Genetic Aspects of Human Obesity: A Review

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Introduction

Obesity is a common disease which has become more prevalent in all countries over the past few years. Obesity involves genetic predisposition but also metabolic, hormonal, behavioral, social and cultural aspects. A considerable amount of research on the genetics of obesity has been reported in the past few years.The most recent obesity gene map indicates that there are >200 genes or marker loci that have the potential to influence obesity. Scientists involved in the study of the causes of human obesity have become optimistic about the possibility of identifying the genes associated with the predisposition to this disease. A growing understanding of the human genome, the high degree of homology between humans and common laboratory animals for a large number of genes and chromosomal regions, and the availability of a whole variety of technologies and tools to study and manipulate DNA in the laboratory are among the most important reasons for the present level of hope in the obesity research community. Efforts are needed to identify among these genes those responsible for modulating the response to diet. Few candidate genes have been investigated for their role in the response of obesity phenotypes to changes in diet. The shift from genetic information to medical application will be possible in the near future, thanks to the development of genomic knowledge in humans. Advances toward a more comprehensive understanding of the molecular mechanisms involved in body weight regulation provide clues for therapeutic intervention in obesity. Genetic approaches can be used in the identification of new physiologic targets for therapeutic agents (i.e.genomic pharmacology).

Body weight and the prevalence of obesity are rising so rapidly in many countries that the World Health Organization has recognized that there is a "global epidemic of obesity.1" Obesity, which can be defined as a body weight more than 20% in excess of the ideal body weight, is a major health problem ,since it is associated with an increased risk for cardiovascular disease, diabetes, and an increased mortality rate.2-5 It is a result of a positive energy balance, which usually amounts to a tiny proportion of the total energy turnover. Energy intake, energy expenditure, and energy accumulation (as fat) may all be primarily disturbed. There is a great, and still insufficiently understood, variation in prevalence of obesity and in the rate of change of the prevalence. The prevailing contention is that the epidemic is due to the changes in the society - the so-called modernization--leading to overnutrition and a sedentary life.6-9 Although rapid globalization of the Westernized way of life is responsible for the large rise in the number of obesity cases (about 1 billion individuals are now overweight or frankly obese), obesity is a typical common multifactorial disease in that environmental and genetic factors interact, resulting in a disease state.10 There is strong evidence for a genetic component to human obesity: e.g., the familial clustering (the relative risk among siblings being 3-7)11and the high concordance of body composition in monozygotic twins.12 According to some estimates 40-70% of variation in obesity related phenotypes is

heritable.13
The aim of this review is to summarize some of the results obtained in genetic studies to identify obesity genes and to emphasize the power of genetic approach to provide clues for therapeutic intervention in obesity.

Human Obesity (OB) Gene and Leptin

Despite early evidence that genes are involved in the variation of body fat in humans, no obesity gene was identified until the Ob gene was discovered in mice.14 Genetic studies in obese mice have revealed the Ob. gene, its products leptin and the leptin receptor to be important factors in the regulation of both appetite and energy expenditure.15-17 A feedback regulatory loop with three distinct steps has been identified: (1) a sensor (leptin production by adipose cells) monitors the size of the adipose tissue mass; (2) hypothalamic centers receive and integrate the intensity of the leptin signal through leptin receptors (LRb); (3) effector systems, including the sympathetic nervous system, control the two main determinants of energy balance-energy intake and energy expenditure.18 Leptin is a 16-kilodaltons adipocyte-derived hormone which circulates in the serum as the free and bound forms. The leptin serum level reflects the amount of energy stored in adipose tissue. The leptin gene is expressed in adipose tissue, gastric epithelium, and placenta.Plasma leptin concentrations correlate with body fat content; they are elevated in obesity and decreased in anorexia nervosa. Moreover, it has been recently shown that in addition to its effects on food intake and energy expenditure, leptin influences the regulation of FSH, LH, ACTH, cortisol, and GH concentrations. Leptin acts through the leptin receptor, which belongs to the cytokine - receptor family.19-26 Leptin influences lipid metabolism by stimulating the expression of the proopiomelanocortin (POMC) gene in melanocortinergic neurons of the hypothalamus. POMC is the precursor of alpha-melanocyte-stimulating hormone (alpha-MSH), which binds to the melanocortin receptor MC4-R in the brain, decreases appetite, and activates lipid metabolism.27-30 In rodents as well as in humans, homozygous mutations in genes encoding leptin or the leptin receptor cause early-onset morbid obesity, hyperphagia, and reduced energy expenditure. Recent studies have demonstrated that Ob. gene expression is increased in human obesity.31

By the fluorescence in situ hybridization technique, the ob gene was assigned to human chromosome 7q31.3. The human ob gene spanned approximately 20 kilobases (kb) and contained three exons separated by two introns. The first intron, approximately 10.6 kb in size, occurred in the 5'-untranslated region, 29 base pair (bp) upstream of the ATG start codon. The second intron of 2.3 kb in size was located at glutamine +49. By rapid amplification of 5'-cDNA ends, the transcription initiation sites were mapped 54-57 bp upstream of the ATG start codon. The 172-bp 5'-flanking region of the human ob gene contained a TATA box-like sequence and several cis-acting regulatory elements (three copies of GC boxes, an AP-2-binding site, and a CCAAT/enhancer-binding protein-binding site).32-35

A complex, genetically variable region (polymorphism) close to the human obesity (OB) gene is associated with obesity in young women, but not young men. It is found that the genetic variants at the OB gene are also associated in these women with depression and anxiety, two of the behaviors most often associated with obesity. The results suggest the depression was a direct result of the OB gene variants and not just secondary to the

obesity.The cloning and sequencing of the mouse and the human obesity (OB) genes have been greeted with enormous excitement. When mice have a defective OB gene on both chromosomes, they are very obese and treatment with leptin, the product of the OB gene, causes rapid weight loss. This led to the hope that obese humans also had a defective OB gene, and treatment with leptin would also cause weight loss. However, many subsequent studies have shown that obese humans have too much leptin, not too little, and no mutations of the OB gene itself were found. Thus, the OB gene - leptin story is far more complex than originally thought. Obesity being the result of many different genes (polygenic), with a greater involvement of genetic factors in women and younger subjects, and suggest that variants of the OB gene are causally involved not only with human obesity but with its associated behavioral disorders.36

Role of melanocortin system in the control of body weight

The key role of the melanocortin system in the control of body weight in humans is evidenced by the discovery of mutations in POMC and MC4R genes that also result in severe obesity.The POMC gene expessed in human brain, gut, placenta and pancreas, is involved in the leptin/melanocortin pathway.37 Furthermore POMC is the precursor of other peptides which include adrenocorticotrophin (ACTH) and melanocyte stimulating hormone (MSH) involved in energy homeostasis.38 POMC-knockout mice have obesity, a defective adrenal development and an altered pigmentation.39 The MC4R gene is the most prevalent obesity gene, being involved in 1 to 4% of cases of obesity.40 MC4R mutations generally segregate in families under an autosomal dominant mode of inheritance with variable penetrance. Human obesity caused by MC4R mutations is similar to the more common forms of obesity , but with an earlier age of onset and a trend for hyperphagia in infancy, a trait that disappears with age.41

Gene-nutrient interactions in human obesity

A considerable amount of research on the genetics of obesity has been reported in the past few years. Despite evidence that genetic factors play a significant role in the etiology of this nutritional disease and the increasing number of obesity genes identified, relatively little is known about the role of genes in the response of obesity phenotypes to alterations in energy balance or diet composition. Recent evidence suggests that quantitative trait loci identified from animal models of diet-induced obesity could influence body fat in humans. The role of dietary fat in the etiology of obesity was addressed in several studies but remains controversial.42-47 It is generally accepted that high-fat diets induce an overconsumption of energy, which can lead to the development of obesity. Animal models of diet-induced obesity could be of benefit in understanding the role of gene-environment interactions in obesity. One benefit is the possibility of controlling rigorously the diet and other relevant environmental factors affecting obesity and the possibility of performing selective breeding studies. In a comparison of the response of 9 mouse strains to a high-fat diet, West et al found a range in adiposity gain of 6-fold between the sensitive AKR/J strain and the resistant SWR/J strain. Examination of the segregation of this trait in the progeny of crosses between the sensitive and the resistant strains showed a polygenic pattern of inheritance with a minimum of 3 loci determining the response to dietary lipids. Using the quantitative-trait-loci (QTL) mapping method, West et al identified 3 dietary obese (Dob) QTL. These loci-Dob1,

Dob2, and Dob3-were located on mouse chromosomes 4, 9, and 15, respectively. On the basis of the synteny between the mouse and human genomes, these QTL map to human chromosomes 1p36-1p35 and 9p13 for Dob1, 3p21 for Dob2, and 8q23-q24 for Dob3. Other QTL from the same cross were reported, but only in abstract forms.These positional candidate genes in rodents can be used to test for linkage with body fat phenotypes in humans.48,49 Using data from the Quebec Family Study, linkage between markers syntenic to Dob1 on human chromosome 1 and various obesity phenotypes was studied. The phenotypes investigated included BMI, subcutaneous fat assessed by the sum of 6 skinfold-thickness measures, and percentage body fat and fat mass derived from underwater weighing.These obesity phenotypes were adjusted for age and sex and were tested for linkage with the sibpair linkage method. Significant evidence of linkage was observed between BMI, subcutaneous fat, percentage body fat, fat mass, and the markers D1S193 and D1S200, whereas the marker D1S255 was found to be linked only to subcutaneous fat and percentage body fat.50,51

Recently recognized genes associated with obesity

Adipogene

Using the SSH (suppression subtractive hybridization, a technique which combines subtractive hybridization with PCR, to generate a population of PCR fragments enriched for transcripts of high or low abundance from differentially expressed genes) a new gene is identified, called Adipogene, which is overexpressed in the adipose tissue of the obese individuals and could be involved in obesity. Adipogene is encoded on chromosome 8, less than 1 centiMorgan (cM) from the beta3 adrenergic receptor (ADRB3) locus. Weak linkages were observed with body mass index (BMI) and three microsatellite markers located within 10 cM of Adipogene.52 Many appetite-regulating related peptides or receptors and some reproduction-related genes are found to be expressed in adipose tissue. Eight autocrine/paracrine systems are also described in the visceral adipose tissue. The visceral adipose tissue has important secretory functions and there is a complex local autocrine/paracrine regulatory network. It is suggested that the visceral adipose tissue is an important component of the neuroendocrine-immune network and plays an important role in regulating appetite not only via endocrine but also via autocrine/paracrine system.53,54

Gherlin Gene

Gherlin is a recently recognized gut-brain peptide originally derived from the gastric mucosa. It stimulates growth hormone release, increases appetite and facilitates fat storage and may interact with glucose metabolism.Variations in the gherlin gene contribute to obesity in children and may contribute glucose-induced insulin secretion.55

Lipoprotein lipase gene

Lipoprotein lipase is the enzyme responsible for the hydrolysis of triacylglycerol-rich lipoproteins and plays an important role in the regulation of plasma lipoprotein composition and concentrations and in the partitioning of exogenous triacylglycerol between adipose tissue for storage and skeletal muscle for oxidation. Moreover, it was shown recently that transgenic mice that overexpress lipoprotein lipase in the skeletal muscle were protected against diet-induced obesity only The lipoprotein lipase gene

located on chromosome 8p22 could therefore be considered a strong candidate for gene-environment interactions in obesity. Using data from our intervention studies in monozygotic twins, we found that a BamHI restriction length fragment polymorphism in the lipoprotein lipase gene was associated with the response to overfeeding .Changes in body weight and percentage body fat in response to overfeeding were more important in carriers of the BamHI restriction site (9.1 kg weight and 7.9% body fat) compared with noncarriers (7 kg weight and 5.6%).56,57 Similarly, a lipoprotein lipase HindIII polymorphism located in intron 8 of the gene was found to modulate the relation between visceral fat and plasma triacylglycerol.58 Other data suggest that the apo A-II MspI polymorphism is associated with lower HDL2-cholesterol concentrations, but only in men with high amounts of abdominal visceral fat or with evidence of an insulin-resistance state.59

b3-AR (adrenocepter) and UCP(uncoupling protein) genes

In human beings, the b3-AR are expressed in fat and adipocytes lining the gastrointestinal tract.In mature brown adipocyte cells, stimulation of b3-AR by norepinephrine activates UCP via the cyclic adenosine monophosphate (cAMP)metabolic pathway. UCPs are inner mitochondrial membrane transporters that dissipate the proton gradient, releasing stored energy in the form of heat. An A to G variation in UCP1 was associated with a gain in fat mass in a Quebec family study.Trp®Arg mutation of b3-AR gene occurred in the French morbid obese population.60-66

TH, INS and IGF2 genes

The subtelomeric region of 11p harbours three closely linked genes, TH, INS and IGF2, that have been associated with obesity, size at birth, type I diabetes, polycystic ovary syndrome and possibly hypertension.67

BBS1 Gene

Bardet-Biedl syndrome is a complex human obesity syndrome, a genetic disorder with the primary features of obesity, pigmentary retinopathy,polydactyly, renal malformations, mental retardation and hypogenitalism. Missense mutation of BBS1 gene is the cause of this syndrome.68

X chromosome and obesity

Many research workers have completed autosomal genome scans aimed at detecting linkage to obesity-related phenotypes. Only few groups have completed scans of the X chromosome, however. A French group found linkage to a marker in chromosome region Xp22 and Xq and a Finnish group reported linkage to a marker in Xq24. Both studies used qualitative thresholds of BMI(Body mass index)as the obesity phenotype. Two genetic syndromes with obesity as a feature map to a broad interval on Xp, MEHMO (mental retardation, epileptic seizures, hypogonadism and genitalism, microcephaly, obesity) syndrome and Simpson-Golabi-Behmel syndrome. Quantitative trait loci have also been mapped to this region, one for body weight in mice and another for back-fat thickness in swine. There is a suggestive evidence of linkage of a measure of fat patterning, the WHR(waist/hip ratio), to markers in human chromosome region Xp21-22.69-71

Pharmacogenetics of obesity

Validating the usefulness of gene screening in humans is the successful example of leptin replacement in a child with congenital leptin deficiency. In this 9 year old girl daily subcutaneous injection of recombinant human leptin for a year was well tolerated and led to an important and sustained fat mass loss.The most profound effect was reduction of energy intake and a definite improvement in her eating behaviour,confirming the role of leptin in regulation of appetite.72 This strategy of genetic screening for the defective component will probably be extended to the treatment of other monogenic forms of obesity. Following the discovery of the leptin as an adiposity signal, clinical trials using recombinant leptin have been developed in large obese populations and dose related body weight loss was noted.73,74 The question remains as to whether molecules that are clinically active in monogenic forms of obesity might be used in situations of obesity with variable expressivity and penetrance,and as well as in commoner (polygenic)forms. Significant reduction of body fat after treatment with intranasal melanocortin melanocyte-stimulating hormone MSH/Adrenocorticcotrophin fragment (MSH/ACTH4-10)was recently observed in small group of individuals.75

Knowledge of the regulation of ob gene expression and factors implicated therein will therefore be important in the prevention and treatment of obesity. Administration of high doses of glucocorticoids have a dramatic catabolic action, resulting in a marked decrease in food intake and body weight. In addition, glucocorticoid treatment induces ob gene expression.The effects of corticosteroids on ob gene expression are due to a direct action of these hormones on ob gene transcription. Alternatively, these hormones may have indirect effects. Administration of high doses of glucocorticoids may, for instance, influence the plasma concentrations of other hormones that regulate food intake, such as dehydroepiandrosterone or corticotropin-releasing hormone. Alternatively, high doses of glucocorticoids increase gluconeogenesis, predispose to diabetes, and may therefore increase plasma glucose concentrations. According to the glucostasis theory, decreased plasma glucose concentrations would be a signal, triggering food intake.Thus, glucocorticoids may act by increasing plasma glucose concentrations, which in its turn may induce ob gene expression resulting in a reduction of food consumption act by increasing plasma glucose concentrations, which in its turn may induce ob gene expression resulting in a reduction of food consumption.76-79

Drugs that play a role in energy expenditure have also been developed. The use of reagents with b3-AR agonistic pharmacologic properties has gained renewed interest thanks to the discovery of b3-AR mutation and its phenotypic consequence.80

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