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Nutrigenetics in Obesity

- Gene and environment interaction in obesity -

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The World Health Organization (WHO) has identified obesity as "one of today's most blatantly visible – yet most neglected – public health problems," with an estimated 300 million affected adults worldwide. This epidemic of overweight and obesity has been called by some as "globesity" to emphasize that is a global problem and that, unless action is taken, billions worldwide will suffer as they get older from the debilitating conditions associated with obesity including cardiovascular disease, stroke, some cancers, adult-onset diabetes and osteoarthritis.

Obesity is developed by multiple factors including various actions of several genes and environmental factors. In general, the inherited factors are known to be responsible for about one-half of the variation in body mass, an index of obesity, within a population. However, it is uncertain what types of variants practically have an effect on complex genetic traits such as obesity.

Human studies investigating the specific variants associated with obesity have been achieved mainly by a linkage analysis and association studies. Linkage analysis has been used principally in mapping genes responsible for single gene disorders, but in general, it has been less successful for studying multigenic diseases such as obesity. Actually, individuals affected with monogenic forms of obesity (Mendelian obesity syndromes or single-gene disorders) represent only a small portion of the obese population and cannot explain the magnitude of the problem involved with obesity that industrialized societies are facing today. Although whole genome scans identify similar regions as being linked to obesity, there is diversity of the results, possibly due to the low power of linkage to find genes with modest effects or different study designs or a variation of populations.

Association studies, another way identifying genes involved in obesity, have supplied a noteworthy information for the characterization of genes with a small contribution to obesity. Genes and variants that have a role in metabolism in obesity or that is located within an area of linkage are selected as candidates for obesity. They are selected on the basis of their function in biochemical pathways related to the adipose tissue or the regulation of energy balance (intake/expenditure). More than 70 genes have been recently reported to be positively associated with phenotypes of obesity. For example, diverse obesity phenotype indicators such as body mass index and central fat distribution, have shown positive associations with the variants of some genes such as apolipoprotein B (apoB), apoD, apoA2, apoA4, apoE, adiponectin (ADIPOQ), β-adrenergic receptor 2 and 3 (β2-AR, β3-AR), tumor necrosis factor α (TNF-α), lymphotoxin, leptin (LEP), peroxisome proliferators activated receptors (PPAR), perilipin (PLIN), uncoupling proteins 1, 2 and 3 (UCP1, UCP2, UCP3) and others.

Influences of the adiponectin gene on obesity-related risk in response to weight reduction

Adiponectin, an insulin-sensitizing and anti-inflammatory adipokine, synthesized primarily in the adipose tissue has been suggested as a promise candidate factor for mediating the weight loss effects on the features of insulin resistance (IR) through the involvement in the metabolic action and its potential role in the development of obesity and type 2 diabetes. Plasma levels of adiponectin are lower in obese subjects, and these low levels have been associated with several risk factors for obesity-related risk including IR. It was recently described that several single nucleotide polymorphisms (SNPs) and haplotypes of adiponectin (ADIPOQ) gene were associated with plasma adiponectin levels.

Two hundred and ninety four nondiabetic/overweight-obese Koreans participated in a clinical intervention study lasting 12 weeks involving an intake reduction of -300kcal/day to determine whether two SNPs (45T>G/276G>T) at the ADIPOQ locus influence changes in circulating adiponectin and the features of IR in response to a weight loss interventions. Especially, the G/G homozygotes at ADIPOQ SNP276 have beneficial effects on the improvement in IR after modest weight loss by modulation of circulating adiponectin levels.

The perilipin (PLIN) gene and mild weight reduction in cardiovascular disease risk factors related obesity

Perilipin is the predominant protein associated with adipocyte lipid droplets. The key roles of perilipin in regulating lipid storage in adipocytes and the accumulation of body fat have been demonstrated in both *in vitro* and *in vivo* studie. Genetic variation at the perilipin (PLIN) gene has been associated with modulation of the perilipin content and lipolytic rate in humans. Consistent with those functional observations, significant associations between genetic variants at this locus, body-weight and obesity risk in several ethnic groups were found. We investigated the allelic associations for each of the SNPs of the PLIN gene with circulating FFA concentrations and abdominal fat distribution in response to weight loss. 177 nondiabetic/overweight-obese Koreans participated in a 12-week clinical intervention study of －300kcal of intake /day (24). Of 7 PLIN SNPs (6209T>C, 10076C>G, 10171A>T, 11482G>A, 13042A>G, 13048C>T and 14995A>T), the 10171A>T and 10076C>G were in the strongest positive linkage disequilibrium (D'=0.923, R^2=0.839, P<0.001). The 11482G>A and the 14995A>T were in relatively strong positive linkage disequilibrium (D'=0.824, R^2=0.578, P<0.001). Low calorie diet induced a mild weight loss of 4.6% with reduced abdominal fat. For PLIN 10076C>G, GG subjects showed higher reduction of FFA than those with CC (P=0.010). However, subjects with homozygous rare alleles of either 11482G>A (P=0.045) or 14995A>T (P=0.029) showed increased FFA levels. There were no significant allelic differences of SNPs 6209T>C, 10171A>T, 13042A>G and 13048C>T in changes in FFA levels. For 11482G>A/14995A>T haplotypes, compared to GA/GA subjects who were G/G at 11482 and A/A at 14995, those with nGA/nGA haplotype (non-GA haplotype carriers) showed greater reduction in waist circumference (P=0.042) and visceral fat area (P=0.004) at L4 level than those with GA/GA. Subjects with GA/GA haplotype showed the highest concentration of urinary excretion of PGF2α and circulating oxidized LDL at baseline and had greater reduction after weight loss. Our results have shown that genetic variants at the PLIN locus respond differently to mild weight loss in changes in circulating FFA levels, abdominal fat areas and lipid peroxides.

However, most findings have not come to the same conclusion for many of obesity-related genes. Only a part of reported associations are likely to be probable but difficult to replicate with small studies that are underpowered to detect the main effect of the genes to obesity-related risk. Therefore, further studies that comprise a more productive approach using multiple genes as well as a functional study need to be evaluated for the nutrigenetics in obesity.