Single Nucleotide Polymorphisms (SNPs) and the Search for Obesity-Related Genes

editorial

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Obesity is implicated in a variety of chronic problems, among them diabetes, cardiovascular diseases and cancer. Worldwide, its economic burden is thought to be around billion of dollars in direct health care costs and also the cost of lost productivity in affected individuals. Official data from Instituto Brasileiro de Geografia e Estatístistica (IBGE) released in December 2004 showed that 38.8 million of Brazilians are either overweight or obese. How and why some individuals gain weight and the mechanisms that make it not easy to sustain weight loss can provide insights into the pathways that regulate food intake.

The last two decades have seen an explosion of information regarding the relationship between genome variation and biological function of a given protein in the hope that single nucleotide polymorphisms (SNPs), which account for over 90% of genetic variation in the human genome, will allow genes that are related to complex diseases to be identified. Single nucleotide polymorphisms (SNPs) and small insertions or deletions (indels) are the most common type of genetic polymorphisms and are appropriate for molecular marker development due to their abundance within the genome and their slow mutation rate.

In this issue, Dr. Hinuy and colleagues (1) report the association between the leptin polymorphism G-2548A and obesity-related trait in a sample of 228 Brazilian women and their work confirm previous data about LEP in obese women. Leptin (*LEP*; MIM +164160), whose name is derived from the Greek word "leptos", meaning "thin", is an adipocyte-specific hormone that regulates adipose-tissue mass through hypothalamic effects on satiety and energy expenditure. The *LEP* gene is the human homolog of the ob gene mutant in the mouse '*obese*' phenotype cloned by Zhang e col. in 1994 (2). The gene, located at 7q31.3, encodes a 4.5-kb adipose tissue mRNA with a highly conserved 167-amino acid open reading frame and consists of 3 exons and 2 introns and spans about 18 kb (Gong e col., 1996(3). It acts through the leptin receptor (*LEPR*, MIM *601007), a single-transmembrane-domain receptor of the cytokine receptor family which is found in many tissues in several alternatively spliced forms. Genetic leptin deficiency is extremely rare, and elevated plasma leptin usually accompanies obesity, suggesting leptin resistance. In addition to its role in obesity, leptin has also been associated with breast cancer tissue. Indeed, results of the Million Woman Study in the United Kingdom established that being overweight or obese is associated with a higher risk of postmenopausal breast cancer and lower survival. Another important finding is that some antipsychotic drugs are associated with weight gain potential as well as with adiposity-dependent and possibly adiposity-independent changes in insulin sensitivity and lipid metabolism, increasing the risk of metabolic disease. However, the role of leptin in health and disease remains to be fully established. Therefore, in the 18 yr since the original paper

by Zhang e col. (1994), there has been a continuing search for other genes whose polymorphisms contribute to obesity.

The major breakthrough in obesity genetics was the discovery of *FTO* (fat mass and obesity-associated) gene through genome-wide association. It was the first locus harboring a predisposing obesity gene. Large-scale data by Scuteri e col. (2007) (3) and Frayling e col. (2007) (4) unequivocally demonstrated that the *FTO* gene is associated with substantial changes in body mass index (BMI), hip circumference, and body weight. Newly data published in Nature Genetics (5) provide strong evidence that common variants near *MC4R* gene are associated with fat mass, weight and risk of obesity in individuals of European descent. In addition, the authors showed that common variants near the *MC4R* and *FTO* genes seem to have an additive effect on body mass index (BMI) and suggested that further studies are needed to firmly establish the genetics determinants of monogenic as well as multi-factorial forms of the same disease. In a soon to be published report, Ng e col. (2008)(6) studied 13 associated single nucleotide polymorphisms (SNPs) near *TCF7L2*, *SLC30A8*, *HHEX*, *CDKAL1*, *CDKN2A/B*, *IGF2BP2* and *FTO* genes in type 2 diabetes and obesity in individuals of Asian ancestry from Hong Kong and Korea. Their findings supported the relevant but differential contribution of these polymorphisms for type 2 diabetes and obesity in Asians as compared to Europeans. To date, most of these large-scale studies discussed above have been conducted in European and Asian populations. The Brazilian population is the result of five centuries of interethnic crosses between the trihybrid populations of the Americas, forming the fifth largest and one of the most heterogeneous populations in the world. Since ethnic differences have been demonstrated worldwide, data dealing with polymorphisms must be replicated in other populations and such studies should be performed in Brazil. In addition, it is time to investigate not only genetic variation but also the functional impact of these variations in cells and organs. Studies in peripheral tissues from humans and the use of animal models to determine changes in pathways that are supposed to affect lipid metabolism, insulin response and energy expenditure are on the way. The quest to unveil the complexity of the obesity phenotype is paramount and only identifying those key molecular elements will allow an effective strategy to prevent and/or treat this deleterious condition.

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