Gene/Locus[a]	Marker[b]	Scientific Strength[c]
APOA2	rs5082	4
ADIPOQ	rs17300539	3
FTO	rs9939609	3
KCTD10	rs10850219	3
LIPC	rs1800588	3
MMAB	rs2241201	3
PPARG	rs1801282	3

[a]Gene or locus containing the tested marker

[b]Marker tested

[c]"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.

References

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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.[1,2] Genetic variants have also been shown to be associated with resting metabolic rate.[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 ≤ 30 kg/m^2).[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 ≤ 30 kg/m^2).

References

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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

Gene/Locus[a]	Marker[b]	Risk Allele[c]	Scientific Strength[d]
FTO	rs9939609	A	4
MC4R	rs17782313	C	4

[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.

References

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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).[1] 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.[2] 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.[3] 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.[4] 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 (r^2=1) and concentration of EPA; preliminary evidence extended this association to African, Chinese and Hispanic cohorts.[5] 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 maker 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.

References

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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.[1] Genetic variants have been shown to be associated with response to MUFAs.[2,3]

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.[2,3] 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

Gene/Locus[a]	Marker[b]	Associated Allele[c]	Scientific Strength[d]
ADIPOQ	rs17300539	A	3
PPARG	rs1801282	G	3

[a]Gene or locus containing the tested marker

[b]Marker tested

[c]"Associated Allele" refers to the allele that is associated with increased benefit from monounsaturated fats.

[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 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.

References

1. Monounsaturated Fats. American Heart Association web site. http://www.heart.org/HEARTORG/GettingHealthy/FatsAndOils/Fats101/Monounsaturated-Fats_UCM_301460_Article.jsp. Updated October 2010. Accessed June 14, 2013.
2. Warodomwichit D, Shen J, Arnett DK, et al. ADIPOQ polymorphisms, monounsaturated fatty acids, and obesity risk: the GOLDN study. *Obesity (Silver Spring, Md.).* 2009;17:510-7.
3. Memisoglu A, Hu FB, Hankinson SE, et al. Interaction between a peroxisome proliferator-activated receptor gamma gene polymorphism and dietary fat intake in relation to body mass. *Human molecular genetics.* 2003;12:2923-9.

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.[1] Genetic variants have been shown to be associated with response to PUFAs.[2]

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/m^2 while BMI in the lowest quintile was 26.6 kg/m^2.[2] However, there was no observed association between the P:S ratio and BMI in individuals with a G allele at rs1801282.[2] 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.

References

1. Polyunsaturated Fats. American Heart Association web site. http://www.heart.org/HEARTORG/GettingHealthy/FatsAndOils/Fats101/Polyunsaturated-Fats_UCM_301461_Article.jsp. Updated October 2010. Accessed June 14, 2013.
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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.

References

1. Wardle J, Carnell S, Haworth CM, et al. Obesity associated genetic variation in FTO is associated with diminished satiety. *The Journal of clinical endocrinology and metabolism.* 2008;93:3640-3.

2. den Hoed M, Westerterp-Plantenga MS, Bouwman FG, Mariman EC, Westerterp KR. Postprandial responses in hunger and satiety are associated with the rs9939609 single nucleotide polymorphism in FTO. *The American journal of clinical nutrition.* 2009;90:1426-32.
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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/m^2 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/m^2. 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.

References

1. de Krom M, van der Schouw YT, Hendriks J, et al. Common genetic variations in CCK, leptin, and leptin receptor genes are associated with specific human eating patterns. *Diabetes.* 2007;56:276-80.

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.

References

1. Orkunoglu-Suer FE, Gordish-Dressman H, Clarkson PM, et al. INSIG2 gene polymorphism is associated with increased subcutaneous fat in women and poor response to resistance training in men. *BMC medical genetics.* 2008;9:117.

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.[1] Genetic variants have been shown to be associated with sensitivity to sweetness.[2]

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.[2] 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.[2] 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.

References

1. Mainland JD, Matsunami H. Taste perception: how sweet it is (to be transcribed by you). *Current biology : CB.* 2009;19:R655-6.
2. Fushan AA, Simons CT, Slack JP, Manichaikul A, Drayna D. Allelic polymorphism within the TAS1R3 promoter is associated with human taste sensitivity to sucrose. *Current biology : CB.* 2009;19:1288-93.

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/m^2. 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/m^2. 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.

References

1. Eny KM, Wolever TM, Fontaine-Bisson B, El-Sohemy A. Genetic variant in the glucose transporter type 2 is associated with higher intakes of sugars in two distinct populations. *Physiological genomics.* 2008;33:355-60.

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.[1,2,3,4] Genetic variants have been shown to be associated with levels of vitamin A.[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 *in vitro*.[5] The *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.[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

Gene/Locus[a]	Marker[b]	Associated Allele[c]	Scientific Strength[d]
BCMO1	rs7501331	T	2
BCMO1	rs12934922	T	2

[a]Gene or locus containing the tested marker

[b]Marker tested

[c]"Associated Allele" refers to the allele that is associated with decreased vitamin A levels.

[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.

References

1. Gerster H. Vitamin A--functions, dietary requirements and safety in humans. *International journal for vitamin and nutrition research. Internationale Zeitschrift fur Vitamin- und Ernahrungsforschung. Journal international de vitaminologie et de nutrition.* 1997;67:71-90.
2. Semba RD. The role of vitamin A and related retinoids in immune function. *Nutrition reviews.* 1998;56:S38-48.
3. Dawson MI. The importance of vitamin A in nutrition. *Current pharmaceutical design.* 2000;6:311-25.
4. Ross AC, Gardner EM. The function of vitamin A in cellular growth and differentiation, and its roles during pregnancy and lactation. *Advances in experimental medicine and biology.* 1994;352:187-200.
5. Leung WC, Hessel S, Méplan C, et al. Two common single nucleotide polymorphisms in the gene encoding beta-carotene 15,15'-monoxygenase alter beta-carotene metabolism in female volunteers. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology.* 2009;23:1041-53.

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.[1] 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.[2,3,4]

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.[2,3,4] A genome-wide association study (GWAS) with replication identified an association between rs602662 and vitamin B12 levels.[4] A second GWAS with replication that looked at a population of women also found an association between rs602662 and vitamin B12 levels.[3] Additionally, a meta-analysis came to the same conclusion, although it should be noted that the study included individuals from the second GWAS.[2] 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.

References

1. Zittoun J, Zittoun R. Modern clinical testing strategies in cobalamin and folate deficiency. *Seminars in hematology.* 1999;36:35-46.
2. Hazra A, Kraft P, Lazarus R, et al. Genome-wide significant predictors of metabolites in the one-carbon metabolism pathway. *Human molecular genetics.* 2009;18:4677-87.
3. Hazra A, Kraft P, Selhub J, et al. Common variants of FUT2 are associated with plasma vitamin B12 levels. *Nature genetics.* 2008;40:1160-2.
4. Tanaka T, Scheet P, Giusti B, et al. Genome-wide association study of vitamin B6, vitamin B12, folate, and homocysteine blood concentrations. *American journal of human genetics.* 2009;84:477-82.

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.[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.[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.[5,6] As high homocysteine levels are known to be a risk factor for cardiovascular disease and stroke,[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.

References

1. McNulty H, Pentieva K, Hoey L, Ward M. Homocysteine, B-vitamins and CVD. *The Proceedings of the Nutrition Society.* 2008;67:232-7.
2. McNulty H, Strain JJ, Pentieva K, Ward M. C(1) metabolism and CVD outcomes in older adults. *The Proceedings of the Nutrition Society.* 2012;71:213-21.
3. Hustad S, Midttun Ø, Schneede J, et al. The methylenetetrahydrofolate reductase 677C-->T polymorphism as a modulator of a B vitamin network with major effects on homocysteine metabolism. *American journal of human genetics.* 2007;80:846-55.
4. Yazdanpanah N, Uitterlinden AG, Zillikens MC, et al. Low dietary riboflavin but not folate predicts increased fracture risk in postmenopausal women homozygous for the MTHFR 677 T allele. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* 2008;23:86-94.
5. Horigan G, McNulty H, Ward M, et al. Riboflavin lowers blood pressure in cardiovascular disease patients homozygous for the 677C-->T polymorphism in MTHFR. *Journal of hypertension.* 2010;28:478-86.
6. McNulty H, Dowey le RC, Strain JJ, et al. Riboflavin lowers homocysteine in individuals homozygous for the MTHFR 677C->T polymorphism. *Circulation.* 2006;113:74-80.

Genetic risk for decreased vitamin B6

Report Type: Nutrition

About: Vitamin B6 contributes to nervous system function and protein and sugar metabolism.[1] 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.[2,3]

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.[2] 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.[3] 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.

References

1. Dietary Supplement Fact Sheet: Vitamin B6. Office of Dietary Supplements, National Institutes of Health web site. http://ods.od.nih.gov/factsheets/VitaminB6-HealthProfessional/. Reviewed September 2011. Accessed June 14, 2013.

2. Tanaka T, Scheet P, Giusti B, et al. Genome-wide association study of vitamin B6, vitamin B12, folate, and homocysteine blood concentrations. *American journal of human genetics.* 2009;84:477-82.
3. Hazra A, Kraft P, Lazarus R, et al. Genome-wide significant predictors of metabolites in the one-carbon metabolism pathway. *Human molecular genetics.* 2009;18:4677-87.

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 µmol/L per A allele in the discovery cohort and -5.98 µmol/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.

References

1. Cahill LE, El-Sohemy A. Vitamin C transporter gene polymorphisms, dietary vitamin C and serum ascorbic acid. *Journal of nutrigenetics and nutrigenomics.* 2009;2:292-301.

2. Timpson NJ, Forouhi NG, Brion MJ, et al. Genetic variation at the SLC23A1 locus is associated with circulating concentrations of L-ascorbic acid (vitamin C): evidence from 5 independent studies with >15,000 participants. *The American journal of clinical nutrition.* 2010;92:375-82.

Genetic risk for decreased vitamin D

Report Type: Nutrition

About: Vitamin D is important for the absorption and use of calcium.[1] 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.[2,3]

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.[2,3] 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.

References

1. Holick MF. Vitamin D and bone health. *The Journal of nutrition.* 1996;126:1159S-64S.
2. Ahn J, Albanes D, Berndt SI, et al. Vitamin D-related genes, serum vitamin D concentrations and prostate cancer risk. *Carcinogenesis.* 2009;30:769-76.

3. Wang TJ, Zhang F, Richards JB, et al. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. *Lancet (London, England).* 2010;376:180-8.

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;[1,2] increased levels are associated with decreased frailty and disability in old age.[3] Genetic variants have been shown to be associated with increased vitamin E plasma levels.[4]

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.[4] 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.[4] 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.

References

1. Beharka A, Redican S, Leka L, Meydani SN. Vitamin E status and immune function. *Methods in enzymology.* 1997;282:247-63.
2. Morrissey PA, Sheehy PJ. Optimal nutrition: vitamin E. *The Proceedings of the Nutrition Society.* 1999;58:459-68.
3. Bartali B, Frongillo EA, Guralnik JM, et al. Serum micronutrient concentrations and decline in physical function among older persons. *JAMA.* 2008;299:308-15.
4. Ferrucci L, Perry JR, Matteini A, et al. Common variation in the beta-carotene 15,15'-monooxygenase 1 gene affects circulating levels of carotenoids: a genome-wide association study. *American journal of human genetics.* 2009;84:123-33.

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.

References

1. Vimaleswaran KS, Li S, Zhao JH, et al. Physical activity attenuates the body mass index-increasing influence of genetic variation in the FTO gene. *The American journal of clinical nutrition.* 2009;90:425-8.
2. Li S, Zhao JH, Luan J, et al. Cumulative effects and predictive value of common obesity-susceptibility variants identified by genome-wide association studies. *The American journal of clinical nutrition.* 2010;91:184-90.

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.

References

1. Goyenechea E, Collins LJ, Parra D, et al. The - 11391 G/A polymorphism of the adiponectin gene promoter is associated with metabolic syndrome traits and the outcome of an energy-restricted diet in obese subjects. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme.* 2009;41:55-61.