Gene SNP™

DNA Analysis

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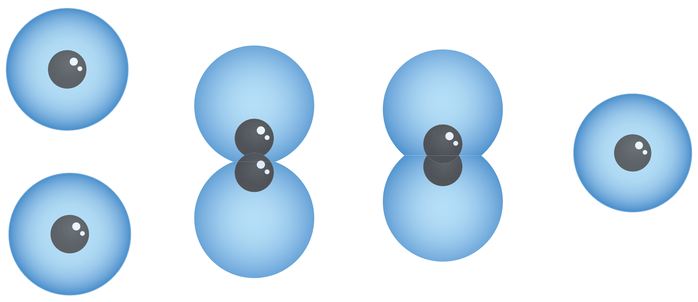
This genetic profile contains information about the specific genetic material your cells contain. Remember that even though your genetic material influences how your body responds to your world, it is only one part of that response. For example, you may have a genetic tendency toward high blood pressure, but your blood pressure is normal. On the other hand, you may not have a genetic tendency toward high cholesterol, but your cholesterol levels may still be elevated. Your genetic material is just one piece of the puzzle—definitely an important piece, but one that is influenced by many other factors. Some of these factors, like diet, exercise, and how you respond to cravings, you are able to control. Others may not be controllable, but understanding why you are the way you are can help.

GENETICS 101

DNA is the genetic material in our cells that makes us who we are. You inherit this genetic material, half from your mother and half from your father. It determines your physical appearance, like your hair and eye color.



You get half of your DNA from your mother and half from your father.

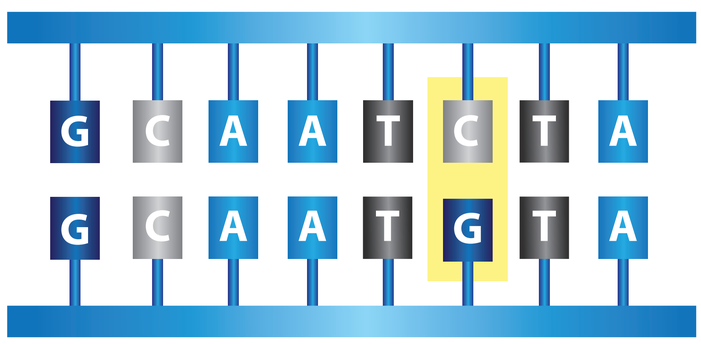
It can also influence how your body functions, such as whether you are able to process fat efficiently or tend to have high blood pressure. Knowing what your individual genetic profile says can help you understand your body, recognize your deficiencies, and possibly overcome any negative genetic tendencies.

Your genotype is your genetic makeup, your actual strands of DNA comprised of a 3 billion base strand in which each individual base is one of four possible molecules. The four types of bases are: adenine (A), thymine (T), guanine (G), and cytosine (C). These bases form long, twisted-chains of DNA, and a piece of DNA containing millions of base pairs packed tightly is called a "chromosome."

DNA is made up of billions of base pairs.

The base pairs of DNA give instructions to the body to perform certain actions. For example, some base pairs contain instructions on making enzymes to digest food. The base pairs may give very specific instructions, too, such as telling only certain skin cells to make hair while other skin cells do not.

Sometimes, when DNA is being copied to make new cells, "mistakes" are made in the copying of bases. These variations are called **SNPs** or single-nucleotide polymorphisms. For example, in a series where the original base says "AATC," the copied base may say "AATG."



Sometimes mistakes called SNPs occur in our DNA.

This mistake, like a typo or a mistake in a computer program, can change the instructions the DNA gives to the body. The change may be minor or not have any noticeable effect. Or it may be a major change that affects the body significantly, such as failing to make a protein that leaves the body susceptible to disease.

The other genes you have and your environment determine how your body responds to the SNPs that you have. For example, you may have other genes that compensate for the "mistake" in the copying. Or you may have compensated for the error by eating (or not eating) certain foods. You and another person may have the same SNP but respond to it differently and thus have different phenotypes.

This genetic report contains information about your genetic profile or genotype. It tells you what SNPs you have, or where alterations happened in copying your genetic material. Understanding the potential issues your personal genotype contains will help you deal with and possibly even overcome the way those genes may be expressed. This report gives you practical suggestions to potentially improve your phenotype, or the expression of your genetic material, and potentially live a healthier lifestyle.

TERMS YOU SHOULD KNOW

DNA *(DeoxyriboNucleic Acid)*: A nucleic acid that carries genetic information contained in each cell

Genotype: The genetic makeup of an organism

Phenotype: The expression of a certain trait based on genetic and environmental influences

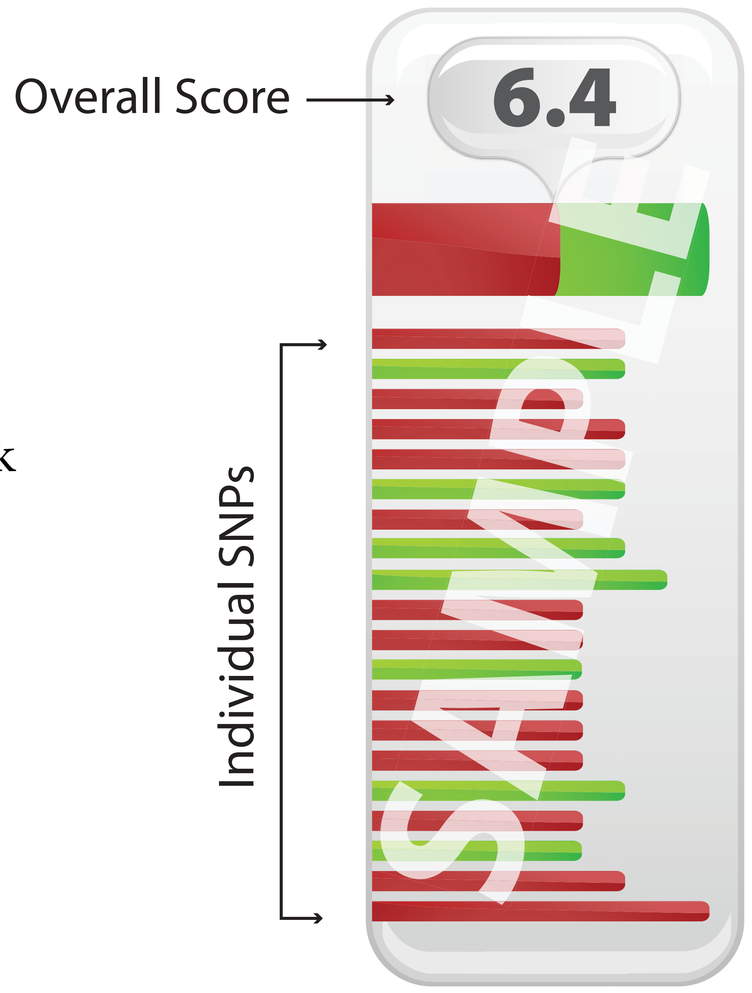
SNP *(Single-Nucleotide Polymorphism)*: A commonly found change in a single nucleotide base in a DNA sequence

HOW TO READ THIS REPORT

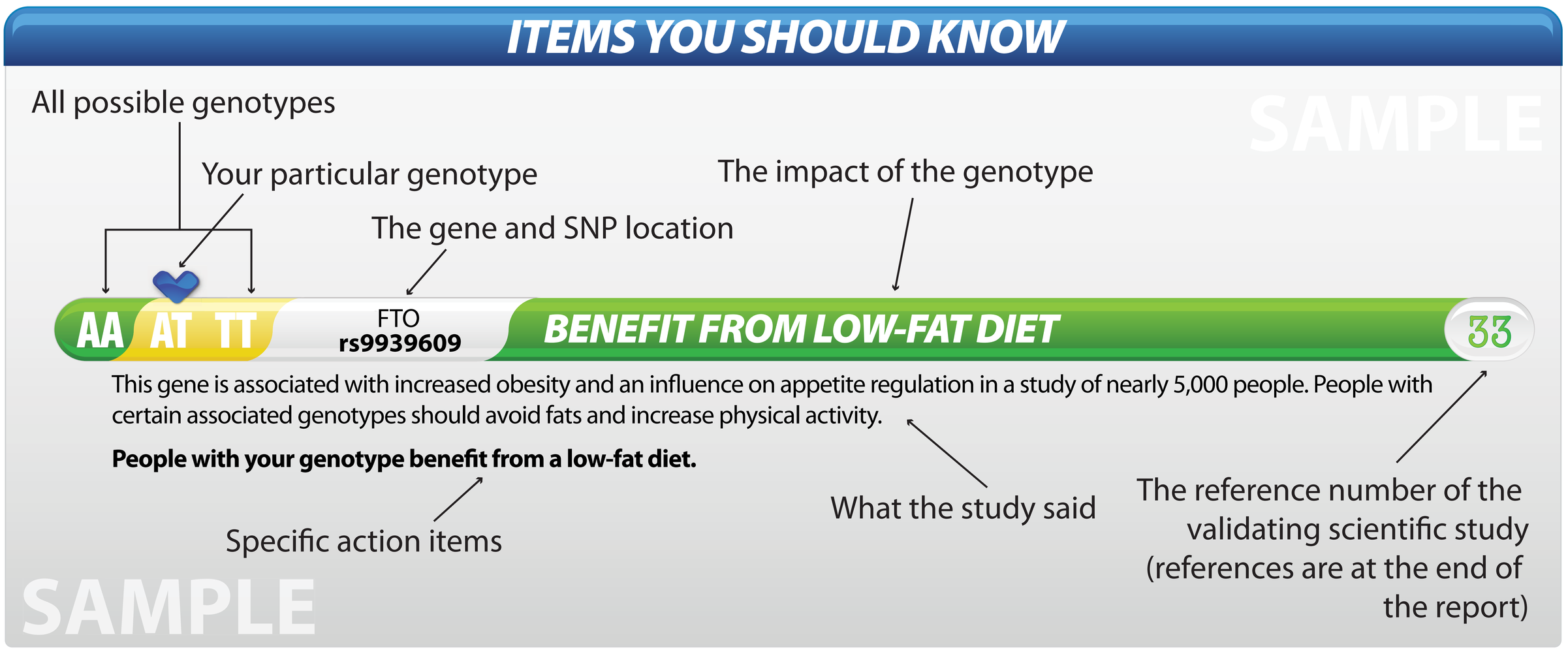
This report details the findings from an analysis of 48 SNPs of your genetic material. (For more info about basic genetics and definitions of unfamiliar terms, see Genetics 101.) The first section, Personal Genetic Profile is a summary of the most significant findings from the areas examined:

- Your General Obesity Index
- Your Food Choices
- Your Exercise and Activity
- Your Health
- Your Behavior
- Vitamins & You

The first section shows your overall score on a "general obesity index." This score evaluates 22 SNPs that have been studied and shown to be related to a genetic risk of obesity. Each green (positive) or red (negative) bar shows a SNP and how it relates to your personal risk of obesity. These findings are weighted and calculated to give you an overall score.



The rest of these two pages gives you a quick overview of positive (green), negative (red), and neutral (grey or yellow) findings along with action items—what you can do to work with the genes you've got. The sections that follow each give further details on one of the above-listed categories. They show the following:

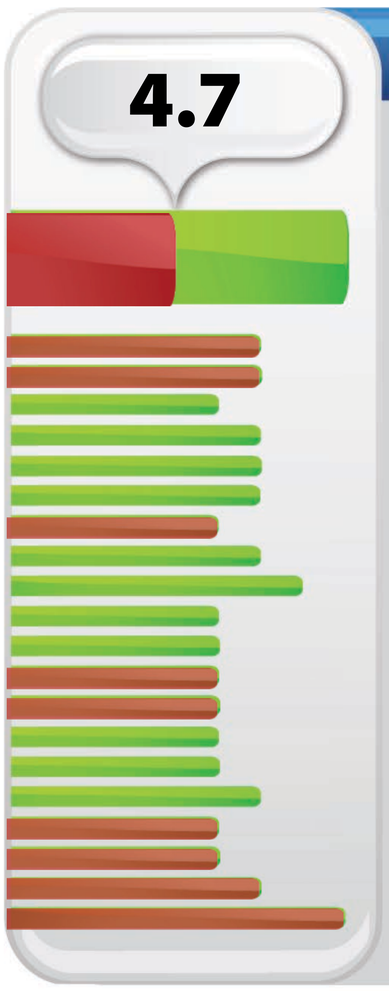


You may have some conflicting genetic information, which is normal. For example, you may have some SNPs that show that you have no increased risk of obesity, while other SNPs show that your obesity risk is increased. Remember that many factors contribute to the effect your genes have on your health, including foods you eat, your exercise level, and other environmental factors. **Knowing your genotype gives you the power to control many oft hese environmental factors and improve your overall health.**

PERSONAL GENETIC PROFILE

Summary of YOUR Most Significant Findings

Welcome to your genetic wellness profile! **This report is tailored to you, based on your individual and unique DNA.** Using the latest discoveries in genetic research, we've analyzed how *your* genes impact *your* health and wellness. More importantly, we've highlighted the steps you can take to achieve optimal health, by taking advantage of your genetic strengths and countering your genetic weaknesses. By following the guidelines we provide you can reach your full wellness potential!



YOUR GENERAL OBESITY INDEX

Your Obesity Index is a number, between 1 and 10, calculated by examining 22 base pairs in your DNA that have been associated with weight issues including BMI, waist circumference, and body fat percentage.

Your score is 4.7, which indicates a moderate genetic propensity for obesity. Eat a reasonably healthy diet and stay somewhat active, and you shouldn't have to worry too much about excessive weight gain.

See the other panels for specific steps you can take to reduce your obesity risk.

YOUR FOOD CHOICES

USE MONOUNSATURATED FATS

Your genotype shows an association between fat intake and BMI and waist and hip circumference. Even more than most people, you will benefit from a very low-fat diet.

Your genotype shows a strong benefit for avoiding fats as much as possible.

LIMIT CARBS TO DECREASE LDLS

Your genotype shows a relationship to the amount of carbohydrates you eat and an increase in LDL and HDL. More than others with a different genotype, you will need to limit carb intake to offset this tendency.

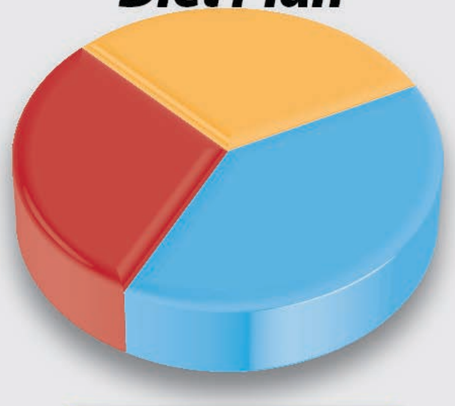
Limit dietary carbohydrate intake. Eat unsaturated fats, lean protein, fresh produce, and whole grains.

DECREASED ABILITY TO TASTE SUCROSE

You may have a weakened ability to taste sweetness.

Watch your sweets intake. People who cannot taste sweetness as easily tend to overeat sweet things in an effort to fulfill the desire for sweet foods.

Genetically Optimized Diet Plan



YOUR EXERCISE & ACTIVITY

USE FAST-TWITCH MUSCLES

You share a genotype with many world-class athletes. Your body uses alpha-actinin-3 protein more efficiently to provide a boost to fast-twitch muscle fibers that generate force at high velocity.

Discover your abilities by exploring activities that use fast-twitch muscle fibers, such as weight training, sprinting, jumping, and other explosive activities.

EXERCISE FOR FAT REDUCTION

Exercise will have a greater beneficial impact on your body fat and BMI than for those with a different genotype.

Develop a habit of exercising daily. Any type of exercise (strength training, aerobic, etc.) will significantly reduce body fat and BMI.

YOUR HEALTH

LIMIT CARBS TO LOWER BAD CHOLESTEROL

The amount of carbohydrates that you consume will impact your levels of LDL (bad) and HDL (good) cholesterol to a greater extent than for those with a different genotype.

Avoid high dietary carbohydrate intake. Focus on eating healthy fats, lean protein, fresh produce, and whole grains.

NO KNOWN REDUCTION OF CHOLESTEROL

Your genotype does not indicate any tendency toward reduced cholesterol levels.

You can still keep your cholesterol levels reasonable; keep exercising and monitor dietary triggers.

NO ASSOCIATED HIGH BLOOD PRESSURE RISK

There is no known increased risk of high blood pressure with your genotype.

Even if you do not have a genetic tendency toward high blood pressure, make regular exercise a normal part of your health routine to increase cardiovascular health.

YOUR BEHAVIOR

POSSIBLE TENDENCY TO OVEREAT

Your genotype shows that if you are female, you may be prone to overeating because of a genetic tendency toward disinhibition.

Watch portion sizes and stop eating after a reasonable amount.

BE AWARE OF INCREASED DESIRE FOR SWEETS

You have more of a sweet tooth than people with a different genotype and may experience increased cravings for sweet foods.

When you find yourself thinking about sweets, replace them with a healthy snack or an activity that you enjoy.

NORMAL FEELING OF FULLNESS

Your genotype shows no genetically related difficulty in feeling full.

Even if you are not genetically inclined toward overeating, it is easy to do. Eat reasonable portions for overall good health.

VITAMINS & YOU

POSSIBLE VITAMIN D DEFICIENCY

Your genotype indicates that you may be prone to Vitamin D deficiency.

Consider Vitamin D (cholecalciferol) supplementation and regular serum 25-hydroxy Vitamin D testing, especially if you live in a northern climate.

POSSIBLE VITAMIN E DEFICIENCY

Your genotype indicates that you may be prone to Vitamin E deficiency.

Consider supplementing with all four tocopherol isomers of Vitamin E.

POSSIBLE VITAMIN B12 DEFICIENCY

Your genotype indicates that you may be prone to Vitamin B12 deficiency.

Consider B12 supplementation (as methylcobalamin) and H. pylori testing.

4.7 YOUR GENERAL OBESITY INDEX

GENOTYPE	GENE LOCATION	IMPACT OF GENOTYPE	STUDY REF

The General Obesity Index is made up of 22 SNPs that are all correlated in various ways to the buildup of fat tissue in the body. How much a person weighs and how that fat tissue is distributed depends on that person's genetic makeup. Some of the most compelling studies on weight and genetics investigate separated twins to determine the "nature vs nurture" effect in obesity. These studies show that genetics can account for 77% of variation in body weight. Studies that look into adopted and biological parents and children show that much body type variation is genetic. However, no single SNP is capable of making someone obese. Genetic markers have an additive effect and are sometimes "turned on and off" by other factors.

The General Obesity Index is a number between 1 and 10 that you can use as an indication of how your body responds genetically to weight gain. Remember, though, that this number is not the last word in this equation. Your behavior has a significant impact on your tendency toward obesity. Even if you have a high General Obesity Index, you can overcome it by eating well and exercising. If you burn the same amount of calories that you consume, you will not gain weight. The opposite is also true—even if your General Obesity Index is low, you can still gain weight if you stick to the all-American diet of salt, sugar, and fat.

AA AG GG | FAIM2 **rs7138803** | **INCREASED RISK OF OBESITY** | 2

Your genotype was associated with increased risk of obesity in the same study that identified many other similar genes.

Even though you have a genetic tendency to obesity, this tendency can be overcome with lifestyle changes. Work at maintaining a healthy diet and increase your exercise level to get and stay healthy.

AA AG GG | MC4R **rs12970134** | **INCREASED RISK OF HIGH BMI** | 7

This gene was associated with increased waist circumference, increased BMI, and insulin resistance in a study of over 13,000 people.

Even though you have a genetic tendency to obesity, this tendency can be overcome with lifestyle changes. Work at maintaining a healthy diet and increase your exercise level to get and stay healthy.

CC CT TT | SEC16B **rs10913469** | **NO INCREASE IN CHILDHOOD OBESITY RISK** | 2

Your genotype does not include this SNP which is related to increased risk of obesity. However, many other factors can affect weight gain and overall health. Eat healthy foods and keep exercising to increase your chances of avoiding disease.

AG GG AA | TMEM18 **rs7561317** | **NO KNOWN INCREASED RISK OF OBESITY** | 2

This gene has been associated with raising the risk of extreme childhood obesity and obesity as an adult.

Your genotype does not include this SNP which is related to increased risk of obesity. However, many other factors can affect weight gain and overall health. Eat healthy foods and keep exercising to increase your chances of avoiding disease.

4.7 YOUR GENERAL OBESITY INDEX

GENOTYPE	GENE LOCATION	IMPACT OF GENOTYPE	STUDY REF

AA AT TT — FTO rs9939609 — NORMAL FEELING OF FULLNESS — 3

This gene has been associated with obesity and diabetes. Some genotypes seem to have difficulty feeling full after eating, even when food intake is more than adequate. Thus, people with those genotypes tend to overeat and gain weight.

Your genetic profile does not show that you have difficulty feeling satiated, but it is a good idea to measure out reasonable portions.

CC GC GG — INSIG2 rs7566605 — NO KNOWN INCREASED RISK OF OBESITY — 25

This gene is associated with obesity in adults and children, especially in women. In men, it has been associated with increased body fat when strength training.

Your genotype has no known association with increase in subcutaneous fat with weight training. Adding strength training to your exercise routine benefits your overall health.

CC CT TT — ETV5 rs7647305 — INCREASED RISK OF OBESITY — 2

This genotype has been associated with the risk of obesity as an adult.

Even though you have a genetic tendency to obesity, this tendency can be overcome with lifestyle changes. Work at maintaining a healthy diet and increase your exercise level to get and stay healthy.

GG AA GA — COMT rs4680 — NO GENETIC TENDENCY TO OVEREAT — 18

This gene is tied to dopamine, serotonin, and noradrenaline production in the brain. These neurotransmitters are, in turn, related to emotional patterns, which can affect eating behaviors. Certain genotypes for this gene are associated with obesity, type 2 diabetes, and impaired glucose tolerance.

Your genotype has no known association with overeating or addictive behaviors. However, watching portion size and avoiding high-sugar and high-calorie foods will help you maintain a healthy BMI.

TT GT GG — FTO rs3751812 — NO RISK OF INCREASED BMI — 16

This particular location on the FTO gene was shown to contribute to early onset of obesity in adolescents and children that continued into adulthood for some genotypes.

Your genotype does not include this SNP which is related to increased risk of obesity. However, many other factors can affect weight gain and overall health. Eat healthy foods and keep exercising to increase your chances of avoiding disease.

4.7 YOUR GENERAL OBESITY INDEX

GENOTYPE	GENE LOCATION	IMPACT OF GENOTYPE	STUDY REF

CC TC TT — MC4R rs17782313 — NO KNOWN RISK OF HIGHER BMI — 7

This gene is associated with an increased BMI. In a study of over 60,000 people, this gene was shown to influence fat mass, weight, and risk of obesity.

Your genotype does not include this SNP which is related to increased risk of obesity. However, many other factors can affect weight gain and overall health. Eat healthy foods and keep exercising to increase your chances of avoiding disease.

TT CT CC — DRD2 rs1800497 — NO KNOWN TENDENCY TO OVEREAT — 8

This SNP plays a role in the reward system of the brain. It influences how the brain uses dopamine, a neurotransmitter relating to rewards and behavior, which may lead to increased behaviors that provide immediate rewards, like smoking or overeating, and is also related to addictive behaviors.

Your genotype has no known association with extreme food-seeking behaviors. However, watching portion size and avoiding sugary and fatty foods will help you maintain a healthy BMI.

AA AG GG — NEGR1 rs2568958 — INCREASED BMI IN CHILDHOOD — 2

This gene SNP is nearly always found in children who experience extreme obesity in childhood and is associated with obesity in adults. Little is known about this gene, but it is thought to be related to neurological processes that take place in the hypothalamus, such as energy balance and appetite, that contribute to obesity.

Even though you have a genetic tendency to obesity, this tendency can be overcome with lifestyle changes. Work at maintaining a healthy diet and increase your exercise level to get and stay healthy. Make sure you teach your children healthy habits. This genetic tendency can show up in childhood.

GT TT GG — NCR3_AIF1 rs2844479 — INCREASED BMI IN CHILDHOOD — 2

Your genotype is associated with raising the risk of extreme childhood obesity and obesity as an adult.

Even though you have a genetic tendency to obesity, this tendency can be overcome with lifestyle changes. Work at maintaining a healthy diet and increase your exercise level to get and stay healthy. Make sure you teach your children healthy habits. This genetic tendency can show up in childhood.

AA GA GG — SH2B1 rs4788102 — NO KNOWN RISK OF INCREASED BMI — 2

This gene was associated with increased risk of obesity in the same large study that identified many similar genes.

Your genotype does not include this SNP which is related to increased risk of obesity. However, many other factors can affect weight gain and overall health. Eat healthy foods and keep exercising to increase your chances of avoiding disease.

4.7 YOUR GENERAL OBESITY INDEX

GENOTYPE	GENE LOCATION	IMPACT OF GENOTYPE	STUDY REF

AA AG GG — LEP rs7799039 — NO GENETIC TENDENCY FOR HIGHER BMI — 26

This gene is associated with risk of significant obesity, especially among those with Pacific Islander heritage. It is also associated with increased weight gain in children who take risperidone (used to treat schizophrenia or bipolar disorder).

Your genotype does not include this SNP which is related to increased risk of obesity. However, many other factors can affect weight gain and overall health. Eat healthy foods and keep exercising to increase your chances of avoiding disease.

AA AG GG — BDNF rs6265 — NO KNOWN INCREASED RISK OF OBESITY — 2

This gene was associated with increased risk of obesity in the same study that identified many other similar genes. This particular one also has a relationship to increased risk for depression, linking it to neurotransmitter function.

Your genotype does not include this SNP which is related to increased risk of obesity. However, many other factors can affect weight gain and overall health. Eat healthy foods and keep exercising to increase your chances of avoiding disease.

CG CC GG — PCSK1_2 rs6235 — RISK OF INCREASED BMI — 22

Your genotype is strongly and consistently associated with obesity in a study of over 13,000 individuals of European descent. It is thought that this gene affects the way protein is used by the body.

Even though you have a genetic tendency to obesity, this tendency can be overcome with lifestyle changes. Work at maintaining a healthy diet and increase your exercise level to get and stay healthy.

CC CT TT — DRD2 rs6277 — BE AWARE OF FOOD CRAVINGS — 23

This gene plays a role in the reward system of the brain. Some genotypes for this gene influence how the brain uses dopamine, a neurotransmitter relating to rewards and behavior, which may lead to increased behaviors that provide immediate rewards, like smoking or overeating. This genotype is also related to addictive behaviors.

Your genotype shows a tendency toward addictive behaviors, which may manifest as seeking out food for pleasure or rewards. Addiction is associated with low levels of certain neurotransmitters, including dopamine and serotonin. When experiencing food cravings, try incorporating activities that facilitate the natural release of endorphins such as light exercise, talking with a friend or loved one, doing an activity you enjoy, or going for brisk walk.

CT TT CC — HTR2A rs6311 — INCREASED RISK OF OBESITY — 18

Your genotype is associated with increased BMI, increased waist measurements, and other markers of obesity risk, such as glucose intolerance.

Even though you have a genetic tendency to obesity, this tendency can be overcome with lifestyle changes. Work at maintaining a healthy diet and increase your exercise level to get and stay healthy.

4.7 YOUR GENERAL OBESITY INDEX

GENOTYPE	GENE LOCATION	IMPACT OF GENOTYPE	STUDY REF
CC CT TT	NEAR-KCTD15 rs29941	STRONG ASSOCIATION WITH INCREASED BMI	2

In a large study of over 16,000 people of European descent that identified several genes associated with increased risk of obesity, your genotype had one of the strongest associations. This finding was confirmed in another large study involving Chinese people. Current thinking is that this gene acts as a transcription factor, a piece of DNA that controls how other important genes are processed by the body.

Even though you have a genetic tendency to obesity, this tendency can be overcome with lifestyle changes. Work at maintaining a healthy diet and increase your exercise level to get and stay healthy.

GENOTYPE	GENE LOCATION	IMPACT OF GENOTYPE	STUDY REF
AA GA GG	ADIPOQ rs17366568	LOWER RISK OF OBESITY	36

In a nested case control study with over 1,200 cases and over 1,200 controls, 29 SNPs were evaluated for their relationship to adeponectin, which is inversely related to obesity levels and some types of cancer.

Your genotype is related to normal levels of adiponection. Adiponectin is a hormone produced by the body to help control fat metabolism and overall health. Having higher blood levels of adiponectin increases your ability to process fat. The control of this hormone is partially genetic based, and this SNP contributes to its control.

GENOTYPE	GENE LOCATION	IMPACT OF GENOTYPE	STUDY REF
CC GC GG	LEPR rs8179183	NORMAL RESTING METABOLIC RATE	33

One major contributor to weight gain and loss is the metabolism rate of individuals. People with a higher resting metabolism rate will naturally burn more calories than others doing the same basic activities. This leads to lower average weight and slower weight gain. This SNP in the LEPR gene shows direct correlation with resting metabolic rate.

Your genotype shows that you have a tendency to burn calories at a typical rate. This may make it more difficult for you to lose weight only using exercise.

YOUR FOOD CHOICES

GENOTYPE | GENE LOCATION | IMPACT OF GENOTYPE | STUDY REF

Humans vary greatly when it comes to metabolism and food processing. The process of breaking down and storing or using energy from food is extremely complicated, and we are just beginning to learn about the genes involved in metabolism. This section identifies some of the genetic variations that are related to food processing and preferences and how your body reacts to fats, proteins, and carbs. As a general rule, whole, unprocessed foods, especially fruits and vegetables, are the best fuel you can feed your body, but this section will also show you some strengths and weaknesses that will enable you to better plan your diet. These SNPs all have an environmental component that relates to the genetic hand you have been dealt. This means that how you eat and treat yourself is as important (if not more important!) than your genetics. None of these SNPs alone should be a great cause of concern, but they should be treated seriously as these have been scientifically proven to contribute to overall wellness.

CC CT TT | APOA2 **rs5082** | **NO KNOWN BENEFIT TO LOW-FAT DIET** | 19

A large study of over 3,000 people from 3 independent populations found a gene-diet interaction associated with increased BMI (6.2%) and obesity. This gene is associated with extremely efficient fat processing; people with certain associated genotypes should avoid saturated fats.

Maintain appropriate total calorie intake for your body weight and incorporate regular exercise to maintain a healthy weight.

AA AT TT | FTO **rs9939609** | **NO INCREASED RISK OF OBESITY** | 3

This genotype is associated with increased obesity and an influence on appetite regulation in a study of nearly 5,000 people. People with certain associated genotypes should avoid fats and increase physical activity.

Maintain appropriate total calorie intake for your body weight and incorporate regular exercise to maintain a healthy weight.

AA AG GG | ADIPOQ **rs17300539** | **STRICTLY MONITOR FAT INTAKE** | 6

Your genotype has increased benefits from eating monounsaturated fats. Your genotypes may also protect against regaining weight after dieting.

Your genetic profile shows that you may have a lower BMI and waist-to-hip ratio when incorporating monounsaturated fats such as olive, avocado, and walnut oils. Aim to iincoprorate 1 -3 svgs a day of these types of fats.

GG CC GC | PPARG **rs1801282** | **NO KNOWN BENEFIT WITH A LOW-FAT DIET** | 29

Your genotype is not associated with a negative physiological response to fat. Diets high in fat do not appear to influence obesity or increase major cardiac risk factors such as the development of atherosclerotic plaque in people with this genotype.

Although you may not receive additional benefits from fat restriction, fat intake should be monitored along with total calorie intake.

GG CC GC | KCTD10 **rs10850219** | **LIMIT CARBS TO DECREASE LDLS** | 15

In a study evaluating various genes for their relationship to high-density lipoprotein (HDL), or good cholesterol, your genotype was linked to increased levels of low-density lipoprotein (LDL), or bad cholesterol, and decreased levels of HDL with a high-carb diet.

Limit dietary carbohydrate intake. Eat unsaturated fats, lean protein, fresh produce, and whole grains.

YOUR FOOD CHOICES

GENOTYPE	GENE LOCATION	IMPACT OF GENOTYPE	STUDY REF

GG CC GC — MMAB rs2241201 — NO KNOWN BENEFIT FROM LOW-CARB DIET — 15

In a study evaluating various genes for their relationship to high-density lipoprotein (HDL), or good cholesterol, this gene was linked to increased levels of low-density lipoprotein (LDL), or bad cholesterol, and decreased levels of HDL with a high-carb diet.

Although carbohydrate restriction does not have a significant impact on your cholesterol ratio, continue to exercise regularly, monitor overall calorie intake , and consume a balanced ratio of healthy fats, carbohydrates, and proteins for a potentially positive impact on blood lipids.

TT CT CC — LIPC rs1800588 — NO KNOWN HDL BENEFIT WITH LOW-FAT DIET — 10

This gene is associated with the amount of high-density lipoprotein (HDL), or good cholesterol, produced by the body. Those with lower HDL levels should avoid low-carb, high-fat diets.

Eat a balanced diet that incorporates quality fats.

AA GA GG — TAS1R3 rs35744813 — DECREASED ABILITY TO TASTE SUCROSE — 34

The genes TAS1R2 and TAS1R3 are both tied to taste perception in humans. Scientists have located a SNP on the genome just upstream of the TAS1R3 gene that is correlated to the ability to taste sucrose. People deficient in sucrose tasting may be subject to increased sugar intake to satisfy their need for something sweet.

Your genotype shows that you have a decreased ability to taste sweet foods. This may lead to an increase in the amount of sweets you eat so that you will satisfy your need for something sweet. Try to limit the amount of sweet foods you eat to overcome this genetic tendency.

CC TT TC — MCM6 rs4988235 — INCREASED RISK OF LACTOSE INTOLERANCE — 30

A study involving four different populations found a very strong correlation between this SNP and lactose intolerance. The fact that it is widespread over populations that are only distantly related suggests that this SNP is very old.

This genotype is associated with lactose intolerance, the inability to digest milk products containing lactose. This condition manifests as abdominal pain, bloating, gas, diarrhea, and/or nausea. If you experience these symptoms, contact your healthcare provider for help in modifying your diet to include other calcium sources.

AA GA GG — ALDH2 rs671 — NO INCREASED RISK OF FLUSH RESPONSE — 35

Some people become flush in their face and shoulders and experience severe hangovers when they drink alcohol. This is due to defective alcohol metabolism caused by the gene aldehyde dehydrogenase 2 or ALDH2. This genetic issue is often accompanied by a lower likelihood to suffer from alcoholism possibly because with these negative effects, those with this genotype may avoid drinking alcohol.

Drinking moderate amounts of alcohol can provide some health benefits. However, there are also many negatives associated with drinking. If you choose to drink alcohol, always do so moderately.

YOUR FOOD CHOICES

GENOTYPE	GENE LOCATION	IMPACT OF GENOTYPE	STUDY REF

CC CG GG — TAS2R38 rs713598 — INCREASED SENSITIVITY TO BITTER TASTE — 31

Sensitivity to PTC or bitter taste has long been known to have a genetic component with evolutionary and anthropological implications. Many poisonous things taste bitter, and being able to taste and avoid these things is an evolutionary advantage. The TAS2R38 gene on chromosome 7 is linked to this trait in humans with two SNPs that signal the ability to taste bitterness. However, this genotype is often acompanied by the desire to eat salt to mask bitter flavor.

You may eat more salt than others with a different genotype who are not as sensitive to bitter taste. Salt can mask the bitterness in foods, so watch how much salt you are adding at the table.

AA CC CA — CYP1A2 rs762551 — TYPICAL EFFECT OF CAFFEINE — 32

Caffeine metabolism rate varies according to genetics. The CYP1A2 gene has a SNP that controls the variation in caffeine metabolism and other similar compounds.

Your genotype is not associated with greater sensitivity to caffeine. However, limiting the amount of caffeine intake is associated with a healthy lifestyle, particularly for those who also smoke.

YOUR EXERCISE & ACTIVITY

GENOTYPE | GENE LOCATION | IMPACT OF GENOTYPE | STUDY REF

One of the keys to living a long and healthy life is a good amount of safe, structured, physical activity. Whether you enjoy going out for a walk, running 15 miles, playing sports for an hour, or practicing yoga, the benefits of exercise are hard to quantify. They include stronger bones, healthy heart, more calories burned, less excess fat and many more. Our muscles are made of two kinds of fibers, fast twitch and slow twitch. We have yet to uncover the exact genetics behind muscle type, but we do know that one person's body generally favors one over the other. Fast-twitch muscle fibers help people excel at power-based sports (sprinting, short-distance swimming, weight lifting, fast-paced sports) while slow-twitch fibers help people excel at endurance sports (distance running, cycling, hiking, etc.). To date scientists have found some SNPs that correlate with what type of exercise will be most beneficial to a certain person from many angles including fat loss, blood pressure and cholesterol levels. Use this section to plan out how you are going to incorporate exercise in your drive for a more healthy you.

GG AA GA | PPARD **rs2016520** | **NO ENHANCED ENDURANCE EXERCISE BENEFIT** | 14

In a study of over 700 subjects, this SNP was linked to an increased impact on HDL levels with endurance exercise for some genotypes.

Even though you may not experience an enhanced benefit, make endurance /aerobic exercise a part of your health routine; any type of exercise will reduce your risk of heart disease.

CC CT TT | ACTN3 **rs1815739** | **USE FAST-TWITCH MUSCLES** | 13

This gene has been associated with the ability of the body to use alpha-actinin-3 protein, a protein that enhances fast-twitch in muscle fibers. This means that the body can generate force at a high velocity; for example, male and female world-class sprinters have significantly higher frequencies of one of these genotypes.

Discover your abilities by exploring activities that use fast-twitch muscle fibers, such as weight training, sprinting, jumping, and other"explosive activities.

TT TC CC | FTO **rs1121980** | **NO INCREASED BENEFIT WITH EXERCISE** | 3

This gene has been associated with increased fat mass and obesity. However, in a large study of over 20,000 participants, it was shown that for some genotypes, physical activity helps greatly in overcoming this tendency and enhances the ability to lower BMI and risk of obesity.

It is always a good idea to include stamina and endurance exercises along with strength and flexibility training to help you maintain an ideal weight.

CC GC GG | INSIG2 **rs7566605** | **NO KNOWN INCREASED RISK OF OBESITY** | 25

This gene is associated with obesity in adults and children, especially in women. In men, it has been associated with increased body fat when strength training.

Your genotype has no known association with increase in subcutaneous fat with weight training. Adding strength training to your exercise routine benefits your overall health.

YOUR EXERCISE & ACTIVITY

GENOTYPE	GENE LOCATION	IMPACT OF GENOTYPE	STUDY REF

GG GA AA — LEP rs7799039 — EXERCISE FOR FAT REDUCTION — 26

This gene has been associated with levels of leptin, a substance that helps regulate body weight and metabolism. Thus, the different genotypes associated with this gene respond to exercise differently.

Develop a habit of exercising daily. Any type of exercise (strength training, aerobic, etc.) will significantly reduce body fat and BMI.

AA AT TT — FTO rs9939609 — DIETARY FAT, ACTIVITY, AND OBESITY — 3

This gene is associated with increased obesity and an influence on appetite regulation in a study of nearly 5,000 people. People with certain associated genotypes should avoid fats and increase physical activity.

Regular exercise can help you maintain a healthy body weight.

TT GG TG — EDN1 rs5370 — NO KNOWN RISK OF HIGH BLOOD PRESSURE — 20

In a nearly 10-year study with over 1,000 people, this gene was associated with a higher risk of high blood pressure. However, certain genotypes show an ability to keep a near-normal blood pressure with exercise.

Include stamina and endurance exercises along with strength and flexibility training. Even without an improvement in blood pressure, exercise can help you maintain an ideal body weight.

CC CT TT — LIPC rs1800588 — NO ENHANCED ENDURANCE EXERCISE BENEFIT — 10

Though anyone will benefit from endurance training (a deliberate act of exercising to increase stamina and endurance), this gene has been associated with enhanced benefits from this type of exercise for certain genotypes.

Make sure you include exercises known to increase stamina and endurance (running, cycling, swimming) in your fitness plan. These types of exercise will help you maintain an ideal body weight even though you may not see an improvement in HDL levels.

YOUR HEALTH

GENOTYPE	GENE LOCATION	IMPACT OF GENOTYPE	STUDY REF

GG GC CC — PPARG rs1801282 — NO KNOWN REDUCTION OF CHOLESTEROL — 29

In a large study of over 2,000 people, men with this genotype showed a decreased risk of cardiovascular disease due to lower cholesterol levels.

Though exercise and diet will always have an impact on cholesterol levels, your genotype was not associated with an added benefit. Speak with your healthcare provider to develop a multi-pronged strategy for improving blood lipid levels if you are concerned about them.

TT GG TG — EDN1 rs5370 — NO ASSOCIATED HIGH BLOOD PRESSURE RISK — 20

In a nearly 10-year study with over 1,000 people, this gene was associated with a higher risk of high blood pressure. However, certain genotypes show an ability to keep a near-normal blood pressure with exercise.

Include stamina and endurance exercises along with strength and flexibility training to maintain a healthy body weight.

GG AA GA — PPARD rs2016520 — NO KNOWN ENDURANCE EXERCISE BENEFIT — 14

Though anyone will benefit from endurance training (a deliberate act of exercising to increase stamina and endurance), this gene has been associated with enhanced benefits from this type of exercise for some genotypes.

Even though you may not experience an enhanced benefit, make sure you include exercises known to increase stamina and endurance (running, cycling, swimming) in your fitness plan.

GG CC GC — KCTD10 rs10850219 — LIMIT CARBS TO LOWER BAD CHOLESTEROL — 15

In a study evaluating various genes for their relationship to high-density lipoprotein (HDL), or good cholesterol, your genotype was linked to increased levels of low-density lipoprotein (LDL), or bad cholesterol, and decreased levels of HDL with a high-carb diet.

Your genotype indicates that carbohydrate intake of more than 241 grams per day or approximately 45% of a 2,000 calorie diet may have a negative impact on blood lipid levels. Emphasize unsaturated fats, lean protein, produce, and whole grains when eating carbs.

GG CC GC — MMAB rs2241201 — NO KNOWN BENEFIT FROM LOW-CARB DIET — 15

In a study evaluating various genes for their relationship to high-density lipoprotein (HDL), or good cholesterol, this gene was linked to increased levels of low-density lipoprotein (LDL), or bad cholesterol, and decreased levels of HDL with a high-carb diet for some genotypes.

Although carbohydrate restriction does not have a significant impact on your cholesterol ratio, continue to exercise regularly, monitor overall calorie intake , and consume a balanced ratio of healthy fats, carbohydrates, and proteins for a potentially positive impact on blood lipids.

YOUR HEALTH

GENOTYPE	GENE LOCATION	IMPACT OF GENOTYPE	STUDY REF
CC CT TT	LIPC **rs1800588**	NO ENHANCED ENDURANCE EXERCISE BENEFIT	10

Though anyone will benefit from endurance training (a deliberate act of exercising to increase stamina and endurance), this gene has been associated with enhanced benefits from this type of exercise for certain genotypes.

Make sure you include exercises known to increase stamina and endurance (running, cycling, swimming) in your fitness plan.

YOUR BEHAVIOR

GENOTYPE	GENE LOCATION	IMPACT OF GENOTYPE	STUDY REF

Genetic markers work in tandem with the environment and how you treat your body. It seems simple—eat less and exercise more to be thinner and healthier. But we also know that there are some genetic inclinations that determine just how easy it is for us to make good choices concerning food. As a species, our natural instinct is to eat as much as we can when we have food available. Nature's way is survival of the fittest, which means survival of the one who obtains the most nutrients. In today's society, however, food is readily available for most people, and unfortunately, the food that is the most available tends to be the least healthy food.

In this section are a number of genetic markers that tell you about your own behaviors concerning cravings and reactions to different substances. If you know your pitfalls, you will be better able to fight them.

TT TC CC — TAS2R38 rs1726866 — POSSIBLE TENDENCY TO OVEREAT — 5

This gene has been associated with a difference in taste perception that allows disinhibition, or the inability to stop eating. In a large study (over 700 people), it was linked to eating behavior for women, but not for men, for certain genotypes.

Your genetic profile indicates that if you are female, you may experience disinhibition, or the inability to stop eating. Try filling your plate with a reasonable amount of food, then putting any other food away so you are not tempted to keep eating. Work with your healthcare provider to establish portion-control techniques.

AA AT TT — FTO rs9939609 — NORMAL FEELING OF FULLNESS — 3

This gene has been associated with obesity and diabetes. Some genotypes seem to have difficulty feeling full after eating, even when food intake is more than adequate. Thus, people with those genotypes tend to overeat and gain weight.

Your genetic profile does not show that you have difficulty feeling satiated, but it is always a good idea to measure out reasonable portions.

TT CT CC — DRD2 rs1800497 — NO INCREASED RISK OF ADDICTIVE BEHAVIOR — 8

This SNP plays a role in the reward system of the brain. It influences how the brain uses dopamine, a neurotransmitter relating to rewards and behavior, which may lead to increased behaviors that provide immediate rewards, like smoking or overeating, and is also related to addictive behaviors.

Your genotype has no known association with increased risk of obesity due to neurotransmissions in the reward center of the brain.

TT TC CC — SLC2A2 rs5400 — BE AWARE OF INCREASED DESIRE FOR SWEETS — 21

This gene has been associated with a higher level of sugar intake, possibly due to the way the brain senses glucose intake.

Your genetic profile indicates a tendency to seek out and overeat sweets. Keep sweet foods out of reach and limit yourself when you allow a sweet snack. Sugar and carbohydrate cravings can often occur as a result of an underlying issue, such as blood sugar disorders, candida, or food allergies. Work with your healthcare provider to determine if any of these may be an issue for you.

VITAMINS & YOU

GENOTYPE | GENE LOCATION | IMPACT OF GENOTYPE | STUDY REF

Some genetic markers allow us to see gaps in our ability to process foods in a way that will maximize their potential. Some people lack the ability to fully process vitamins from their food. This section provides information that will help you decide if you need to complement your diet with a daily vitamin supplement and, if so, which vitamins may be most beneficial to you.

GG GA AA — NEAR-CYP2R1 rs10741657 — POSSIBLE VITAMIN D DEFICIENCY — 1

In a study of nearly 34,000 people of European descent, this gene was associated with insufficiency of Vitamin D, an important vitamin for skeletal health.

Your genetic profile shows an association with Vitamin D deficiency. If you live in a southern latitude (below 37 degrees), try to get 10-15 minutes of sunshine exposure each day before you put on sunscreen. If you live in a northern latitude, supplementation with Vitamin D3 (cholecalciferol) may be necessary to optimize Vitamin D levels. Consider having serum 25-hydroxy Vitamin D tested regularly and aim to maintain vitamin D status no less than 50 ng/mol.

CC AA CA — INTERGENIC rs12272004 — POSSIBLE VITAMIN E DEFICIENCY — 4

In a study of nearly 4,000 people, this gene was associated with decreased levels of Vitamin E. Though there is no consensus about recommended levels of Vitamin E, many experts recommend supplementation, claiming improved metabolism, boosted immune response, and less risk of chronic disease.

Your genotype shows an association with decreased levels of alpha tochoperol, an active isomer of Vitamin E which is essential for antioxidant activity. Nuts are an especially good source of Vitamin E , including almonds, peanuts, and pine nuts. If supplementing, choose a product that contains mixed-tocopherols. Supplementing with all four tocopherol isomers has been shown to be more beneficial to overall health.

GG GT TT — NEAR-DHCR7 rs12785878 — NO ASSOCIATED VITAMIN D DEFICIENCY — 1

In a study of nearly 34,000 people of European descent, this gene was associated with insufficiency of Vitamin D, an important vitamin for skeletal health.

Ensure a sufficient amount of Vitamin D in your diet for healthy bones and muscles.

TT TA AA — BCMO1 rs12934922 — ABILITY TO CONVERT BETA-CAROTENE — 24

This gene has been associated with converting beta-carotene into Vitamin A so it can be used by the body. People with some genotypes will benefit from a diet rich in beta-carotene (carrots, pumpkin, sweet potato, spinach) and will benefit from a multivitamin containing Vitamin A.

Maintain reasonable Vitamin A levels by eating green and orange fruits and vegetables that are rich in carotenoids.

TT TC CC — MTHFR rs1801133 — NO ASSOCIATION WITH FOLATE DEFICIENCY — 11

Many biochemical processes in the body use folate.This gene has been associated with a genotype that may interrupt necessary biochemical pathways by reducing folate metabolism.

Your genotype is not associated with folate deficiency. However, it is a good idea to ensure a sufficient amount of folate in your diet for healthy production of neurotransmitters and red blood cells.

VITAMINS & YOU

GENOTYPE	GENE LOCATION	IMPACT OF GENOTYPE	STUDY REF

CC CA AA — GC rs2282679 — NO ASSOCIATED VITAMIN D DEFICIENCY — 1

In a study of nearly 34,000 people of European descent, this gene was associated with insufficiency of Vitamin D, an important vitamin for skeletal health.

Ensure a sufficient amount of Vitamin D in your diet for healthy bones and muscles.

CC CT TT — NBPF3 rs4654748 — NO ASSOCIATED VITAMIN B6 DEFICIENCY — 17

This gene has been associated with decreased levels of Vitamin B6, an important part of brain function, glucose metabolism, and heart health. People with some genotypes will benefit from increased Vitamin B6 supplementation.

Ensure a sufficient amount of Vitamin B6 in your diet for healthy metabolism.

GG GA AA — FUT2 rs602662 — POSSIBLE VITAMIN B12 DEFICIENCY — 17

Your genotype has been associated with decreased levels of Vitamin B12, an important part of brain function, glucose metabolism, and heart health. People with your genotype will benefit from increased Vitamin B12 supplementation.

Your genotype shows an association with Vitamin B12 deficiency. B12 is an essential cofactor in pathways involved in the synthesis of neurotransmitters and red blood cell production. B12 is predominantly found in animal-derived foods, including meat and dairy; you may be increasing your risk of deficiency if your diet is low in these foods. Additionally, low secretion of the glycoprotein intrinsic factor by the stomach can be a root cause of B12 deficiency. Consider sublingual supplementation or supplementing with intrinsic factor to reduce deficiency risk. Your genotype is also associated with increased risk of infection with H. pylori, a microrganism associated with GERD. Consider working with your healthcare provider to determine if treatment is needed.

TT TC CC — BCM01 rs7501331 — REDUCED ABILITY TO CONVERT BETA-CAROTENE — 24

This gene has been associated with converting beta-carotene into Vitamin A so it can be used by the body. People with some genotypes will benefit from a diet rich in beta-carotene (carrots, pumpkin, sweet potato, spinach) and will benefit from a multivitamin containing Vitamin A.

Your genotype indicates that you may insufficiently convert the carotenoids (plant-based Vitamin A) to active Vitamin A (retinoic acid) in the body. Vitamin A deficiency and impairments in Vitamin A metabolism can lead to changes in cellular replication and vision problems. You may benefit from a Vitamin A supplement that contains active Vitamin A as retinyl palmitate. If you are pregnant or planning to conceive, work with your healthcare provider to determine a safe dose as high doses of Vitamin A can be teratogenic.

REFERENCES

1 **Wang, T.J. et al, 2010, Common genetic determinants of vitamin D insufficiency: a genome-wide association study. The Lancet, 376 (9736). 180-188.**

Background Vitamin D is crucial for maintenance of musculoskeletal health, and might also have a role in extraskeletal tissues. Determinants of circulating 25-hydroxyvitamin D concentrations include sun exposure and diet, but high heritability suggests that genetic factors could also play a part. We aimed to identify common genetic variants affecting vitamin D concentrations and risk of insufficiency. Methods We undertook a genome-wide association study of 25-hydroxyvitamin D concentrations in 33,996 individuals of European descent from 15 cohorts. Five epidemiological cohorts were designated as discovery cohorts (n=16,125), five as in-silico replication cohorts (n=9,367), and five as de-novo replication cohorts (n=8,504). 25-hydroxyvitamin D concentrations were measured by radioimmunoassay, chemiluminescent assay, ELISA, or mass spectrometry. Vitamin D insufficiency was defined as concentrations lower than 75 nmol/L or 50 nmol/L. We combined results of genome-wide analyses across cohorts using Z-score-weighted meta-analysis. Genotype scores were constructed for confirmed variants. Findings Variants at three loci reached genome-wide significance in discovery cohorts for association with 25-hydroxyvitamin D concentrations, and were confirmed in replication cohorts. Variants at an additional locus (20q13, CYP24A1) were genome-wide significant in the pooled sample. Participants with a genotype score (combining the three confirmed variants) in the highest quartile were at increased risk of having 25-hydroxyvitamin D concentrations lower than 75 nmol/L or lower than 50 nmol/L compared with those in the lowest quartile. Interpretation Variants near genes involved in cholesterol synthesis, hydroxylation, and vitamin D transport affect vitamin D status. Genetic variation at these loci identifies individuals who have substantially raised risk of vitamin D insufficiency.

2 **Willer, C.J. et al , 2009, Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. Nature Genetics, 41(1). 25-34.**

Common variants at only two loci, FTO and MC4R, have been reproducibly associated with body mass index (BMI) in humans. To identify additional loci, we conducted meta-analysis of 15 genome-wide association studies for BMI (n > 32,000) and followed up top signals in 14 additional cohorts (n > 59,000). We strongly confirm FTO and MC4R and identify six additional loci (P < 5 x 10(-8)): TMEM18, KCTD15, GNPDA2, SH2B1, MTCH2 and NEGR1 (where a 45-kb deletion polymorphism is a candidate causal variant). Several of the likely causal genes are highly expressed or known to act in the central nervous system (CNS), emphasizing, as in rare monogenic forms of obesity, the role of the CNS in predisposition to obesity.

3 **Vimaleswaran, K. S. et al, 2009, Physical activity attenuates the body mass index increasing influence of genetic variation in the FTO gene. American Journal Clinical Nutrition, 90(2). 425-428.**

Background: Intronic variation in the FTO (fat mass and obesity-associated) gene has been unequivocally associated with increased body mass index (BMI; in kg/m2) and the risk of obesity in populations of different ethnicity. Objective: We examined whether this robust genetic predisposition to obesity can be attenuated by being more physically active. Design: The FTO variant rs1121980 was genotyped in 20,374 participants (39 to 79 y of age) from the European Prospective Investigation into Cancer and Nutrition Norfolk Study, an ethnically homogeneous population-based cohort. Physical activity (PA) was assessed with a validated self-reported questionnaire. The interaction between rs1121980 and PA on BMI and waist circumference (WC) was examined by including the interaction term in mixed-effect models. Results: We confirmed that the risk (T) allele of rs1121980 was significantly associated with BMI (0.31-unit increase per allele; P < 0.001) and WC (0.77-cm increase per allele; P < 0.001). The PA level attenuated the effect of rs1121980 on BMI and WC; ie, whereas in active individuals the risk allele increased BMI by 0.25 per allele, the increase in BMI was significantly (P for interaction = 0.004) more pronounced (76%) in inactive individuals (0.44 per risk allele). We observed similar effects for WC (P for interaction = 0.02): the risk allele increased WC by 1.04 cm per allele in inactive individuals but by only 0.64 cm in active individuals. Conclusions: Our results showed that PA attenuates the effect of the FTO rs1121980 genotype on BMI and WC. This observation has important public health implications because we showed that a genetic susceptibility to obesity induced by FTO variation can be overcome, at least in part, by adopting a physically active lifestyle.

4 **Ferrucci, L. et al, 2009, Common variation in the beta-carotene 15,15'-monooxygenase 1 gene affects circulating levels of carotenoids: a genome-wide association study. American Journal of Human Genetics, 84(2). 123-33.**

Low plasma levels of carotenoids and tocopherols are associated with increased risk of chronic disease and disability. Because dietary intake of these lipid-soluble antioxidant vitamins is only poorly correlated with plasma levels, we hypothesized that circulating carotenoids (vitamin A-related compounds) and tocopherols (vitamin E-related compounds) are affected by common genetic variation. By conducting a genome-wide association study in a sample of Italians (n = 1190), we identified novel common variants associated with circulating carotenoid levels and known lipid variants associated with alpha-tocopherol levels. Effects were replicated in the Women's Health and Aging Study (n = 615) and in the alpha-Tocopherol, beta-Carotene Cancer Prevention (ATBC) study (n = 2136). In meta-analyses including all three studies, the G allele at rs6564851, near the beta-carotene 15,15'-monooxygenase 1 (BCMO1) gene, was associated with higher beta-carotene (p = 1.6 x 10(-24)) and alpha-carotene (p = 0.0001) levels and lower lycopene (0.003), zeaxanthin (p = 1.3 x 10(-5)), and lutein (p = 7.3 x 10(-15)) levels, with effect sizes ranging from 0.10-0.28 SDs per allele. Interestingly, this genetic variant had no significant effect on plasma retinol (p > 0.05). The SNP rs12272004, in linkage disequilibrium with the S19W variant in the APOA5 gene, was associated with alpha-tocopherol (meta-analysis p = 7.8 x 10(-10)) levels, and this association was substantially weaker when we adjusted for triglyceride levels (p = 0.002). Our findings might shed light on the controversial relationship between lipid-soluble anti-oxidant nutrients and human health.

5 **Dotson, C.D. et al, 2010, Variation in the gene TAS2R38 is associated with the eating behavior disinhibition in Old Order Amish women. Appetite, 54(1). 93-9.**

Insensitivity to the bitter-tasting compound 6-n-propylthiouracil (PROP) has been proposed as a marker for individual differences in taste perception that influence food preference and intake. The principal genetic determinants of phenotypic variation in PROP taste sensitivity are alleles of the TAS2R38 gene, which encodes a chemosensory receptor sensitive to thiourea compounds including PROP and phenylthiocarbamide. Members of the TAS2R family are expressed in the gustatory system, where they function as bitter taste receptors, and throughout the gut, where their physiological roles in prandial, gut-derived hormone release are beginning to be elucidated. To better understand the relationship between TAS2R function and ingestive behaviors, we asked if TAS2R38 variants are associated with one or more of three eating behaviors: restraint, disinhibition, and hunger. We genotyped a single nucleotide polymorphism (SNP) located within the TAS2R38 gene, rs1726866 (T785C, Val262Ala) in 729 nondiabetic individuals (381 females, 348 males) within the Amish Family Diabetes Study. Eating behaviors were assessed using the Three-Factor Eating Questionnaire. An association analysis between rs1726866 and these three traits revealed a significant association of the PROP-insensitive T allele with increased disinhibition (p=0.03). Because eating behaviors differ substantially between males and females, we subsequently performed sex-stratified analyses, which revealed a strong association in females (p=0.0002) but not in males. Analyses with other SNPs in close proximity to rs1726866 suggest that this locus is principally responsible for the association. Therefore, our results indicate that a polymorphism in TAS2R38 is associated with differences in ingestive behavior.

6 **Warodomwichit, D. et al, 2009, The monounsaturated fatty acid intake modulates the effect of ADIPOQ polymorphisms on obesity. Obesity (Silver Spring), 17(3). 510-7.**

Serum adiponectin levels have been positively associated with insulin sensitivity and are decreased in type 2 diabetes (T2D) and obesity. Genetic and environmental factors influence serum adiponectin and may contribute to risk of metabolic syndrome and T2D. Therefore, we investigated the effect of ADIPOQ single-nucleotide polymorphisms (SNPs), -11377C>G and -11391G>A, on metabolic-related traits, and their modulation by dietary fat in white Americans. Data were collected from 1,083 subjects participating in the Genetics of Lipid Lowering Drugs and Diet Network study. Mean serum adiponectin concentration was higher for carriers of the -11391A allele (P = 0.001) but lower for the -11377G allele carriers (P = 0.017). Moreover, we found a significant association with obesity traits for the -11391G>A SNP. Carriers of the -11391A allele had significantly lower weight (P = 0.029), BMI (P = 0.019), waist (P = 0.003), and hip circumferences (P = 0.004) compared to noncarriers. Interestingly, the associations of the -11391G>A with BMI and obesity risk were modified by monounsaturated fatty acids (MUFAs) intake (P-interaction = 0.021 and 0.034 for BMI and obesity risk, respectively). In subjects with MUFA intake above the median (> or =13% of energy intake), -11391A carriers had lower BMI (27.1 kg/m(2) for GA+AA vs. 29.1 kg/m(2) for GG, P = 0.002) and decreased obesity risk (odds ratio for -11391A = 0.52, 95% confidence interval (CI); 0.28-0.96; P = 0.031). However, we did not detect genotype-related differences for BMI or obesity in subjects with MUFA intake <13%. Our findings support a significant association between the -11391G>A SNPs and obesity-related traits and the potential to moderate such effects using dietary modification.

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7 **Loos, R.J. et al, 2008, Common variants near MC4R are associated with fat mass, weight and risk of obesity. Nature Genetics, 40(6). 768-75.**

To identify common variants influencing body mass index (BMI), we analyzed genome-wide association data from 16,876 individuals of European descent. After previously reported variants in FTO, the strongest association signal (rs17782313, P = 2.9 x 10(-6)) mapped 188 kb downstream of MC4R (melanocortin-4 receptor), mutations of which are the leading cause of monogenic severe childhood-onset obesity. We confirmed the BMI association in 60,352 adults (per-allele effect = 0.05 Z-score units; P = 2.8 x 10(-15)) and 5,988 children aged 7-11 (0.13 Z-score units; P = 1.5 x 10(-8)). In case-control analyses (n = 10,583), the odds for severe childhood obesity reached 1.30 (P = 8.0 x 10(-11)). Furthermore, we observed overtransmission of the risk allele to obese offspring in 660 families (P (pedigree disequilibrium test average; PDT-avg) = 2.4 x 10(-4)). The SNP location and patterns of phenotypic associations are consistent with effects mediated through altered MC4R function. Our findings establish that common variants near MC4R influence fat mass, weight and obesity risk at the population level and reinforce the need for large-scale data integration to identify variants influencing continuous biomedical traits.

8 **Morton, L.M. et al, 2006, DRD2 genetic variation in relation to smoking and obesity in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Pharma Cogenetics Genomics, 16(12). 901-10.**

Cigarette smoking is the leading cause of morbidity and mortality worldwide. We investigated the association between smoking behavior and genetic variations in the D2 dopamine receptor (DRD2), which mediates nicotine dependence. To assess the specificity of genetic effects, we also investigated other reward-motivated characteristics (obesity, alcohol consumption). METHODS: Four single nucleotide polymorphisms in DRD2 were genotyped in 2374 participants selected randomly from the screening arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial after stratifying by sex, age, and smoking status. Smoking, obesity, and alcohol consumption were assessed by questionnaire. Single nucleotide polymorphism and haplotype associations were estimated using odds ratios (ORs) and 95% confidence intervals derived from conditional logistic regression models, adjusted for race/ethnicity. RESULTS: DRD2 polymorphisms were associated with the risk of remaining a current smoker and obesity. Current smokers were more likely than former smokers to possess the variant TaqIA allele in a dose-dependent model (ORCT=1.2, ORTT=1.5, P for linear trend=0.007). The DRD2 haplotype T-C-T-A [TaqIA(C/T)-957(T/C)-IVS6-83(G/T)- -50977(A/G)] was more common among current than former smokers (OR=1.3, P=0.006), particularly among heavy smokers (21+ cigarettes per day; OR=1.6, P=0.006), and was more common among obese than normal weight individuals (OR=1.4, P=0.02). CONCLUSIONS: Genetic variation in DRD2 is a modifier of the reward-motivated characteristics, smoking and obesity. As fewer than 15% of smokers who attempt to quit are able to maintain abstinence for greater than 3 months, our results support that DRD2 is an appropriate molecular target for smoking cessation treatments. Our results further support evaluation of DRD2 antagonists for obesity therapies.

9 **Ordovas, J.M. et al, 2002, Dietary fat intake determines the effect of a common polymorphism in the hepatic lipase gene promoter on high-density lipoprotein metabolism: evidence of a strong dose effect in this gene-nutrient interaction in the Framingham Study. Circulation, 106(18). 2315-21.**

BACKGROUND: Gene-nutrient interactions affecting high-density lipoprotein cholesterol (HDL-C) concentrations may contribute to the interindividual variability of the cardiovascular disease risk associated with dietary fat intake. Hepatic lipase (HL) is a key determinant of HDL metabolism. Four polymorphisms in linkage disequilibrium have been identified in the HL gene (LIPC), defining what is known as the -514T allele. This allele has been associated with decreased HL activity and increased HDL-C concentrations. However, the effect is variable among populations. METHODS AND RESULTS: We have examined interaction effects between the -514(C/T) LIPC polymorphism, dietary fat, and HDL-related measures in 1020 men and 1110 women participating in the Framingham Study. We found a consistent and highly significant gene-nutrient interaction showing a strong dose-response effect. Thus, the T allele was associated with significantly greater HDL-C concentrations only in subjects consuming <30% of energy from fat (P<0.001). When total fat intake was > or =30% of energy, mean HDL-C concentrations were lowest among those with the TT genotype, and no differences were observed between CC and CT individuals. We found similar gene-nutrient interactions when the outcome variables were HDL2-C (P<0.001), large HDL subfraction (P<0.001), or HDL size (P=0.001). These interactions were seen for saturated and monounsaturated fat intakes (highly correlated with animal fat in this population), but not for polyunsaturated fat. CONCLUSIONS: Dietary fat intake modifies the effect of the -514(C/T) polymorphism on HDL-C concentrations and subclasses. Specifically, in the Framingham Study, TT subjects may have an impaired adaptation to higher animal fat diets that could result in higher cardiovascular risk.

10 **Hautala, A.J. et al, 2007, Peroxisome proliferator-activated receptor-delta polymorphisms are associated with physical performance and plasma lipids: the HERITAGE Family Study. American Journal of Physiology Heart and Circulatory Physiology, 292(5). H2498-505.**

We tested the hypothesis that peroxisome proliferator-activated receptor-delta (PPARdelta) gene polymorphisms are associated with cardiorespiratory fitness and plasma lipid responses to endurance training. Associations between the PPARdelta exon 4 +15 C/T and exon 7 +65 A/G polymorphisms and maximal exercise capacity and plasma lipid responses to 20 wk of endurance training were investigated in healthy white (n = 477) and black (n = 264) subjects. In black subjects, the exon 4 +15 C/C homozygotes showed a smaller training-induced increase in maximal oxygen consumption (P = 0.028) than the C/T and T/T genotypes. Similarly, a lower training response in maximal power output was observed in the exon 4 +15 C/C homozygotes (P = 0.005) compared with the heterozygotes and the T/T homozygotes in black subjects, and a similar trend was evident in white subjects (P = 0.087). In white subjects, baseline apolipoprotein A-1 (Apo A-1)levels were higher in the exon 4 +15 C/C (P = 0.011) and exon 7 +65 G/G (P = 0.05) genotypes compared with those in the other genotypes. In white subjects, exon 4 +15 C/C (P = 0.0025) and exon 7 +65 G/G (P = 0.011) genotypes showed significantly greater increases in plasma high-density lipoprotein-cholesterol (HDL-C) levels with endurance training than in the other genotypes, whereas in black subjects the exon 4 +15 CC homozygotes tended to increase (P = 0.057) their Apo A-1 levels more than the T allele carriers. DNA sequence variation in the PPARdelta locus is a potential modifier of changes in cardiorespiratory fitness and plasma HDL-C in healthy individuals in response to regular exercise.

11 **Warren, R.B. et al, 2009, Outcomes of methotrexate therapy for psoriasis and relationship to genetic polymorphisms. British Journal of Dermatology, 160(2). 438-41.**

The use of methotrexate is limited by interindividual variability in response. Previous studies in patients with either rheumatoid arthritis or psoriasis suggest that genetic variation across the methotrexate metabolic pathway might enable prediction of both efficacy and toxicity of the drug. Objectives To assess if single nucleotide polymorphisms (SNPs) across four genes that are relevant to methotrexate metabolism [folypolyglutamate synthase (FPGS), gamma-glutamyl hydrolase (GGH), methylenetetrahydrofolate reductase (MTHFR) and 5-aminoimidazole-4-carboxamide ribonucleotide transformylase (ATIC)] are related to treatment outcomes in patients with psoriasis. Methods DNA was collected from 374 patients with psoriasis who had been treated with methotrexate. Data were available on individual outcomes to therapy, namely efficacy and toxicity. Haplotype-tagging SNPs (r2 > 0.8) for the four genes with a minor allele frequency of > 5% were selected from the HAPMAP phase II data. Genotyping was undertaken using the Mass ARRAY spectrometric method (Sequenom). Results There were no significant associations detected between clinical outcomes in patients with psoriasis treated with methotrexate and SNPs in the four genes investigated. Conclusions Genetic variation in four key genes relevant to the intracellular metabolism of methotrexate does not appear to predict response to methotrexate therapy in patients with psoriasis.

12 **Memisoglu, A. et al, 2003, Interaction between a peroxisome proliferator-activated receptor gamma gene polymorphism and dietary fat intake in relation to body mass. Human Molecular Genetics, 12(22). 2923-29.**

The peroxisome proliferator-activated receptor gamma (PPAR gamma) is a critical regulator of adipogenesis. PPAR gamma+/- mice are resistant to high-fat diet-induced obesity and thus PPAR gamma may mediate physiological responses to dietary fat in other mammals. The aim of this study was to determine whether the human PPAR gamma proline to alanine substitution polymorphism (Pro12Ala) modifies the association between dietary fat and adiposity and plasma lipids. Subjects (n=2141) were controls selected for three case-control studies nested within the Nurses' Health Study, a large ongoing prospective cohort study. Associations between intake of total fat, fat subtypes and BMI were different in PPAR gamma 12Ala variant allele-carriers compared with non-carriers. Among homozygous wild-type Pro/Pro individuals, those in the highest quintile of total fat intake, had significantly higher mean body mass index (BMI) compared with those in the lowest quintile (27.3 versus 25.4 kg/m2, respectively; P-trend<0.0001) whereas among 12Ala variant allele-carriers there was no significant trend observed between dietary fat intake and BMI (P-trend=0.99; P-interaction=0.003). In contrast, intake of monounsaturated fat was not associated with BMI among homozygous wild-type women but was inversely associated with BMI among 12Ala variant allele-carriers (mean in lowest quintile=27.6 versus mean in highest quintile=25.5 kg/m2; P-trend=0.006; P-interaction=0.003). The relationship between dietary fat intake and plasma lipid concentrations also differed according to PPAR gamma genotype. These data suggest that PPAR gamma genotype is an important factor in physiological responses to dietary fat in humans.

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13 **Yang, N. et al, 2003, ACTN3 genotype is associated with human elite athletic performance. American Journal of Human Genetics, 73(3). 627-31.**

There is increasing evidence for strong genetic influences on athletic performance and for an evolutionary trade-off between performance traits for speed and endurance activities. We have recently demonstrated that the skeletal-muscle actin-binding protein alpha-actinin-3 is absent in 18% of healthy white individuals because of homozygosity for a common stop-codon polymorphism in the ACTN3 gene, R577X. Alpha-actinin-3 is specifically expressed in fast-twitch myofibers responsible for generating force at high velocity. The absence of a disease phenotype secondary to alpha-actinin-3 deficiency is likely due to compensation by the homologous protein, alpha-actinin-2. However, the high degree of evolutionary conservation of ACTN3 suggests function(s) independent of ACTN2. Here, we demonstrate highly significant associations between ACTN3 genotype and athletic performance. Both male and female elite sprint athletes have significantly higher frequencies of the 577R allele than do controls. This suggests that the presence of actinin-3 has a beneficial effect on the function of skeletal muscle in generating forceful contractions at high velocity, and provides an evolutionary advantage because of increased sprint performance. There is also a genotype effect in female sprint and endurance athletes, with higher than expected numbers of 577RX heterozygotes among sprint athletes and lower than expected numbers among endurance athletes. The lack of a similar effect in males suggests that the ACTN3 genotype affects athletic performance differently in males and females. The differential effects in sprint and endurance athletes suggests that the R577X polymorphism may have been maintained in the human population by balancing natural selection.

14 **Teran-Garcia, M. et al, 2005, Hepatic lipase gene variant -514C>T is associated with lipoprotein and insulin sensitivity response to regular exercise: the HERITAGE Family Study. Diabetes, 54(7). 2251-55.**

We investigated the associations between the hepatic lipase gene (LIPC) eC514C>T polymorphism and lipases, lipoproteins, and insulin sensitivity (Si) responses to exercise training. Hepatic lipase and lipoprotein lipase activities, plasma lipoprotein levels, and Si were measured in the sedentary state and post-exercise training in the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) Family Study (n = 662). The LIPC eC514C allele frequency was 0.516 (blacks) and 0.796 (whites). Baseline and post-exercise training hepatic lipase activities were 40% higher in CC homozygotes ($P < 0.0001$) in both races. Black CC homozygotes had lower baseline lipoprotein lipase activity, HDL cholesterol, HDL3, and apolipoprotein (apo)A-1 concentrations. White CC homozygotes had lower baseline HDL cholesterol, apoA-1, LDL cholesterol, and apoB levels that remained low post-exercise training. Baseline Si was not associated with the LIPC genotypes. However, training-induced improvements in Si both in blacks and whites were greater in CC homozygotes than in the TT genotype. The LIPC eC514C allele was associated with higher hepatic lipase activity in sedentary and physically active states and better Si responses to regular exercise both in black and white individuals. The benefits from an exercise program on Si are likely to be substantial in the general population given the high frequency of the LIPC eC514C allele, particularly in whites.

15 **Junyent, M. et al, 2009, Novel variants at KCTD10, MVK, and MMAB genes interact with dietary carbohydrates to modulate HDL-cholesterol concentrations in the Genetics of Lipid Lowering Drugs and Diet Network Study. American Journal Clinical Nutrition, 90(3). 686-94.**

Background: Several genome-wide association studies have identified novel loci (KCTD10, MVK, and MMAB) that are associated with HDL-cholesterol concentrations. Of the environmental factors that determine HDL cholesterol, high-carbohydrate diets have been shown to be associated with low concentrations. Objective: The objective was to evaluate the associations of 8 single nucleotide polymorphisms (SNPs) located within the KCTD10, MVK, and MMAB loci with lipids and their potential interactions with dietary carbohydrates. Design: KCTD10, MVK, and MMAB SNPs were genotyped in 920 subjects (441 men and 479 women) who participated in the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) Study. Biochemical measurements were made by using standard procedures. Dietary intakes were estimated by using a validated questionnaire. Results: For the SNPs KCTD10_i5642GC and MVK_S52NGA, homozygotes for the major alleles (G) had lower HDL-cholesterol concentrations than did carriers of the minor alleles ($P = 0.005$ and $P = 0.019$, respectively). For the SNP 12inter_108466061AG, homozygotes for the minor allele (G) had higher total cholesterol and LDL-cholesterol concentrations than did AG subjects ($P = 0.030$ and $P = 0.034$, respectively). Conversely, homozygotes for the major allele (G) at MMAB_3U3527GC had higher LDL-cholesterol concentrations than did carriers of the minor allele ($P = 0.034$). Significant gene-diet interactions for HDL cholesterol were found ($P < 0.001$-0.038), in which GG subjects at SNPs KCTD10_i5642GC and MMAB_3U3527GC and C allele carriers at SNP KCTD10_V206VTC had lower concentrations only if they consumed diets with a high carbohydrate content ($P < 0.001$-0.011). Conclusion: These findings suggest that the KCTD10 (V206VTC and i5642GC) and MMAB_3U3527GC variants may contribute to the variation in HDL-cholesterol concentrations, particularly in subjects with high carbohydrate intakes.

16 **Okuda, M. et al, 2011, Association between the FTO gene and overweight in Japanese children and adolescents. Pediatric Diabetes, 12. 494-500.**

Association between the FTO gene and overweight in Japanese children and adolescents. Background: The association between the fat mass- and obesity-associated (FTO) gene and a predisposition to obesity is inconsistent in adult Asian populations. We investigated the association of the FTO gene with weight status in Japanese children and adolescents. Design/setting: Nested case-control study and 3-yr longitudinal study - In the Shunan Child Cohort Study, fifth and eighth grade students attending all schools of Shunan completed the questionnaires. Overweight, including obesity, was defined as a percentage of overweight of 20% or in accordance with the International Obesity Task Force. We recruited 133 obese subjects and randomly selected controls from the 2006 cohort. We genotyped three FTO single nucleotide polymorphisms (SNPs): rs3751812, rs9939609, and rs1558902. Results: The three genotyped SNPs were in tight linkage disequilibrium, with the exception of one case. The minor SNP allele of rs3751812 conferred a predisposition to obesity, and its odds ratio was 2.2 [95% confidence interval (CI), 1.5-3.4] in the additive model and 2.7 (95% CI, 1.6-4.4) in the dominant model ($p < 0.001$). Although blood parameters and some lifestyle behaviors were significantly different between the cases and controls ($p < 0.01$), these traits were not significantly different among the genotypes. In addition, we did not find an association between the genotypes and body mass index change during the 3 yr. Conclusion: The FTO gene is associated with the early onset of overweight in the Japanese population as well as in European populations. The results suggest that obesity-related risk factors in fifth and eighth graders appear because of their overweight status.

17 **Tanaka, T. et al, 2009, Genome-wide association study of vitamin B6, vitamin B12, folate, and homocysteine blood concentrations. American Journal of Human Genetics, 84(4). 477-82.**

The B vitamins are components of one-carbon metabolism (OCM) that contribute to DNA synthesis and methylation. Homocysteine, a by-product of OCM, has been associated with coronary heart disease, stroke and neurological disease. To investigate genetic factors that affect circulating vitamin B6, vitamin B12, folate and homocysteine, a genome-wide association analysis was conducted in the InCHIANTI (N = 1175), SardiNIA (N = 1115), and BLSA (N = 640) studies. The top loci were replicated in an independent sample of 687 participants in the Progetto Nutrizione study. Polymorphisms in the ALPL gene (rs4654748, $p = 8.30 \times 10(-18)$) were associated with vitamin B6 and FUT2 (rs602662, [corrected] $p = 2.83 \times 10(-20)$) with vitamin B12 serum levels. The association of MTHFR, a gene consistently associated with homocysteine, was confirmed in this meta-analysis. The ALPL gene likely influences the catabolism of vitamin B6 while FUT2 interferes with absorption of vitamin B12. These findings highlight mechanisms that affect vitamin B6, vitamin B12 and homocysteine serum levels.

18 **Kring, S.I. et al, 2009, Polymorphisms of serotonin receptor 2A and 2C genes and COMT in relation to obesity and type 2 diabetes Public Library of Science One, 4(8). e6696.**

Candidate genes of psychological importance include 5HT2A, 5HT2C, and COMT, implicated in the serotonin, noradrenaline and dopamine pathways, which also may be involved in regulation of energy balance. We investigated the associations of single nucleotide polymorphisms (SNPs) of these genes with obesity and metabolic traits. Methodology/Principal Findings In a population of 166 200 young men examined at the draft boards, obese men (n = 726, BMI 31.0 kg/m2) and a randomly selected group (n = 831) were re-examined at two surveys at mean ages 46 and 49 years (S-46, S-49). Anthropometric, physiological and biochemical measures were available. Logistic regression analyses were used to assess age-adjusted odds ratios. No significant associations were observed of 5HT2A rs6311, 5HT2C rs3813929 and COMT rs4680 with obesity, except that COMT rs4680 GG-genotype was associated with fat-BMI (OR = 1.08, CI = 1.01-1.16). The SNPs were associated with a number of physiological variables; most importantly 5HT2C rs3813929 T-allele was associated with glucose (OR = 4.56, CI = 1.13-18.4) and acute insulin response (OR = 0.65, CI = 0.44-0.94) in S-49. COMT rs4680 GG-genotype was associated with glucose (OR = 1.04, CI = 1.00-1.09). Except for an association between 5HT2A rs6311 and total-cholesterol at both surveys, significant in S-46 (OR = 2.66, CI = 1.11-6.40), no significant associations were observed for the other phenotypes. Significant associations were obtained when combined genotype of 5HT2C rs3813929 and COMT rs4680 were examined in relation to BMI (OR = 1.12, CI = 1.03-1.21), fat-BMI (OR = 1.22, CI = 1.08-1.38), waist (OR = 1.13, CI = 1.04-1.22), and cholesterol (OR = 5.60, CI = 0.99-31.4). Analyses of impaired glucose tolerance (IGT) and type 2 diabetes (T2D) revealed, a 12.3% increased frequency of 5HT2C rs3813929 T-allele and an 11.6% increased frequency of COMT rs4680 GG-genotype in individuals with IGT or T2D (2, $p = 0.05$ and $p = 0.06$, respectively). Examination of the combined genotypes of 5HT2C and COMT showed a 34.0% increased frequency of IGT or T2D (2, $p = 0.01$). Conclusions The findings lend further support to the involvement of serotonin, noradrenaline and dopamine pathways on obesity and glucose homeostasis, in particular when combined genotype associations are explored.

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19 **Corella, D. et al, 2009, APOA2, dietary fat, and body mass index: replication of a gene-diet interaction in 3 independent populations. Archives of Internal Medicine, 169(20). 1897-906.**

BACKGROUND: Nutrigenetics studies the role of genetic variation on interactions between diet and health, aiming to provide more personalized dietary advice. However, replication has been low. Our aim was to study interaction among a functional APOA2 polymorphism, food intake, and body mass index (BMI) in independent populations to replicate findings and to increase their evidence level. METHODS: Cross-sectional, follow-up (20 years), and case-control analyses were undertaken in 3 independent populations. We analyzed gene-diet interactions between the APOA2 -265T>C polymorphism and saturated fat intake on BMI and obesity in 3462 individuals from 3 populations in the United States: the Framingham Offspring Study (1454 whites), the Genetics of Lipid Lowering Drugs and Diet Network Study (1078 whites), and Boston-Puerto Rican Centers on Population Health and Health Disparities Study (930 Hispanics of Caribbean origin). RESULTS: Prevalence of the CC genotype in study participants ranged from 10.5% to 16.2%. We identified statistically significant interactions between the APOA2 -265T>C and saturated fat regarding BMI in all 3 populations. Thus, the magnitude of the difference in BMI between the individuals with the CC and TT+TC genotypes differed by saturated fat. A mean increase in BMI of 6.2% (range, 4.3%-7.9%; P = .01) was observed between genotypes with high- (> or =22 g/d) but not with low- saturated fat intake in all studies. Likewise, the CC genotype was significantly associated with higher obesity prevalence in all populations only in the high-saturated fat stratum. Meta-analysis estimations of obesity for individuals with the CC genotype compared with the TT+TC genotype were an odds ratio of 1.84 (95% confidence interval, 1.38-2.47; P < .001) in the high-saturated fat stratum, but no association was detected in the low-saturated fat stratum (odds ratio, 0.81; 95% confidence interval, 0.59-1.11; P = .18). CONCLUSION: For the first time to our knowledge, a gene-diet interaction influencing BMI and obesity has been strongly and consistently replicated in 3 independent populations.

20 **Rankinen, T. et al, 2007, Effect of endothelin 1 genotype on blood pressure is dependent on physical activity or fitness levels. Hypertension, 50(6). 1120-5.**

Contributions of the DNA sequence variation at the endothelin 1 locus to the risk of hypertension and to endurance training-induced changes in blood pressure were investigated in the Aerobics Center Longitudinal Study and the Health, Risk Factors, Exercise Training and Genetics Family Study cohorts. We identified 586 normotensive control subjects and 607 incident hypertensive case subjects from the Aerobics Center Longitudinal Study cohort (all whites) who were normotensive and healthy at their first clinic visit. The case subjects were diagnosed with hypertension during an average follow-up of 9.5 years, whereas the control subjects remained normotensive. The allele and genotype frequencies of 5 endothelin 1 haplotype tagging single nucleotide polymorphisms did not differ significantly between the case and control subjects. However, we observed a significant (P=0.0025) interaction between the endothelin 1 rs5370 (G/T; Lys198Asn) genotype and cardiorespiratory fitness level on the risk of hypertension: among low-fit subjects, the rs5370 minor allele (T; 198Asn) was associated with higher risk of hypertension (odds ratio: 1.95; 95% CI: 1.36 to 2.81; P=0.0003), whereas the risk did not differ among genotypes in high-fit subjects. In the white Health, Risk Factors, Exercise Training and Genetics subjects (N=480), the rs5370 T allele was associated with blunted systolic blood pressure (P=0.0046) and pulse pressure (P=0.0016) responses to a 20-week endurance training program. The Lys198Asn variant of the endothelin 1 locus is associated with blood pressure phenotypes in whites. However, the expression of the genotype effect is modulated by physical activity or cardiorespiratory fitness level. Our study provides an illustrative example of how physical activity and fitness level modifies the associations between a candidate gene and outcome phenotype.

21 **Eny, K.M. et al, 2008, Genetic variant in the glucose transporter type 2 is associated with higher intakes of sugars in two distinct populations. Physiological Genomics, 33(3). 355-60.**

Glucose sensing in the brain has been proposed to be involved in regulating food intake, but the mechanism is not known. Glucose transporter type 2 (GLUT2)-null mice fail to control their food intake in response to glucose, suggesting a potential role for this transporter as a glucose sensor in the brain. Here we show that individuals with a genetic variation in GLUT2 (Thr110Ile) have a higher daily intake of sugars in two distinct populations. In the first population, compared with individuals with the Thr/Thr genotype, carriers of the Ile allele had a significantly higher intake of sugars as assessed from 3-day food records administered on two separate visits (visit 1: 112 vs. 86 g/day, P = 0.01; visit 2: 111 vs. 82 g/day, P = 0.003), demonstrating within-population reproducibility. In a second population, carriers of the Ile allele also reported consuming a significantly greater intake of sugars (131 vs. 115 g/day, P = 0.007) over a 1-mo period as measured from a food frequency questionnaire. GLUT2 genotypes were not associated with fat, protein, or alcohol intake in either population. These observations were consistent across older and younger adults as well as among subjects with early Type 2 diabetes and healthy individuals. Taken together, our findings show that a genetic variation in GLUT2 is associated with habitual consumption of sugars, suggesting an underlying glucose-sensing mechanism that regulates food intake.

22 **Benzinou, M. et al, 2008, Common nonsynonymous variants in PCSK1 confer risk of obesity. Nature Genetics, 40(8). 943-5.**

Mutations in PCSK1 cause monogenic obesity. To assess the contribution of PCSK1 to polygenic obesity risk, we genotyped tag SNPs in a total of 13,659 individuals of European ancestry from eight independent case-control or family-based cohorts. The nonsynonymous variants rs6232, encoding N221D, and rs6234-rs6235, encoding the Q665E-S690T pair, were consistently associated with obesity in adults and children (P = 7.27 10-8 and P = 2.31 10-12, respectively). Functional analysis showed a significant impairment of the N221D-mutant PC1/3 protein catalytic activity.

23 **Doehring A, Kirchhof A, Lotsch J., 2009, Genetic diagnostics of functional variants of the human dopamine D2 receptor gene. Psychiatric Genetics, 19(5). 259-68.**

Introduction: The importance of dopamine D2 receptors (DRD2) for central nervous dopaminergic signalling makes variants in the DRD2 gene potential modulators of the risk or course of various behavioural, psychiatric or neurologic diseases (e.g. addiction, schizophrenia, Parkinson's disease). We developed Pyrosequencing genetic screening assays for single nucleotide polymorphisms spanning the whole range of the DRD2 gene locus up to the functionally related ankyrin repeat and kinase domain containing 1 gene (ANKK1) located at approximately 10 kb downstream of DRD2. Methods: Assays for 11 genetic variants with reported functional association were developed in DNA samples from 300 unrelated healthy Caucasians and validated by independent conventional sequencing. Results: In all DNA samples the DRD2/ANKK1 genetic variants were identified correctly as verified by the control samples. The observed frequencies of homozygous, heterozygous and noncarriers of the minor alleles were in agreement with the Hardy-Weinberg equilibrium. Observed minor allele frequencies were DRD2 rs12364283T>C: 6.5%, rs1799978A>G: 4.8%, rs1799732C del: 14.2%, rs4648317C>T: 12.8%, rs1079597G>A: 13.8%, rs1076560G>T: 14.5%, rs1800496C>T: 0.2%, rs1801028C>G: 3.0%, rs6275C>T: 32.7%, rs6277C>T: 53.0% and ANKK1 rs1800497C>T: 17.5%. Conclusion: The presently developed Pyrosequencing assays are provided to facilitate further research toward personalized approaches to pathophysiological conditions involving behavioural, psychiatric and neurologic disorders including addiction, schizophrenia and Parkinson's disease.

24 **Leung, W.C. et al, 2009, Two common single nucleotide polymorphisms in the gene encoding beta-carotene 15,15'-monoxygenase alter beta-carotene metabolism in female volunteers. FASEB J, 23(4). 1041-53.**

The key enzyme responsible for beta-carotene conversion into retinal is beta-carotene 15,15'-monoxygenase (BCMO1). Since it has been reported that the conversion of beta-carotene into vitamin A is highly variable in up to 45% of healthy individuals, we hypothesized that genetic polymorphisms in the BCMO1 gene could contribute to the occurrence of the poor converter phenotype. Here we describe the screening of the total open reading frame of the BCMO1 coding region that led to the identification of two common nonsynonymous single nucleotide polymorphisms (R267S: rs12934922; A379V: rs7501331) with variant allele frequencies of 42 and 24%, respectively. In vitro biochemical characterization of the recombinant 267S + 379V double mutant revealed a reduced catalytic activity of BCMO1 by 57% (P<0.001). Assessment of the responsiveness to a pharmacological dose of beta-carotene in female volunteers confirmed that carriers of both the 379V and 267S + 379V variant alleles had a reduced ability to convert beta-carotene, as indicated through reduced retinyl palmitate:beta-carotene ratios in the triglyceride-rich lipoprotein fraction [-32% (P=0.005) and -69% (P=0.001), respectively] and increased fasting beta-carotene concentrations [+160% (P=0.025) and +240% (P=0.041), respectively]. Our data show that there is genetic variability in beta-carotene metabolism and may provide an explanation for the molecular basis of the poor converter phenotype within the population.

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25 **Orkunoglu-Suer, F.E. et al, 2008, INSIG2 gene polymorphism is associated with increased subcutaneous fat in women and poor response to resistance training in men. BMC Medical Genetics, 9. 117.**

Background A common SNP upstream of the INSIG2 gene, rs7566605 (g.-10,1025G>C, Chr2:118,552,255, NT 022135.15), was reported to be associated with obesity (Body Mass Index, [BMI]) in a genome-wide association scan using the Framingham Heart Study but has not been reproduced in other cohorts. As BMI is a relatively insensitive measure of adiposity that is subject to many confounding variables, we sought to determine the relationship between the INSIG2 SNP and subcutaneous fat volumes measured by MRI in a young adult population. Methods We genotyped the INSIG2 SNP rs7566605 in college-aged population enrolled in a controlled resistance-training program, (the Functional Polymorphism Associated with Human Muscle Size and Strength, FAMuSS cohort, n = 752 volunteers 18-40 yrs). In this longitudinal study, we examined the effect of the INSIG2 polymorphism on subcutaneous fat and muscle volumes of the upper arm measured by magnetic resonance imaging (MRI) before and after 12 wks of resistance training. Gene/phenotype associations were tested using an analysis of covariance model with age and weight as covariates. Further, the % variation in each phenotype attributable to genotype was determined using hierarchical models and tested with a likelihood ratio test. Results Women with a copy of the C allele had higher levels of baseline subcutaneous fat (GG: n = 139; 243473 mm3 vs. GC/CC: n = 181; 268521 mm3; p = 0.0011); but men did not show any such association. Men homozygous for the G ancestral allele showed a loss of subcutaneous fat, while those with one or two copies of the C allele gained a greater percentage of subcutaneous fat with resistance training (GG: n = 103; 1.02% vs. GC/CC: n = 93; 6.39% p = 0.035). Conclusion Our results show that the INSIG2 rs7566605 polymorphism underlies variation in subcutaneous adiposity in young adult women and suppresses the positive effects of resistance training on men. This supports and extends the original finding that there is an association between measures of obesity and INSIG2 rs7566605 and further implicates this polymorphism in fat regulation.

26 **Furusawa, T.et al, 2010, The Q223R polymorphism in LEPR is associated with obesity in Pacific Islanders. Human Genetics, 127(3). 287-294.**

Various Pacific Island populations have experienced a marked increase in the prevalence of obesity in past decades. This study examined the association of a promoter polymorphism of the leptin gene (LEP), G-2548A (rs7799039), and two non-synonymous single nucleotide polymorphisms of the leptin receptor gene (LEPR), K109R (rs1137100) and Q223R (rs1137101), with body weight, body mass index (BMI) and obesity in Pacific Islanders. A total of 745 Austronesian (AN)-speaking participants were analyzed after adjusting for age, gender, and population differences. The results revealed that carriers of the 223Q alleles of LEPR had significantly higher body weight (P=0.0009) and BMI (P=0.0022) than non-carriers (i.e., 223R homozygotes); furthermore, the 223Q carriers also had a significantly higher risk of obesity in comparison to non-carriers (P=0.0222). The other two polymorphisms, G-2548A and K109R, were associated with neither body weight, BMI, nor obesity. The 223Q allele was widely found among the AN-speaking study subjects, thus suggesting that the LEPR Q223R polymorphism is one of the factors contributing to the high prevalence of obesity in the Pacific Island populations.

27 **Huuskonen, A. et al, 2010, Genetic variations of leptin and leptin receptor are associated with body composition changes in response to physical training. Cell Biochemistry and Function, 28(4). 306-12.**

Leptin regulates body weight, metabolism, and tissue adaptations to environmental stressors. We examined the association of single nucleotide polymorphism (SNP) of leptin promoter G-2548A (rs7799039) and leptin receptor Gln223Arg (rs1137101) with body composition, plasma leptin levels, and peak oxygen uptake (VO(2)peak) in response to 8 weeks of physical training in 48 male military conscripts. AA homozygotes of leptin promoter SNP-2548 showed higher body fat and BMI values than G allele carriers. Acute exercise decreased leptin levels in G allele carriers, but increased in AA homozygotes. Physical training significantly decreased BMI values and also a tendency for decreased plasma leptin levels was observed in all subjects. In G allele carriers, BMI loss was mainly due to decreased fat mass, whereas in AA homozygotes due to loss of fat-free mass. Training increased VO(2)peak in all subjects with most prominent effects in G allele carriers. Regarding leptin receptor SNP, there were no statistically significant differences in BMI values between the genotype groups at baseline or after physical training. Our results suggest that physical training-induced alterations in body composition and plasma leptin may be influenced by a genetic variation of leptin promoter but not of leptin receptor.

28 **den Hoed, M. et al, 2009, Postprandial responses in hunger and satiety are associated with the rs9939609 single nucleotide polymorphism in FTO. American Journal of Clinical Nutrition, 90(5). 1426-32.**

Background: The common rs9939609 single nucleotide polymorphism (SNP) in the fat mass and obesity-associated (FTO) gene is associated with adiposity, possibly by affecting satiety responsiveness. Objective: The objective was to determine whether postprandial responses in hunger and satiety are associated with rs9939609, taking interactions with other relevant candidate genes into account. Design: Sixty-two women and 41 men [age: 31 plus or minus 14 y; body mass index (in kg/m2): 25.0 plus or minus 3.1] were genotyped for 5 SNPs in FTO, DNMT1, DNMT3B, LEP, and LEPR. Individuals received fixed meals provided in energy balance. Hunger and satiety were determined pre- and postprandially by using visual analog scales. Results: A general association test showed a significant association between postprandial responses in hunger and satiety with rs9939609 (P = 0.036 and P = 0.050, respectively). Individuals with low postprandial responses in hunger and satiety were overrepresented among TA/AA carriers in rs9939609 (FTO) compared with TT carriers (dominant and additive model: P = 0.013 and P = 0.020, respectively). Moreover, multifactor dimensionality reduction showed significant epistatic interactions for the postprandial decrease in hunger involving rs9939609 (FTO), rs992472 (DNMT3B), and rs1137101 (LEPR). Individuals with a low postprandial decrease in hunger were overrepresented among TA/AA (dominant), CC/CA (recessive), and AG/GG (dominant) carriers in rs9939609 (FTO), rs992472 (DNMT3B), and rs1137101 (LEPR), respectively (n = 39), compared with TT, AA, and/or AA carriers in these SNPs, respectively (P = 0.00001). Each SNP had an additional effect. Conclusions: Our results confirm a role for FTO in responsiveness to hunger and satiety cues in adults in an experimental setting. The epistatic interaction suggests that DNA methylation, an epigenetic process, affects appetite.

29 **Regieli J.J. et al, 2009, PPAR gamma variant influences angiographic outcome and 10-year cardiovascular riski in male symptomatic coronary artery disease patients. Diabetes Care, 32(5). 839-44.**

Carriers of the 12Ala allele of PPAR have less widespread CAD and are considerably protected against 10-year (cardio) vascular morbidity and mortality. These long-term findings in patients with manifest CAD support an important role of PPAR in determining vascular risk.

30 **Enattah, N.S.; Sahi, T; Savilahti, E. et al, 2002, Identification of a variant associated with adult-type hypolactasia. Nature Genetics, 30(1). 233-7.**

Adult-type hypolactasia, also known as lactase non-persistence (lactose intolerance), is a common autosomal recessive condition resulting from the physiological decline in activity of the lactase-phlorizin hydrolase (LPH) in intestinal cells after weaning. LPH hydrolyzes lactose into glucose and galactose. Sequence analyses of the coding and promoter regions of LCT, the gene encoding LPH, has revealed no DNA variations correlating with lactase non-persistence. An associated haplotype spanning LCT, as well as a distinct difference in the transcript levels of 'non-persistence' and 'persistence' alleles in heterozygotes, suggest that a cis-acting element contributes to the lactase non-persistence phenotype. Using linkage disequilibrium (LD) and haplotype analysis of nine extended Finnish families, we restricted the locus to a 47-kb interval on 2q21. Sequence analysis of the complete region and subsequent association analyses revealed that a DNA variant, C/T-13910, roughly 14 kb upstream from the LCT locus, completely associates with biochemically verified lactase non-persistence in Finnish families and a sample set of 236 individuals from four different populations. A second variant, G/A-22018, 8 kb telomeric to C/T-13910, is also associated with the trait in 229 of 236 cases. Prevalence of the C/T-13910 variant in 1,047 DNA samples is consistent with the reported prevalence of adult-type hypolactasia in four different populations. That the variant (C/T-13910) occurs in distantly related populations indicates that it is very old.

31 **Kim, U.K. et al, 2003, Positional cloning of the human quantitative trait locus underlying taste sensitivity to phenylthiocarbamide. Science, 299(5610). 1221-5.**

The ability to taste the substance phenylthiocarbamide (PTC) has been widely used for genetic and anthropological studies, but genetic studies have produced conflicting results and demonstrated complex inheritance for this trait. We have identified a small region on chromosome 7q that shows strong linkage disequilibrium between single-nucleotide polymorphism (SNP) markers and PTC taste sensitivity in unrelated subjects. This region contains a single gene that encodes a member of the TAS2R bitter taste receptor family. We identified three coding SNPs giving rise to five haplotypes in this gene worldwide. These haplotypes completely explain the bimodal distribution of PTC taste sensitivity, thus accounting for the inheritance of the classically defined taste insensitivity and for 55 to 85% of the variance in PTC sensitivity. Distinct phenotypes were associated with specific haplotypes, which demonstrates that this gene has a direct influence on PTC taste sensitivity and that sequence variants at different sites interact with each other within the encoded gene product.

REFERENCES (cont.)

32 **Sachae, C. et al, 1999, Functional significance of a C-->A polymorphism in intron 1 of the cytochrome P450 CYP1A2 gene tested with caffeine. British Journal of Clinical Pharmacology, 47(4). 445-9.**

Aims: The cytochrome P450 enzyme CYP1A2 metabolises several drugs and carcinogens. We wanted to determine how much of the variability of CYP1A2 activity is explained by a newly discovered gene polymorphism in intron 1.Methods: A single nucleotide polymorphism in intron 1 of the CYP1A2 gene at position 734 downstream of the first transcribed nucleotide was identified by DNA sequence analysis. The functional significance of this C/A polymorphism was assessed in 185 healthy Caucasian non-smokers and in 51 smokers by genotyping and phenotyping using caffeine (100 mg oral dose).Results: Out of the total sample, 46% were homozygous for the variant A, 44% were heterozygous, and 10% were homozygous for the variant C. The ratio of 1,7-dimethylxanthine (17X) plus 1,7-dimethyluric acid divided by caffeine in 0-5 h urine samples from 185 non-smokers did not differ significantly between the three CYP1A2 genotypes. In the 51 smokers, analysis of variance revealed significant differences in the 5 h plasma 17X/caffeine ratios between the genotypes (P=0.008, F-test). The mean ratio was 1.37 in carriers of the A/A genotype, 0.88 in heterozygotes and 0.82 in carriers of C/C. The mean difference between the A/A and C/A groups was 0.48 (95% confidence interval 0.15-0.81; P=0.01). Conclusions: The A/A genotype, which may represent a CYP1A2 high inducibility genotype, may either be a direct cause of increased CYP1A2 activity, or be genetically linked to polymorphisms conferring high inducibility. Further studies are needed to define the role of this polymorphism on the pharmacokinetics of drugs metabolised by CYP1A2 and in the activation of carcinogens.

33 **Loos, R.J. et al, 2006, Polymorphisms in the leptin and leptin receptor genes in relation to resting metabolic rate and respiratory quotient International Journal of Obesity, 30(1). 183-190.**

Leptin (LEP) is an endocrine hormone that participates in many metabolic pathways, including those associated with the central regulation of energy homeostasis. Objective: We examined the associations between polymorphisms in the LEP and leptin receptor (LEPR) genes and resting metabolic rate (RMR) and respiratory quotient (RQ) in the Quebec Family Study. RQ45 was associated with the LEPR-K109R (P=0.004) and Q223R (P=0.03) polymorphisms, and RMR showed association with the LEPR-K656N polymorphism (P=0.006). For the LEP-19A>G polymorphism, no significant associations were observed. However, LEP-A19A homozygotes who were carriers of the LEPR N656 allele had a significantly lower RQ45 compared to other genotype combinations (P for interaction=0.003). Conclusion: These findings suggest that DNA sequence variation in the LEPR gene contributes to human variation in RMR and in the relative rates of substrate oxidation during low-intensity exercise in steady state but not in a resting state.

34 **Fushan, A.A. et al, 2009, Allelic polymorphism within the TAS1R3 promoter is associated with human taste sensitivity to sucrose. Current Biology, 19(15). 1288-93.**

Human sweet taste perception is mediated by the heterodimeric G protein-coupled receptor encoded by the TAS1R2 and TAS1R3 genes . Variation in these genes has been characterized, but the functional consequences of such variation for sweet perception are unknown. We found that two C/T single-nucleotide polymorphisms (SNPs) located at positions 1572 (rs307355) and 1266 (rs35744813) upstream of the TAS1R3 coding sequence strongly correlate with human taste sensitivity to sucrose and explain 16% of population variability in perception. By using a luciferase reporter assay, we demonstrated that the T allele of each SNP results in reduced promoter activity in comparison to the C alleles, consistent with the phenotype observed in humans carrying T alleles. We also found that the distal region of the TAS1R3 promoter harbors a composite cis-acting element that has a strong silencing effect on promoter activity. We conclude that the rs307355 and rs35744813 SNPs affect gene transcription by altering the function of this regulatory element. A worldwide population survey reveals that the T alleles of rs307355 and rs35744813 occur at lowest frequencies in European populations. We propose that inherited differences in TAS1R3 transcription account for a substantial fraction of worldwide differences in human sweet taste perception.

35 **Matsuo, K. et al, 2006, Alcohol dehydrogenase 2 His47Arg polymorphism influences drinking habit independently of aldehyde dehydrogenase 2 Glu487Lys polymorphism Cancer Epidemiology, Biomarkers & Prevention, 15(5). 1009-13.**

Although the functional effect of alcohol dehydrogenase 2 (ADH2) His47Arg polymorphism has been elucidated, its effect on habitual drinking remains unknown. Here, we conducted a cross-sectional study in 2,299 nonalcoholic Japanese subjects (989 men and 1,310 women). Drinking status, ethanol consumption, and physical reaction to one glass of beer were examined with regard to ADH2 and aldehyde dehydrogenase 2 (ALDH2) polymorphism. Strength of associations were assessed by age-, sex-, smoking status-, and genotype-adjusted odds ratios and their 95% confidence intervals. ADH2 His/Arg and Arg/Arg genotypes showed higher risk for habitual drinking. Among men, ALDH2 genotype- and confounder-adjusted odds ratios (95% confidence intervals) were 1.30 (0.89-1.89) and 3.16 (1.03-9.70), and this trend was significant (P = 0.024). A similar trend was observed among women. The combination genotypes of two polymorphisms revealed the clear effect of the ADH2 Arg allele among those with ALDH2 Glu/Lys in both sexes (Ptrend = 0.007 for men and 0.024 for women). Physical reactions, such as flushing and palpitation, were significantly less common in those with Arg/Arg compared with other ADH2 genotypes, and this was marked when combined with ALDH2 Glu/Lys. Heavy drinker status was also strongly associated with ADH2 Arg alleles. In conclusion, this study showed the strong effect of ADH2 His47Arg polymorphism on habitual drinking regardless of ALDH2 genotype.

36 **Dhillon, P.K., 2011, Common Polymorphisms in the Adiponectin and Its Receptor Genes, Adiponectin Levels and the Risk of Prostate Cancer. Cancer Epidemiology, Biomarkers & Prevention, 20. 2618-2627.**

Results: Among the 12 tagging polymorphisms in ADIPOQ, four (rs266729, rs182052, rs822391, and rs2082940) were significantly associated (P < 0.05) with overall prostate cancer risk, with no significant difference by tumor grade or clinical stage. Two of the risk SNPs (rs266729 and rs182052) plus four other SNPs (rs16861209, rs17366568, rs3774261, and rs7639352) were also associated with plasma adiponectin levels, and three of these (rs1686109, rs17366568, and rs3774261) were also significantly associated with IR expression in prostate tumor tissue. One additional SNP was associated with IGFI-R tumor tissue expression (rs16861205). None of the 16 variants in ADIPOR1/R2 were related to cancer risk or circulating adiponectin levels. Conclusions: Common variants in the adiponectin gene were associated with prostate cancer risk, plasma adiponectin levels, and IR or IGF-IR expression in the prostate tumor. Impact: These genotype-phenotype associations support the biological relevance of adiponectin for prostate carcinogenesis, particularly in earlier stages of development.