THE SCIENCE BEHIND THE

Weight Management genetic test

Introduction to the Summary of Scientific Evidence

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Obesity has become an increasingly important clinical and public health challenge worldwide. According to the International Obesity Taskforce estimates, there are about 1.1 billion overweight and 350 million obese individuals worldwide **(1)** and this number is expected to grow to alarming levels in the next decade. In the U.S., prevalence of obesity has more than doubled in the past 25 years. Nearly two-thirds of adults are either overweight or obese **(2)**, as characterized by an excess of fat (adipose) tissue. The World Health Organization (WHO) and other public health agencies recommend determination of overweight/obesity status for an individual by the measurement of three different parameters which include, body mass index (BMI), total body fat, and waist/hip ratio (WHR). The cutoff points for classification of an individual as overweight or obese have been well defined for each of these parameters **(3)**. The overweight and obese subjects are at a higher risk of developing one or more serious medical conditions, including hypertension, dyslipidemia, heart diseases and diabetes. Together these conditions are the second leading cause of preventable death.

Human obesity arises from the interactions of multiple genes, environmental factors and behaviors, rendering management and prevention of obesity very challenging. Lack of physical activity and easy availability of palatable foods are generally regarded as the primary aspects of our modern lifestyle that have contributed to the increase in obesity worldwide. Despite the fact that we are all exposed to the same environment, not everyone becomes obese. This could be attributed to individual genetic differences. Genetics determines an individual's susceptibility to obesity when exposed to an unfavorable environment as well as the way he/she can respond to diet and exercise. There have been multiple reports that describe the heritability of obesity and also utilize genetic association studies to identify the gene-gene, gene-environment and gene-diet interactions involved in the development of obesity. These studies have identified a small number of single nucleotide polymorphisms (SNPs) that respond to diet and/or exercise. For example, people with certain SNPs are more sensitive to the amount of fat in the diet, while individuals with other SNPs are more resistant to exercise-induced weight loss.

Interleukin Genetics has developed a genetic test panel in the area of Weight Management (WM), which includes the genes that have been validated as significant modifiers of body weight and responsiveness to diet and exercise. The genes were selected from the Obesity Gene Map Database based on a comprehensive review of the existing scientific literature using very stringent selection criteria by a team of experts from genetics, nutrition, obesity and weight management areas.

Process Used to Develop the Weight Management Genetic Test Panel

1. Dr. Louis Perusse, one of the authors of the Obesity Gene Map review **(4)**, screened the evidence for all genetic variations that were associated with body weight, body mass index, or body fat and identified those that had been replicated in at least three clinical studies. Out of hundreds of genes reported in the scientific literature relative to obesity, only 16 met this first criterion.

2. A team of experts then reviewed all evidence on the 16 gene variations to determine which of those met the following criterion:
   - Had proven biological function. In fact, all of the genetic variations in the test panel produce a change in the amino acid structure of the protein and change the activity of the protein.
   - Had a plausible biological role in weight management. For example, some of the gene variations produce a change in the amount of fat absorbed from a meal or change carbohydrate metabolism.
   - Had evidence from clinical studies that individuals with the different genotypes had a differential response to either certain diets or physical activity.

3. Five variations in four genes met all of the above scientific criterion and are included in the Weight Management Genetic Test Panel. These gene variations thus impact various pathways that influence body weight and have been associated with elevated risk for obesity and for their ability to differentiate a subject's response to weight management interventions by genotypes. Weight Management Panel genes and variants include:
   - Fatty acid binding protein 2 (FABP2) Ala54Thr;
   - Peroxisome proliferator-activated receptor-gamma (PPARG or γ) Pro12Ala;
   - Beta-2 adrenergic receptor (ADRB2) Arg16Gly and Gln27Glu; and
   - Beta-3 adrenergic receptor (ADRB3) Arg64Trp

The weight management (WM) test panel is designed to assist with effective management of body weight by guiding diet and exercise programs based on genetic differences in metabolism and fat absorption. Following are summaries of scientific evidence for each of the polymorphisms included in the Weight Management Genetic Test.

FABP2 Ala54Thr (A54T) Polymorphism

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The FABP2 gene encodes the intestinal form of fatty acid binding protein2 (FABP2). FABP2 protein is found in small intestine epithelial cells where it strongly influences fat absorption. Variations in DNA or polymorphisms in the gene result in greater binding of the fatty acids (released in the intestine from dietary fat consumption) which in turn results in higher absorption of fat **(5, 6)**. One such polymorphism, Ala54Thr, has been found to be associated with obesity. Multiple clinical research studies have indicated that individuals with the Thr54 form of the protein show increased absorption and/or processing of dietary fatty acids by the intestine. The Thr54 variant has been associated with elevated BMI and body fat **(7)**, increased abdominal fat **(8)**, and obesity and higher leptin levels (protein hormone that plays a key role in regulating energy intake and energy expenditure, including appetite and metabolism) **(9)**. Multiple dietary intervention clinical research studies show that the Ala54Thr polymorphism affects the response to changes in dietary fat in test meals. It has been reported that individuals with two copies of the 54Thr/Thr variant show increased levels of postprandial triglycerides **(10, 11)** and increased levels of 14-18-carbon fatty acids **(12, 13)** compared with the 54Ala/Ala form of the protein. A group of obese, non-diabetic patients analyzed before and three months after a lifestyle modification program, consisting of hypocaloric diet (1,520 kcal/day) and aerobic exercise three times per week, **(14)** showed that carriers of the Thr54 allele (compared to the wild-type 54Ala/Ala homozygotes) failed to have a significant reduction in fat mass, LDL-cholesterol levels, and leptin levels. Other studies have demonstrated an association between FABP2 genotype and dietary fat intake, with moderate carbohydrate intake **(15, 16)**.

PPARG Pro12Ala (P12A) Polymorphism

Peroxisome proliferator-activated receptor-gamma (PPARG) protein is abundantly expressed in fat cells and plays a key role in the formation of fat cells. It is crucial to lipid (fat) metabolism. Polymorphisms in this gene that are responsible for expression of variant forms of the protein have been associated with the development of type 2 diabetes. The variant form of the protein (Ala12) is associated with a decreased binding affinity to its target genes and thus with a reduction in its ability to regulate the expression of these target genes **(17)**. According to the 2005 obesity gene map **(18)**, multiple studies show association between PPARG gene and obesity involving the Pro12Ala polymorphism. Multiple clinical studies showed that individuals with the 12Pro/Pro form of the protein were more affected by the amount of fat in the diet **(19)** and had a direct association between higher BMI and the amount of fat intake as opposed to the Ala12 carriers **(20)**. These findings clearly indicated that 12Pro/Ala (carriers of one copy of the allele) individuals are more sensitive to the amount of fat in the diet **(21)**. Similarly, in a 3-year dietary and exercise intervention study, 12Ala/Ala subjects showed higher weight loss than in Pro12/Ala or in 12Pro/Pro subjects. Clinical studies consistently show that Pro12 allele is the high-risk allele and 12Pro/Pro subjects are more sensitive to the amount of fat in the diet, more resistant to weight loss and at increased risk of diabetes. The evidence of gene-diet interaction is strong.

PPARG protein is abundantly expressed in fat cells and plays a key role in the formation of fat cells.

ADRB2 Arg16Gly (R16E) and Gln27Glu (Q27E) Polymorphisms

The beta-2 adrenergic receptor (ADRB2) gene product ADRB2 protein is expressed in fat cells. This receptor protein is involved in the mobilization of fat from the fat cells for energy in response to hormones called catecholamines (adrenaline, noradrenaline and dopamine). Several polymorphisms of this gene that result in amino acid changes have been identified. The two main well-characterized polymorphisms Arg16Gly and Gln27Glu are the most common in Caucasians. Laboratory studies indicate that these polymorphisms affect the overall expression (production) of the receptor **(22)**. The recent obesity gene map **(18)** shows association between variants in the ADRB2 gene and obesity, with most of the positive findings involving the Arg16Gly or Gln27Glu polymorphisms. Multiple studies show association between Glu27 and Gly16 alleles carriers and abdominal **(23, 24)** and central obesity **(25)**. A long-term clinical study showed that weight gain from childhood to adulthood **(26)** and weight gain during adulthood **(27, 28)** are higher in individuals who carry the Gly16 allele. A clinical study involving women with high carbohydrate diet reported that women with 27Gln/Glu genetic makeup had increased risk of obesity, while no association of obesity was observed in 27Gln/Gln women **(29)**. 27Gln/Gln was found to be a risk genetic profile in studies involving overfeeding of identical twins where higher weight gain and subcutaneous fat were observed compared to those with the Glu27 allele **(30)**. A study of overweight Japanese men enrolled in a 24-month weight loss program (1,600 kcal/day and aerobic exercise one hour daily) showed that men with the Gly16 allele were more resistant to weight loss and more likely to regain body weight after 6 months **(27)**. Women who were more active during their leisure time and were carriers of the Glu27 allele had higher BMI compared to similarly-active carriers, suggesting that these women may be more resistant to losing weight **(31)**. Results from intervention studies (exercise or diet) involving the Arg16Gly polymorphism indicate Gly16 allele is the high-risk allele, especially in studies involving exercise and endurance training. Long-term studies suggest that the Gly16 allele is associated with greater weight gain over time. Results from association studies suggest that the Glu27 allele is associated with an increased risk of obesity, abdominal obesity and obesity when adhering to a high carbohydrate diet.

ADRB2 receptor protein is involved in the mobilization of fat from the fat cells for energy in response to hormones called catecholamines (adrenaline, noradrenaline, and dopamine).

ADRB3 Trp64Arg (R64W) Polymorphism

The beta-3 adrenergic receptor (ADRB3) protein is expressed in visceral adipose tissue and the fat depot where it is involved in the regulation of fat breakdown (lipolysis). Laboratory studies on isolated fat cells (adipocytes) show that the Trp64Arg polymorphism in the gene results in reduced lipolysis in response to a specific agonist in cells carrying the Arg64 allele **(32)**. Multiple clinical studies showed that Arg64 variant on the ADRB3 gene is strongly associated with increased BMI **(33-36)**. A case-control study (158 obese, 154 normal weight) showed an increased risk of obesity (OR = 2.98) in Arg64 carriers, but only in subjects who were sedentary **(37)**. A study of 61 obese women with type 2 diabetes enrolled in a 3-month intervention combining low-calorie diet and exercise showed that women with the Arg64 variant lost less weight (4.6 kg vs. 8.3 kg) and body mass (1.9 kg/m2 vs. 3.4 kg/m2) than 64Trp/Trp women **(38)**. A study performed in 76 perimenopausal women enrolled in a 3-month intervention combining exercise and diet found that 48% of the women with the Arg64 variant lost weight compared to 69% of the women without the variant **(39)**. These two studies suggest that the variant is associated with difficulty in losing weight through diet and exercise. A study **(40)** performed on 29 men and 41 women showed that ADRB3 Arg64 carriers experienced greater loss of fat mass and trunk fat following 24 weeks of supervised aerobic exercise training compared to non-carriers.

The ADRB3 protein is involved in the regulation of fat breakdown (lipolysis).

ADRB2 Arg16Gly (R16E) and ADRB3 Trp64Arg (R64W) Polymorphisms and Exercise

A number of studies have investigated the role of ADRB 2 and 3 polymorphisms on the risk of developing obesity and assessed the effect of physical activity on this risk. In a case-control study it was observed that the effect of the ADRB3 variant on obesity changes depending on the recreational physical activity levels **(41)**. Physical activity for each individual was evaluated based on a validated questionnaire about their leisure-time physical activities. Metabolic Equivalent Task (MET) value was assigned to each activity and a composite value of total weekly MET-hours per participant was computed. The ratio (M/S) between METs hours/week in physical activity (M) and the time spent sitting down during leisure time (S) was used to predict recreational energy expenditure. An increased obesity risk among carriers of the mutation (Arg64) was dramatically diminished when subjects had recreational energy expenditure levels higher than the median (M/S > 0.5). In the HERITAGE Family Study, it was observed that carriers of Arg16 and Arg64 alleles, respectively, for ß2- and ß3- adrenergic receptors showed a greater decrease in fat mass in response to endurance training (METs > 6) than subjects with other allelic combinations **(42)**. In a study conducted on 313 Spanish subjects, it was observed that carriers of Arg64 alleles in the ADRB3 gene could reduce the risk of developing obesity if their physical activity level was ≥ 20 MET hours/week **(41)**. Several observational studies have reported that women, who are overweight or obese at the time of diagnosis as well as who gain weight after diagnosis, are at greater risk for breast cancer recurrence and death than the non-overweight women **(43)**. To determine whether ADRB3 polymorphism (Trp64Arg) is associated with obesity and levels of subcutaneous or visceral fat in African-American breast cancer cases, a clinical study was conducted on 219 African-American breast cancer patients **(43)**. Each household or recreational activity was categorized as light (<3 METs), moderate (3-6 METs) or vigorous (>6 METs) intensity based on The Compendium of Physical Activities by Ainsworth et. al. **(44)**. The results from this study showed that physical activity modifies the effect of ADRB3 on obesity **(43)**. Consistent with the study of Spanish subjects **(37)**, these findings also indicated that the higher risk of obesity among carriers of the ADRB3 variant (Arg64) may be altered by moderate levels of physical activity (>13 MET hours/week).

ADRB2 and ADRB3 polymorphisms respond differently to differing amounts of physical activity.

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