Accessed on 12th June, 2013]

Chagnon CY, Perusse L, Bouchard C. 2000. The molecular and epidemiological Genetics of Obesity. In: Dean H, Lockwood MD., Thomas C (eds.), Handbook of Experimental Pharmacology, Springer, Germany. pp 57-89.

Chagnon YC, Chung WK, Perusse L, Chagnon M, Leibel RL, Bouchard C. Linkages and associations between the leptin receptor (LEPR) gene and human body composition in the Quebec Family Study. Int J Obes, 1999; 23:278–86.

Chagnon YC, Wilmore JH, Borecki IB. Associations between the leptin receptor gene and adiposity in middle-aged Caucasian males from the HERITAGE family study. J Clin Endocrinol Metab, 2000; 85(1):29-34.

Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care , 1994; 17:961-9.

Chen Y, Zhu J, Lum PY, Yang X, Pinto S, MacNeil DJ, Zhang C, Lamb J, Edwards S, Sieberts SK, Leonardson A, Castellini LW, Wang S, Champy MF, Zhang B, Emilsson V, Doss S, Ghazalpour A, Horvath S, Drake TA, Lusis AJ, Schadt EE. Variations in DNA elucidate molecular networks that cause disease. Nature, 2008; 452:429-35.

Chial H, Craig J. Genome-wide association studies (GWAS) and obesity. Nature Education 2008;1(1). Available from http://www.nature.com/scitable/topicpage/genome-wide-association-studies-gwas-and-obesity-752 [Accessed on 10th September 2013]

Clément J, Vaisse V, Manning BSJ, Basdevant A, Guy-Grand B, Ruiz J, Silver KD, Shuldiner AR, Froguel P, Strosberg AD, Genetic Variation in the β3-Adrenergic-Receptor and Increased Capacity to Gain Weight in Patients with Morbid Obesity. N Engl J Med, 1995; 333:352-54.

Clément K, Philippi A, Jury C, Pividal R, Hager J, Demenais F, Basdevant A, Guy-Grand B, Froguel P.Candidate gene approach of familial morbid obesity: linkage analysis of the glucocorticoid receptor gene. Int J Obes Relat Metab Disord, 1996; 20(6):507-12.

Clément K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D, Gourmelen M , Dina C, Chambaz J, Lacorte JM, Basdevant A, Bougnères P, Lebouc Y, Froguel P, Guy-Grand B. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature, 1998; 392(6674):398-401.

Considine RV, Sinha MV, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohannesian JP, Marco CC, McKee LJ, Bauer TL, Caro JF. Serum immune reactive leptin concentrations in normal-weight and obese humans. N Engl J Med, 1996; 334:292-5.

Cummings ED, Schwartz WM. Genetics and pathophysiology of human obesity. Annu Rev Med, 2003; 54:453-71.

David R. Mann, DR, Plant TM. Leptin and Pubertal Development. Semin Reprod Med, 2002; 20(2).

Digirolamo M, Harp J, Stevens, J. 2000. Obesity: Definition and Epidemiology. In: Dean H, Lockwood MD., Thomas C (eds.), Handbook of Experimental Pharmacology, Springer, Germany. pp 3-28.

Elangbam CS. Review Paper: Current Strategies in the Development of Anti-obesity Drugs and Their Safety Concerns. Vet Pathol, 2009; 46:10–24 Available from http://vet.sagepub.com/content/46/1/10.full [Accessed on 16th September 2013]

Emilsson V, Thorleifsson G, Zhang B, Leonardson AS, Zink F, Zhu J, Carlson S, Helgason A, Walters GB, Gunnarsdottir S, Mouy M, Steinthorsdottir V, Eiriksdottir GH, Bjornsdottir G, Reynisdottir I, Gudbjartsson D, Helgadottir A, Jonasdottir A, Jonasdottir A, Styrkarsdottir U, Gretarsdottir S, Magnusson KP, Stefansson H, Fossdal R, Kristjansson K, Gislason HG, Stefansson T, Leifsson BG, Thorsteinsdottir U, Lamb JR, Gulcher JR, Reitman ML, Kong A, Schadt EE, Stefansson K. Genetics of gene expression and its effect on disease. Nature, 2008; 452:423–28.

Farooqi IS, Drop S, Clements A, Keogh JM, Biernacka J, Lowenbein S, Challis BG, O'Rahilly S. Heterozygosity for a POMC-null mutation and increased obesity risk in humans. Diabetes, 2006; 55(9):2549-53.

Farooqi IS, O'Rahilly S. Monogenic obesity in humans. Annu Rev Med, 2005; 56:443-58.

Farooqi IS, Wangensteen T, Collins S, Kimber W, Matarese G, Keogh JM, Lank E, Bottomley B, Lopez-Fernandez J, Ferraz-Amaro I, Dattani MT, Ercan O, Myhre AG, Retterstol L, Stanhope R, Edge JA, McKenzie S, Lessan N, Ghodsi M, Rosa VD, Perna F, Fontana S, Barroso I, Undlien DE, O'Rahilly S. Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. N Engl J Med, 2007; 356(3):237-47.

Finkelstein EA, Trogdon JG, Cohen JW, Dietz W. Annual Medical Spending Attributable To Obesity: Payer- And Service-Specific Estimates. Health Affairs, 2009; 28(5):w822-w831. Available from http://content.healthaffairs.org/content/28/5/w822.full.pdf+html [Accessed on 16th September 2013]

Flier JS. AgRP in energy balance: Will the real AgRP please stand up? Cell Metab, 2006;3(2):83-5.

Flier JS. Obesity wars: molecular progress confronts an expanding epidemic. Cell, 2004; 116(2):337-50.

Hainer V, Toplak H, Mitrakou A. Treatment Modalities of Obesity. What fits whom? Diabetes Care 2008; 31 (Suppl. 2):S269–S277. Available from http://care.diabetesjournals.org /content/31/Supplement_2/S269.full.pdf+html [Accessed on 16th September 2013]

Hampp C, Hartzema AG, Kauf TL, Cost-Utility Analysis of Rimonabant In The Treatment Of Obesity. Value Health. 2008; 11(3):389-99. doi: 10.1111/j.1524-4733.2007.00281. Available from

http://www.valueinhealthjournal.com/article/S1098-3015(10)70006-1/ [Accessed on 17th September 2013]

Haslam DW, James WPT: Obesity. Lancet 2005; 366 (9492):1197–209.

Helali AM, Iti FM, Mohamed IN. Cathepsin K Inhibitors: A Novel Target but Promising Approach in the Treatment of Osteoporosis. Curr Drug Targets, 2013 (Epub ahead of print); PMID: 23957815.

Huxley R, Mendis S, Zheleznyakov E, Reddy S, Chan J. Body mass index, waist circumference and waist:hip ratio as predictors of cardiovascular risk--a review of the literature. Eur J Clin Nutr, 2010; 64(1):16-22.

Inui A. Transgenic Approach to the Study of Body Weight Regulation. Pharmacological Reviews, 2000; 52(1):35-62.

Ismail MN, Chee SS, Nawawi H, Yusoff K, Lim TO, James WPT. Obesity in Malaysia. Obesity Reviews, 2002; 3: 203–208. doi: 10.1046/j.1467-789X.2002.00074.x

Iwaniec UT, Boghossian S, Lapke PD, Turner RT, Kalra SP. Central Leptin Gene Therapy Corrects Skeletal Abnormalities in Leptin-deficient ob/ob Mice. Peptides, 2007; *28*(5):1012–19.

Janssen I, Katzmarzyk PT, Ross R. Body mass index, waist circumference, and health risk: evidencein support of current National Institutes of Health guidelines. Arch Intern Med, 2002; 162: 2074–9.

Janssen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesityrelated health risk. Am J Clin Nutr, 79:2004; 379–84.

Kalra PS, Kalra SP. Obesity and metabolic syndrome: long-term benefits of central leptin gene therapy. Drugs Today, (Barc). 2002; 38(11):745-57.

Kang JG, Park CY. Anti-Obesity Drugs: A Review about Their Effects and Safety. Diabetes Metab J. 2012 Feb; 36(1):13-25. doi.org/10.4093/dmj.2012.36.1.13 Available from http://synapse.koreamed.org/DOIx.php?id=10.4093/dmj.2012.36.1.13 [Accessed on 16th September 2013]

Kievit P, Howard JK, Badman MK, Balthasar N, Coppari R, Mori H, Lee CE, Elmquist JK, Yoshimura A, Flier JS. Enhanced leptin sensitivity and improved glucose homeostasis in mice lacking suppressor of cytokine signaling-3 in POMC-expressing cells. Cell Metab, 2006;4(2):123-32.

Kobayashi H, Ogawa Y, Shintani M, Ebihara K, Shimodahira M, Iwakura T et al. A Novel homozygous missense mutation of melanocortin-4 receptor (MC4R) in a Japanese woman with severe obesity. Diabetes, 2002; 51(1):243-6.

Kroll D. Why Does Arena's Obesity Drug Have Abuse Potential? Pharma & Healthcare. 5/11/2013 @ 9:53AM. Available from http://www.forbes.com/sites/davidkroll/2013/05/11/why-does-arenas-obesity-drug-have-abuse-potential/ [Accessed on 16th September 2013]

Krude H, Biebermann H, Luck W, Horn R, Brabant G, Grüters A. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. Nat Genet, 1998;19(2):155-7.

Maffei M, Stoffel M, Barone M, Moon B, Dammerman M, Ravussin E, Bogardus C, Ludwig DS, Flier JS, Talley M, Auerbach S, Friedman JM. Absence of mutations in the human Ob gene in obese/diabetic subjects. Diabetes, 1996; 45:679-82.

Martin SS, Qasim A, Reilly MP. Leptin Resistance: A Possible Interface of Inflammation and Metabolism in Obesity-Related Cardiovascular Disease. J Am Coll Cardiol 2008; 52(15):1201-10.

Mergen M, Mergen H, Ozata M, Oner R, Oner C. A novel melanocortin 4 receptor (MC4R) genemutation associated with morbid obesity. J Clin Endocrinol Metab. 2001; 86(7):3448.

Mohamad WB, Mokhtar N, Mafauzy M, Mustaffa BE, Musalmah M. Prevalence of obesity and overweight in north-eastern peninsular Malaysia and their relationship with cardiovascular risk factors. Southeast Asian J Trop Med Public Health. 1996; 27(2):339-42. Available from http://elib.uum.edu.my/kip/Record/um647647 [Accessed on 16th September 2013]

Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, Wareham NJ et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature, 1997; 387:903-08.

National Institutes of Health, National Heart, Lung, and Blood Institute. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. NIH Publication no 98-4083, 1998. Available at: http://www.nhlbi.nih.gov/guidelines/obesity/ob_gdlns.pdf [Accessed on 20th July, 2013].

New Medical. The pros and cons of new anti-obesity drugs. 2006. Available from http://www.news-medical.net/news/2006/02/16/15937.aspx [Accessed on 16th September 2013]

O'Rahilly S, Farooqi IS. Genetics of obesity. Phil Trans R Soc B, 2006; 361:1095–1105.

Pomerleau J, McKeigue PM, Chaturvedi N. Factors associated with obesity in South Asian, Afro-Caribbean and European women. Int J Obes Relat Metab Disord. 1999 Jan;23(1):25-33. Available from http://www.researchgate.net/publication/13195760 [Accessed on 16th September 2013]

Rankinen T, Bray MS, Hagberg JM, Pérusse L, Roth SM, Wolfarth B, Bouchard C. The human gene map for performance and health-related fitness phenotypes: the 2005 update. Med Sci Sports Exerc, 2006; 38(11):1863-88.

Remacle C, Bieswal F, Reusens B. Programming of obesity and cardiovascular disease. Int J Obes Relat Metab Disord, 2004; 28(3):S46-53.

Sailaja AK, Bhatnagar P. PPARG Polymorphisms and their association with Type 2 Diabetes in South Indian population. IJPT, 2010; 2(3):623-33.

Shafique S, Akhter N, Stallkamp G, de Pee S, Panagides D, Bloem MW. Trends of under- and overweight among rural and urban poor women indicate the double burden of malnutrition in Bangladesh. International Journal of Epidemiology, 2007; 36:449–457.

Shuldiner RA, Munir MK. Genetics of Obesity: More Complicated Than Initially Thought. Lipids, 2003; 38(2):97-9.

Soyka M. Rimonabant and depression. Pharmacopsychiatry 2008; 41(5): 204-205. DOI: 10.1055/s-2008-1078744

Speakman JR. 2007. Genetics of Obesity**.** In**:** Fantuzzi G, Mazzone T (eds.), Adipose Tissue and Adipokines in Health and Disease**,** Springer, Germany. pp 221-236.

Starr R, Willson TA, Viney EM, Murray LJ, Rayner JR, Jenkins BJ, Gonda TJ, Alexander WS, Metcalf D, Nicola NA, Hilton DJ. A family of cytokine-inducible inhibitors of signaling. Nature, 1997;387: 917-21.

Stevens J, Couper D, Pankow J, Folsom AR, Duncan BB, Nieto FJ, Jones D, Tyroler HA.Sensitivity and specificity of anthropometrics for the prediction of diabetes in a biracial cohort. Obes Res, 2001; 9:696-705.

Vaisse C, Clement K, Guy-Grand B, Froguel P. A frameshift mutation in human MC4R is associated awith a dominant form of obesity. Nat Genet, 1998; 20(2):113-4.

Van Baal PH, van den Berg M, Hoogenveen RT, Vijgen SM, Engelfriet PM. Cost-effectiveness of a low-calorie diet and orlistat for obese persons: modeling long-term health gains through prevention of obesity-related chronic diseases. Value Health. 2008;11(7):1033-40. doi: 10.1111/j.1524-4733.2008.00328.x. Available from http://www.valueinhealthjournal.com/article/S1098-3015(10)60584-0/[Accessed on 17th September 2013]

Walley JA, Blakemore FIA, Froguel P. Genetics of obesity and the prediction of risk for health. Human Molecular Genetics, 2006; 15(2):R124-30.

Walston J, Silver K, Bogardus C, Knowler WC, Celi FS, Austin S, Manning B, Strosberg AD, Stern MP, Raben N, Sorkin JD, Roth J, Shuldiner AR.Time of Onset of Non-insulin-Dependent Diabetes Mellitus and Genetic Variation in the β3-Adrenergic-Receptor Gene. N Engl J Med, 1995; 333:343-47.

Wei M, Gaskill SP, Haffner SM. Waist circumference as the best predictor of noninsulin dependent diabetes mellitus (NIDDM) compared to body mass index, waist/hip ratio and other anthropometric measurements in Mexican Americans—a 7-year prospective study. Obes Res, 1997; 5:16-23.

Widen E, Lehto M, Kanninen T, Walston J, Shuldiner AR, Groop LC. Association of a Polymorphism in the β3-Adrenergic-Receptor Gene with Features of the Insulin Resistance Syndrome in Finns. N Engl J Med, 1995; 333:348-51.

World Health Organization. Controlling the global obesity epidemic. Available at: http://www.who.int/nutrition/topics/obesity/en/ [Accessed on 20th July, 2013].

Wyatt HR, Hill JO. What role for weight-loss medication? Weighing the pros and cons for obese patients. Postgrad Med, 2004; 115(1):38-40, 43-5, 58.

Yang R, Barouch LA. Leptin Signaling and Obesity: Cardiovascular Consequences. Circulation Research , 2007; 101:545-59.

Yen CJ, Beamer BA, Negri C, Silver K, Brown KA, Yarnall DP, Burns DK, Jesse Roth J, Alan R. Shuldiner AR. Molecular Scanning of the Human Peroxisome Proliferator Activated Receptor γ (hPPAR γ) Gene in Diabetic Caucasians: Identification of a Pro12Ala PPAR γ2 Missense Mutation. Biochem Biophys Res Commun, 1997;241(2):270-74.

Yeo GS, Farooqi IS, Aminian S, Halsall DJ, Stanhope RG, O'Rahilly S. A frameshift mutation in MC4R associated with dominantly inherited human obesity. Nat Genet, 1998; 20(2):111-2.

Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature, 1994; 372(6505):425-32.

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