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Healthy Weight DNA Insight

Technical Bulletin

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Genetic risk for decreased adiponectin

Report Type: Body and Weight

About: Adiponectin is a hormone that stimulates liver and muscles to access fat reserves.[1] Higher adiponectin levels are beneficial for weight loss and health.[2] Genetic variants have been shown to be associated with adiponectin levels.[3]

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.[3] 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.[3] Other variants in ADIPOQ have been also linked to adiponectin levels.[4,5,6,7] 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

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Clopidogrel metabolism

(DC:TB-0237.001 06DEC2012)

Report Type: Pharmacogenetics

About: Clopidogrel (Plavix) is an oral anti-platelet agent used to inhibit blood clots in patients with coronary artery disease, peripheral vascular disease, and cerebrovascular disease. Clopidogrel is a prodrug that must be metabolized to an active form to be effective. The CYP2C19 enzyme, a member of the cytochrome P450 superfamily, metabolizes clopidogrel to the active metabolite via a two-step reaction. Multiple cytochrome P450 enzymes contribute to the metabolism of clopidogrel, but CYP2C19 acts in both steps of the reaction, accounting for 45% of the first oxidation step and for 20% of the second step.[1]

Genetics: Variants of the CYP2C19 gene that lead to reduced enzyme function have been shown to be associated with reduced metabolism of clopidogrel to its active form in many ethnic populations.[2,3,4,5,6] Individuals can be classified based on their CYP2C19 enzyme activity into four metabolizer groups: Ultrarapid Metabolizer (higher than normal enzyme activity), Extensive Metabolizer (normal enzyme activity), Intermediate Metabolizer (intermediate enzyme activity) and Poor Metabolizer (low or no enzyme activity).[7]

In 2010, FDA added a boxed warning to the Plavix label indicating that clopidogrel can be less effective in CYP2C19 poor metabolizers and that genetic tests can help define a therapeutic strategy. In 2011, the NIH Clinical Pharmacogenetics Implementation Consortium issued guidelines describing clinical actions that can be implemented based on metabolizer status (see "Recommendations" below).[7]

The evidence is strongest for patients who are being treated with clopidogrel and receive percutaneous coronary intervention (PCI). Poor or intermediate metabolizers who receive PCI are at significantly increased risk of stent thrombosis, which can result in myocardial infarction and death.[8,9,10] For other indications, many studies have shown that poor metabolizers (2% to 15% of patients) and intermediate metabolizers (18% to 45% of patients) may be at risk for adverse cardiac events, such as myocardial infarction and stroke, when treated with clopidogrel;[7,11] however, recent studies dispute this claim.[9,12,13]

Recommendations: FDA's boxed warning on the Plavix label recommends that alternative treatments should be considered for patients identified as CYP2C19 poor metabolizers.[14] The NIH Clinical Pharmacogenetics Implementation Consortium Guidelines recommend that prasugrel or another alternative be considered for intermediate and poor metabolizers.[7] The Royal Dutch Association for the Advancement of Pharmacy's Pharmacogenetics Working Group also recommends alternative therapies, such as prasugrel.[15]

Concurrent use of clopidogrel with CYP2C19 inhibitors may affect clopidogrel response, particularly in extensive and ultra-rapid metabolizers. In these individuals, concurrent use of clopidogrel with CYP2C19 inhibitors (see "Known CYP2C19

Inhibitors" table below) may result in a poor metabolizer phenotype; as such, these individuals may have increased risk for cardiac adverse events when being treated with clopidogrel.[14]

Concurrent use of clopidogrel with omeprazole or esomeprazole should be avoided.[14] Concurrent use of clopidogrel with other CYP2C19 substrates (see "Known CYP2C19 Substrates" table below) may affect clopidogrel response.[16]

A patient's CYP2C19 metabolizer status may result in unexpected responses to other drugs, such as benzodiazepines, phenytoin, barbiturates and others[17] (see "Known CYP2C19 Substrates" table below).

Possible Outcomes: Poor Metabolizer, Intermediate Metabolizer, Extensive Metabolizer, Ultrarapid Metabolizer

Markers or Alleles Tested: CYP2C19 [CYP2C19*2, CYP2C19*3, CYP2C19*4, CYP2C19*5, CYP2C19*6, CYP2C19*8, CYP2C19*17]

Ethnic Distribution of Tested Alleles

The CYP2C19 panel detects alleles that have a combined frequency of over 99% in major ethnic groups.[7]

CYP2C19	Allele	Caucasian	African	East Asian	Middle Eastern	Enzyme activity
Wild-type	*1	63%	68%	60%	87%	Normal
rs4244285	*2	15%	15%	29%	12%	None
rs4986893	*3	0.42%	0.52%	8.9%	1.1%	None
rs28399504	*4	0.25%	0.093%	0.049%	ND[a]	None
rs56337013	*5	0.0073%	ND	0.062%	ND	Reduced
rs72552267	*6	0.017%	0%	0%	ND	None
rs41291556	*8	0.35%	0%	0%	ND	Reduced
rs12248560	*17	21%	16%	2.7%	ND	Increased

[a]Not Determined

Predicted CYP2C19 Metabolizer Status[7]

CYP2C19 Diplotype	Predicted Metabolizer Status
*2-*8/*2-*8	Poor Metabolizer
*1/*2-*8, *17/*2-*8	Intermediate Metabolizer
*1/*1	Extensive Metabolizer
*1/*17, *17/*17	Ultrarapid Metabolizer

Limitations and Warnings: Many rare CYP2C19 variants have been identified, but are not part of this test. It is possible, but unlikely, that the patient may have a variant that is not included in this test.

In addition to the genetic variants included in this test, other genetic and nongenetic factors can influence the effective dose of clopidogrel, including variants in other genes, age, sex, nutrition, lifestyle, other medications and route of administration.[16]

CYP2C19 genotype and metabolizer status may also affect responses to other drugs[17].

Known CYP2C19 Inhibitors and Substrates Tables

Known CYP2C19 Substrates[18]	Known CYP2C19 Inhibitors[18]
Proton-pump Inhibitors lansoprazole omeprazole pantoprazole rabeprazole **Anti-epileptics** diazepam phenytoin S-mephenytoin phenobarbitone **Other** amitriptyline carisoprodol citalopram chloramphenicol clomipramine clopidogrel cyclophosphamide hexobarbital imipramine N-deME indomethacin R-mephobarbital moclobemide nelfinavir nilutamide primidone progesterone proguanil propranolol teniposide R-warfarin	**Proton-pump Inhibitors** lansoprazole omeprazole pantoprazole rabeprazole **Other** chloramphenicol cimetidine felbamate fluoxetine fluvoxamine indomethacin ketoconazole modafinil oxcarbazepine probenicid ticlopidine topiramate

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)
995.29 Unspecified adverse effect of other drug, medicinal and biological substance Applies to: • Unspecified adverse effect of medicinal substance NEC properly administered	N/A

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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

Gene/Locus[a]	Marker[b]	Risk Allele[c]	Scientific Strength[d]
ABCA1	rs1883025	A	4
ANGPTL4	rs2967605	A	4
CETP	rs173539[e]	C	4
FADS1	rs174547	C	4
GALNT2	rs4846914	G	4
HNF4A	rs1800961	T	4
KCTD10	rs2338104	C	4
LCAT	rs2271293	G	4
LIPC	rs10468017	C	4
LIPG	rs4939883	T	4
LPL	rs12678919	A	4
PLTP	rs7679	C	4
TTC39B	rs471364	G	4
ZNF259	rs964184	G	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 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.

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Diabetes, type 2

Report Type: Health Conditions

About: Type 2 diabetes (T2D) accounts for approximately 90% of individuals with diabetes. It is estimated that over 6% of individuals in the world between the ages of 20 and 79 have the condition.[1] This chronic disease is characterized by high blood glucose levels that are caused by a defect in the insulin signaling pathway.[2] Risk factors for T2D include family history and obesity, and research indicates that multiple genetic factors are also associated with the disease.[1]

Genetics: T2D arises from a combination of genetic and environmental factors.[1] The hereditability of T2D is well-established by familial studies, yet environmental and lifestyle factors must also play a role in the development of T2D because the prevalence of T2D has increased dramatically in the last 50 years, a period of time too brief to be explained by changes in gene frequencies. Most of the genetic variants associated with an increased risk for T2D impact the development or function of pancreatic beta-cells, which produce, store and secrete the hormone insulin.[3] In addition, genetic factors associated with fat mass and increased risk for obesity also contribute to the development of T2D.[1]

Genes in the T2D test that affect pancreatic beta-cells include CDKAL1,[4] CDKN2B,[5] HHEX,[6,7,8] HNF1B,[9] JAZF1,[10] KCNJ11,[11,12] KCNQ1,[13] NOTCH2,[14] SLC30A8,[6,7,15,16] TCF7L2[17,18,19] and WFS1.[20]

The T2D test also includes genes associated with fat mass and obesity risk, such as FTO,[21] IGF2BP2,[22,23] PPARG,[24,25] ADIPOQ[26] and ESR1.[27,28]

The most consistent evidence for the association of genetic markers with T2D has come from large-scale T2D genetic studies in European populations.

Individuals of African American ancestry are twice as likely to develop Type 2 Diabetes (T2D) as those of Caucasian ancestry, particularly African American women. African American populations have been studied for most of the Caucasian T2D-associated gene markers. Due to differences in allele frequencies in the two ethnic population and the smaller number of African Americans studied, only a few of the Caucasian markers have been found to be associated with T2D in Africans.

Recently, many studies initially conducted in Caucasian populations have been replicated in Japanese populations, and an overlap in disease variants has been discovered. In addition, the shared variants appear to confer a higher disease risk in Japanese versus Caucasians. This may be due to the fact that the Japanese (in Japan) are a leaner and more homogenous population in comparison. A large proportion of Asian type 2 diabetics are non-obese, and studies have shown that non-obese T2D patients progress to insulin dependence faster. Non-obese T2D Europeans or Japanese-Americans have a higher prevalence of TCF7L2 and PPARG risk alleles, respectively, compared to individuals who do not have T2D.[29,30,31] Furthermore, it has been shown that although they are not obese, the fat distribution of non-obese type 2 diabetics tends to be abdominal. The gene variants repeatedly showing the highest odds ratios associated with T2D in Japanese are TCF7L2, CDKAL1, CDKN2B and KCNQ1. As with other populations, recently replicated studies in Chinese populations show an overlap in disease variants compared to those discovered in Caucasian populations.[32]

Recommendations: The U.S. Preventative Services Task Force recommends screening for type 2 diabetes in asymptomatic adults with sustained blood pressure (either treated or untreated) greater than 135/80 mmHg.[33]

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
WFS1	rs10010131	G	1.12	Caucasian	67.7%	Validated	18040659
CDKN2B	rs10811661	T	1.27	Asian	57.7%	Validated	18477659
CDKN2B	rs10811661	T	1.20	Caucasian	80.1%	Validated	17463246
MTNR1B	rs10830963	G	1.16	Asian	41.7%	Validated	19241057
MTNR1B	rs10830963	G	1.09	Caucasian	30.0%	Validated	19060907
NOTCH2	rs10923931	T	1.13	Caucasian	9.3%	Validated	18372903
CDKAL1	rs10946398	C	1.16	Caucasian	33.6%	Validated	17463249
HHEX	rs1111875	G	1.27	Asian	31.5%	Validated	18477659
HHEX	rs1111875	G	1.15	Caucasian	58.4%	Validated	17463246
SLC30A8	rs13266634	C	1.17	Asian	53.0%	Validated	18469204
SLC30A8	rs13266634	C	1.12	Caucasian	76.1%	Validated	17463249
IGF2BP2	rs1470579	C	1.18	Asian	26.2%	Validated	18477659
IGF2BP2	rs1470579	C	1.19	Caucasian	29.6%	Validated	17463246
PPARG	rs1801282	C	1.75	Asian	95.2%	Validated	11289058
PPARG	rs1801282	C	1.23	Caucasian	90.3%	Validated	17463249
KCNQ1	rs2237892	C	1.43	Asian	65.5%	Validated	18711367
KCNQ1	rs2237892	C	1.29	Caucasian	92.5%	Validated	18711367
KCNJ11	rs5219	T	1.25	Asian	35.5%	Validated	18162508
KCNJ11	rs5219	T	1.15	Caucasian	36.0%	Validated	17463246
HNF1B	rs7501939	T	1.15	Caucasian	43.4%	Validated	17603484
CDKAL1	rs7754840	C	1.27	Asian	42.3%	Validated	18766326
TCF7L2	rs7903146	T	1.51	African	33.7%	Validated	17601994
TCF7L2	rs7903146	T	1.59	Asian	2.4%	Validated	19012045
TCF7L2	rs7903146	T	1.38	Caucasian	27.9%	Validated	17463246
FTO	rs8050136	A	1.27	Caucasian	46.0%	Validated	17463249
JAZF1	rs864745	T[i]	1.10	Caucasian	48.7%	Validated	18372903
ESR1	rs1569788	C	1.25	African	52.9%	Preliminary	18305958
ADIPOQ	rs182052	A	1.24	African	38.7%	Preliminary	19056609
ESR1	rs3020314	C	1.23	Caucasian	25.7%	Preliminary	18854778
Intergenic_6q24	rs4897081	A	1.28	African	51.0%	Preliminary	18560894

[a]Gene or locus containing the tested marker

[b]Marker tested

[c]Allele associated with disease risk

[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele

[e]Ethnicity of the population in the corresponding study

[f]Percentage of people who have the associated allele in the population studied

[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

[h]PubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

[i]This marker can be assayed on either strand of DNA. Therefore, the associated allele could be reported as either an A or a T in the patient report.

Limitations and Warnings: NA

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)
250.00 Diabetes mellitus without mention of complication, type II or unspecified type, not stated as uncontrolled	V77.1 Screen-diabetes mellitus

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OmeCare

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.

References

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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,[1] 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.[2] 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.[2] 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.[2] 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.[2]

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.[3]

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

Markers Tested and Scientific Strength

Gene/Locus[a]	Marker[b]	Risk Allele[c]	Scientific Strength[d]
ABCG8	rs6544713	T	4
APOB	rs515135	G	4
CELSR2	rs12740374	G	4
HMGCR	rs3846663	T	4
HNF1A	rs2650000	A	4
intergenic	rs1501908	G	4
LDLR	rs6511720	G	4
MAFB	rs6102059	C	4
NCAN	rs10401969	T	4
PCSK9	rs11206510	T	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 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.

Limitations and Warnings: These genetic variants together account for approximately 7.7% of the variance in LDL cholesterol levels[2] 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.

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,[1] 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.[2] 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.[2] 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.[2]

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

Recommendations: N/A

Markers Tested and Scientific Strength

Gene/Locus[a]	Marker[b]	Risk Allele[c]	Scientific Strength[d]
ANGPTL3	rs10889353	A	4
APOB	rs7557067	A	4
FADS1	rs174547	C	4
GCKR	rs1260326	T	4
LPL	rs12678919	A	4
MLXIPL	rs714052	T	4
NCAN	rs17216525	C	4
PLTP	rs7679	C	4
TRIB1	rs2954029	A	4
XKR6	rs7819412	A	4
ZNF259	rs964184	G	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 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.

Limitations and Warnings: These genetic variants together account for approximately 7.4% of the variance in triglyceride levels[2] 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.

References

1. ATP III at-a-glance: quick desk reference. National Heart Lung and Blood Institute web site. http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.htm. Updated 2004. Accessed August 3, 2012.
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OmeCare

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

Gene/Locus[a]	Marker[b]	Associated Allele[c]	Scientific Strength[d]
LIPC	rs1800588	C	3
PPARD	rs2016520	G	3
LPL	rs328	G	2

[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

1. Garenc C, Pérusse L, Bergeron J, et al. Evidence of LPL gene-exercise interaction for body fat and LPL activity: the HERITAGE Family Study. *Journal of applied physiology (Bethesda, Md. : 1985).* 2001;91:1334-40.
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3. Hautala AJ, Leon AS, Skinner JS, et al. Peroxisome proliferator-activated receptor-delta polymorphisms are associated with physical performance and plasma lipids: the HERITAGE Family Study. *American journal of physiology. Heart and circulatory physiology.* 2007;292:H2498-505.

OmeCare

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.

References

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2. Yang QH, Botto LD, Gallagher M, et al. Prevalence and effects of gene-gene and gene-nutrient interactions on serum folate and serum total homocysteine concentrations in the United States: findings from the third National Health and Nutrition Examination Survey DNA Bank. *The American journal of clinical nutrition.* 2008;88:232-46.
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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.[1] Genetic variants have been shown to be associated with levels of food reinforcement.[2]

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.[2] 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;[3,4] 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.[5]

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

References

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2. Epstein LH, Temple JL, Neaderhiser BJ, et al. Food reinforcement, the dopamine D2 receptor genotype, and energy intake in obese and nonobese humans. *Behavioral neuroscience.* 2007;121:877-86.
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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.[1] 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.[2] 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.[3]

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.[3] 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.

References

1. Natarajan P, Ray KK, Cannon CP. High-density lipoprotein and coronary heart disease: current and future therapies. *Journal of the American College of Cardiology.* 2010;55:1283-99.
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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.

References

1. Teran-Garcia M, Santoro N, Rankinen T, et al. Hepatic lipase gene variant -514C>T is associated with lipoprotein and insulin sensitivity response to regular exercise: the HERITAGE Family Study. *Diabetes*. 2005;54:2251-5.

∞ OmeCare

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.[1,2,3,4,5,6] 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.[7,8] 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.[1,2,3,4] 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.[1] 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.[7,8] 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.[9] In another instance, a patient with a genetic predisposition towards decreased HDL cholesterol levels could be recommended a diet low in carbohydrates,[10,11] while a patient with a genetic predisposition towards elevated levels of LDL cholesterol could be recommended a diet low in fats, particularly saturated fats.[10,12] 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

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.

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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.

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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.

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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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Osteoarthritis

Report Type: Health Conditions

About: Osteoarthritis is the most common form of arthritis and is a major cause of disability in the U.S.[1] This progressive bone disease is characterized by cartilage loss, which can lead to pain and reduced joint function. Risk factors for osteoarthritis include age, obesity, gender and trauma. Research indicates that genetic factors are also associated with the disease.[2]

Genetics: Some rare forms of early-onset osteoarthritis (OA) are caused by mutations in single genes, but uncovering the genetic basis of the most common form of OA, which appears after age 45, has been more elusive. Variants in three genes that have been shown to increase the risk of developing OA are included on the test: GDF5, DVWA and PTGS2.

The GDF5 gene encodes a member of the transforming growth factor-beta superfamily and is involved in the development and maintenance of bone and cartilage. Mutations in GDF5 are known to cause disorders of skeletal development including chondrodysplasia, synphalangism and type C brachydactyly. In the largest meta-analysis study of OA to date, researchers found an association of a variant in the GDF5 gene with OA of the knee in Caucasian and Asian women.[3]

The DVWA gene encodes a protein that binds beta-tubulin, which is the building block of the microtubules that serve a structural and kinetic role in the cell. In Asians, a variant in the DVWA gene is associated with susceptibility to OA of the knee.[4]

The PTGS2 gene encodes prostaglandin G/H synthase 2, which is involved in a key step in the synthesis of prostaglandins. Prostaglandins are regulators of important biological processes such as inflammation, cell division, and formation of new blood vessels. In Caucasians, a variant in the PTGS2 gene is associated with OA in the knee.[5]

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/ Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
GDF5	rs143383	T	1.55	Asian	77.9%	Preliminary	18299287
GDF5	rs143383	T	1.13	Caucasian	66.7%	Preliminary	19479880
PTGS2	rs4140564	C	1.55	Caucasian	8.0%	Preliminary	18471798
DVWA	rs7639618	G[i]	1.43	Asian	54.2%	Preliminary	19181678

aGene or locus containing the tested marker.

bMarker tested.

cAllele associated with disease risk.

dMeasure of the likelihood that an individual will get the disease if carrying a specific allele.

eEthnicity of the population in the corresponding study.

fPercentage of people who have the associated allele in the population studied.

gValidated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

hPubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

iThis marker can be assayed on either strand of DNA. Therefore, the associated allele could be reported as either a C or a G in the patient report.

Limitations and Warnings: NA

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)
715.89 Osteoarthrosis involving, or with mention of more than one site, but not specified as generalized, multiple sites	N/A

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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

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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.

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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

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Simvastatin-induced myopathy

(DC:TB-0229.001 06DEC2012)

Report Type: Pharmacogenetics

About: Simvastatin is a member of the statins, a class of cholesterol-lowering drugs whose major adverse effect is skeletal muscle toxicity. Approximately 5% to 10% of patients taking statins experience muscle pain (myalgia).[1] A small portion of patients, (1.5% to 5.0%) may develop more severe symptoms indicating muscle degradation (myopathy).[1] In rare cases (0.1 to 0.2 cases per 1,000 person-years), severe muscle damage leads to acute, potentially lethal kidney failure (rhabdomyolysis).[1,2]

Genetics: Simvastatin-induced myopathy has been shown to be influenced by variation in the SLCO1B1 gene.[3] Approximately 60% of myopathy cases in a simvastatin (80 mg/day) clinical trial were attributed to the C allele of the rs4149056 marker in the SLCO1B1 gene.[3] SLCO1B1 encodes the organic anion-transporting polypeptide 1B1 (OATP1B1, also known as OATP-C or OATP2), which regulates the hepatic uptake of statins and other drugs. The C allele at rs4149056 reduces the activity of the OATP1B1 transporter,[4] leading to increased blood simvastatin levels and the potential for increased toxicity to the muscles. However, available clinical data are insufficient to show whether the SLCO1B1 variant also alters myopathy risk associated with the use of statins other than simvastatin.[5]

The risk of myopathy varies with the type of statin and is dose-related. Some statins are associated with lower risk of myopathy compared with others,[1] and the pharmacokinetic effects of variants of rs4149056 are not uniform for different statins.[6,7] The incidences of myopathy and rhabdomyolysis while taking 80 mg simvastatin daily are disproportionally higher than those with lower doses.[8]

Genetic variation in SLCO1B1 also affects pharmacokinetics of other drugs, such as methotrexate and HIV protease inhibitors.[9]

Recommendations: The NIH Clinical Pharmacogenetics Implementation Consortium (CPIC) published guidelines for SLCO1B1 genotyping and simvastatin-induced myopathy, recommending reduced dose or alternative statins for patients with the C allele at rs4149056. The CPIC also recommends routine surveillance of serum creatine kinase levels for those patients.[5]

Possible Outcomes: Increased Risk, Typical Risk

Markers and Alleles Tested: SLCO1B1 [rs4149056]

Ethnic Distribution of Tested Allele

Frequency of C allele of the rs4149056 marker in major ethnic groups.[5]

Ethnicity	C allele frequency (rs4149056)
Caucasian	15%
African	3%
Middle Eastern	20%
Asian	13%

Limitations and Warnings: Although the tested SLCO1B1 variant has the most significant genetic effect on the risk of simvastatin-induced myopathy in clinical studies, rarer mutations in SLCO1B1 that may also affect the function of the encoded protein are not screened in this test. Current knowledge is limited on the involvement of other genes in the metabolism and clinical effects of simvastatin. In addition to genetic effects, the risk of simvastatin-induced myopathy varies with the patient's age, gender, body mass index, ethnicity and other clinical factors.[5]

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)
359.4 Toxic myopathy	N/A

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OmeCare

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.

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

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Venous thrombosis

Report Type: Health Condition

About: Venous thrombosis is the formation of a blood clot in the veins that can potentially lead to thromboembolism. The individual risk of venous thromboembolism (VTE) is determined by a complex interaction of genetic, circumstantial and environmental factors. Risk factors include immobility, surgery, trauma, cancer, hormonal therapy, pregnancy, advanced age and family history.[1,2] Genetic factors are also associated with the risk of VTE development.

Genetics: Factor V Leiden, a mutation in the F5 gene, is the most common and most studied genetic prothrombotic defect, with an overall prevalence in Caucasians of approximately 5%. It is found in 20% of all patients with venous thrombosis, and in up to 50% of patients with thrombophilia.[3] The F5 gene encodes coagulation factor V, an important cofactor that accelerates the activation of prothrombin to thrombin in the blood coagulation cascade. The Factor V Leiden mutation impairs down-regulation of coagulation factor V, resulting in increased risk of clotting.

Individuals who are heterozygous for the Factor V Leiden mutation have a 3.5-fold increase in risk of VTE.[1,4,5,6] Homozygous patients are at a higher risk than heterozygous patients.[1,4]

After Factor V Leiden, the most common mutation associated with heritable thrombophilia is prothrombin G20210A,[7] which is located in the 3'-untranslated region of the gene and is associated with increased levels of prothrombin.[3] Increased levels of prothrombin are a risk factor for thrombosis.[8] Individuals with the mutation are at increased risk of VTE,[1,4,5,6] and risk further increases in individuals who have the Factor V Leiden mutation.[9,10] Individuals who are heterozygous for both mutations have a 20-fold increase in risk, whereas individuals who are heterozygous for either mutation only have a four- to five-fold increase in VTE risk.[11]

Among women with history of VTE, the Factor V Leiden and prothrombin G20210A mutations are independently associated with increased risk of VTE during pregnancy and puerperium.[10] Risk of thrombosis increases more than 100-fold in pregnant women who have both mutations compared to women without the mutations.[10,12]

MTHFR is an important enzyme in folate metabolism and DNA synthesis. The homozygous MTHFR C677T genotype has been associated with an increased risk of elevated plasma homocysteine levels[13] and hyperhomocysteinemia, an independent risk factor for VTE.[14,15,16] The homozygous C677T genotype has also been associated with risk of VTE in Chinese and Korean populations.[5,14,17,18] A meta-analysis found that, in studies of non-Americans, the homozygous C677T genotype was associated with a 20% higher risk of VTE compared to the homozygous wild-type genotype.[16] In contrast, the homozygous C677T genotype had no effect on VTE in North America, possibly due to the higher intake rates of folate and riboflavin. In support of this hypothesis, one study found that homocysteine levels in homozygous C677T individuals were significantly higher than in homozygous wild-type individuals only if folate levels were below 15.4 nmol/L.[15,19] Thus, individuals who are homozygous for C677T may require more dietary folate than individuals who are wild-type.

Recommendations: The American College of Medical Genetics, the American College of Obstetricians and Gynecologists and the European International Thrombophilia Guidelines recommend Factor V Leiden and/or G20210A testing in populations that are likely to have a mutation.[7,20,21]

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers and Alleles Tested: F5 [Factor V Leiden/R506Q]; F2 [G20210A]; MTHFR [C677T]

Ethnic Distribution of Tested Alleles: The Factor V Leiden and prothrombin G20210A mutations are common in Caucasians but extremely rare in Asians and Africans.[22] The allele frequency of Factor V Leiden in the U.S. population is 5% in Caucasians, 2.2% in Hispanics and 1.2% in blacks.[1,23] Prothrombin G20210A has a prevalence of approximately 2% in the US population and occurs primarily in Caucasians.[1] Double heterozygosity for Factor V Leiden and prothrombin G20210A is estimated to affect 1 in 1,000 individuals in the general population.

There is significant ethnic and geographic variation in the frequency of C677T. The prevalence of the homozygous C677T genotype ranges from around 1% in Black populations in the US, sub-Saharan Africa, and South America to more than 20% in US Hispanics, Colombians and Amerindians in Brazil. The homozygous C677T genotype occurs at a frequency of 8-20% in Caucasians in Europe, North America, and Australia and at 12% in Japanese.[24]

Limitations and Warnings: Genetic variants in other proteins, such as protein S, protein C and antithrombin are known to increase the risk of venous thrombosis, but are not part of this test. Non-genetic factors known to increase the risk of venous thrombosis include age, obesity, trauma/surgery, smoking, pregnancy and airplane travel.[25]

According to the American College of Medical Genetics (ACMG) Consensus Statement on Factor V Leiden Mutation Testing, the MTHFR C677T only accounts for a third of hyperhomocysteinemia cases, and plasma measurements of homocysteine may be more informative than molecular methods.[7]

Dietary factors, such as folic acid intake, may influence the association between MTHFR and VTE.[19]

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)
453.9 Other venous embolism and thrombosis of unspecified site • Embolism of vein • Thrombosis (vein)	N/A

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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.

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OmeCare

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.

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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.

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OmeCare

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.

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∞ OmeCare

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

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OmeCare

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.
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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

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Warfarin

(DC:TB-0230.002 31JUL2013)

Report Type: Pharmacogenetics

About: Warfarin is the most frequently used oral anticoagulant worldwide, prescribed for prophylaxis and treatment of thrombotic disorders and thromboembolic events. Such indications include venous thrombosis, pulmonary embolism, atrial fibrillation and cardiac valve replacement. Warfarin is highly efficacious, but its narrow therapeutic index and large interindividual dosing variability lead to a high incidence of adverse events. Improper warfarin dosing is the second leading cause of drug-related emergency room visitation[1] and the number one cited reason for drug-related mortality.[2]

Warfarin acts as an anticoagulant through its ability to inhibit reduction of vitamin K by the vitamin K epoxide reductase complex subunit 1 (VKORC1) enzyme complex. Reduced vitamin K is an essential cofactor of gamma-glutamyl carboxylase, the enzyme that activates coagulation factors II, VII, IX and X. By decreasing the amount of reduced vitamin K available, warfarin depresses the activation of factors II, VII, IX and X into functional, coagulant proteins, and, therefore, decreases the ability of blood to clot. The primary metabolizing enzyme of warfarin is cytochrome P450 2C9 (CYP2C9).[3]

In 2010, the United States Food and Drug Administration (FDA) released a table of dosing recommendations for initiation of warfarin therapy based on VKORC1 and CYP2C9 genotypes. This pharmacogenetics-based dosing table significantly improved accuracy of therapeutic dose prediction compared to the traditional strategy of empirically determined dose.[4]

Genetics: The A allele of the -1639G>A mutation in the VKORC1 gene has been shown to decrease hepatic expression of VKORC1 and, therefore, increase patient sensitivity to warfarin.[5,6,7] Research studies have shown that the therapeutic dose of warfarin in patients with two copies of the A allele was less than the dose of patients with two copies of the G allele, with a difference up to 2.0 to 4.5-fold.[7,8,9]

Individuals carrying *2 or *3 genetic variants of CYP2C9 clear warfarin at a 30% to 50% or 80% to 90% slower rate, respectively, and exhibit increased serum levels of warfarin compared to carriers of only the reference wild-type variant *1.[10,11] CYP2C9*2 and CYP2C9*3 variants may decrease the dose required for effective anticoagulation and may increase the time necessary to achieve stable, therapeutic effect.[9,12] The CYP2C9*6 variant may also reduce metabolic activity and the dose required for effective anticoagulation.[11,13]

Customizing initial warfarin dose to VKORC1 and CYP2C9 genotypes may decrease patient risk of bleeding complications and may reduce the time required to achieve a stable, therapeutic effect.[12,14,15]

Recommendations: The FDA-approved label for warfarin recommends initial dosing based on VKORC1 and CYP2C9 genotypes in addition to clinical factors.[16] The National Institutes of Health (NIH) Clinical Pharmacogenetics Implementation Consortium guidelines recommend initial dosing based on VKORC1 and CYP2C9 genotypes.[11]

Standard doses of warfarin may cause bleeding complications in patients whose genotypes indicate increased or substantially increased sensitivity to warfarin. These patients may require lower initial doses of warfarin. Increased laboratory monitoring may be appropriate.

Classes of drugs that potentially interact with warfarin include the following:[16] inhibitors or inducers of CYP2C9, CYP1A2 and/or CYP3A4, anticoagulants, antiplatelet agents, nonsteroidal anti-inflammatory agents, serotonin reuptake inhibitors, antibiotics, antifungals, and botanical (herbal) products and foods. This list is not complete. Consult the warfarin drug label[16] and the labels of all concurrently used drugs for more specifics about warfarin drug interactions.

Possible Outcomes: Substantially Increased Sensitivity, Increased Sensitivity, Typical Sensitivity

Markers or Alleles Tested: VKORC1 -1639G>A [rs9923231]; CYP2C9 [CYP2C9*2/rs1799853, CYP2C9*3/rs1057910, CYP2C9*6/rs9332131]

Ethnic Distribution of Tested Alleles

Frequency of VKORC1 and CYP2C9 alleles differs significantly between racial and ethnic groups.[17]

Gene	Allele	Caucasian	African American	Asian	Hispanic
VKORC1	-1639: G	59.4%	89.2%	33.3%	56.4%
VKORC1	-1639: A	40.6%	10.8%	66.7%	43.6%
CYP2C9	*1	78.8%	86.7%	92.2%	82.2%
CYP2C9	*2	15.1%	2.8%	2.9%	6.9%
CYP2C9	*3	5.7%	2.0%	3.9%	6.4%
CYP2C9	*6	0.0%	1.0%	0.0%	0.5%

Predicted Warfarin Sensitivity Status

CYP2C9 genotype (below)	VKORC1 -1639G>A genotype		
	G/G	G/A	A/A
*1/*1	Typical sensitivity	Typical sensitivity	Increased sensitivity
*1/*2	Typical sensitivity	Increased sensitivity	Increased sensitivity
*1/*3	Increased sensitivity	Increased sensitivity	Substantially increased sensitivity
*1/*6	Increased sensitivity	Increased sensitivity	Substantially increased sensitivity
*2/*2	Increased sensitivity	Increased sensitivity	Substantially increased sensitivity
*2/*3	Increased sensitivity	Substantially increased sensitivity	Substantially increased sensitivity
*2/*6	Increased sensitivity	Substantially increased sensitivity	Substantially increased sensitivity
*3/*3	Substantially increased sensitivity	Substantially increased sensitivity	Substantially increased sensitivity
*3/*6	Substantially increased sensitivity	Substantially increased sensitivity	Substantially increased sensitivity
*6/*6	Substantially increased sensitivity	Substantially increased sensitivity	Substantially increased sensitivity

Limitations and Warnings: Warfarin can cause major or fatal bleeding. Additional genetic variants within VKORC1, CYP2C9, and other genes not included in this test are known to affect warfarin sensitivity. Not all genetic factors influencing warfarin sensitivity have been identified. Regular monitoring of INR (international normalized ratio) should be performed on all treated patients.

Not all factors influencing warfarin response are known. Important non-genetic factors include age, sex, weight, height, race, ethnicity, comorbidities, warfarin indication, target INR, and use of tobacco and interacting medications.[11]

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)
E934.2 Anticoagulants causing adverse effects in therapeutic use	N/A

References

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OmeCare

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.

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