Pathway Fit®

Technical Bulletin
Achilles tendinopathy

Report Type: Exercise

About: The Achilles tendon is a band of tissue that connects the calf muscle to the heel bone. Achilles tendinopathy is characterized by inflammation and lesions in the tendon. Exercise-induced pain is the primary symptom, and the condition is more common in athletes. However, not all patients who suffer from Achilles tendinopathy take part in vigorous physical activity, suggesting other factors may contribute to the etiology of the condition. Genetic variants have been shown to be associated with risk of Achilles tendinopathy.

Genetics: The risk of Achilles tendinopathy is associated with variants in the MMP3 gene, which encodes an enzyme involved in breaking down the extracellular matrix. In a small study, genetic variants within MMP3 in individuals with symptoms of Achilles tendon pathology were compared to variants in a control group. Individuals who were homozygous for the G allele of the rs679620 marker had 2.5-times higher risk of Achilles tendinopathy than individuals with other genotypes. Thus, patients who are homozygous for the G allele of rs679620 receive an outcome of “Injury Prone”.

Possible Outcomes: Injury Prone, Typical

Recommendations: N/A

Markers Tested and Scientific Strength: MMP3 [rs679620]

The rs679620 marker is rated “2”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: The association of rs679620 with risk of Achilles tendinopathy was detected in Caucasians, mostly males, and may or may not apply to other ethnicities.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

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References

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A CAP and CLIA Accredited Laboratory | 4045 Sorrento Valley Blvd., San Diego, CA 92121

Aerobic capacity (VO2max)

Report Type: Exercise

About: Maximal oxygen uptake (VO2max) is widely used as the best measure of an individual's cardiorespiratory fitness. VO2max is defined as the maximum volume of oxygen per unit time that an individual uses at maximum exertion. Anyone can increase fitness and VO2max by endurance training, but baseline VO2max levels can vary depending on age, gender, past medical history, current health and level of physical activity. Genetic variants have also been shown to be associated with baseline VO2max.¹

Genetics: Aerobic capacity is associated with variants in the PPARGC1A gene, which encodes a transcription factor that is a key regulator of energy metabolism. In a study of Spanish and British world-class male cyclists and runners, the rs8192678 marker was associated with baseline VO2max (L/min).¹ Men who had the G allele at rs8192678 were more likely to have typical VO2max, whereas men who were homozygous for the A allele were more likely to have a decreased VO2max. In this study, the association was not analyzed in women. Individuals who are homozygous for the A allele receive an outcome of “Decreased”.

Possible Outcomes: Decreased, Typical

Recommendations: N/A

Nutritionist's Recommendations:

Markers Tested and Scientific Strength: PPARGC1A [rs8192678]

The rs8192678 marker is rated “2”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: The association of rs8192678 with aerobic capacity was detected in Caucasian, male, world-class endurance athletes and may or may not apply to females, other ethnicities or non-athletes.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.
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Alcohol flush

Report Type: Food Reactions

About: In some individuals, drinking even small amounts of alcohol causes the person's face to flush red and, possibly, feel warm and itchy. People who experience this condition called alcohol flush may also experience other unpleasant symptoms in response to alcohol, such as rapid heartbeat, nausea or dizziness. Genetic variants have been shown to be associated with alcohol flush.¹²³

Genetics: Alcohol flush is associated with variants in the ALDH2 gene, which encodes the enzyme aldehyde dehydrogenase 2. This enzyme converts the carcinogen and product of alcohol oxidation, acetaldehyde, to the less toxic compound acetate. The A allele at the rs671 marker causes a less active aldehyde dehydrogenase 2 enzyme, leading to a buildup of acetaldehyde, which causes facial flushing and other symptoms.¹ This association has been replicated in multiple studies.²³ Approximately 36% of East Asians (Japanese, Chinese and Koreans) have at least one copy of the deficient enzyme and experience alcohol flush. The rs671 allele is very rare in Caucasians and Africans. Variants in ALDH2 are also associated with overall reduced consumption of alcohol.⁴

Possible Outcomes: More Likely, Less Likely

Recommendations: N/A

Markers Tested and Scientific Strength: ALDH2 [rs671]

The rs671 marker is rated “4”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: The association of rs671 with alcohol flush was detected in East Asians. The A allele at rs671 is very rare in Caucasians and Africans. While these ethnicities may also experience flushing symptoms after alcohol consumption, the underlying mechanisms are still under investigation.

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Bitter taste

Report Type: Food Reactions

About: The ability to taste bitterness may affect a person’s diet because individuals who have the ability may prefer salty food to mask bitterness. Bitter taste perception can be tested by exposing individuals to compounds that may be perceived as bitter, such as phenylthiocarbamide (PTC) and propylthiouracil (PROP). Genetic variants have been shown to be associated with perceiving bitterness when tasting these compounds. Genetics: Sensitivity to PTC is associated with variants in the TAS2R38 gene, which encodes a taste receptor. In a study that included Caucasians and Asians, the rs713598 and rs1726866 markers were shown to account for 55-85% of the variance in PTC sensitivity. In a study of PROP taste perception in Caucasians, the same two markers were also highly associated with taste sensitivity. Individuals who receive an outcome of “Taster” may be more sensitive to bitter compounds, whereas individuals who receive an outcome of “Non-taster” may be less sensitive. An outcome of “Inconclusive” means that there is not enough scientific evidence to determine how an individual’s genotype is associated with bitter taste sensitivity.

Possible Outcomes: Non-taster, Taster, Inconclusive

Recommendations: N/A

Markers Tested and Scientific Strength

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<tr>
<th>Gene/Locus</th>
<th>Marker</th>
<th>Scientific Strength</th>
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<tbody>
<tr>
<td>TAS2R38</td>
<td>rs1726866</td>
<td>3</td>
</tr>
<tr>
<td>TAS2R38</td>
<td>rs713598</td>
<td>3</td>
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</tbody>
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Gene or locus containing the tested marker

Marker tested

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: The association of rs1726866 and rs713598 with bitter taste sensitivity was detected in Caucasians and Asians and may or may not apply to individuals other ethnicities. The reporting strategy in this genetic test is based on studies of sensitivity to the synthetic compounds, PROP and PTC, and the perception for different bitter compounds is associated with different genetic factors.
**Compatible ICD-9 Codes:** Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

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Blood pressure response to exercise

Report Type: Exercise

About: The prevalence of hypertension is estimated to be 29% in the U.S. The condition can lead to stroke, heart attack and kidney failure. Risk factors for hypertension include high salt intake, being overweight and high alcohol consumption. Physical activity is an important part of blood pressure control, and genetic variants have been shown to be associated with blood pressure response to exercise.

Genetics: Blood pressure response to exercise is associated with variants in the EDN1 gene, which encodes the vasoconstrictor endothelin 1. A study of U.S. patients showed that there was an interaction between the rs5370 marker in the EDN1 gene, cardiorespiratory fitness levels, and the risk of hypertension. Among subjects with low cardiorespiratory fitness levels, which was defined as having maximal metabolic equivalents below the sex-specific median, individuals who had the T allele at the rs5370 marker had higher risk of hypertension than individuals who were homozygous for the G allele. However, the risk did not differ among genotypes in individuals with high cardiorespiratory fitness.

In the same study, the authors reported consistent findings in a longitudinal cohort that underwent 20-week endurance training. The T allele was associated with blunted response to the training program in systolic blood pressure and pulse pressure, and individuals who have the T allele receive an outcome of “Exercise Strongly Recommended”. The study recruited both Caucasian and black individuals, but the effect of the variant on exercise-induced blood pressure benefits was significant only in Caucasian subjects.

Possible Outcomes: Exercise Strongly Recommended, Exercise Recommended

Recommendations: N/A

Markers Tested and Scientific Strength: EDN1 [rs5370]

The rs5370 marker is rated “3”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: The association of rs5370 with blood pressure response to exercise was detected in Caucasian but not African-American patients; applicability to other ethnicities is unknown.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing
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BMI response to exercise

Report Type: Exercise

About: Obesity, clinically defined as a body mass index (BMI) > 30 kg/m$^2$, affects at least 20% of individuals in Western countries, while 50% of people are classified as overweight (BMI > 25 kg/m$^2$) or obese by the World Health Organization’s definition. Physical activity is an important part of maintaining a healthy BMI, and genetic variants have been shown to be associated with BMI response to physical activity.$^1$

Genetics: The response of an individual’s Body Mass Index (BMI) to physical activity is associated with variants in the FTO (fat mass and obesity-associated) gene. Variants of the rs1121980 marker in the FTO gene were shown to be strongly associated with obesity measures such as body mass index (BMI) and waist circumference in a genome wide association (GWA) study of Caucasian individuals.$^2$ Furthermore, in a large study of Caucasian individuals from the same study population (EPIC-Norfolk study), the association of this variant with BMI and waist circumference was shown to be modified by physical activity levels. The study compared individuals with at least one T allele to individuals who were homozygous for the C allele. For active individuals, presence of the T allele was associated with a BMI increase of 0.25 kg/m$^2$ per allele, whereas for inactive individuals presence of the T allele was associated with BMI increase of 0.44 kg/m$^2$ per allele. Also, for active individuals, presence of the T allele was associated with a waist circumference increase of 0.64 cm per allele, whereas for inactive individuals presence of the T allele was associated with a waist circumference increase of 1.04 cm per allele.$^1$ Inactive individuals were characterized as having a sedentary job and no recreational activity. Individuals who have the T allele receive an outcome of “Exercise Strongly Recommended” because physical activity reduces the propensity for increased BMI associated with this genotype.

Possible Outcomes: Exercise Strongly Recommended, Exercise Recommended

Recommendations: N/A

Markers Tested and Scientific Strength: FTO [rs1121980]

The rs1121980 marker is rated “3”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: The association of rs1121980 with BMI response to exercise was detected in Caucasians and may or may not apply to other ethnicities.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing
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Caffeine metabolism

**Report Type:** Pharmacogenetics

**About:** Caffeine is the most widely consumed stimulant in the world. It acts as an adenosine receptor antagonist and thus modulates cAMP activity. The drug is metabolized to an inactive product by the liver enzyme cytochrome P450 1A2.\(^1\)

**Genetics:** Cytochrome P450 1A2 is encoded by the CYP1A2 gene. Variants of CYP1A2 can affect enzyme activity and, thus, a patient’s ability to metabolize caffeine. The A allele of the rs762551 marker in the CYP1A2 gene (CYP1A2*1F)\(^\dagger\) increases the activity of the enzyme, resulting in significantly enhanced caffeine metabolism.\(^1,2\) Individuals homozygous for the A allele are classified as “fast” caffeine metabolizers, whereas individuals with a C allele (CYP1A2*1A) are classified as “slow” caffeine metabolizers.\(^3\) However, increased caffeine metabolism by A allele homozygotes was observed in smokers but not in non-smokers, suggesting that in the absence of an inducer like smoking, A allele homozygotes may not be significantly different than C carriers.\(^2\)

Coffee intake has been observed to be associated with increased risk for myocardial infarction in "slow" caffeine-metabolizing individuals with a C allele at rs762551 in the CYP1A2 gene.\(^3\) In a study assessing the relationship between coffee drinking habits and myocardial infarction, researchers found that young (less than 59 years) individuals with the “slow” CYP1A2 genotype have an increased risk for heart attack if they are heavy coffee drinkers. Risk was greater for individuals who drank more than four cups of coffee per day than for individuals who drank two to three cups per day. The risk was not gender-specific and was not affected by smoking status.\(^3\) Caffeine is the only major compound found in filtered coffee that is known to be metabolized by the cytochrome P450 1A2 (CYP1A2) enzyme, suggesting that caffeine is the component of coffee that increases the risk of heart attack.

\(^\dagger\)The CYP1A2 allele designation is based upon the recommendations of the International Human CYP Allele Nomenclature Committee\(^4\) and is reflected in this report.

**Recommendations:** N/A

**Possible outcomes:** Slow Metabolizer, Fast Metabolizer

**Markers or Alleles Tested:** CYP1A2 [rs762551]

**Ethnic Distribution of Tested Alleles:** The C allele frequency at rs762551 was reported to be approximately 29% to 33% in Caucasians, 30% to 39% in Asians and 40% to 51% in Africans.\(^5\)

**Limitations and Warnings:** An important consideration regarding A homozygotes (“fast” caffeine metabolizers) is that some studies have found that they do not differ from the C homozygotes (“slow” caffeine metabolizers) in the absence of a CYP1A2 inducer like tobacco or omeprazole.\(^2,6\) Therefore, it is possible that “fast” caffeine metabolizers who are non-smokers, or not taking an inducer of CYP1A2, might have similar caffeine-associated, heart attack risk as the “slow” caffeine metabolizer.
Moreover, the A allele of rs762551 is also found in other haplotypes besides CYP1A2*1F (CYP1A2 Allele Nomenclature table). Importantly, the frequency of the A allele of is not significantly different between Asians (63%, Koreans) and Caucasians (71%, Swedes), but the frequency of CYP1A2*1F haplotype was found to be significantly lower in Asians (0.4 to 7.7%) compared to Caucasians (57%). In Caucasians, the A allele is mostly found in the CYP1A2*1F haplotype, while in Asians, it is mostly found in other haplotypes that contain additional mutations. In Asians, the CYP1A2*1F haplotype cannot be identified by testing for rs762551 alone and there is a lack of association of the A allele of rs762551 with increased enzyme activity or inducibility. Therefore, this test is not recommended for Asians.

The CYP1A2 enzyme can metabolize a variety of compounds in addition to caffeine, such as the arthritis drug leflunomide. C homozygous individuals had a 9.7-fold higher risk for overall leflunomide-induced toxicity than did heterozygotes. Some of the known CYP1A2 substrates, inhibitors and inducers are listed below in a table reproduced from Cytochrome P450 drug interaction table.

In addition to genetics, a patient's ability to metabolize caffeine may also depend on nongenetic factors. Smoking, diet, oral contraceptives, and a variety of other drugs affect CYP1A2 activity.

<table>
<thead>
<tr>
<th>Known CYP1A2 Substrates</th>
<th>Known CYP1A2 Inhibitors</th>
<th>Known CYP1A2 Inducers</th>
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<tr>
<td>amitriptyline</td>
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<td>(R)warfarin</td>
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<td>zolmitriptan</td>
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References

Eating disinhibition

**Report Type:** Eating Behaviors

**About:** Eating disinhibition is the tendency of an individual to eat more than normal in response to a stimulus, such as certain food, or in situations that trigger overeating, such as emotional stress or specific social situations. This eating behavior can be quantified through the use of questionnaires, such as the Three-Factor Eating Questionnaire (TFEQ). This method of quantification has been used to identify genetic variants that are associated with eating disinhibition.¹

**Genetics:** The likelihood of eating disinhibition is associated with variants in the TAS2R38 gene, which encodes a chemosensory receptor. TAS2R38 belongs to a family of receptors that are expressed in the stomach and small intestine and function as bitter taste receptors in the gustatory system. A study of an Amish population tested whether TAS2R38 variants were associated with eating restraint, eating disinhibition and/or hunger. The TFEQ was used to assess three behavioral traits related to the control of food intake: restraint, disinhibition, and hunger. In women, the T allele of the rs1726866 marker was more likely to be associated with eating disinhibition, whereas the homozygous C genotype was less likely to be associated with eating disinhibition. This association was not observed in men.¹

**Possible Outcomes:** More Likely, Less Likely

**Recommendations:** N/A

**Markers Tested and Scientific Strength:** TAS2R38 [rs1726866]

The rs1726866 marker is rated “2”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

**Limitations and Warnings:** The association of rs1726866 with eating disinhibition was detected in Caucasian women but not men. Thus, the test result does not apply to men and may or may not apply to women of other ethnicities.

**Compatible ICD-9 Codes:** Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

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Endurance training

**Report Type:** Exercise

**About:** Endurance training generally describes exercise to improve stamina. The health benefits of endurance training are well-established, but some individuals benefit to a greater degree than others. Genetic variants have been shown to be associated with the extent of the benefits received from endurance training.1,2,3

**Genetics:** Benefit from endurance training is associated with variants in multiple genes, including LIPC, PPARD and LPL. Three studies tested people’s responses to a 20-week endurance training program and identified genetic variants that correlate with enhanced benefit from endurance training.1,2,3 The C allele (reported as “G” in this genetic test for technical reasons) of the rs2016520 marker in the PPARD gene is associated with a greater endurance exercise-induced increase in HDL cholesterol,3 and the C allele of the rs1800588 marker in the LIPC gene is associated with greater increase in insulin sensitivity in response to endurance exercise.2 In Caucasian women, the G allele of the rs328 marker in the LPL gene is associated with greater reductions of BMI, fat mass and percent body fat; the same allele is associated with greater reductions in abdominal visceral fat in African-American women.1

**Possible Outcomes:** Enhanced Benefit, Normal Benefit

**Recommendations:** N/A

**Markers Tested and Scientific Strength**

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<th>Gene/Locus</th>
<th>Marker</th>
<th>Associated Allele</th>
<th>Scientific Strength</th>
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<td>PPARD</td>
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<tr>
<td>LPL</td>
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\( ^a \)Gene or locus containing the tested marker

\( ^b \)Marker tested

\( ^c \)“Associated Allele” refers to the allele that is associated with enhanced benefit from endurance training.

\( ^d \)“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

**Limitations and Warnings:** The association of rs2016520 with HDL cholesterol response to endurance exercise was detected in Caucasians but not in African-Americans. The association between rs328 and endurance exercise-induced changes in body fat was detected in women but not in men.
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References

Food desire

Report Type: Eating Behaviors

About: The reinforcing value of food is a measurement of how much effort an individual is willing to put forth to gain access to food. Although there is no objective method to quantify someone's feeling of hunger or desire for a particular type of food, behavioral scientists have devised techniques to measure an individual's motivation to consume food relative to other people's motivation. The reinforcing value can be determined through a series of tests in which an individual is asked to complete a task in exchange for his or her favorite foods. Tasks increase in difficulty until the participant feels that the food is no longer worth the effort. Early quitters, when compared with late quitters, are considered low in food reinforcement. Genetic variants have been shown to be associated with levels of food reinforcement.

Genetics: Food desire is associated with variants near the DRD2 gene, which encodes a dopamine receptor. Using the technique described above, a study identified a genetic component of food reinforcement. Among people who were considered obese, individuals who had the T allele at the rs1800497 marker were more likely to make more of an effort to obtain their favorite foods. In contrast, the individuals who were homozygous for the C allele had typical levels of food reinforcement. The rs1800497 allele is located in the ANKK1 gene, which is located near the DRD2 gene. The T allele is associated with reduced DRD2 gene expression; therefore, it has been hypothesized that individuals with the T allele have reduced expression of the DRD2 gene, leading to less satisfaction with natural rewards such as food and sex.

Possible Outcomes: Increased, Typical

Recommendations: N/A

Markers Tested and Scientific Strength: ANKK1/DRD2 [rs1800497]

The rs1800497 marker is rated “2”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: N/A

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.
References

Genetic risk due to decreased vitamin B2

Report Type: Nutrition

About: Vitamin B2, or riboflavin, is a cofactor of the enzyme MTHFR, which is involved in folate metabolism. Folate can lower plasma levels of homocysteine, which, at high levels, is a risk factor for cardiovascular disease and stroke.\textsuperscript{1,2} An individual's genotype can indicate how riboflavin levels may affect levels of homocysteine.

Genetics: The rs1801133 marker is located in the MTHFR gene. In European individuals who were homozygous for the T allele at this marker, riboflavin was the second strongest predictor of homocysteine levels (after folate levels), with there being an inverse relationship between riboflavin and plasma homocysteine levels.\textsuperscript{3,4} In individuals who were homozygous for the T allele, homocysteine levels were highest in people with low riboflavin or vitamin B2 levels. Furthermore, riboflavin supplementation reduced homocysteine levels in these individuals.\textsuperscript{5,6} As high homocysteine levels are known to be a risk factor for cardiovascular disease and stroke,\textsuperscript{1,2} individuals who are homozygous for the T allele receive an outcome of “Optimize Intake” of riboflavin. On the other hand, vitamin B2 supplementation had a relatively small impact on homocysteine levels in people who have a C allele; therefore, these individuals receive a ”Stay Balanced” outcome.

Possible Outcomes: Optimize Intake, Stay Balanced

Recommendations: Please also see the genetic test results for related conditions: “Genetic risk for decreased folate” and “Methotrexate toxicity”.

Markers Tested and Scientific Strength: MTHFR [rs1801133]

The rs1801133 marker is rated “3”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: This test reports on genetic predisposition for increased homocysteine levels due to lower levels of vitamin B2. Other tests are available to assess a patient’s levels of homocysteine and riboflavin in blood. An “Optimize Intake” genetic result does not indicate that the patient’s actual blood levels of riboflavin are too low, but rather that the patient may be genetically predisposed to have lower levels of riboflavin in blood. Similarly, a “Stay Balanced” genetic result does not indicate that the patient’s actual riboflavin levels in blood are optimal.

The association of rs1801133 with risk due to vitamin B2 levels was detected in Caucasians and may or may not apply to other ethnicities.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing
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References


Genetic risk for decreased adiponectin

Report Type: Body and Weight

About: Adiponectin is a hormone that stimulates liver and muscles to access fat reserves. Higher adiponectin levels are beneficial for weight loss and health. Genetic variants have been shown to be associated with adiponectin levels.

Genetics: Adiponectin levels are associated with variants in the ADIPOQ gene, which encodes adiponectin. The rs17366568 marker explains 3.8% of the plasma adiponectin variance in Caucasians. In a large study of Caucasians, individuals who had the A allele had low levels of adiponectin compared to individuals who were homozygous for the G allele, who had typical levels. Other variants in ADIPOQ have been also linked to adiponectin levels. However, the contributions of those markers to the variability in adiponectin levels remain low.

Possible Outcomes: Possibly Low, Typical

Recommendations: N/A

Markers Tested and Scientific Strength: ADIPOQ [rs17366568]

The rs17366568 marker is rated “4”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: N/A

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

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References


Genetic risk for decreased folate

Report Type: Nutrition

About: Folate, a B-vitamin, plays a role in protein metabolism and DNA repair\(^1\) and can lower the blood level of homocysteine, a substance linked to cardiovascular disease at high levels.\(^2\) Diets rich in folate have also been associated with reduced risk of cardiovascular disease.\(^3\) The vitamin is particularly important early in pregnancy for preventing some birth defects\(^1\). The recommended dietary allowance for most adults is 400 micrograms per day, while 600 micrograms of folate per day is recommended by the Institute of Medicine for pregnant women.

Genetics: The C677T variant in the methylenetetrahydrofolate reductase gene (MTHFR, which encodes a folate-metabolizing enzyme), has been associated with lowered folate levels in the blood in a study that included over six thousand Caucasian, African and Hispanic individuals from the third National Health and Nutrition Examination Survey (NHANES III).\(^2\) The study also showed that dietary intake of folic acid could significantly reduce the negative impact of this variant on serum folate levels in individuals taking supplements containing greater than 400 micrograms folate per day. Therefore, people with a T allele are recommended to optimize their intake of folate by eating foods rich in folate. People who are homozygous for the C allele should maintain a healthy, balanced diet.

Possible Outcomes: Optimize Intake, Stay Balanced

Recommendations: Please also see the genetic test results for the related phenotypes: "Methotrexate toxicity" and "Genetic risk due to decreased vitamin B2".

Markers Tested and Scientific Strength: MTHFR [rs1801133]

The rs1801133 marker is rated a “3”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: This test reports on genetic predisposition for decreased folate levels. Other tests are available to assess a patient’s levels of blood folate. An ‘Optimize Intake’ genetic result does not indicate that the patient’s actual blood folate levels are too low, but rather that the patient may be genetically predisposed to have lower blood folate levels. Similarly, a ‘Stay Balanced’ genetic result does not indicate that the patient’s actual blood folate levels are optimal.

These interpretations and recommendations are made in the context of studies that included Caucasian, African and Hispanic participants, and the results may or may not be relevant to tested individuals who are of Asian ancestry.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test,
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<tr>
<td>266.2 Other B-complex deficiencies</td>
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</tbody>
</table>

Applies to:
- Deficiency:
  - cyanocobalamin
  - folic acid
  - vitamin B12

References

Genetic risk for decreased HDL cholesterol

Report Type: Metabolic Health Factors

About: High levels of high-density lipoprotein (HDL) cholesterol may protect against heart attack, while low levels may increase the risk of heart disease.\(^1\) Though multiple mechanisms are known to account for the effects of HDL cholesterol levels, the major one is thought to be the role of HDL in transporting excess cholesterol away from the arteries and back to the liver, where it is passed from the body.\(^2\) According to the National Cholesterol Education Program (NCEP) guidelines, levels lower than 40 mg/dl (for men) and lower than 50 mg/dl (for women) are considered risk factors for heart disease.\(^3\)

Genetics: Fourteen genetic variants associated with decreased HDL cholesterol levels were identified in a large genome-wide association study that included over 19,000 Caucasian individuals from the Framingham Heart Study.\(^4\) The association was replicated in another set of over 20,000 Caucasian individuals within the same study. While the function of these genetic variants is still being investigated, most are in genes such as CETP (cholesteryl ester transfer protein), FADS1 (fatty acid desaturase 1), LIPC (hepatic lipase), LIPG (endothelial lipase), LPL (lipoprotein lipase), PLTP (phospholipid transfer protein), amongst others, that are known to be involved in lipid metabolism.

An allele counting algorithm, in which risk alleles are weighted based on their effect size, was used to assign risk outcomes for each patient. This algorithm is based on a genome-wide association study (GWAS) that identified a set of 14 loci associated with HDL cholesterol levels. The authors used the alleles at each locus to assign a cumulative allelic dosage score for each individual. Based on dosage scores, individuals were divided into deciles and assessed for HDL cholesterol concentrations. The authors observed a significant trend in average HDL cholesterol concentration relative to allelic dosage score. Additionally, individuals with higher allelic dosage scores were more likely to have HDL levels below 40 mg/dl, a risk factor for heart disease.\(^4\)

An outcome of “High Risk” indicates that the patient has a genetic profile similar to individuals in the study who fell into the two highest allelic dosage deciles. The average HDL cholesterol levels of these individuals were below 46 mg/dl. Approximately 37% of individuals in this group had levels below 40 mg/dl.\(^4\) An outcome of “Above Average Risk” indicates that the patient has a genetic profile similar to individuals in the study who fell into the two next highest deciles; these individuals had HDL cholesterol levels that were, on average, below 50 mg/dl. Additionally, approximately 30% of individuals in this group had HDL cholesterol levels below 40 mg/dl.\(^4\) An outcome of “Average Risk”, “Below Average Risk” or “Low Risk” indicates that the patient has a genetic profile similar to individuals in the study whose HDL cholesterol levels were, on average, above 50 mg/dl.\(^4\)

Possible Outcomes: High Risk, Above Average Risk, Average Risk, Below Average Risk, Low Risk

Recommendations: Routine screening for blood cholesterol levels should be performed at appropriate ages, as recommended by the U.S. Preventive Services Task Force and other groups.\(^5\)

Markers Tested and Scientific Strength

Pathway Genomics Corporation | www.pathway.com | 877.505.7374 | clientservices@pathway.com
A CAP and CLIA Accredited Laboratory | 4045 Sorrento Valley Blvd., San Diego, CA 92121
<table>
<thead>
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\(^a\)Gene or locus containing the tested marker

\(^b\)Marker tested

\(^c\)“Risk Allele” refers to the allele that is associated with increased risk for the condition.

\(^d\)“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

\(^e\)A proxy marker (rs247616) may be used on the test. The rs247616 marker can be assayed on either strand of DNA. Therefore, the associated allele for rs247616 could be reported as either a C or a G in the patient report.

Limitations and Warnings: These genetic variants together account for approximately 9.3% of the variance in HDL cholesterol levels\(^4\) and, therefore, need to be considered together with other known risk factors for decreased HDL cholesterol levels. Specifically, an outcome of “High Risk” or “Above Average Risk” does not indicate that the patient has decreased HDL cholesterol levels; rather it indicates that the patient may have a genetic propensity for decreased HDL cholesterol levels. Similarly, an outcome of “Low” or “Below Average” does not indicate that the patient has optimal HDL cholesterol levels; rather it indicates that the patient has a lower than average genetic likelihood for decreased HDL cholesterol levels. To identify a patient’s actual blood HDL cholesterol levels, a standard blood test could be considered.

The genetic risk for decreased HDL cholesterol has been studied and observed in Caucasian populations. The interpretation and recommendations are made in the context of Caucasian studies, and the results may or may not be relevant to tested individuals who are of non-Caucasian or mixed ethnicities.
**Compatible ICD-9 Codes:** Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

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**References**

Genetic risk for decreased omega-6 and omega-3

Report Type: Diet Recommendation

About: The two main types of polyunsaturated fatty acids (PUFAs) are omega-6 and omega-3, both of which are important for heart health, according to the American Heart Association (AHA). Historically, the ratio of omega-6 to omega-3 fatty acids in the diet was maintained close to a healthy 1:1, while in the current Western diet, it is estimated to be about 15:1, indicating relative deficiency of omega-3 and overabundance of omega-6 fatty acids. Long-chain PUFAs that are synthesized in the body originate from precursor essential fatty acids, such as linoleic acid (LA, omega-6) and alpha-linolenic acid (ALA, omega-3). The most important enzymes involved in the elongation and desaturation of these precursors into their active long-chain forms are the rate-limiting delta-5 and delta-6 desaturases. Genetic variants have been shown to be associated with levels of omega-6 and omega-3 fatty acids.

Genetics: Omega-6 and omega-3 plasma levels are associated with variants in the FADS1 gene, which encodes delta-5 desaturase. In a large genome-wide association study (GWAS) of Italian patients, individuals with the minor allele of the rs174537 marker had decreased blood levels of arachidonic acid (AA), a long-chain omega-6 fatty acid, and eicosapentaenoic acid (EPA), a long-chain omega-3 fatty acid. Individuals who were homozygous for the major allele had typical levels of AA and EPA. These results were replicated in an independent study of individuals from the United States. A meta-analysis of five GWAS cohorts of European ancestry found an association between the rs174547 marker, which is in perfect linkage disequilibrium with rs174537 (r²=1) and concentration of EPA; preliminary evidence extended this association to African, Chinese and Hispanic cohorts. Individuals with the C allele receive an outcome of “Decreased”.

Possible Outcomes: Decreased, Typical

Recommendations: N/A

Markers Tested and Scientific Strength: FADS1 [rs174547]

The rs174547 marker is rated “4”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: The association of rs174547 with omega-3 and omega-6 fatty acid levels was detected in Caucasians; the data that extend the association to non-Caucasian patients are preliminary.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing
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References


Genetic risk for decreased vitamin A

Report Type: Nutrition

About: Vitamin A consists of a many related compounds, including retinol, retinal and retinoic acid. It is critical for vision, immune system function, bone growth, reproduction and regulation of gene expression.\textsuperscript{1,2,3,4} Genetic variants have been shown to be associated with levels of vitamin A.\textsuperscript{5}

Genetics: Vitamin A levels are associated with variants in the BCMO1 gene, which encodes an enzyme that converts beta-carotene to retinal, the precursor of vitamin A. Screening of the BCMO1 gene identified two common variants that resulted in reduced activity of BCMO1 by almost 57 percent \textit{in vitro}.\textsuperscript{5} The \textit{in vitro} results were confirmed using healthy female volunteers that were given a pharmacological dose of beta-carotene and assessed for beta-carotene metabolism. Female individuals who had the R267S (rs12934992) or A379V (rs7501331) allele showed approximately 69% reduction in beta-carotene metabolism as measured by retinyl palmitate:beta-carotene ratios.\textsuperscript{5}

An outcome of "Inconclusive," means that there was not enough clinical evidence to determine how the patient’s genotype relates to the efficiency of converting beta-carotene to vitamin A.

Possible Outcomes: Optimize Intake, Stay Balanced, Inconclusive

Recommendations: N/A

Markers Tested and Scientific Strength

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\textsuperscript{a}Gene or locus containing the tested marker

\textsuperscript{b}Marker tested

\textsuperscript{c}“Associated Allele” refers to the allele that is associated with decreased vitamin A levels.

\textsuperscript{d}“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: This test reports on genetic predisposition for decreased vitamin A levels. Other tests are available to assess a patient’s vitamin A plasma levels. An ‘Optimize Intake’ genetic result does not indicate that the patient’s actual vitamin A plasma levels are too low, but rather that the patient may be genetically predisposed to have lower
vitamin A plasma levels. Similarly, a ‘Stay Balanced’ genetic result does not indicate that the patient's actual vitamin A plasma levels are optimal.

The association of rs7501331 and rs12934922 with decreased vitamin A levels was detected in female patients from the United Kingdom and may or may not be applicable to males or other ethnicities.

**Compatible ICD-9 Codes:** Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

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**References**

Genetic risk for decreased vitamin B12

Report Type: Nutrition

About: Vitamin B12 contributes to brain and nervous system function and the health of red blood cells. It is also a critical component for DNA synthesis and regulation. Symptoms of vitamin B12 deficiency can vary but may include fatigue, weakness, bloating, or numbness and tingling in the hands and feet. The recommended intake for adults is 2.4 micrograms per day. Genetic variants are associated with vitamin B12 levels.

Genetics: Vitamin B12 plasma levels are associated with variants in the FUT2 gene, which encodes a protein involved in protein maturation. Multiple studies have found that individuals with the G allele of the rs602662 marker had lower plasma levels of vitamin B12 than individuals who were homozygous for the A allele. A genome-wide association study (GWAS) with replication identified an association between rs602662 and vitamin B12 levels. A second GWAS with replication that looked at a population of women also found an association between rs602662 and vitamin B12 levels. Additionally, a meta-analysis came to the same conclusion, although it should be noted that the study included individuals from the second GWAS. Individuals who have the G allele of rs602662 receive an outcome of “Optimize Intake”.

Possible Outcomes: Optimize Intake, Stay Balanced

Recommendations: N/A

Markers Tested and Scientific Strength: FUT2 [rs602662]

The rs602662 marker is rated “4”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: This test reports on genetic predisposition for decreased vitamin B12 levels. Other tests are available to directly assess a patient’s vitamin B12 plasma levels. An ‘Optimize Intake’ genetic result does not indicate that the patient’s actual vitamin B12 plasma levels are too low, but rather that the patient may be genetically predisposed to have lower vitamin B12 plasma levels. Similarly, a ‘Stay Balanced’ genetic result does not indicate that the patient’s actual vitamin B12 plasma levels are optimal.

The association of rs602662 with vitamin B12 levels was detected in Caucasians and may or may not apply to other ethnicities.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing
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<td>266.2 Other B-complex deficiencies</td>
<td>N/A</td>
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Applies to:
- Deficiency: vitamin B12

References

Genetic risk for decreased vitamin B6

Report Type: Nutrition

About: Vitamin B6 contributes to nervous system function and protein and sugar metabolism. Vitamin B6 deficiency is rare in the United States because most people receive sufficient amounts of vitamin B6 from a healthy diet. Genetic variants are associated with levels of vitamin B6.

Genetics: Vitamin B6 levels are associated with variants of the NBPF3 gene. In multiple studies, patients who had the C allele of the rs4654748 marker had lower levels of B6 than patients who were homozygous for the T allele. In a genome-wide association (GWA) study of Caucasian individuals, the association of rs4654748 with vitamin B6 levels was identified and replicated. A meta-analysis of the original and replicated groups showed that vitamin B6 levels were 1.45 ng/mL lower per C allele. Another meta-analysis of three GWA studies looked at levels of plasma PLP, an active form of vitamin B6. This study found that individuals who were homozygous for the T allele at rs4654748 had higher plasma PLP levels than individuals with one or more C alleles. Individuals who have the C allele receive an outcome of “Optimize Intake”.

Possible Outcomes: Optimize Intake, Stay Balanced

Recommendations: N/A

Markers Tested and Scientific Strength: NBPF3 [rs4654748]

The rs4654748 marker is rated “4”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: This test reports on genetic predisposition for decreased vitamin B6 levels. Other tests are available to directly assess a patient's vitamin B6 plasma levels. An ‘Optimize Intake’ genetic result does not indicate that the patient's actual vitamin B6 plasma levels are too low, but rather that the patient may be genetically predisposed to have lower vitamin B6 plasma levels. Similarly, a ‘Stay Balanced’ genetic result does not indicate that the patient's actual vitamin B6 plasma levels are optimal.

The association of rs4654748 with vitamin B6 levels was detected in Caucasians and may or may not apply to other ethnicities.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.
<table>
<thead>
<tr>
<th>Primary ICD-9 Code(s)</th>
<th>Screening ICD-9 Code(s)</th>
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</thead>
<tbody>
<tr>
<td>266.1 Vitamin B6 deficiency</td>
<td>N/A</td>
</tr>
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</table>

Applies to:
- Deficiency:
  - Pyridoxine

References

Genetic risk for decreased vitamin C

Report Type: Nutrition

About: Vitamin C, or L-ascorbic acid, must be acquired from dietary sources. Severe vitamin C deficiency ultimately leads to scurvy. Variations in vitamin C levels have been associated with a wide range of chronic complex diseases, such as atherosclerosis, type 2 diabetes and cancer.\(^1\) These associations are thought to result from a contribution of vitamin C as an antioxidant, as well as its role in the synthesis of collagen and various hormones. Genetic variants have been shown to be associated with vitamin C levels.\(^2\)

Genetics: Vitamin C plasma levels are associated with variants in the SLC23A1 gene, which encodes a protein that transports vitamin C into cells. A large study that examined circulating levels of L-ascorbic acid in Caucasians found that the A allele of the rs33972313 marker in SLC23A1 was associated with decreased levels of circulating L-ascorbic acid in a discovery cohort, four replication cohorts and a meta-analysis.\(^2\) The rs33972313 marker was associated with reduction of L-ascorbic acid levels of -4.15 \(\mu\)mol/L per A allele in the discovery cohort and -5.98 \(\mu\)mol/L per A allele in the pooled analysis.\(^2\)

Possible Outcomes: Optimize Intake, Stay Balanced

Recommendations: N/A

Markers Tested and Scientific Strength: SLC23A1 [rs33972313]

The rs33972313 marker is rated “4”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: This test reports on genetic predisposition for decreased vitamin C levels. Other tests are available to assess a patient’s vitamin C plasma levels. An ‘Optimize Intake’ genetic result does not indicate that the patient’s actual vitamin C plasma levels are too low, but rather that the patient may be genetically predisposed to have lower vitamin C plasma levels. Similarly, a ‘Stay Balanced’ genetic result does not indicate that the patient’s actual vitamin C plasma levels are optimal.

The association of rs33972313 with vitamin C levels was detected in Caucasians and may or may not apply to other ethnicities.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing
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<table>
<thead>
<tr>
<th>Primary ICD-9 Code(s)</th>
<th>Screening ICD-9 Code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>267 Ascorbic acid deficiency</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Applies to:
- Deficiency of vitamin C
- Scurvy

References


Genetic risk for decreased vitamin D

Report Type: Nutrition

About: Vitamin D is important for the absorption and use of calcium. Exposure to sunlight is an important determinant of a person’s vitamin D level because there are few natural dietary sources of vitamin D. In addition to environmental factors, genetic variants have also been shown to be associated with plasma levels of vitamin D.

Genetics: Vitamin D plasma levels are associated with variants in the GC gene, which encodes a vitamin D-binding protein. The G allele of the rs2282679 marker is associated with decreased plasma levels of 25-hydroxyvitamin D, the major circulating form of vitamin D. Individuals who have the G allele of the rs2282679 marker may have lower plasma levels of vitamin D than patients who are homozygous for the T allele. This result may be due to a reduced ability to transport vitamin D in the body. Individuals who have the G allele of rs2282679 receive an outcome of "Optimize Intake".

Possible Outcomes: Optimize Intake, Stay Balanced

Recommendations: N/A

Markers Tested and Scientific Strength: GC [rs2282679]

The rs2282679 marker is rated “4”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: This test reports on genetic predisposition for decreased vitamin D levels. Other tests are available to assess a patient’s vitamin D plasma levels. An ‘Optimize Intake’ genetic result does not indicate that the patient’s actual vitamin D plasma levels are too low, but rather that the patient may be genetically predisposed to have lower vitamin D plasma levels. Similarly, a ‘Stay Balanced’ genetic result does not indicate that the patient’s actual vitamin D plasma levels are optimal.

The association of rs2282679 with vitamin A levels was detected in Caucasians and may or may not apply to other ethnicities.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.
References


Genetic risk for elevated blood sugar

Report Type: Metabolic Health Factors

About: The term “elevated blood sugar” refers to a higher than normal amount of glucose in the blood. The American Diabetes Association defines normal blood sugar as glucose concentration less than 100 mg/dl (5.6 mmol/l) in the fasting state, or less than 140 mg/dl (7.8 mmol/l) in an oral glucose tolerance test (OGTT). Elevated blood sugar often indicates the presence of insulin resistance and is the hallmark of type 2 diabetes. Pre-diabetes is a risk factor for type 2 diabetes and is defined as abnormally elevated glucose that is not high enough to be classified as diabetic. Pre-diabetes typically precedes overt disease in patients who develop type 2 diabetes. Fasting glucose greater than or equal to 126 mg/dl (7.0 mmol/l) or OGTT glucose greater than or equal to 200 mg/dl (11.1 mmol/l) is diagnostic for type 2 diabetes.

Genetics: Sixteen genetic markers associated with blood glucose concentration were identified in a large genome-wide association study that included over 120,000 euglycemic or pre-diabetic Caucasian individuals. In the study, a genotype risk score composed of the sixteen markers significantly influenced fasting glucose levels. Risk scores in the top 5.6% were associated with a fasting glucose 7.2 mg/dl higher than those in the bottom 2.9%. In a follow-up study, the same genetic risk score was tested longitudinally and shown to influence fasting glucose over a 10-year period in a population of Swedish patients. All of the Swedish patients were diabetes-free at baseline and follow-up. Risk scores in the top 20 percent were associated with a 64% higher risk of developing pre-diabetes during the ten-year follow-up period compared to risk scores in the bottom 20 percent.

Possible Outcomes: High Risk, Above Average Risk, Average Risk, Below Average Risk, Low Risk

Recommendations: N/A

Markers Tested and Scientific Strength

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<th>Gene/Locus</th>
<th>Marker</th>
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<tr>
<td>ADRA2A</td>
<td>rs10885122</td>
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<tr>
<td>CRY2</td>
<td>rs11605924</td>
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<tr>
<td>FADS1</td>
<td>rs174550</td>
<td>T</td>
<td>4</td>
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<td>G6PC2</td>
<td>rs560887</td>
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<tr>
<td>GCK</td>
<td>rs4607517</td>
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<tr>
<td>GCKR</td>
<td>rs780094</td>
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<tr>
<td>GLIS3</td>
<td>rs7034200</td>
<td>A</td>
<td>4</td>
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<tr>
<td>MADD</td>
<td>rs7944584</td>
<td>A</td>
<td>4</td>
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<tr>
<td>MTNR1B</td>
<td>rs10830963</td>
<td>G</td>
<td>4</td>
</tr>
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</table>
PROX1 | rs340874 | C | 4
SLC2A2 | rs11920090 | T | 4
TCF7L2 | rs7903146 | T | 4

Gene or locus containing the tested marker

Marker tested

“Risk Allele” refers to the allele that is associated with increased risk for the condition.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: These genetic variants together account for approximately 10% of the variance in blood glucose level and, therefore, need to be considered with other known risk factors for elevated blood glucose. Specifically, an outcome of "High Risk" or "Above Average Risk" does not indicate that the patient has an elevated glucose level; rather, it indicates that the patient may have a genetic propensity for elevated glucose. Similarly, an outcome of "Low Risk" or "Below Average Risk" does not indicate that the patient has optimal blood glucose levels; rather, it indicates that the patient has a lower than average genetic likelihood for elevated blood glucose. To identify a patient's actual blood glucose levels, a standard blood test could be considered.

The genetic risk for elevated blood sugar has been studied and observed in Caucasian populations. The interpretation and recommendations are made in the context of Caucasian studies, and the results may or may not be relevant to tested individuals who are of non-Caucasian or mixed ethnicities.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

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<tbody>
<tr>
<td>790.29 Other abnormal glucose</td>
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</table>

References

Genetic risk for elevated LDL cholesterol

Report Type: Metabolic Health Factors

About: At high levels, low-density lipoprotein (LDL) cholesterol can put a patient at risk for conditions such as heart attack or stroke. According to the National Cholesterol Education Program (NCEP) guidelines, optimal LDL levels should be less than 100 mg/dl. Near-optimal levels range from 100 to 129 mg/dl and borderline-high from 130 to 159 mg/dl. A score greater than 160 mg/dl is high, and a score greater than 190 mg/dl is considered very high.

Genetics: Ten genetic variants associated with elevated LDL cholesterol levels were identified in a large genome-wide association study that included over 19,000 Caucasian individuals from the Framingham Heart Study. The association was replicated in another set of over 20,000 Caucasian individuals within the same study. While the function of these genetic variants is still being investigated, most are in genes that are directly involved in lipid metabolism, such as APOB (apolipoprotein B) and LDLR (low density lipoprotein receptor). Others, such as HNF1A (hepatic nuclear transcription factor 1A), regulate genes involved in lipid metabolism.

An allele counting algorithm, in which risk alleles are weighted based on their effect size, was used to assign risk outcomes for each patient. An outcome of “High Risk” indicates that the patient has a genetic profile similar to individuals in the study whose LDL cholesterol levels were, on average, borderline-high. Approximately 25% of individuals in this group had levels in the high range. An outcome of “Above Average Risk” indicates that the patient has a genetic profile similar to individuals in the study whose LDL cholesterol levels were on average borderline-high; approximately 17% of individuals in this group had levels in the high range. An outcome of “Average Risk”, “Below Average Risk” or “Low Risk” indicates that the patient has a genetic profile similar to individuals in the study whose LDL cholesterol levels were on average in the near-optimal range.

Recommendations: Routine screening for blood cholesterol levels should be performed at appropriate ages, as recommended by the U.S. Preventive Services Task Force and other groups.

Possible Outcomes: High Risk, Above Average Risk, Average Risk, Below Average Risk, Low Risk

Markers Tested and Scientific Strength

<table>
<thead>
<tr>
<th>Gene/Locus</th>
<th>Marker</th>
<th>Risk Allele</th>
<th>Scientific Strength</th>
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<td>ABCG8</td>
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<tr>
<td>APOB</td>
<td>rs515135</td>
<td>G</td>
<td>4</td>
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<tr>
<td>CELSR2</td>
<td>rs12740374</td>
<td>G</td>
<td>4</td>
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<tr>
<td>HMGCR</td>
<td>rs3846663</td>
<td>T</td>
<td>4</td>
</tr>
<tr>
<td>HNF1A</td>
<td>rs2650000</td>
<td>A</td>
<td>4</td>
</tr>
<tr>
<td>Intergenic</td>
<td>rs1501908</td>
<td>G</td>
<td>4</td>
</tr>
</tbody>
</table>

Pathway Genomics Corporation | www.pathway.com | 877.505.7374 | clientservices@pathway.com

A CAP and CLIA Accredited Laboratory | 4045 Sorrento Valley Blvd., San Diego, CA 92121
<table>
<thead>
<tr>
<th>Gene or locus containing the tested marker</th>
<th>Marker tested</th>
<th>&quot;Risk Allele&quot; refers to the allele that is associated with increased risk for the condition.</th>
<th>&quot;Scientific Strength&quot; refers to the strength of research evidence for the genetic marker and the associated result. A rating of &quot;4&quot; indicates a study of over 2,000 people and at least one study that replicated the results. A rating of &quot;3&quot; indicates a study of over 400 people. A rating of &quot;2&quot; indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of &quot;1&quot; indicates that results are extremely preliminary.</th>
</tr>
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<tbody>
<tr>
<td>LDLR</td>
<td>rs6511720</td>
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<tr>
<td>MAFB</td>
<td>rs6102059</td>
<td>C</td>
<td>4</td>
</tr>
<tr>
<td>NCAN</td>
<td>rs10401969</td>
<td>T</td>
<td>4</td>
</tr>
<tr>
<td>PCSK9</td>
<td>rs11206510</td>
<td>T</td>
<td>4</td>
</tr>
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</table>

**Limitations and Warnings:** These genetic variants together account for approximately 7.7% of the variance in LDL cholesterol levels and, therefore, need to be considered together with other known risk factors for elevated LDL cholesterol levels. Specifically, an outcome of "High Risk" or "Above Average Risk" does not indicate that the patient has elevated LDL cholesterol levels; rather it indicates that the patient may have a genetic propensity for elevated LDL cholesterol levels. Similarly, an outcome of "Low Risk" or "Below Average Risk" does not indicate that the patient has optimal LDL cholesterol levels; rather it indicates that the patient has a lower than average genetic likelihood for elevated LDL cholesterol levels. To assess a patient’s actual LDL cholesterol levels, a standard blood test could be considered.

The genetic risk for elevated LDL cholesterol has been studied and observed in Caucasian populations. The interpretation and recommendations are made in the context of Caucasian studies, and the results may or may not be relevant to tested individuals who are of non-Caucasian or mixed ethnicities.

**Compatible ICD-9 Codes:** Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

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<thead>
<tr>
<th>Primary ICD-9 Code(s)</th>
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</thead>
<tbody>
<tr>
<td>272.0 Pure hypercholesterolemia</td>
<td>V77.91 Screening for lipoid disorders</td>
</tr>
</tbody>
</table>

Applies to:
- Familial hypercholesterolemia
- Fredrickson Type IIa hyperlipoproteinemia
- Hyperbetalipoproteinemia
- Hyperlipidemia, Group A
- Low-density-lipoid-type [LDL] hyperlipoproteinemia

**References**

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Genetic risk for elevated triglycerides

Report Type: Metabolic Health Factors

About: Elevated triglycerides are a risk factor for conditions such as coronary artery disease and type 2 diabetes. According to the National Cholesterol Education Program (NCEP) guidelines, a normal triglyceride score is under 150 mg/dl. Triglyceride levels in the range of 150 to 199 mg/dl are defined as borderline-high, with over 200 mg/dl considered high and over 500 mg/dl very high.

Genetics: Eleven genetic variants associated with elevated triglyceride levels were identified in a large genome-wide association study that included over 19,000 Caucasian individuals from the Framingham Heart Study. The association was replicated in another set of over 20,000 Caucasian individuals within the same study. While the function of these genetic variants is still being investigated, most are in genes such as APOB (apolipoprotein B), FADS1 (fatty acid desaturase 1), LPL (lipoprotein lipase), PLTP (phospholipid transfer protein), amongst others, that are known to be involved in lipid metabolism.

An allele counting algorithm, in which risk alleles are weighted based on their effect size, was used to assign risk outcomes for each patient. An outcome of “High Risk” indicates that the patient has a genetic profile similar to individuals in the study whose triglyceride levels were, on average, borderline-high. Approximately 31% of individuals in this group had levels in the high range. An outcome of “Above Average Risk”, “Average Risk”, “Below Average Risk” or “Low Risk” indicates that the patient has a genetic profile similar to individuals in the study whose triglyceride levels were on average under 150 mg/dl.

Possible Outcomes: High Risk, Above Average Risk, Average Risk, Below Average Risk, Low Risk

Recommendations: N/A

Markers Tested and Scientific Strength

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<tr>
<th>Gene/Locus</th>
<th>Marker</th>
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<th>Scientific Strength</th>
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<td>APOB</td>
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<td>4</td>
</tr>
<tr>
<td>FADS1</td>
<td>rs174547</td>
<td>C</td>
<td>4</td>
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<tr>
<td>GCKR</td>
<td>rs1260326</td>
<td>T</td>
<td>4</td>
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<td>LPL</td>
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<tr>
<td>MLXIPL</td>
<td>rs714052</td>
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<td>4</td>
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<td>NCAN</td>
<td>rs17216525</td>
<td>C</td>
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<td>PLTP</td>
<td>rs7679</td>
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<tr>
<td>TRIB1</td>
<td>rs2954029</td>
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</table>
Gene or locus containing the tested marker

Marker tested

“Risk Allele” refers to the allele that is associated with increased risk for the condition.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: These genetic variants together account for approximately 7.4% of the variance in triglyceride levels and, therefore, need to be considered together with other known risk factors for elevated triglyceride levels. Specifically, an outcome of "High Risk" or "Above Average Risk" does not indicate that the patient has elevated triglyceride levels; rather it indicates that the patient may have a genetic propensity for elevated triglyceride levels. Similarly, an outcome of "Low Risk" or "Below Average Risk" does not indicate that the patient has optimal triglyceride levels; it indicates that the patient has a lower than average genetic likelihood for elevated triglyceride levels. To assess a patient's actual triglyceride levels, a standard blood cholesterol test could be considered.

The genetic risk for elevated triglyceride levels has been studied and observed in Caucasian populations. The interpretation and recommendations are made in the context of Caucasian studies, and the results may or may not be relevant to tested individuals who are of non-Caucasian or mixed ethnicities.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

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<th>Primary ICD-9 Code(s)</th>
<th>Screening ICD-9 Code(s)</th>
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</thead>
<tbody>
<tr>
<td>272.2 Mixed hyperlipidemia</td>
<td>V77.91 Screening for lipoid disorders</td>
</tr>
</tbody>
</table>

Applies to:
- Broad- or floating-betalipoproteinemia
- Combined hyperlipidemia
- Elevated cholesterol with elevated triglycerides NEC
- Fredrickson Type IIb or III hyperlipoproteinemia
- Hypercholesterolemia with endogenous hyperglyceridemia
- Hyperbetalipoproteinemia with prebetalipoproteinemia
- Tubo-eruptive xanthoma
- Xanthoma tuberosum
References

Genetic risk for increased vitamin E

Report Type: Nutrition

About: Vitamin E is a group of eight antioxidant molecules, with alpha-tocopherol being the most abundant in the body. Vitamin E functions in the immune system and regulates metabolic processes; increased levels are associated with decreased frailty and disability in old age. Genetic variants have been shown to be associated with increased vitamin E plasma levels.

Genetics: Vitamin E plasma levels are associated with variants near the APOA5 gene, which encodes an apolipoprotein involved in the regulation of triglyceride plasma levels. Vitamin E absorption and distribution follows processes similar to those used in fatty acid digestion and metabolism. In a genome-wide association study, individuals with the A allele of the rs12272004 marker, which is near the APOA5 gene, had increased plasma levels of alpha-tocopherol compared to individuals who were homozygous for the C allele. The association was identified in one population and replicated in two other, separate populations. A meta-analysis of all three studies confirmed the result. Individuals who have the A allele receive an outcome of “Stay Balanced”.

Possible Outcomes: Optimize Intake, Stay Balanced

Recommendations: N/A

Markers Tested and Scientific Strength: Intergenic [rs12272004]

The rs12272004 marker is rated “4”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: This test reports on genetic predisposition for elevated vitamin E levels. Other tests are available to assess a patient’s vitamin E plasma levels. An ‘Optimize Intake’ genetic result does not indicate that the patient’s actual vitamin E plasma levels are too low, but rather that the patient may be genetically predisposed to have lower vitamin E plasma levels. Similarly, a ‘Stay Balanced’ genetic result does not indicate that the patient’s actual vitamin E plasma levels are optimal.

The association of rs12272004 with vitamin E levels was detected in Caucasians and may or may not apply to other ethnicities.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient.
laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

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</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

References

HDL cholesterol response to exercise

Report Type: Exercise

About: High levels of high-density lipoprotein (HDL) cholesterol may protect against heart attack, while low levels may increase the risk of heart disease. According to the National Cholesterol Education Program (NCEP) guidelines, levels lower than 40 mg/dl (for men) or lower than 50 mg/dl (for women) are considered risk factors for heart disease. While physical activity is an important aspect of cardiovascular health, genetic variants have also been shown to be associated with the response of a person's HDL cholesterol levels to exercise.

Genetics: The response of an individual’s HDL cholesterol (HDL-C) levels to exercise is associated with variants in the PPARD (peroxisome proliferator-activated receptor delta) gene. Members of the PPAR family of nuclear hormone receptors are involved in the modulation of many genes, some of which affect lipid metabolism. In a study involving healthy Caucasians who underwent a 20-week endurance training program, the C allele of the rs2016520 marker in the PPARD gene was associated with a greater exercise-induced HDL-C increase. In response to exercise, HDL-C levels increased three times more in people who were homozygous for the C allele than in people who were homozygous for the T allele. Thus, individuals who have the C allele (reported as “G” in this genetic test for technical reasons) receive an outcome of “Enhanced Benefit”.

Possible Outcomes: Enhanced Benefit, Normal Benefit

Recommendations: N/A

Markers Tested and Scientific Strength: PPARD [rs2016520]

The rs2016520 marker is rated “3”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: The association of rs2016520 with HDL cholesterol response to exercise was detected in Caucasians but not in African Americans. This test may or may not apply to other non-Caucasian ethnicities.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.
References


Hunger

**Report Type:** Eating Behaviors

**About:** Eating behaviors can be quantified through the use of questionnaires. For example, the Three-Factor Eating Questionnaire (TFEQ) measures cognitive dietary restraint, disinhibition and susceptibility to hunger. These quantification methods provide an entry point for studies into the genetics of eating behaviors, and one study suggests that genetic variants are associated with susceptibility to hunger.¹

**Genetics:** Feelings of hunger are associated with variants in the NMB gene. In a study of Canadians, susceptibility to hunger, which can be described as an individual's perceived need for food, was measured based on responses to 14 questions of the TFEQ about eating behaviors. The study found that people who were homozygous for the T allele at the rs1051168 marker were more likely to report an increased susceptibility to hunger. In contrast, individuals with a G allele were more likely to have a typical hunger response.¹ The results of this study are extremely preliminary. Individuals who are homozygous for the T allele receive an outcome of “Increased”.

**Possible Outcomes:** Increased, Typical

**Recommendations:** N/A

**Markers Tested and Scientific Strength:** NMB [rs1051168]

The rs1051168 marker is rated “1”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

**Limitations and Warnings:** The association of rs1051168 with susceptibility to hunger was detected in Caucasians and may or may not apply to other ethnicities. This association is based on a single preliminary study.

**Compatible ICD-9 Codes:** Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

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**References**
Insulin sensitivity response to exercise

Report Type: Exercise

About: Insulin sensitivity describes the body’s response to insulin, a hormone that regulates the metabolism of sugar. For most people, exercise results in the benefit of increased insulin sensitivity, but some individuals benefit to a greater degree than others. Genetic variants have been shown to be associated with the sizes of these benefits.¹

Genetics: Insulin sensitivity response to exercise is associated with variants in the LIPC gene, which is involved in lipid metabolism. One study looked at the change in insulin sensitivity in Caucasians and African Americans after 20 weeks of endurance training. Individuals who had the C allele at the rs1800588 marker showed a greater exercise-induced increase in insulin sensitivity compared to individuals who were homozygous for the T allele. This difference was significant in both Caucasians and African Americans recruited in the study. This genetic marker had no effect on baseline insulin sensitivity.¹ Based on this study, individuals with a C allele receive an outcome of “Enhanced Benefit”, whereas individuals who are homozygous for the T allele receive an outcome of “Less Benefit”.

Possible Outcomes: Enhanced Benefit, Less Benefit

Recommendations: N/A

Markers Tested and Scientific Strength: LIPC [rs1800588]

The rs1800588 marker is rated “3”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: The association of rs1800588 with insulin sensitivity response to exercise was detected in Caucasians and African Americans and may or may not apply to other ethnicities.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

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References
Lactose intolerance

Report Type: Food Reactions

About: Lactose intolerance is the inability to digest lactose, the sugar found in milk and milk products. This condition is caused by the decreased activity of an enzyme called lactase. Genetic variants have been shown to be associated with lactase activity and lactose intolerance.¹,²,³,⁴

Genetics: Lactose intolerance is associated with variants near the lactase (LCT) gene. The rs4988235 marker is located in the MCM6 gene, which is close to LCT, and has been shown to regulate lactase levels.⁵,⁶,⁷ A case-control study of a Finnish population examined the trait of reduced lactase activity, or lactase non-persistence, as measured by disaccharidase activity assays. Individuals who were homozygous for the C allele at rs4988235 were more likely to have lactase non-persistence.¹ These results were replicated in a Polish population.² Another study asked Finnish adults to fill out a questionnaire about milk consumption and gastrointestinal problems. This study concluded that over a three month period, individuals who were homozygous for the C allele at the same marker drank less milk and were significantly more likely to report gastrointestinal symptoms compared to individuals with the T allele.³ Another small study found that Hispanics in Chile who were homozygous for the C allele were more likely to have lactase non-persistence.⁴ Homozygosity for the C allele indicates a predisposition to lactose intolerance; however, the effects can vary between individuals and might depend on the presence of additional factors.

Possible Outcomes: More Likely, Less Likely

Recommendations: N/A

Markers Tested and Scientific Strength: MCM6 [rs4988235]

The rs4988235 marker is rated “3”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: The association of rs4988235 with lactose intolerance was detected in Caucasians and may or may not apply to other ethnicities. Other genetic variants might play an important role in other ethnicities, including Africans and Asians.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.
Primary ICD-9 Code(s) | Screening ICD-9 Code(s)
--- | ---
271.3 Intestinal disaccharidase deficiencies and disaccharide malabsorption | N/A

References


Loss of body fat response to exercise

Report Type: Exercise

About: Endurance training is a well-established method of reducing body fat, but the magnitude of the effect can vary from person to person. At least part of this interindividual variability can be attributed to genetics. The HERITAGE Family Study has examined the role of genetics in an individual’s response to exercise. One of the studies that came out of the project provides evidence that genetic variants are associated with loss of body fat in response to exercise.

Genetics: Loss of body fat in response to exercise is associated with variants in the LPL gene, which encodes a lipoprotein lipase. In a small study of Caucasians and African Americans, individuals underwent 20 weeks of endurance training; fat mass and percent body fat were measured before and after the training. Caucasian women who had the G allele at the rs328 marker had a greater decrease of fat mass and percent body fat compared to women who did not have the G allele. The same study did not find an association between the G allele and loss of body fat in Caucasian males or African American females or males.

Possible Outcomes: Enhanced Benefit, Normal Benefit

Recommendations: N/A

Markers Tested and Scientific Strength: LPL [rs328]

The rs328 marker is rated “2”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: The association of rs328 with loss of body fat in response to exercise was detected in Caucasian women. The same study did not detect an association between rs328 and loss of body fat in response to exercise in Caucasian men or African American women or men.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

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References


Matching diet type

**Report Type:** Diet recommendation

**About:** The patient's diet type is selected by evaluating many genetic variants that are associated with how individuals respond to a variety of macronutrients. Genetic risk profiles of metabolic health factors, such as LDL and HDL cholesterol levels, are also evaluated and incorporated into a proprietary algorithm to determine a patient's recommended diet. The combination of the patient's genetic results determines which of the following diets may be best for overall health: "Low Fat," "Low Carb," "Mediterranean" or "Balanced Diet."

**Genetics:** The algorithm used to determine a patient's recommended diet is based on multiple genetic markers. Some of these markers are associated with responses to diet, while others are associated with benefits from eating particular foods or restricting particular foods or nutrients. For example, the hepatic lipase gene (LIPC) is known to play a major role in the regulation of plasma lipid levels. It was found that in people who are homozygous for the T allele of the rs1800588 marker in this gene, higher levels of HDL cholesterol were associated with lower intake of animal fat. This association suggests that a diet low in animal fats would benefit people who are homozygous for the T allele at this LIPC marker.

The algorithm also incorporates genetic markers associated with disease risk and related conditions, such as elevated blood sugar, elevated LDL cholesterol, elevated triglycerides and decreased HDL cholesterol. For these conditions, there may be known methods of reducing one's risk by making changes to the diet and nutritional intake. For example, patients with risk for elevated blood sugar could be recommended to reduce their intake of (high glycemic index) carbohydrates. In another instance, a patient with a genetic predisposition towards decreased HDL cholesterol levels could be recommended a diet low in carbohydrates, while a patient with a genetic predisposition towards elevated levels of LDL cholesterol could be recommended a diet low in fats, particularly saturated fats. The diet recommendation algorithm combines genetic markers from diet-based association studies and those that relate to a genetic predisposition for health conditions to provide an output that is one of four possible diets.

**Possible Outcomes:** Balanced Diet, Mediterranean Diet, Low Carb Diet, Low Fat Diet

**Recommendations:** N/A

**Markers Tested and Scientific Strength**

<table>
<thead>
<tr>
<th>Gene/Locus</th>
<th>Marker</th>
<th>Scientific Strength</th>
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<tr>
<td>APOA2</td>
<td>rs5082</td>
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<tr>
<td>ADIPOQ</td>
<td>rs17300539</td>
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<td>FTO</td>
<td>rs9939609</td>
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<td>KCTD10</td>
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<td>LIPC</td>
<td>rs1800588</td>
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| Gene or locus containing the tested marker | Marker tested | "Scientific Strength" refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

**Limitations and Warnings:** It is recommended to review any change in diet plan in relation to the medical history of the patient.

**Compatible ICD-9 Codes:** Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

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**References**


Metabolism

Report Type: Body and Weight

About: Metabolism refers to processes involved in the conversion and use of energy. Resting metabolic rates vary among individuals and may be influenced by weight, fat-free mass and fat mass.\textsuperscript{1,2} Genetic variants have also been shown to be associated with resting metabolic rate.\textsuperscript{3}

Genetics: Resting metabolic rate is associated with variants in the LEPR gene, which encodes the leptin receptor. In a study of Caucasians, individuals who were homozygous for the C allele of the rs8179183 marker tended to have an increased resting metabolic rate, or "Fast" metabolism, compared to individuals who have the G allele. This association was only observed in non-obese individuals (body mass index \( \leq 30 \text{ kg/m}^2 \)).\textsuperscript{3}

Possible Outcomes: Fast, Normal

Recommendations: N/A

Markers Tested and Scientific Strength: LEPR [rs8179183]

The rs8179183 marker is rated “3”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: The association of rs8179183 with resting metabolic rate was only detected in Caucasians and may or may not apply to other ethnicities; it has not been replicated and only applies to non-obese individuals (defined as BMI \( \leq 30 \text{ kg/m}^2 \)).

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

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References


Obesity

Report Type: Body and Weight

About: Obesity, clinically defined as a body mass index (BMI) greater than 30 kg/m\(^2\) affects at least 20% of individuals in Western countries; 50% of people are classified as overweight (BMI > 25 kg/m\(^2\)) or obese by the World Health Organization's definition. This condition is characterized by an increase in fat mass that can result in adverse health consequences. Obesity is associated with increased risks for cardiovascular disease, type 2 diabetes and various types of cancer.\(^1\) Risk factors for obesity include low physical activity and consumption of high-energy foods. Research indicates that approximately 40% to 70% of an individual's susceptibility to obesity is inherited\(^2\) and that genetic factors are associated with the disease.\(^3\)

Genetics: Obesity is associated with variants of the MC4R (melanocortin-4 receptor) and FTO (fat mass and obesity associated) genes. The MC4R gene is expressed in the brain's hunger center and is involved in regulating energy balance.\(^4\) Rare mutations in the MC4R gene have been shown to cause a rare, inherited form of obesity. FTO is less well-understood but is also believed to be important for controlling feeding behavior and energy balance.\(^5\) This genetic test includes common variants that were associated with a predisposition for high BMI and/or obesity in many large studies in European\(^6,7,8,9,10\) and Asian populations.\(^10,11,12\) Lifestyle also has a considerable impact on obesity, and a patient can mitigate risks through proper diet, exercise and stress reduction.\(^13,14\)

Possible Outcomes: Above Average, Average

Recommendations: N/A

Markers Tested and Scientific Strength

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<th>Marker(^b)</th>
<th>Risk Allele(^c)</th>
<th>Scientific Strength(^d)</th>
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<td>MC4R</td>
<td>rs17782313</td>
<td>C</td>
<td>4</td>
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</tbody>
</table>

\(^a\)Gene or locus containing the tested marker
\(^b\)Marker tested
\(^c\)“Risk Allele” refers to the allele that is associated with increased risk for obesity.
\(^d\)“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.
Limitations and Warnings: The association of the tested markers (rs9939609 and rs17782313) with obesity was detected in Caucasians and Asians. It is known that these markers are not associated with BMI in populations of African descent. 15 Applicability to other ethnicities is unknown.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

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<td>278.01 Morbid obesity</td>
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<td>V85.3X - Body mass index between 30-39, adult</td>
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<td>V85.4X - Body mass index between 40 and over, adult</td>
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References


Response to monounsaturated fats

Report Type: Diet Recommendation

About: Monounsaturated fats (MUFAs) contain one double-bonded carbon and are considered a healthy dietary fat found in avocados, olives, some nuts and oils. These fats can decrease a person’s risk of heart disease and stroke. Genetic variants have been shown to be associated with response to MUFAs.

Genetics: A person’s response to MUFAs is associated with variants in the ADIPOQ gene, which encodes adiponectin, and the PPARG gene, which encodes a transcription factor that regulates adipogenesis. The A allele of the rs17300539 marker in ADIPOQ and the G allele of the rs1801282 marker in PPARG are the minor alleles. In studies of these variants, the consumption of MUFAs was measured by questionnaire. Individuals who consumed higher MUFAs (more than 13% of total calories) and had the minor alleles of ADIPOQ or PPARG had lower body mass indexes (BMIs) than individuals who were homozygous for the major allele. Thus, individuals who have a minor allele at either of the tested markers will receive an outcome of “Increased Benefit” from MUFAs, while individuals who are homozygous for the major allele at both markers will receive an outcome of “Neutral”. While the ADIPOQ study was done in a population of both men and women, the PPARG study was done only in women. There is not enough scientific evidence to support if the PPARG association holds true in men.

Possible Outcomes: Increased Benefit, Neutral

Recommendations: N/A

Markers Tested and Scientific Strength

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<th>Marker</th>
<th>Associated Allele</th>
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<td>PPARG</td>
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Gene or locus containing the tested marker

Marker tested

“Associated Allele” refers to the allele that is associated with increased benefit from monounsaturated fats.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: The associations of rs1730059 and rs1801282 with response to monounsaturated fats were detected in Caucasians and may or may not apply to other ethnicities. The association of rs1801282 with response to monounsaturated fats was detected in women and may or may not apply to men.
**Compatible ICD-9 Codes**: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

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**References**

Response to polyunsaturated fats

Report Type: Diet Recommendation

About: Omega-6 and omega 3 fats are examples of polyunsaturated fats (PUFAs), which contain more than one double-bonded carbon. PUFAs can decrease a person's risk of heart disease and are important for heart and brain function, as well as growth and development. Genetic variants have been shown to be associated with response to PUFAs.

Genetics: A patient’s response to PUFAs is associated with variants in the PPARG gene, which encodes a transcription factor that regulates adipogenesis. In one study of over 2,000 women, PUFA intake was measured using a questionnaire. Individuals who were homozygous for the C allele at the rs1801282 marker in the PPARG gene had lower BMI when they consumed more polyunsaturated fats than saturated fats; BMI in the highest quintile of polyunsaturated to saturated fat (P:S) ratio was 25.4 kg/m² while BMI in the lowest quintile was 26.6 kg/m². However, there was no observed association between the P:S ratio and BMI in individuals with a G allele at rs1801282. Individuals who are homozygous for the C allele at rs1801282 receive an outcome of “Increased Benefit”, while individuals who have a G allele receive an outcome of “Neutral”.

Possible Outcomes: Increased Benefit, Neutral

Recommendations: N/A

Markers Tested and Scientific Strength: PPARG [rs1801282]

The rs1801282 marker is rated “3”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: The association of rs1801282 with response to polyunsaturated fats was detected in Caucasian women and may or may not apply to other ethnicities or men.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

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Satiety - feeling full

Report Type: Eating Behaviors

About: Satiety is the feeling of fullness after eating. There are a variety of methods for measuring satiety, one of which is the Satiety Responsiveness scale, a questionnaire-based measure of the ease with which satiety is achieved. Genetic variants have been shown to be associated with satiety.\(^1\),\(^2\)

Genetics: Satiety is associated with variants in the FTO (fat mass and obesity-associated) gene,\(^1\) which is also associated with body mass index (BMI).\(^3\) In a study of children in the U.K., habitual appetitive behavior was measured using the Satiety Responsiveness scale. Individuals who were homozygous for the A allele at the rs9939609 marker in the FTO gene scored lower on this scale than individuals who had a T allele. This result indicated that homozygous A allele individuals were more likely to have difficulty feeling full. This association was also significant after adjustment for gender, age, family socioeconomic status and BMI.\(^1\)

Although this study was done in children, there are preliminary data that support an association in adults.\(^2\) A study of adults determined satiety before and after a meal using questionnaire-based methods. Individuals with low satiety after a meal were overrepresented among individuals with an A allele compared to individuals who were homozygous for a T allele.\(^2\) Based on these two studies, individuals who are homozygous for the A allele receive an outcome of “Difficulty Feeling Full” in this genetic test.

Possible Outcomes: Difficulty Feeling Full, Typical

Recommendations: N/A

Markers Tested and Scientific Strength: FTO [rs9939609]

The rs9939609 marker is rated “3”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: The association of rs9939609 with satiety was detected in children 8 to 11 years old; applicability to adults is based on a replication study that is considered preliminary. The studies used as the basis of the recommendations include Caucasians, and the satiety algorithm may or may not apply to other ethnicities.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing
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References

Snacking

Report Type: Eating Behaviors

About: Eating behaviors can be quantified through the use of questionnaires. These quantification methods provide an entry point for studies into the genetics of these behaviors, such as the frequency of snacking. One study suggests that genetic variants may be associated with snacking behavior.¹

Genetics: Snacking behavior is associated with variants in the LEPR gene, which encodes a leptin receptor. Leptin is a hormone that is essential for the regulation of food intake. The association of genotype with snacking behavior is based on a small study of European women. A group of obese women with a body mass index (BMI) greater than or equal to 33 kg/m² were defined as having “extreme snack behavior” because they scored in the top 5ᵗʰ percentile on a survey of eleven questions about snacking frequency. The genotypes of these women were compared to genotypes of randomly selected control women with a mean BMI of 26 kg/m². Increased snacking behavior was associated with homozygosity for the G allele at the tested marker.¹ Individuals who are homozygous for the G allele receive an outcome of “Increased”, which indicates that they are more likely to experience increased snacking.

Possible Outcomes: Increased, Typical

Recommendations: N/A

Markers Tested and Scientific Strength: LEPR [rs2025804]

The rs2025804 marker is rated “2”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: The association between rs2025804 and snacking was detected in Caucasians and may or may not apply to other ethnicities. This association was only studied in women and may or may not apply to men.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

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Strength training

Report Type: Exercise

About: Strength training can be described as exercises that incorporate the use of opposing forces to build muscle. This type of training is often incorporated into workout regimens aimed at reducing weight and body fat. Genetic variants have been shown to be associated with the amount of increase in fat volume in response to strength training.\(^1\)

Genetics: The increase in subcutaneous fat volume in response to strength training is associated with variants in the INSIG2 gene, which encodes a protein involved in cholesterol synthesis. In a small study, young adult men who had the C allele at the rs7566605 marker were more likely to experience increased fat volume after participating in twelve weeks of resistance training;\(^1\) individuals who have a C allele at rs7566605 receive an outcome of "Less Beneficial". While this study also included women, they did not experience a significant increase in fat volume after strength training.

Possible Outcomes: Less Beneficial, Beneficial

Recommendations: N/A

Markers Tested and Scientific Strength: INSIG2 [rs7566605]

The rs7566605 marker is rated "2".

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of "4" indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: The association of rs7566605 with the amount of increase in fat in response to exercise was detected in Caucasian men and may or may not apply to other ethnicities. The association was not detected in women.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

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Sweet taste

Report Type: Food Reactions

About: “Sweet taste” can be described as the sensitivity to sweetness. Receptors in the TAS1R taste receptor gene family serve as the primary mediator of sweetness perception. The proteins encoded by the TAS1R2 and TAS1R3 genes form heterodimeric receptors that bind chemicals in sweet foods. Genetic variants have been shown to be associated with sensitivity to sweetness.

Genetics: Sensitivity to sweetness is associated with variants in the TAS1R3 gene, which encodes the TAS1R3 taste receptor. In one study, sensitivity was measured by requiring participants to sort nine different sucrose solutions from least sweet to most sweet. Individuals who had the T allele at the rs35744813 marker had decreased ability to discriminate between the sweetness of the different solutions. In vitro, functional analysis indicated the T allele was also associated with reduced expression of the TAS1R3 gene, suggesting a mechanism for the decreased sensitivity. Individuals with a T allele (reported as “A” for technical reasons) receive an outcome of “Decreased” because they may have lower sensitivity to sucrose than individuals who are homozygous for the C allele (reported as “G” for technical reasons).

Possible Outcomes: Decreased, Typical

Recommendations: N/A

Markers Tested and Scientific Strength: TAS1R3 [rs35744813]

The rs35744813 marker is rated “2”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: The association of rs35744813 with sensitivity to sweetness was detected in a combined sample population of Europeans, Asians and Africans.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

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Sweet tooth

Report Type: Eating Behaviors

About: "Sweet tooth" can be described as the craving of sweet foods. Consumption of some of these foods can lead to an increase in blood glucose levels and the secretion of insulin. Entry of glucose into the pancreatic b-cell is the first step in glucose-induced insulin secretion. This step is facilitated by the glucose transporter type 2 (GLUT2), which is expressed in the pancreas, liver, small intestine, kidney and brain. GLUT2 is thought to be important in the postprandial state and in glucose homeostasis. Genetic variants in the SLC2A2 gene, which encodes GLUT2, have been shown to be associated with sweet tooth.

Genetics: An association between variants in the SLC2A2 gene and sweet tooth was shown in a study of Canadians. The T allele of rs5400 marker was associated with increased consumption of dietary sugar.¹ This result was observed in two independent populations within the study using two different methods of dietary assessment. The first population consisted of patients who were diagnosed with Type 2 diabetes within two months before the start of the study, did not require medication, and had an average BMI of 30.7 kg/m². Habitual food and beverage intake was assessed using a 3-day food record. Individuals with the T allele consumed a greater amount of sugar compared to individuals who were homozygous for the C allele.

The second population consisted of diabetes-free patients with an average BMI of 22.5 kg/m². A food frequency questionnaire was used to assess food and beverage intake. Individuals with the T allele consumed more sugar than individuals who were homozygous for the C allele. A specific analysis of sugar subtype showed that people with the T allele consumed more sucrose, fructose and glucose, but not lactose or maltose, than C allele homozygotes. In addition, this increased sugar intake resulted from increased consumption of sweetened beverages and sweets.

Possible Outcomes: Increased, Typical

Recommendations: N/A

Markers Tested and Scientific Strength: SLC2A2 [rs5400]

The rs5400 marker is rated “3”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: The association of rs5400 with sweet tooth was detected in adults and may or may not apply to children and adolescents.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test,
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Weight loss-regain

Report Type: Body and Weight

About: Weight loss is beneficial to overweight and obese patients, but keeping excess weight off is also important for maintaining good health. The propensity to regain weight after it is lost varies among individuals, and genetic variants have been shown to be associated with weight regain.¹

Genetics: Weight loss-regain is associated with variants in the ADIPOQ gene, which encodes adiponectin, a hormone that is often lower in obese patients. In one study of obese Spanish people, individuals were enrolled in an 8-week, low-calorie diet. Measurements were conducted at baseline and at 0, 32 and 60 weeks after the diet. Clinical manifestations of metabolic syndrome disappeared after the diet in individuals who were homozygous for the G allele at the rs17300539 marker in the ADIPOQ gene. Specifically, no differences associated with the genotype were observed at week 8 for insulin resistance, insulin values or triacylglyceride values. By week 32, individuals who were homozygous for the G allele had recovered the risk of metabolic co-morbidities; by week 60, the improvement in these individuals disappeared.¹ At week 60, the individuals who were homozygous for the G allele showed an average regain of 1.4±1.0 kg and increased insulin resistance, while the individuals who had the A allele showed no significant weight regain and no increased insulin resistance. Thus, individuals who are homozygous for the G allele receive an outcome of “More Likely to Regain Weight” and individuals with other genotypes receive an outcome of “Weight Loss Maintained”.

Possible Outcomes: More Likely to Regain Weight, Weight Loss Maintained

Recommendations: N/A

Markers Tested and Scientific Strength: ADIPOQ [rs17300539]

The rs17300539 marker is rated “2”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: The association of rs17300539 with weight loss regain was detected in a small study of Spanish individuals and may or may not apply to other ethnicities.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.
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