ApoE Report v1

Source: Cooper_Beaman_23andmenew_v4_Full_20190517100124.zip
Created at February 23 at 3:44 PM PDT

Apolipoprotein E is a class of proteins involved in the transport of fatty acids and cholesterol throughout the body and brain. Polymorphisms in this gene can affect the risk of Alzheimer's disease and cardiovascular disease in a way that may also interact with lifestyle factors, such as diet, sleep, alcohol intake, omega-3 fatty acid status, and more.

Noteworthy

These genotypes are the ones that are potentially worth being aware of.

Gene	SNPs involved	Status	More information

Less noteworthy

These genotypes are normal.

Gene	SNPs involved	Status	More information
APO-E3/E3	rs429358(T;T) rs7412(C;C)	Normal risk of alzheimer's, normal risk of hypertriglyceridemia	This genotype is the APO-E3/E3 genotype. **Cardiovascular disease** This genotype is defined as the "benchmark" for normal lipid homeostasis, is the standard by which other APOE isoforms are compared and is considered to have normal lipid and cholesterol transport mechanisms. This genotype has normal cardiovascular disease risk and normal Alzheimer's disease risk. **LDL Cholesterol** Alcohol consumption does not affect LDL levels in APOE3 carriers after controlling for age, body mass index, smoking status, and fat and energy intake. • View the SNPedia page about ApoE. SNPs Involved rs429358(T;T) rs7412(C;C)

Cholesterol Report v3

Source: Cooper_Beaman_23andmenew_v4_Full_20190517100124.zip
Created at February 23 at 3:44 PM PDT

This report is focused on SNPs relevant to cholesterol metabolism which can affect cholesterol levels. This report also focuses on HMG-CoA reductase inhibitors such as statins.

Statins are drugs that lower blood cholesterol levels by blocking the production of an enzyme in the liver called hydroxy-methylglutaryl-coenzyme A reductase (HMG-CoA reductase). Taking statins may reduce the risk of cardiovascular disease in some people.

Although statins are generally well tolerated, as many as 10 – 20 percent of people taking the drugs experience complications, including myopathy (muscle damage) or liver damage. Certain SNPs may increase the risk of experiencing complications.

Noteworthy

These genotypes are the ones that are potentially worth being aware of.

Gene	SNPs involved	Status	More information
HMGCR	rs17244841(A;A)	More responsive to some statins	Rs17244841, also known as SNP 12, is an SNP in the gene that provides instructions for hydroxy-methylglutaryl-coenzyme A reductase(HMGCR), an enzyme that is crucial to cholesterol production. Statins block the production of HMGCR. **This genotype, rs17244841(A;A), was associated with a greater response to pravastatin** in a study of more than 1,500 ethnically diverse men and women, with total blood cholesterol reductions of approximately 42.0mg/dL. • Read more on SNPedia SNPs Involved rs17244841(A;A)
SLCO1B1	rs4149056(C;T)	Increased risk for myopathy with statin use	This gene, SLCO1B1, encodes for a protein transports drugs and other substances from the blood into the liver, where they can be broken down and used by the body or excreted. People who have variants of the rs4149056 SNP may respond differently to statins. This altered response may be due to changes in the amino acid makeup of the OATP1B1 protein, leading to reduced clearance of drugs from the blood. **This genotype, rs4149056(C;T), has been associated in a study of more than 500 men and women taking atorvastatin, simvastatin, or pravastatin with a greater likelihood of experiencing muscle-related drug complications.** A genome-wide association study involving 12,000 participants who were taking 80 mg of simvastatin (a type of statin) and 20,000 participants taking 40 mg of simvastatin daily also revealed an association between having the rs4149056(C;T) genotype and a 4.5-fold increased risk for developing myopathy. Statin-related myopathy following administration of simvastatin or atorvastatin appears to be dose-dependent. Increased risk of myopathy has not been observed with rosuvastatin, however. Bilirubin is a byproduct of the normal breakdown process of red blood cells. Abnormal bilirubin levels are associated with altered cardiovascular disease risk and drug metabolism. Variants of the rs4363657 SNP on SLCO1B1 may influence bilirubin levels. • Read more on SNPedia **Statins, myopathy & supplemental CoQ10** Statins are able to reduce cholesterol by inhibiting the action of an enzyme known as HMG-CoA reductase. This inhibition prevents the production of mevalonate, which is a precursor for both cholesterol *and* coenzyme Q10 (CoQ10), a fat-soluble substance found in the mitochondria of respiring cells. CoQ10 is essential for cellular energy production in the form of ATP. It also protects against oxidative stress and helps the body recycle key antioxidants such as vitamin E. Blood levels of CoQ10 can drop by more than half with statin treatment, and some research suggests that in the setting of CoQ10 deficiency, a concurrent ATP deficiency might induce painful myopathy. In addition, a decrease in CoQ10 levels tends to be accompanied by a higher lactate to pyruvate ratio in the blood, which is commonly seen in myopathy – an indication that the mitochondrial respiratory system is not functioning properly. Some research suggests that taking CoQ10 supplements may reduce symptoms of myopathy; however, larger randomized controlled trials need to be done to establish definitive conclusions. In a small, randomized controlled study, 32 adults who had symptoms of myopathy when taking statins were given either CoQ10 or vitamin E for 30 days. Those who took CoQ10 reported having 40% less pain, but those who took vitamin E saw no improvement in their symptoms. In a randomized, placebo-controlled trial, 51 adults with coronary artery disease who were taking statins were given either a CoQ10 supplement or a placebo for 12 weeks. At the end of the trial, those who were taking the CoQ10 supplement had higher levels of vitamin E and antioxidant enzymes and lower levels of inflammatory markers in their blood compared to those taking the

placebo.

An analysis of 5 randomized controlled studies involving more than 250 people taking CoQ10 supplementation for symptoms of statin-induced myopathy concluded that most of the participants experienced some reduction in their myopathy symptoms; however, the findings were not statistically significant.

- Read more about CoQ10 in *Coenzyme Q10 (CoQ10): In Depth*, an article from the NIH's Office of Dietary Supplements

SNPs Involved

rs4149056(C;T)

SLCO1B1	rs4363657(C;T)	Increased risk for myopathy with statin use	This gene, SLCO1B1, encodes for a protein that transports drugs and other substances from the blood into the liver, where they can be broken down and used by the body or excreted. People who have variants of the rs4363657 SNP may respond differently to statins. **This genotype, rs4363657(C;T), has been associated with a 4.5-fold increased risk for developing myopathy from statin use** according to a genome-wide association study involving 12,000 participants who were taking 80 mg of simvastatin (a type of statin) and 20,000 participants taking 40 mg of simvastatin daily. Statin-related myopathy following administration of simvastatin or atorvastatin appears to be dose-dependent. Increased risk of myopathy has not been observed with osuvastatin, however. Bilirubin is a byproduct of the normal breakdown process of red blood cells. Abnormal bilirubin levels are associated with altered cardiovascular disease risk and drug metabolism. Variants of the rs4363657 SNP on SLCO1B1 may influence bilirubin levels. - Read more on SNPedia **Statins, myopathy & supplemental CoQ10** Statins are able to reduce cholesterol by inhibiting the action of an enzyme known as HMG-CoA reductase. This inhibition prevents the production of mevalonate, which is a precursor for both cholesterol *and* coenzyme Q10 (CoQ10), a fat-soluble substance found in the mitochondria of respiring cells. CoQ10 is essential for cellular energy production in the form of ATP. It also protects against oxidative stress and helps the body recycle key antioxidants such as vitamin E. Blood levels of CoQ10 can drop by more than half with statin treatment, and some research suggests that in the setting of CoQ10 deficiency, a concurrent ATP deficiency might induce painful myopathy. In addition, a decrease in CoQ10 levels tends to be accompanied by a higher lactate to pyruvate ratio in the blood, which is commonly seen in myopathy – an indication that the mitochondrial respiratory system is not functioning properly. Some research suggests that taking CoQ10 supplements may reduce symptoms of myopathy; however, larger randomized controlled trials need to be done to establish definitive conclusions. In a small, randomized controlled study, 32 adults who had symptoms of myopathy when taking statins were given either CoQ10 or vitamin E for 30 days. Those who took CoQ10 reported having 40% less pain, but those who took vitamin E saw no improvement in their symptoms. In a randomized, placebo-controlled trial, 51 adults with coronary artery disease who were taking statins were given either a CoQ10 supplement or a placebo for 12 weeks. At the end of the trial, those who were taking the CoQ10 supplement had higher levels of vitamin E and antioxidant enzymes and lower levels of inflammatory markers in their blood compared to those taking the placebo. An analysis of 5 randomized controlled studies involving more than 250 people taking CoQ10 supplementation for symptoms of statin-induced myopathy concluded that most of the participants experienced some reduction in their myopathy symptoms; however, the findings were not statistically significant. - Read more about CoQ10 in *Coenzyme Q10 (CoQ10): In Depth*, an article from the NIH's Office of Dietary Supplements SNPs Involved rs4363657(C;T)

Less noteworthy

These genotypes are normal.

Gene	SNPs involved	Status	More information
COQ2	rs4693596(C;T)	Normal risk for myopathy with statin use	This gene encodes for coenzyme Q10 (CoQ10), an enzyme produced by every cell in the body. It plays a key role in energy metabolism and is a powerful antioxidant. People who have variants of the gene for CoQ10 (known as COQ2) may be at greater risk for developing statin-related myopathy.

While **this genotype, rs4693596(C;T), is still generally considered normal** the C;C variant has been associated twice the risk of developing statin-related myopathy in a study of nearly 300 people of European ancestry who were taking statins.

- Read more on SNPedia

Statins, myopathy & supplemental CoQ10

Statins are able to reduce cholesterol by inhibiting the action of an enzyme known as HMG-CoA reductase. This inhibition prevents the production of mevalonate, which is a precursor for both cholesterol *and* coenzyme Q10 (CoQ10), a fat-soluble substance found in the mitochondria of respiring cells. CoQ10 is essential for cellular energy production in the form of ATP. It also protects against oxidative stress and helps the body recycle key antioxidants such as vitamin E.

Blood levels of CoQ10 can drop by more than half with statin treatment, and some research suggests that in the setting of CoQ10 deficiency, a concurrent ATP deficiency might induce painful myopathy. In addition, a decrease in CoQ10 levels tends to be accompanied by a higher lactate to pyruvate ratio in the blood, which is commonly seen in myopathy – an indication that the mitochondrial respiratory system is not functioning properly.

Some research suggests that taking CoQ10 supplements may reduce symptoms of myopathy; however, larger randomized controlled trials need to be done to establish definitive conclusions.

In a small, randomized controlled study, 32 adults who had symptoms of myopathy when taking statins were given either CoQ10 or vitamin E for 30 days. Those who took CoQ10 reported having 40% less pain, but those who took vitamin E saw no improvement in their symptoms.

In a randomized, placebo-controlled trial, 51 adults with coronary artery disease who were taking statins were given either a CoQ10 supplement or a placebo for 12 weeks. At the end of the trial, those who were taking the CoQ10 supplement had higher levels of vitamin E and antioxidant enzymes and lower levels of inflammatory markers in their blood compared to those taking the placebo.

An analysis of 5 randomized controlled studies involving more than 250 people taking CoQ10 supplementation for symptoms of statin-induced myopathy concluded that most of the participants experienced some reduction in their myopathy symptoms; however, the findings were not statistically significant.

- Read more about CoQ10 in *Coenzyme Q10 (CoQ10): In Depth*, an article from the NIH's Office of Dietary Supplements

SNPs Involved

rs4693596(C;T)

HMGCR	rs17238540(T;T)	Normal response to statin treatment	This gene, hydroxy-methylglutaryl coenzyme A reductase (HMGCR), encodes for an enzyme that is crucial to cholesterol production. Statins block the production of HMGCR. This SNP has been associated with a reduced response to statins, as well as an increase in stroke risk and other cardiovascular risk factors. **However, this genotype, rs17238540(T;T), is normal and not associated with these effects.** - Read more on SNPedia SNPs Involved rs17238540(T;T)

PCSK9	rs11591147(G;G)	Normal risk of developing heart disease	Proprotein convertase subtilisin/kexin type 9 (PCSK9), a glycoprotein found in the liver, intestine, and kidney, plays a role in cholesterol and lipid metabolism. PCSK9 is secreted into the bloodstream and transported to the liver, where it binds to low-density cholesterol (LDL-C) receptors on the surface of hepatocytes. Once an LDL-C particle binds to this receptor, the entire complex (PCSK9 + LDL-C + receptor) is taken into the cell and degraded. In the absence of PCSK9, LDL-C alone binds to the receptor and enters the cell, where it is digested and the receptor returns to the cell surface where it can remove more LDL-C particles from circulation. **This genotype, rs11591147(G;G), has been associated with average LDL cholesterol levels and an average risk of developing heart disease.** There are polymorphisms in the gene that codes for PCSK9. The variant form **(T)** of the polymorphism, rs11591147 (also known as 137G > T, R46L), is a loss-of-function variant resulting in the production of a non-functional PSCK9 protein. This polymorphism is somewhat rare, present in 1-3% of individuals depending on the population studied. However, the positive effects on LDL-C reduction and cardiovascular disease risk are so strong that pharmaceutical drugs have been designed to target inhibition of PCSK9, thus mimicking the action of this variant. Two such drugs, recently approved by the FDA, are the monoclonal antibody drugs Repatha (evolocumab) and Praluent (alirocumab). The ARIC study followed 9,524 Caucasian individuals (aged 45 - 64) for 15 years. Individuals with the **T** allele (3.2%) had a 21% reduction in LDL-C (about 20 mg/dL) and a 47% reduction in coronary heart disease (CHD) as compared to **(G;G)** individuals. The authors propose that a lifelong decrease in LDL-C, due to the presence of the **T** allele, may confer protection against cardiovascular events. They maintain that even modest reductions in LDL-C (20 - 40mg/dL) sustained over a lifetime may reduce the incidence of CHD. - Read more about rs11591147 on SNPedia

			SNPs Involved rs11591147(G;G)
PCSK9	rs28362286(C;C)	Normal risk of developing heart disease	Proprotein convertase subtilisin/kexin type 9 (PCSK9), a glycoprotein found in the liver, intestine, and kidney, plays a role in cholesterol and lipid metabolism. PCSK9 is secreted into the bloodstream and transported to the liver, where it binds to low-density cholesterol (LDL-C) receptors on the surface of hepatocytes. Once an LDL-C particle binds to this receptor, the entire complex (PCSK9 + LDL-C + receptor) is taken into the cell and degraded. In the absence of PCSK9, LDL-C alone binds to the receptor and enters the cell, where it is digested and the receptor then returns to the cell surface where it can remove more LDL-C particles from circulation. **This genotype, rs28362286(C;C), has been associated with average LDL cholesterol levels and an average risk of developing heart disease.** There are polymorphisms in the gene that codes for PCSK9. The variant form**(A)** of the polymorphism, rs28362286 (also known as 2037C→A, C679X), introduces a premature stop codon into the gene, resulting in the production of a non-functional PSCK9 protein. This polymorphism is somewhat rare, present in only 0.1 - 2% of individuals depending on the population studied. However, the effects on LDL-C reduction and cardiovascular disease risk are generally seen as sufficiently desirable that, in fact, pharmaceutical drugs have been designed to target inhibition of PCSK9, thus mimicking the action of this variant. Two such drugs, recently approved by the FDA, are the monoclonal antibody drugs Repatha (evolocumab) and Praluent (alirocumab). The ARIC study investigated the effects of two SNPs simultaneously in 3363 individuals of African descent (aged 45 - 64) and followed them for 15 years. Individuals with either the **A** allele of this polymorphism (rs28362286) or the G allele of the PCSK9 variant (rs67608943) had a 28% reduction in LDL-C and a 88% reduction risk of coronary heart disease (CHD) when compared to non-variant individuals. Reduction in CHD risk was observed despite the high incidence of other cardiovascular disease risk factors such as hypertension, type 2 diabetes, and smoking. The authors propose that a life-long decrease in LDL-C, due to the presence of the **A** allele may confer protection against cardiovascular events. They maintain that even modest reductions in LDL-C (20 - 40mg/dL) sustained over a lifetime may reduce the incidence of CHD. • Read more about rs28362286 on SNPedia SNPs Involved rs28362286(C;C)
LIPC	rs2070895(G;G)	Normal hdl-c levels	Hepatic lipase (HL) is an enzyme produced by the liver that plays a role in lipoprotein metabolism. It is involved in regulating HDL cholesterol (HDL-C) levels. When HL enzyme activity is high, HDL-C levels are lower. Low levels of HDL-C have traditionally been with an increased risk for cardiovascular disease, due to the role of HDL-C in reverse cholesterol transport. Although this polymorphism is associated with increased HDL-C levels, studies correlating this SNP with protection from heart disease have been inconclusive. There are common polymorphisms in the *LIPC* gene, which codes for hepatic lipase. The variant form **(A)** of the rs2070895 polymorphism (also known as −250G>A), located in the promoter region of the gene, is associated with decreased enzyme activity. **This genotype, rs2070895(G;G), has been associated with normal HDL-C levels.** In a study of 16,156 Danish individuals, the **A** allele associated with higher fasting serum HDL-C levels. Individuals with the **(A;A)** genotype, who reported exercising vigorously, had a further increase in HDL-C as compared to **(G;G)** individuals. • Read more about rs2070895 on SNPedia SNPs Involved rs2070895(G;G)
APO-E3/E3	rs429358(T;T) rs7412(C;C)	Normal risk of alzheimer's, normal risk of hypertriglyceridemia	This genotype is the APO-E3/E3 genotype. **Cardiovascular disease** This genotype is defined as the “benchmark” for normal lipid homeostasis, is the standard by which other APOE isoforms are compared and is considered to have normal lipid and cholesterol transport mechanisms. This genotype has normal cardiovascular disease risk and normal Alzheimer’s disease risk. **LDL Cholesterol** Alcohol consumption does not affect LDL levels in APOE3 carriers after controlling for age, body mass index, smoking status, and fat and energy intake. • View the SNPedia page about ApoE. SNPs Involved rs429358(T;T) rs7412(C;C)

ABCG8	rs6544713(C;C)	Normal levels of ldl cholesterol	ATP-binding cassette transporter G8 (ABCG8) is involved in the metabolism of cholesterol and plant sterols. Expressed in cells of the liver, the intestines and the gallbladder, ABCG8 works in concert with another transporter called ABCG5. Together these transporters regulate the movement of sterols across intestinal cell membranes and target them to the biliary system for excretion, thus influencing how much cholesterol and plant sterols enter the bloodstream. **This genotype, rs6544713(C;C), has been associated with normal levels of LDL cholesterol.** There are common polymorphisms in the *ABCG8* gene, which codes for the ATP-binding cassette transporter G8. The variant form (**T**) of the rs6544713 polymorphism is located in the intronic region of the gene. In a genome-wide association study (GWAS) involving 19,840 individuals, the **T** allele of this polymorphism was associated with an increase in low-density lipoprotein cholesterol (LDL-C) levels, exhibiting an elevation of 0.15 standard deviation units per copy of the **T** allele. Investigators replicated these results in a cohort of 20,623 individuals. While this genotype (**C;C**) was not associated with elevated LDL-C levels, other polymorphisms in this gene and others may influence plasma LDL-C levels. • Read more about rs6544713 on SNPedia SNPs Involved rs6544713(C;C)

Disclaimer

The results found in this report are NOT FOR MEDICAL PURPOSES and are subject to change in future software updates without notice. Raw data from genetic providers is suitable only for research, educational, and informational use and not for medical or other use.

Circadian Report v4

Source: Cooper_Beaman_23andmenew_v4_Full_20190517100124.zip
Created at February 23 at 3:43 PM PDT

This report focuses on genotypes associated with disruptions in the body's circadian rhythm that affect sleep and mood.

Noteworthy

These genotypes are the ones that are potentially worth being aware of.

Gene	SNPs involved	Status	More information
NPAS2	rs11123857(A;G)	Slightly reduced expression of important circadian gene	The *NPAS2* gene encodes for the protein Npas2, which functions in the brain as a generator and maintainer of circadian rhythm. NPAS2 is paralogous (descending from the same ancestral gene) to the *CLOCK* gene, which encodes for Clock, a more well-known protein regulator of circadian rhythm. In the absence of Clock, Npas2 upregulates to keep rhythms intact in the suprachiasmatic nucleus (SCN), the part of the brain that acts as the master regulator or "pacemaker" of circadian rhythm. Similar to Clock, when Npas2 is knocked out mice show sleep disturbances. **This genotype, rs11123857(A;G), is associated with disturbed circadian rhythms and increased risk of major depressive disorder or bipolar disorder.** The effects of carrying a single allele of a particular variant range from no easily observable effect to a lower magnitude of the effects seen when carrying both alleles. For this reason, the effects of rs11123857 are dose-dependent, based on the number of **G** alleles a person carries. For example, in a study of more than 500 Spanish adults, those who carried one of the **G** alleles**(A;G)** had a 1.44-fold increased risk of major depression or bipolar disorder. **Managing our circadian rhythm may help with depression.** Bright light treatment has long been appreciated as a useful intervention for people experiencing seasonal affective disorder. Recent research, however, suggests it may be effective in treating non-seasonal major depressive disorder as well. One of the ways that bright light, particularly blue light, may be helpful in alertness and mood is by acting as a robust circadian trigger in the morning and during the day. Bright light may interfere with sleep patterns at night, however, by triggering the release of melanopsin, a light-sensitive protein that shifts the activity of cells in the brain's suprachiasmatic nucleus into an active day pattern. More than 80% of depressed patients report poor sleep quality, a common feature of depression. Poor sleep quality is also a strong risk factor for suicide. • Read more on SNPedia about rs11123857. • Listen to circadian biologist Dr. Satchin Panda discuss melanopsin and the role of the SCN in circadian rhythm. • Listen to Dan Pardi talk about using proper light timing to improve sleep. SNPs Involved rs11123857(A;G)
NPAS2	rs2305160(C;C)	Circadian-associated increased breast/prostate cancer risk	There has been increasing evidence that mutations in genes involved in circadian rhythm play a role in cancer growth. The NPAS2 gene controls genes involved in cell growth, metabolism, and DNA repair. When these cellular processes become dysregulated this can allow cancer cells to form and proliferate. **This genotype, rs2305160(C;C), has been associated with *increased risk* of certain human cancers including breast cancer and prostate cancer.** One mechanism by which dysregulation of the *NPAS2* gene increases cancer risk is through its effect on metabolism and energy balance. Published data most strongly support fasting insulin, bioavailable estradiol, and C-reactive protein (CRP) as biomarkers of breast cancer risk. Individually, these biomarkers are associated with an approximate **two-fold** increased risk of incident or recurrent breast cancer. For each 10% increase in the proportion of calories consumed after 5pmwas associated with a 3% increase in the inflammatory biomarker CRP (c-reactive protein). For each 3-hour increase in night-time fasting duration was linked to a 20% lower odds of elevated glycated hemoglobin (HbA1C). Studies have shown that consuming food earlier in the day and only during an11-hour window, can decrease breast cancer risk and recurrence by as much as 36%. Together, these data suggest that time-restricted eating is a viable option to lower biomarkers of inflammation and insulin resistance and lower breast cancer risk and recurrence. **More Information** • More information about practical implications for time-restricted eating and breast cancer. • More information on time-restricted eating, circadian rhythm, and cancer risk. • Read more on SNPedia SNPs Involved rs2305160(C;C)

MTNR1B	rs10830963(C;G)	Slight impaired glucose tolerance with a late dinner time and early breakfast and slight increased risk for type-2 diabetes	Melatonin, a hormone associated with the onset of sleep, is produced by the pineal gland in the brain and its levels are highest at night and lowest during the daytime. Melatonin receptor 1B (MTNR1B) is one of two melatonin transmembrane receptors expressed in a variety of tissues, including pancreatic islet cells. The prevailing theory is that melatonin binds to MTNR1B and acts to inhibit insulin secretion. Current research is studying how melatonin may be involved in glucose homeostasis and insulin release. **This genotype, rs10830963(C;G), has been associated with slight impaired glucose tolerance with a late dinner time and slight increased risk for type-2 diabetes.** There are common polymorphisms in the *MTNR1B* gene, which codes for the melatonin receptor 1B. The variant form (**G**) of the rs10830963 polymorphism, located in the intronic region of the gene, is thought to result in higher mRNA expression. In a genome-wide association study (GWAS) involving 36,610 individuals, the **G** allele was associated with a 0.07 mmol/L increase in fasting glucose per copy, impaired insulin secretion as well as an increased risk for type-2 diabetes (T2DM). In a randomized cross-over study, overweight or obese women (n=20 (**G;G**) and n=20 (**C;C**)) were fed an evening meal either 4 hours before their usual bedtime (early) or one hour before their usual bedtime (late). The following week the mealtimes were reversed. When given the late meal, individuals with the (**G;G**) genotype had a dramatically impaired glucose tolerance as compared to those who received the early meal. Investigators did not observe this pattern in subjects with the (**C;C**) genotype. Based on these findings the authors recommend that individuals with the (**G;G**) genotype eat dinner no later than 2 to 4 hours before their usual bedtime in order to allow blood glucose levels to normalize before melatonin rises. This may be particularly important for pre-diabetic or diabetic individuals as well as those who consume a large portion of their daily food intake at the evening meal. The authors maintain that individuals with the (**G;G**) genotype who eat at night when melatonin levels are high, for example shift workers, may be at risk for metabolic disturbances. Investigators observed that **G** allele carriers had 10% extended melatonin release in the morning as compared to those without the **G** allele. Preliminary findings indicate that early risers with the **G** allele were more likely to have T2DM than late risers, suggesting that the extended high melatonin levels in the morning (coinciding with food intake) were more relevant for early risers. Early risers carrying the **G** allele might benefit from a delayed breakfast to avoid eating when melatonin levels are high. • Time-restricted eating and the effect of late night eating (see 00:00-06:00). • Read more about rs10830963 on SNPedia SNPs Involved rs10830963(C;G)
ADA	rs73598374(A;A)	Deeper sleep and decreased well-being with sleep loss	Adenosine deaminase (ADA) is an enzyme involved in the sleep-wake cycle where it catalyzes the degradation of adenosine, a known sleep factor, into inosine and ammonia. Adenosine is generated and accumulates throughout the day as the body uses ATP (adenosine triphosphate) for energy. Sleepiness is caused when adenosine binds to adenosine receptors. Caffeine can block these receptors which prevents adenosine from binding and results in wakefulness. **This genotype, rs73598374(A;A), has been associated with deeper sleep and decreased well-being with sleep loss.** There are common polymorphisms in the *ADA* gene, which codes for adenosine deaminase. The variant form (**A**) of the rs73598374 polymorphism (also known as Asp8Asn), located in the coding region of the gene, is thought to reduce enzyme activity resulting in higher adenosine levels. Researchers studying individual sleep patterns (n=119), observed that carriers of the **A** allele experienced more deep sleep as compared to individuals with the (**G;G**) genotype. The investigators characterized deep sleep as having fewer awakenings, more slow-wave sleep and more delta waves. A subset of individuals (n=7 (**A;G**), n=7 (**G;G**)) participated in an overnight sleep study. Investigators observed that individuals with the (**A;G**) genotype had twice the deep sleep (stage 4) and 30 minutes more slow-wave sleep than individuals with the (**G;G**) genotype. In a study, 220 subjects kept track of their sleep habits and completed a series of learning, memory and executive function tests. Sleep duration was the same in **A** allele carriers and individuals with the (**G;G**) genotype. A subset of these individuals (n=11 (**A;G**), n=11 (**G;G**)) participated in a sleep-deprivation study and were kept awake for 40 hours. Researchers collected data on sleepiness, mood, EEG, psychomotor vigilance and salivary alpha-amylase (a possible biomarker of sleep drive). Carriers of the **A** allele reported greater sleepiness and fatigue and performed worse on attention tests when sleep deprived as compared to subjects with the (**G;G**) genotype. Participants with the **A** allele had higher salivary alpha-amylase levels as compared to (**G;G**) individuals and exhibited more deep sleep and slow-wave activity during the night prior to and the night following the sleep deprivation period. Researchers studying sleep deprivation (n=24) found that carriers of the **A** allele were more likely to report being sleepy when compared to individuals with the (**G;G**) genotype. The results showed that upon introduction of naps this difference between the genotypes was not observed. Participants with the (**A;G**) genotype performed better on memory tests and experienced greater well-being with the nap protocol while for those with the (**G;G**) genotype, performance and well-being were unchanged. The authors suggest that individuals react differently to sleep deprivation and napping may be beneficial to overcome some of the negative effects experienced by individuals with the **A** allele. • Read more about rs73598374 on SNPedia

			SNPs Involved rs73598374(A;A)
CRY2	rs11605924(A;A)	Increased fasting glucose levels, alters response to high fat diet	Cryptochrome circadian regulator 2 (CRY2) is one of the core proteins involved in the control of the circadian system. Physiological processes such as metabolism, body temperature and sleep-wake cycles are all regulated by the circadian clock. Current research is studying the role of circadian regulating proteins such as CRY2 in glucose homeostasis and insulin release. **This genotype, rs11605924(A;A), has been associated with increased fasting glucose levels.** There are common polymorphisms in the *CRY2* gene, which codes for the cryptochrome circadian regulator 2. The rs11605924 polymorphism is located in the intronic region of the gene. In a genome-wide association study (GWAS) involving 116,479 individuals, the **A** allele was associated with increased fasting glucose levels. In the POUNDS LOST trial, a two-year long dietary intervention study, researchers randomly assigned 721 overweight individuals to one of four hypocaloric diets which varied in the amount of carbohydrate, protein and fat content. Investigators assessed energy expenditure by measuring resting metabolic rate (RMR) and respiratory quotient (RQ). RQ measures substrate utilization and indicates which macronutrient (carbohydrate, protein or fat) an individual is using for fuel. After two years, individuals with the **A** allele had a higher increase in RMR and a greater decrease in RQ as compared to individuals with the (**C;C**) genotype. The reduction in RQ for **A** allele carriers was observed more strongly on a high-fat diet than on a low-fat diet. These observations suggest that carriers of the **A** allele have altered energy expenditure responses to a weight loss diet as compared to (**C;C**) individuals. While the findings that **A** allele carriers respond differently to a high-fat vs low-fat diet are interesting, the authors state that more research is needed to understand the mechanism involved. • Read more about rs11605924 on SNPedia SNPs Involved rs11605924(A;A)
PER2	rs2304672(C;G)	Slight tendency for morning preference and extreme snacking	Period circadian regulator 2 (PER2) is a circadian clock repressor protein involved in the regulation of the circadian rhythm which controls the sleep-wake cycle, hormone secretion and body temperature. Individuals vary in their diurnal preference, for example their habitual sleep and wake times, also referred to as chronotype. **This genotype, rs2304672(C;G), has been associated with a slight tendency for morning preference and extreme snacking.** There are common polymorphisms in the *PER2* gene, which codes for the period circadian regulator 2 protein. The variant form (**C**) of the rs2304672 polymorphism (also known as C111G), located in the 5′ untranslated region of the gene, may result in an altered mRNA structure. Researchers identified two groups of individuals who self-reported as either extreme morningness (early larks) or extreme eveningness (night owls), based on validated questionnaires. Individuals with the **C** allele were more likely to be associated with preferring extreme morningness rather than extreme eveningness. In a year-long weight loss study (n=454 overweight or obese subjects), individuals with the **C** allele were more likely to exhibit obesogenic behaviors, such as extreme snacking, eating while bored, breakfast skipping, stress while dieting and dropping out of the study, as compared to individuals with the (**G;G**) genotype. Research suggests that extreme snacking may disrupt the circadian system, and, vice versa disruptions in the circadian rhythm may lead to excessive snacking. This may be due to the fact that both bright light and food are known zeitgebers, external cues which regulate the circadian rhythm. Investigators examined a group of individuals with metabolic syndrome (n=381) and analyzed their plasma fatty acid concentrations and lipid biomarkers. When comparing subjects with high (> median) plasma saturated fatty acid (SFA) levels, carriers of the **C** allele exhibited higher plasma triglycerides (TG), triglyceride-rich lipoproteins (TRL-TG), apoC-II, apoC-III, and apoB-48 concentrations than participants with the (**G;G**) genotype. However, in subjects with lower (≤ median) plasma SFA, carriers of the **C** allele had lower plasma TG, TRL-TG, total cholesterol, apoC-II, apoC-III, apoB, and apoB-48 versus individuals with the (**G;G**) genotype. The authors categorize **C** allele carriers as high responders to plasma SFA and (**G;G**) subjects as low responders to plasma SFA concentrations. They propose that for individuals with metabolic syndrome, disruptions in the PER2 gene (**C** allele) may have detrimental effects on lipid metabolism when saturated fat intake is high. • Read more about rs2304672 on SNPedia * These alleles have been adjusted for consistency with SNP orientation. Read more about orientation. SNPs Involved rs2304672(C;G)
PER1	rs7221412(A;G)	Associated with being an intermediate riser	Period circadian regulator 1 (PER1) is a circadian clock gene involved in the regulation of the circadian rhythm which controls the sleep-wake cycle, hormone secretion and body temperature.

Individuals vary in their diurnal preference, for example their habitual sleep and wake times, also referred to as chronotype.

This genotype, rs7221412(A;G), has been associated with being an intermediate riser.

There are common polymorphisms near the *PER1* gene, which codes for the period circadian regulator 1 protein. The rs7221412 polymorphism is located in the intergenic region downstream of the *PER1* gene.

In a candidate gene association study, investigators examined the sleep-wake cycle of 587 individuals. To measure the timing of their daily activities, participants wore an actigraph wrist-watch for one week. Researchers evaluated the actigraphic data to determine the midpoint of the 8 hours with the most activity. The activity midpoint was 67 minutes earlier in (**A;A**) subjects as compared to (**G;G**) individuals, with (**A;G**) participants falling in between the two. Investigators replicated these findings in a second cohort of 38 subjects.

- Read more about rs7221412 on SNPedia

SNPs Involved

rs7221412(A;G)

Less noteworthy

These genotypes are normal.

Gene	SNPs involved	Status	More information
MTNR1A	rs12506228(C;C)	Normal risk for late-onset alzheimer's disease	There is a common polymorphism located downstream of melatonin receptor type 1A gene (*MTNR1A)* that codes for the MT1 melatonin receptor. Melatonin is a hormone produced primarily by the pineal gland in the brain. Melatonin, which is secreted in high levels at night, decreases with age and is particularly low in Alzheimer's disease (AD) patients. Along with dementia, sleep disturbances and altered circadian rhythms are commonly observed in AD patients. **This genotype, rs12506228(C;C) is associated with normal risk for late-onset Alzheimer's disease (AD).** However, those with the **A** allele may have an increased risk for late-onset AD. In a study of 512 Finnish individuals, aged 85+ years, subjects were assessed for AD and followed for 10 years. The **A** allele was significantly associated with clinical signs of AD, such as dementia. When brain tissue was examined post-mortem, **A** allele carriers had more amyloid-beta plaques and neurofibrillary tangles (hallmark signs of AD) than those without the **A** allele. In fact, all **(A;A)** subjects had severe amyloid-beta plaques and neurofibrillary tangles upon autopsy. This association was confirmed in a second case-control cohort of 673 AD patients and 686 controls (participants over age 75). This association was not observed in a case-control study of younger individuals (average age 70). SNPs Involved rs12506228(C;C)

Unavailable

Depending on the dataset you provided for report generation, not all possible report entries may be available. *This is normal.* In this case, the following groups were excluded because the data you upload did not contain the requisite SNPs:

DEC2, PER2

Fitness Report v1

Source: Cooper_Beaman_23andmenew_v4_Full_20190517100124.zip
Created at February 23 at 3:45 PM PDT

This report is focused on SNPs related to fitness including endurance, the capacity to improve VO2max with endurance training, reduced lactate transport out of muscle and susceptibility to muscle fatigue in men, and susceptibility to injuries to soft tissues including Achilles tendon, ACL, and tennis elbow.

Noteworthy

These genotypes are the ones that are potentially worth being aware of.

Gene	SNPs involved	Status	More information
SLC30A8	rs13266634(C;C)	Increased risk for type 2 diabetes related to zinc transport, susceptibility to doms	ZnT8 is a zinc transporter found in pancreatic beta (insulin-producing) cells. Zinc is a trace element involved in a variety of cellular processes, for example serving as a cofactor to numerous enzymes as well as its role in insulin secretion and storage. **This genotype, rs13266634(C;C) is associated with an increased risk for type 2 diabetes.** There are common polymorphisms in the *SLC30A8* gene, which codes for the ZnT8 transporter protein. The variant form **(C)** of the rs13266634 polymorphism, located in the terminal (3') region of the gene, results in a ZnT8 protein with reduced activity and thus the synthesis and storage of insulin may be impaired. In a genome-wide association study (GWAS) of type 2 diabetes (T2DM) patients (who also had a first degree relative with T2DM) and control subjects (n=1,363) investigators found that the **C** allele was more common in the T2DM group than in the control group. Based on this observation they suggested that the **C** allele confers a risk of developing T2DM. A GWAS of T2DM cases (n=1,464) and controls (n=1,467) from Finland and Swedenconfirmed the association of the **C** allele with T2DM risk. In a recent meta-analysis of 28 case-control studies (25,912 cases and 26,975 controls), researchers found that subjects with the **C** allele had an increased risk of developing TD2M as compared to individuals without the **C** allele. Recent evidence suggests that this association may vary with ethnicity. In a meta-analysis of 38 studies (65,767 T2DM patients and 100,182 controls) the **C** allele was associated with T2DM risk in Asian and European populations but not in African populations. The authors are unsure if this represents a valid result or whether it is the consequence of limited sample size in the African subgroup. Mechanistic studies are still required to elucidate how this polymorphism affects various populations. In a gene-diet interaction study, researchers investigating a different SNP (rs11558471) in the *SLC30A8* gene showed that subjects with the risk allele and higher zinc intake (food sources and supplements) had lower fasting glucose levels than risk individuals with lower zinc intake. This suggests that individuals with the risk allele may benefit from zinc supplementation to promote adequate glucose homeostasis and reduced risk of T2DM. *Delayed onset muscle soreness (DOMS)* Following a resistance training session, men carrying the **C** allele experienced more muscle soreness and damage as compared to men with the (**T;T**) genotype. Individuals with the **C** allele may require longer recovery times after resistance training or may benefit more from endurance-based activities. The authors suggest a mechanism whereby the *SLC30A8* gene contributes to healthy muscle function by participating as a signaling molecule between pancreatic beta cells and skeletal muscles. • Read more about rs13266634 on SNPedia SNPs Involved rs13266634(C;C)
COL5A1	rs12722(T;T)	Increased risk for achilles tendinopathy	*COL5A1* (collagen type V alpha 1 chain) is a gene involved in the synthesis of type V collagen. Collagens are proteins that perform strength and support functions in connective tissues such as tendons and ligaments. Injuries to soft tissues such as the Achilles tendon, anterior cruciate ligament (ACL) and tennis elbow are prevalent in athletes. Although the causes of these injuries are multifactorial, recent research suggests there may be a genetic component. **This genotype, rs12722(T;T), has been associated with increased risk for Achilles tendinopathy.** There are common polymorphisms in the *COL5A1* gene, which codes for the alpha chain of type V collagen protein, a rate-limiting step in type V collagen assembly. The variant form (**T**) of the rs12722 polymorphism, located in the 3′ untranslated region of the gene, is thought to be associated with increased mRNA stability which may regulate how much of the final protein is made. This in turn may affect the density and stiffness of the resulting tissue. In two case-control genetic association studies involving South African (111 cases and 129 controls) and Australian (85 cases and 210 controls) subjects, individuals with the (**C;C**) genotype had a lower risk of developing Achilles tendinopathy as compared to those with the **T** allele.

			A recent meta-analysis (n=1140 cases and 1410 healthy controls) revealed that subjects with the **(T;T)** genotype were more susceptible to musculoskeletal soft tissue injuries of tendons and ligaments, including Achilles tendon, ACL and tennis elbow, as compared to carriers of the **C** allele. Researchers studied triathlon and ultra-marathon athletes with a history of exercise-associated muscle cramping (EAMC, n=116) and controls (n=150). They found that individuals with the **(C;C)** genotype were more likely to be in the control group than carriers of the **T** allele, suggesting some protection from EAMC. The authors propose that alterations in the type V collagen protein may result in tissues which are weaker and stiffer, thereby impacting the risk of EAMC. While a variety of non-genetic factors influence soft tissue injury, individuals with the (**T;T**) genotype may benefit from consulting a physical therapist or trainer to incorporate preventative strategies (prehabilitation exercises) and to determine the optimal training load to achieve goals while minimizing the risk of injury. • Read more about rs12722 on SNPedia SNPs Involved rs12722(T;T)
VEGFA	rs2010963(G;G)	Decreased endurance capacity (resistance to aerobic training), resistance training may help	Vascular endothelial growth factor A (VEGFA) is a cytokine involved in angiogenesis (the generation of new blood vessels) particularly within skeletal muscles. Angiogenesis is essential in the body's adaptation to exercise by facilitating more oxygen delivery to tissues and thus improving VO2 max. **This genotype, rs2010963(G;G), has been associated with decreased endurance capacity (resistance to aerobic training).** There are common polymorphisms in the *VEGFA* gene, which codes for the vascular endothelial growth factor A. The variant form (**C**) of the rs2010963 polymorphism (also known as G634C), located in the promoter region of the gene, is thought to increase *VEGFA* gene expression. In a study of 670 athletes and 1,073 controls, the **C** allele was found more often in the athlete group. The authors suggest that individuals with the **C** allele have elevated oxygen capacity during exertion as a result of higher levels of *VEGFA* gene expression promoting increased blood vessel growth. Based upon this study and previous investigations, researchers propose that individuals with the **C** allele may have an advantage when it comes to the vascular benefits derived from aerobic training. In a study of 42 male youth soccer players, researchers investigated a haplotype of five SNPs (including rs2010963) thought to be involved in cardiovascular fitness. Participants were classed into groups (low, medium or high) with respect to the number of favorable alleles they possessed. Investigators tested aerobic fitness following an 8-week aerobic training program. While all groups showed improvements, individuals in the high group had a 58% greater improvement as compared to individuals in the medium (35%) and low (7%) groups. The authors propose that knowledge about how an individual responds to training may be beneficial in designing a tailored exercise program whether in athletics, general fitness or the medical sphere. Individuals with the **G** allele may see greater benefits using resistance training and plyometrics (such as jumping and skipping) which increase endurance in ways that are not related to increases in VO2 max. Increasing exercise intensity has been shown in other studies to improve training response in low responders. Increased aerobic fitness may be protective against a variety of diseases. While genetics may contribute to an individual's aerobic fitness, training can enhance aerobic potential. • Read more about rs2010963 on SNPedia SNPs Involved rs2010963(G;G)
ADRB2	rs1042713(G;G)	Decreased endurance capacity	Beta-2 adrenergic receptor (ADRB2) plays a role in the sympathetic nervous system, acting to bind catecholamines including epinephrine. ADRB2 is expressed in various body cells and is thought to be involved in lipolysis, glycogenolysis and smooth muscle relaxation (in the gastrointestinal system, airway and vascular system). **This genotype, rs1042713(G;G), has been associated with decreased endurance capacity.** There are common polymorphisms in the *ADRB2* gene, which codes for the β2-adrenergic receptor. The variant form (**A**) of the rs1042713 polymorphism (also known as Arg16Gly), located in the coding region of the gene, is thought to be associated with increased activity. While not fully understood, some evidence points to an increase in receptor density as well as a resistance to desensitization or degradation of the receptor. In a case-control study of elite endurance athletes (n=313) and sedentary controls (n=297), the **G** allele was found more frequently in sedentary controls and the **A** allele was more common in the athletes. Researchers studied 438 participants of the Mount Olympus marathon in Greece. The **A** allele was associated with a shorter marathon finishing time amongst athletes who stated that running was their preferred sport. In a study of 28 recreationally active men, researchers observed that individuals with the **(G;G)** genotype had a higher fat-free mass and higher maximal voluntary isometric (MCIV) strength as compared to men with the (**A;A**) genotype. The authors state that while this research is preliminary, it may be relevant for assessing how muscles respond to training. • Read more about rs1042713 on SNPedia

SNPs Involved

rs1042713(G;G)

Less noteworthy

These genotypes are normal.

Gene	SNPs involved	Status	More information
ADRB3	rs4994(T;T)	Normal ability to lose weight	Beta-3 adrenergic receptor (ADRB3) plays a role in the sympathetic nervous system, acting to bind catecholamines such as epinephrine. ADRB3 is expressed on the surface of fat cells and the bladder and is thought to be involved in energy expenditure, possibly via lipolysis and thermogenesis. Studies in rodents link ADRB3 to lipolysis in white adipose tissue (WAT) during fasting and to thermogenesis in brown adipose tissue (BAT) during cold exposure. However, these associations have only been preliminarily established in humans. **This genotype, rs4994(T;T) is associated with a normal ability to lose weight.** There are common polymorphisms in the *ADRB3* gene, which codes for the β3-adrenergic receptor. The variant form **(C)** of the rs4994 polymorphism (also known as Trp64Arg), is a missense mutation in the coding region of the gene that may decrease the affinity of the receptor for its target. Although not definitive, several researchers have associated this polymorphism with obesity. In a meta-analysis involving 9,000 individuals, subjects carrying the **C** allele had a higher BMI than individuals with the **(T;T)** genotype. In a study of 329 Saudi individuals, those with the **C** allele had higher weight and BMI as compared to individuals with the **(T;T)** genotype. Individuals with the **C** allele also exhibited higher glucose and insulin levels as well as altered blood lipids. The authors propose that this polymorphism may act by decreasing lipolysis in fat cells (causing lipids to be retained in adipocytes rather than being burned for energy) which may explain the connection to obesity and dyslipidemia. • Read more about rs4994 on SNPedia SNPs Involved rs4994(T;T)

Unavailable

Depending on the dataset you provided for report generation, not all possible report entries may be available. *This is normal.* In this case, the following groups were excluded because the data you upload did not contain the requisite SNPs:

MCT1

Longevity Report v1

Source: Cooper_Beaman_23andmenew_v4_Full_20190517100124.zip
Created at February 23 at 3:46 PM PDT

Many factors influence how long a person lives, such as lifestyle, dietary patterns, socioeconomic status, and access to healthcare. Genetics play a role in longevity, too. Certain SNPs have direct influence on longevity (e.g., they promote long life), while others have indirect influence (e.g., they may increase risk of certain diseases, which could shorten life). The following SNPs have been linked to longevity.

Noteworthy

These genotypes are the ones that are potentially worth being aware of.

Gene	SNPs involved	Status	More information
FOXO3	rs2802288(A;G)	May increase lifespan	Forkhead box O3 protein (FOXO3) is a transcription factor involved in the regulation of genes involved in many cellular processes, including DNA repair, tumor suppression, immune function, and resistance to oxidative stress. Some variants of *FOXO3* are associated with longevity in humans. **This genotype, rs2802288(A;G), has been associated with increased lifespan.** There are common polymorphisms in the *FOXO3* gene, which codes for the forkhead box O3 protein. The variant form (**A**) of the rs2802288 polymorphism, located in the intronic region of the gene, is thought to increase expression of the *FOXO3* gene. In a study involving 1,400 Italian adults, individuals carrying the **A** allele (**A;A** or **A;G**) were more likely to live to the age of 90 years or older. • Read more about rs2802288 on SNPedia SNPs Involved rs2802288(A;G)
FOXO3	rs9400239(C;T)	May increase lifespan	Forkhead box O3 protein (FOXO3) is a transcription factor involved in the regulation of genes involved in many cellular processes, including DNA repair, tumor suppression, immune function, and resistance to oxidative stress. Some variants of *FOXO3* are associated with longevity in humans. **This genotype, rs9400239(C,T), has been associated with increased lifespan.** There are common polymorphisms in the *FOXO3* gene, which codes for the forkhead box O3 protein. The variant form (**T**) of the rs9400239 polymorphism is located in the intronic region of the gene. Findings from a meta-analysis of several studies suggest thatindividuals who had achieved an older age (greater than 90 years) were more likely to carry one or more of the **T** alleles (**C;T** or **T;T**) of this polymorphism. • Read more about rs9400239 on SNPedia SNPs Involved rs9400239(C;T)
FOXO3	rs2802292(G;T)	May increase lifespan	Forkhead box O3 protein (FOXO3) is a transcription factor involved in the regulation of genes involved in many cellular processes, including DNA repair, tumor suppression, immune function, and resistance to oxidative stress. Some variants of *FOXO3* are associated with longevity in humans. **This genotype, rs2802292(G;T), has been associated with increased lifespan.** There are common polymorphisms in the *FOXO3* gene, which codes for the forkhead box O3 protein. The variant form (**G**) of the rs2802292 polymorphism, located in the intronic region of the gene, is thought to increase expression of the *FOXO3* gene. Several large studies investigating the link between longevity and genetics observed that carriers of certain *FOXO3* variants tended to live longer. For example, in a study of more than 600 men of Japanese ethnicity carriers of the **G** allele (**G;G** or **G;T**) of this polymorphism were 2.75 times more likely to live to the age of 95 years or older. The men who lived the longest tended to be leaner and had overall better health than their younger counterparts. In a study of 1,762 German adults, carriers of the rs2802288 variant (a proxy for the rs2802292 variant) of the FOXO3 gene were 1.5 times more likely to live to the age of 100 years or older. Likewise, in a group of 1,400 Italian adults, those carrying the rs2802288 variant were more likely to live to the age of 90 years or older. In two parallel studies involving more than 6,000 Japanese, white, and black elderly adults, carriers of the **G** allele (**G;G** or **G;T**) of the rs2802292 polymorphism were 26% less likely to die of cardiovascular disease and 10% less likely to die from all-cause mortality. • Read more about rs2802292 on SNPedia

			SNPs Involved rs2802292(G;T)
FOXO3	rs2764264(C;T)	May increase lifespan	Forkhead box O3 protein (FOXO3) is a transcription factor which plays a role in the regulation of genes involved in many cellular processes, including DNA repair, tumor suppression, immune function, and resistance to oxidative stress. Some variants of FOXO3 are associated with longevity in humans. **This genotype, rs2764264(C;T), has been associated with increased lifespan.** There are common polymorphisms in the *FOXO3* gene, which codes for the forkhead box O3 protein. The variant form (**C**) of the rs2764264 polymorphism, located in the intronic region of the gene, is thought to increase expression of the *FOXO3* gene. Findings from a study that relied on case-control and longitudinal data from more than 1,000 Danish men and women demonstrated that individuals who had reached older age (greater than 90 years) and in particular males, were more likely to carry one or more **C** alleles (**C;T** or **C;C**). • Read more about rs2764264 on SNPedia SNPs Involved rs2764264(C;T)
AKT1	rs3803304(G;G)	May increase lifespan	AKT serine/threonine kinase 1 (AKT1) is an enzyme that regulates many processes including metabolism, proliferation, cell survival, growth and angiogenesis. It is a component of an intracellular signaling pathway called PI3K/AKT/mTOR, which plays roles in the cell cycle, cancer, and longevity. **This genotype, rs3803304(G;G), has been associated with increased lifespan.** There are common polymorphisms in the *AKT1* gene, which codes for AKT serine/threonine kinase 1 enzyme. The variant form (**G**) of the rs3803304 polymorphism is located in the intronic region of the gene. In a study of elderly Caucasian men and women, individuals carrying one or more copies of the **G** allele (**C;G** or **G;G**) were more likely to reach older age, especially among female subjects. • Read more about rs3803304 on SNPedia * These alleles have been adjusted for consistency with SNP orientation. Read more about orientation. SNPs Involved rs3803304(G;G)
IL-6	rs1800795(G;G)	Associated with longer lifespan and increased risk of certain diseases	**This genotype, rs1800795(G;G), is associated with increased lifespan and increased risk of certain diseases.** In a study of 285 Finnish adults, those who carried one or more of the **G** alleles (**C;G** or **G;G**) of the rs1800795 variant of the IL-6 gene were more likely to achieve older age (between the ages of 90 and 95 years). In a meta-analysis of nearly 100 studies that investigated links between this genotype and cancer risk, 78 of the studies found that people who carried one or more of the **G** alleles (**C;G** or **G;G**) of the rs1800795 variant of the IL-6 gene were more likely to develop certain types of cancer, including cervical, breast, colorectal, prostate, lung, glioma (a type of brain cancer), and lymphoma. In a study of more than 150 older men who had experienced a heart attack, those who carried the **G;G** form of the rs1800795 variant of the IL-6 gene were nearly four times more likely to die within one year of the event. In a study of more than 5,000 men and women that took place over a 9-year period those who carried one or more of the **G** alleles (**C;G** or **G;G**) of the rs1800795 variant of the IL-6 gene were more approximately 30% more likely to develop diabetes. (If they carried four or more diabetes-related variants, their risk increased by nearly 250%.) • Read more about rs1800795 on SNPedia **IL-6** Interleukin-6, or IL-6, is a type of cell-signaling protein. It is produced by cells in the immune system in response to infection or trauma (such as burns). IL-6 plays both pro- and anti-inflammatory roles in the body, depending on the physiological context. For this reason, the rs1800795 variant of the IL-6 gene is both *directly* and *indirectly* associated with longevity. For example, some studies *directly* link variants of this gene with increased lifespan. However, rs1800795 variants are also associated with heart disease, Kaposi's sarcoma, type-2 diabetes, stroke, obesity, Hodgkin's lymphoma, sudden infant death syndrome, cancer (including breast cancer, gastric cancer, and prostate cancer), high blood pressure, gum disease, and organ transplant rejection, all of which can *indirectly* shorten lifespan. In addition, the link between the variants and these conditions isn't always related to increased or decreased risk; rather, the link

may be related to how a person does or does not respond to treatment.

Whereas the **C** allele is associated with *decreased* levels of IL-6, the **G** allele is associated with *increased* levels of IL-6.

SNPs Involved

rs1800795(G;G)

CFH | rs1061170(T;T) | May increase lifespan; slightly lower risk of macular degeneration

This genotype, rs1061170(T;T), is associated with longer lifespan. In a study of nearly 500 Finnish adults over the age of 90 years, those who carried the **T;T** form of the rs1061170 variant of the CFH gene tended to live longer, perhaps due to reduced systemic inflammation.

People with this genotype may have less risk of developing age related macular degeneration, a serious eye condition typically seen among older adults. In studies of adults living in Asia, the US, and Germany, those who carried one or more of the alleles for the **C** form (**C;C or C;T**) of the rs1061170 variant for the CFH gene had approximately 2 to 4 times greater risk of developing age-related macular degeneration, compared to those with the **T;T** form of the variant.

- Read more about rs1061170 on SNPedia

CFH

Complement Factor H, or CFH, helps regulate a part of the body's immune response known as the complement system. This system destroys foreign invaders (such as bacteria and viruses), triggers the body's inflammatory response, and removes debris from cells and tissues. Complement factor H, along with several other proteins, protects healthy cells by preventing the complement system from being activated (and causing widespread inflammation) when it is not needed.

SNPs Involved

rs1061170(T;T)

APOC3 | rs2542052(A;C) | May increase lifespan

This genotype, rs2542052(A;C), may be associated with increased lifespan; however, scientific data for this particular variant are lacking. It is noteworthy, however, that in a study of more than 400 Ashkenazi Jewish centenarians and their offspring and an age-matched Ashkenazi control group, those who carried *both* of the APOC3 alleles **(C;C)** of the rs2542052 variant of the APOC3 gene tended to have healthy lipoprotein levels, better cardiovascular health, and increased insulin sensitivity, and were more likely to achieve older age. The effects of carrying a *single* allele of a particular variant range from no easily observable effect to a lower magnitude of the effects seen when carrying both alleles.

- Read more about rs2542052 on SNPedia

APOC3

Apolipoprotein C-3 (APOC3) plays a key role in how the body metabolizes triglycerides. Mice that lack the APOC3 gene tend to have lower blood triglyceride levels, whereas mice that have high amounts of APOC3 tend to have higher blood triglyceride levels. In humans, some variants of APOC3 are associated with having lower blood triglyceride levels and reduced risk for atherosclerosis and heart disease.

SNPs Involved

rs2542052(A;C)

Less noteworthy

These genotypes are normal.

Gene	SNPs involved	Status	More information
GHR	rs6873545(T;T)	Normal lifespan, increased risk of low bone density in women	**This genotype, rs6873545(T;T), is common. People with this genotype typically live a normal lifespan. In women, this genotype may increase risk for low bone density.** In a study of more than 300 healthy teenage girls and post-menopausal women, those who carried the **T;T** form of the rs6873545 variant of the GHR genetended to have lower total body bone mineral density than those who carried the **C;C** alleles. Lower bone density is associated with increased risk and severity of osteoporosis, a condition common in older women.

- Read more about rs6873545 on SNPedia

GHR

The growth hormone receptor, or GHR, is a type of cell-signaling protein found in many cells of the body, especially liver cells. When a substance called growth hormone binds to this receptor, it triggers the growth and division of cells. It also leads to the production of another important growth-promoting hormone called insulin-like growth factor 1, or IGF-1. Growth hormone and IGF-I work together to play key roles in metabolism, including how the body uses and stores carbohydrates, proteins, and fats from food. In some people, one part of the GHR gene (called exon 3) is missing. In these people, GHR signaling is more active, which may increase risk of some diseases and decrease risk of others.

SNPs Involved

rs6873545(T;T)

FOXO3 | rs1935949(C;C) | Associated with normal lifespan

Forkhead box O3 protein (FOXO3) is a transcription factor involved in the regulation of genes involved in many cellular processes, including DNA repair, tumor suppression, immune function, and resistance to oxidative stress. Some variants of *FOXO3* are associated with longevity in humans.

This genotype, rs1935949(C;C), has been associated with a normal lifespan.

There are common polymorphisms in the *FOXO3* gene, which codes for the forkhead box O3 protein. The variant form (**T**) of the rs1935949 polymorphism is located in the intronic region of the gene.

The (**C;C**) genotype is common, and carriers of this genotype typically live a normal lifespan. However, people with variants of this genotype may live longer. For example, in a study of elderly Caucasian men and women, individuals who carried the (**C;T**) or (**T;T**) genotypes were 27% or 46% more likely to achieve older age, respectively, especially among females.

- Read more about rs1935949 on SNPedia

SNPs Involved

rs1935949(C;C)

IGF1R | rs34516635(G;G) | Associated with normal lifespan

This genotype, rs34516635(G;G), is common. People who carry this genotype typically live a normal lifespan. However, in a study of 384 Ashkenazi Jews between the ages of 95 and 108 years, those who carried one or more of the **A** alleles (**A;A** or **A;G**) of the rs34516635 variant of the IGF-1R gene were more likely to achieve older age, especially females.

- Read more about rs34516635 on SNPedia

IGF-1 Receptor

Insulin-like growth factor-1 (IGF-1) is a protein produced by the liver and many other tissues in the body. Its molecular structure is very similar to that of insulin – hence the name. IGF-1 acts as a hormone and plays a key role in growth. When IGF-1 binds to its receptor, known as the insulin-like growth factor-1 receptor (IGF-1R), IGF-1 activates several cell signaling pathways, some of which may contribute to biological aging.

SNPs Involved

rs34516635(G;G)

TP53 | rs1042522(G;G) | Associated with normal lifespan

This genotype, rs1042522(G;G), is common. People with this genotype typically live a normal lifespan. However**,** people who carry variants of this genotype often live longer. In a study of more than 9,000 Danish older adults, those who carried one or more of the **C** alleles (**C;C** or **C;G)** of the rs1042522 variant of the TP53 gene tended to live longer. Those who carried *both* **C** alleles tended to live approximately 3 years longer than those who carried both of the **G** alleles.

- Read more about rs1042522 on SNPedia

TP53

Tumor protein 53, often called TP53 or p53, is a tumor suppressor protein located in the nucleus of cells throughout the body, where it binds to DNA. If the DNA in a cell is mutated or damaged, p53 helps determine whether the cell's DNA will be repaired or whether the cell will undergo apoptosis, a type of programmed cell death. In this way, p53 helps prevent the development of tumors. Mutations in p53 are common, occurring in more than 50% of all tumors.

However, longevity may depend on a balance between tumor suppression and cell renewal mechanisms. For example, mice that have high levels of p53 tend to be cancer free but they age quickly and have shorter lifespans. Research in humans suggests that some variants of p53 protect against cancer but at the cost of longevity.

			SNPs Involved rs1042522(G;G)
CDKN2B-AS1	rs2811712(A;A)	Normal risk for physical impairment with age	**This genotype, rs2811712(A;A), is common. People with this genotype have normalrisk of physical impairment with age.** However, people with variants of this genotype have less risk for physical impairment. For example, in a study of nearly 3,000 older adults, those who carried the **A;G** form of the rs2811712 variant of the CDKN2B-AS1 gene had an approximately 1.5-fold lower risk of experiencing physical impairment with age. • Read more about rs2811712 on SNPedia **CDKN2B-AS1** CDKN2B-AS is a long, non-coding section of RNA. (Non-coding RNAs don't encode new proteins; rather, they regulate gene expression at the transcriptional and post-transcriptional level.) CDKN2B-AS may play a role in several conditions associated with aging, including impaired physical function, cardiovascular disease, diabetes, and Alzheimer's disease. SNPs Involved rs2811712(A;A)
SIRT1	rs7896005(A;G)	Normal lifespan	Sirtuin1(SIRT1) is a member of the sirtuin protein family. Sirtuins regulate a variety of metabolic processes, including the release of insulin, mobilization of lipids, response to stress, and modulation of lifespan. Sirtuins are also involved in telomere maintenance pathways. Telomeres are specific repeated sequences of nucleotides added to the ends of chromosomes to protect them from degradation and prevent them from binding to other chromosomes. Telomeres shorten with age, and their length is associated with metabolic health. **This genotype, rs7896005(A;G), has been associated with normal lifespan.** There are common polymorphisms in the *SIRT1* gene, which codes for the sirtuin1 enzyme. The rs7896005 polymorphism is located in the intron region of the gene and may affect gene splicing. Researchers studying SIRT1 and its involvement in telomere maintenance (n = 224 nonagenarians (90 to 103 years old) and 293 young controls (21 to 59 years old) observed that the **A** allele was associated with longer telomeres. Investigators observed that the **A** allele was more common in the long-lived group than in the younger individuals. Specifically, they found that subjects with the (**A;A**) genotype were two-fold more likely to be in the long-lived group than those with the (**A;G**) or (**G;G**) genotypes. When the researchers repeated this experiment in centenarians (≥98 years old), the (**A;A**) genotype was associated with longevity at near significant levels. The authors propose that the **A** allele upregulates the SIRT1 enzyme facilitating more efficient telomere maintenance, which may have implications for longevity. A recent study illustrated the interlinked relationship between telomeres and sirtuins. In a mouse model of liver disease, researchers knocked out the telomerase gene and observed that sirtuin expression decreased. When they added an NAD+ precursor (a compound known to stimulate sirtuins) sirtuins, particularly SIRT1, increased, and telomeres stabilized. Researchers hypothesize that compromised telomeres reduce the expression of sirtuins in a feedforward loop, which results in further telomere shortening, possibly contributing to disease progression. *Exercise and fasting* The cofactor nicotinamide adenine dinucleotide (NAD+) regulates the activity of sirtuin enzymes. During exercise and fasting, cellular NAD+ levels rise and activate the expression of sirtuin genes. An increase in sirtuin enzyme activity can delay the processes of aging. Supplemental nicotinamide riboside (NR), a precursor to NAD+, has been shown to raise white blood cell NAD+ levels in humans although more research is needed to determine if NAD+ levels increase in other tissues. Read more about the NAD+ precursors nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN). • Read more about rs7896005 on SNPedia SNPs Involved rs7896005(A;G)
SIRT1	rs12778366(T;T)	Associated with a normal lifespan	Sirtuin1(SIRT1) is a member of the sirtuin protein family. Sirtuins regulate a variety of metabolic processes, including release of insulin, mobilization of lipids, response to stress, and modulation of lifespan. Sirtuins also influence circadian clocks and mitochondrial biogenesis. **This genotype, rs12778366(T;T), has been associated with a normal lifespan.** There are common polymorphisms in the *SIRT1* gene, which codes for the sirtuin1 enzyme. The variant form (**C**) of the rs12778366 polymorphism, located in the promoter region of the gene, is thought to increase gene expression which may result in more SIRT1 enzyme being produced. Researchers followed Dutch adults (n=1,390) for 18 years and observed that carriers of the **C** allele had a 30 percent reduced mortality risk as compared to individuals with the (**T;T**) genotype. The authors suggest that SIRT1 may be acting by regulating glucose metabolism. This hypothesis was supported in a second cohort (n=535 males) whereby **C** allele carriers had better glucose tolerance than subjects with the (**T;T**) genotype.

Exercise and fasting
The cofactor nicotinamide adenine dinucleotide (NAD+) regulates the activity of sirtuin enzymes. During exercise and fasting, cellular NAD+ levels rise and activate the expression of sirtuin genes. An increase in sirtuin enzyme activity can delay the processes of aging.

Supplemental nicotinamide riboside (NR), a precursor to NAD+, has been shown to raise white blood cell NAD+ levels in humans although more research is needed to determine if NAD+ levels increase in other tissues. Read more about the NAD+ precursors nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN).

- Read more about rs12778366 on SNPedia

SNPs Involved

rs12778366(T;T)

Unavailable

Depending on the dataset you provided for report generation, not all possible report entries may be available. *This is normal.* In this case, the following groups were excluded because the data you upload did not contain the requisite SNPs:

GHR, FOXO3, SIRT1

Methylation Report v1

Source: Cooper_Beaman_23andmenew_v4_Full_20190517100124.zip
Created at February 23 at 3:46 PM PDT

Genotypes related to choline and folate metabolism.

Noteworthy

These genotypes are the ones that are potentially worth being aware of.

Gene	SNPs involved	Status	More information
MTHFR	rs1801131(C;C) rs1801133(C;C)	Risk for altered folate metabolism	There are common polymorphisms in the MTHFR gene (5-methylenetetrahydrofolate reductase) that converts 5,10-methylenetetrahydrofolate into 5-methylfolate using riboflavin (vitamin B2) as a cofactor. Folate serves as a precursor in two important pathways: 1. the synthesis of the DNA nucleotide thymine. 2. the generation of methyl groups which are important in epigenetics and also the conversion of homocysteine to methionine, which requires vitamin B12 as a cofactor. MTHFR catalyzes the initial step of this second pathway. **This genotype, rs1801131(C;C) and rs1801133(C;C), has two variant alleles at one polymorphisms and is normal at the other. This genotype may be associated with decreased folate levels.** The rs1801133 polymorphism is in the catalytic domain and encodes for a thermolabile form of the MTHFR enzyme having reduced activity. The rs1801131 polymorphism is in the regulatory domain of the gene and encodes a form of the enzyme that is not thermolabile. This particular polymorphism is thought to be less relevant unless found in combination with the other polymorphism. Even thought decreased enzyme activity may be seen, this genotype has not be shown to increase homocysteine levels in the blood. Elevated homocysteine levels have previously been associated with a variety of vascular diseases including coronary artery disease, stroke, and dementia. A recent meta-analysis showed that moderate elevation of homocysteine did not significantly increase coronary heart disease. It should be noted that research concerning the health-related impacts associated with these common MTHFR polymorphisms is still at the investigational stage. This has led 23andMe to release a statement cautioning against such inferences and supporting folate supplementation only for pregnant women. This genotype complex involves the two most common MTHFR polymorphisms. There are other possible mutations in the MTHFR gene, some of which are thought to lead to serious conditions, such as homocystinuria, which is usually diagnosed in childhood. This is not what this loci refers to. **Supplementation and diet.** *5*-methylfolate*, methylcobalamin, and riboflavin.* Supplementing with 5-methylfolate (MTHF), methylcobalamin (vitamin B12), and riboflavin (vitamin B2) may bring down homocysteine levels in these individuals**.** One study showed that **supplementation with 480µg MTHF per day significantly reduced the mean plasma tHcy concentration by 7% after 4 weeks. Despite these results, clinical trials have not been able to show that this decrease was associated with decreased disease risk.** *Betaine and reductions in homocysteine.* Choline is a precursor of betaine. Betaine aids in the remethylation of homocysteine to methionine via the enzyme betaine-homocysteine methyltransferase (BHMT), which serves to lower homocysteine levels in the blood. A meta-analysis showed that betaine supplementation of 4 to 6 g/d lowered plasma homocysteine concentration by 1.23 µmol/L in healthy adults. Reducing plasma homocysteine levels by 5 µmol/L may decrease the risk of cardiovascular disease by 20% to 30% and stroke by 40% to 60%. Supplementation with betaine was also found to increase total and LDL cholesterol by 5 to 10 mg/dL in some studies. However, for individuals with hyperhomocysteinemia, who may be at increased risk for cardiovascular disease, the beneficial homocysteine lowering effects of betaine supplementation likely outweigh the clinically minor increase in serum lipids. Blood biomarkers such as plasma homocysteine levels and blood lipids can aid the clinician in determining if betaine supplementation is a beneficial course of action. *TMAO and choline supplementation* Recent research has suggested that nutrients such as choline, phosphatidylcholine, L-carnitine and betaine are metabolized by gut bacteria to generate trimethylamine (TMA), which is then converted into trimethylene N-oxide (TMAO) by the liver. Elevated plasma levels of TMAO may enhance platelet aggregation (clotting) and increase heart disease risk. However, the metabolism of TMAO is complex and still poorly understood in humans. Furthermore, choline is an essential nutrient in the human diet. • Read more about rs1801131 on SNPedia • Read more about rs1801133 on SNPedia SNPs Involved rs1801131(C;C) rs1801133(C;C)

MTRR	rs1801394(G;G)	Increased risk for hyperhomocysteinemia and altered choline metabolism	There are common polymorphisms in the MTRR gene that code for the enzymemethionine synthase reductase, which catalyzes the conversion of the inactive form of another enzyme, methionine synthase (MTR), to its active form using riboflavin (vitamin B2) as a cofactor. MTR is involved in the remethylation of homocysteine to methionine with cobalamin (vitamin B12) participating as a cofactor. This reaction is of utmost importance as MTR plays a pivotal role in folate metabolism and methionine cycling. **This genotype, rs1801394(G;G), may be associated with hyperhomocysteinemia and altered choline metabolism.** This polymorphism encodes for an MTRR enzyme with a reduced affinity for MTR resulting in less efficient reactivation of MTR, possibly resulting in elevated homocysteine levels. Some associations have been made between rs1801394 and hyperhomocysteinemia especially in combination with low vitamin B12 levels and the *MTHFR* rs1801133 variant. This polymorphism may be associated with an increased risk for neural tube defects (can be circumvented by folate supplementation), 1.4X risk for meningioma (a form of brain cancer) and altered choline metabolism. This polymorphism has been shown to influence the way choline is partitioned between the Cdp-choline pathway and betaine synthesis. At recommended adequate intake (AI) levels of choline, women with this variant shuttled more choline towards phosphatidylcholine synthesis at the expense of betaine synthesis. However, at levels above the AI, normal partitioning was restored, suggesting that women with this polymorphism may benefit from dietary choline intake above the current AI levels. These recent studies may prompt the Institute of Medicine (IOM) to refine the dietary recommendations to include individuals with increased choline needs. **Dietary choline intake.** Choline is found in foods such as eggs, meat, fish and cruciferous vegetables. Strict vegetarians may need to pay special attention to meeting their choline needs. The Food and Nutrition Board (FNB) of the Institute of Medicine (IOM) has established the Adequate Intake (AI) for choline for men (550 mg) and for women (425 mg) during pregnancy (450 mg) and lactation (550 mg). **Betaine and reductions in homocysteine.** One of the functions of choline is to serve as a precursor of a compound known as betaine or trimethylglycine. Betaine aids in the remethylation of homocysteine to methionine via the enzyme betaine-homocysteine methyltransferase (BHMT), thus serving to lower homocysteine levels in the blood. Multiple studies have now shown that high dose (4-6 grams per day) betaine supplementation can significantly lower plasma homocysteine concentrations by as much as 40% after six weeks, reducing an important risk factor for atherogenesis. High-dose betaine, however, has been associated with a slight *increase* in total and LDL cholesterol by 5 to 10 mg/dL in some studies. Other studies have found that a more conservative and *dietarily* attainable dose of just 1.5 grams per day can also lower homocysteine levels by as much as 23% after six weeks Foods rich in betaine include quinoa, spinach, and beets. **Vitamin B12 and B2.** Cobalamin (vitamin B12) and riboflavin (vitamin B2) balance is thought to be an important factor in people with this polymorphism. When B12 status was low, those with the G allele had higher homocysteine levels than those with the (A;A) genotype. Individuals susceptible to low vitamin B12 status include older adults, those with digestive issues (Crohn's, colitis), post gastric bypass patients and those following vegan diets. *TMAO and choline supplementation* Recent research has suggested that nutrients such as choline, phosphatidylcholine, L-carnitine and betaine are metabolized by gut bacteria to generate trimethylamine (TMA) which is then converted into trimethylene N-oxide (TMAO) by the liver. Elevated plasma levels of TMAO may enhance platelet aggregation (clotting) and increase heart disease risk. However, the metabolism of TMAO is complex and still poorly understood in humans. Furthermore, choline is an essential nutrient in the human diet. • Read more on SNPedia SNPs Involved rs1801394(G;G)

Less noteworthy

These genotypes are normal.

Gene	SNPs involved	Status	More information
MTHFD1L	rs6922269(G;G)	Normal risk for cardiovascular disease	There are common polymorphisms in the MTHFD1L gene that codes for an enzyme (5,10-methylenetetrahydrofolate dehydrogenase NADP+ dependent 1-like) involved in the synthesis of tetrahydrofolate (THF) in the mitochondria. THF is important in several biosynthetic pathways as well as cellular methylation by aiding in the regeneration of methionine from homocysteine. **This genotype, rs6922269 (G;G), is associated with normal risk for cardiovascular disease (CAD).** The polymorphism occurs within the intronic region of the gene and was associated with increased risk for CAD in two large studies (Samani et al,2007) and (Wellcome Trust Case Control Consortium) in carriers of the **A** allele. In addition, a meta-analysis of 12 studies showed that this risk association was not correlated with conventional biomarkers for CAD such as blood lipids, glucose

			etc. This polymorphism was found to be associated with early-onset CAD in a study of1,988 subjects with an MI or vascular surgery before age 66 and with a strong family history of CAD as compared to control subjects. The **A** allele was found in approximately 25% of the study population and the study showed a 23% increased risk of CAD per copy of the **A** allele. The authors suggest rs6922269 may increase CAD risk by altering plasma homocysteine levels. • Read more about rs6922269 on SNPedia SNPs Involved rs6922269(G;G)
MTHFD1	rs2236225(C;C)	Normal and not associated with increased risk of choline deficiency at adequate dietary choline intake levels	There are common polymorphisms in the MTHFD1 gene that codes for a trifunctional enzyme (5,10-methylenetetrahydrofolate dehydrogenase) involved in folate metabolism. Folate and choline metabolism are closely linked and changes in folate status can result in changes in choline status and vice versa. Choline is involved in three major pathways: 1. Phosphatidylcholine synthesis via the CDP-choline pathway 2. Methyl donor to form betaine which facilitates the methylation of homocysteine to methionine, important in DNA synthesis 3. Acetylcholine synthesis **This genotype, rs2236225(C;C), is not associated with an increased risk of choline deficiency at adequate dietary choline intake levels.** Individuals with the (C;T) and (T;T) genotype, however, may have increased risks for neural tube defects, cancer, choline deficiency and susceptibility to non alcoholic fatty liver disease (NAFLD) when individuals are deprived of choline. **Lifestyle interactions** **Dietary choline intake.** Choline is found in foods such as eggs, meat, fish and cruciferous vegetables. Strict vegetarians may need to pay special attention to meeting their choline needs. The Food and Nutrition Board (FNB) of the Institute of Medicine (IOM) has established the Adequate Intake (AI) for choline for men (550 mg) and for women (425 mg) during pregnancy (450 mg) and lactation (550 mg). *TMAO and choline supplementation* Recent research has suggested that nutrients such as choline, phosphatidylcholine, L-carnitine and betaine are metabolized by gut bacteria to generate trimethylamine (TMA), which is then converted into trimethylene N-oxide (TMAO) by the liver. Elevated plasma levels of TMAO may enhance platelet aggregation (clotting) and increase heart disease risk. However, the metabolism of TMAO is complex and still poorly understood in humans. Furthermore, choline is an essential nutrient in the human diet. • Read more on SNPedia SNPs Involved rs2236225(C;C)

Unavailable

Depending on the dataset you provided for report generation, not all possible report entries may be available. *This is normal.* In this case, the following groups were excluded because the data you upload did not contain the requisite SNPs:

PEMT

Telomere Report v1

Source: Cooper_Beaman_23andmenew_v4_Full_20190517100124.zip
Created at February 23 at 3:46 PM PDT

This report is focused on SNPs related to telomere length. Telomeres are found at the ends of chromosomes and they protect them from degradation and damage. Telomeres shorten with age and their length is a biomarker for aging and is associated with risks for certain age-related diseases, such as cardiovascular disease. While telomere length is in part genetically determined, both environmental and lifestyle factors may play a role in delaying telomere shortening or even lengthening them.

Noteworthy

These genotypes are the ones that are potentially worth being aware of.

Gene	SNPs involved	Status	More information
OBFC1	rs9420907(A;A)	Shorter telomere length	Telomeres are specific repeated nucleotide sequences found at the ends of chromosomes to protect them from degradation and prevent them from fusing to other chromosomes. Telomeres shorten with age and their length is associated with risks for certain age-related diseases such as cardiovascular disease. OBFC1 (oligonucleotide/oligosaccharide-binding fold-containing protein 1) is an enzyme thought to be involved in telomere maintenance. **This genotype, rs9420907(A;A), has been associated with shorter telomere length.** There are common polymorphisms near the *OBFC1* gene, which codes for the oligonucleotide/oligosaccharide-binding fold-containing protein 1. The **A** allele is the variant form of the rs9420907 polymorphism. In a genome-wide association study (GWAS) meta-analysis involving 37,684 individuals of European descent, the **A** allele was associated with shorter mean leukocyte telomere length (LTL). Each copy of the **A** allele resulted in a shortening of approximately 82.8 base pairs, which the authors report as equivalent to 2.76 years of aging. *Ways to reduce telomere attrition* While telomere length is in part genetically determined, both environmental and lifestyle factors may play a role in delaying telomere shortening or even lengthening them. *Stress reduction* Chronic anxiety and stress have been associated with shorter telomeres and thus stress reducing practices such as meditation, exercise or yoga may be beneficial. *Nutrition* Diet quality may play a role in maintaining telomere length. Reducing added sugar, especially sugar-sweetened beverages, processed foods and processed meats may all be beneficial. Dietary omega-3 fatty acids may also play a role in protecting against cellular aging. One research study demonstrated that individuals adhering more closely to a Mediterranean diet had longer telomeres. Another study showed that individuals experiencing weight loss following a five-year intervention on the Mediterranean diet had longer telomeres. *Other* Try to get adequate sleep. Don't smoke. Avoid being sedentary. • Read more about rs9420907 on SNPedia SNPs Involved rs9420907(A;A)

Less noteworthy

These genotypes are normal.

Gene	SNPs involved	Status	More information
TERT	rs2736100(G;G)	Normal telomere length	Telomeres are specific repeated nucleotide sequences found at the ends of chromosomes to protect them from degradation and to prevent them from fusing to other chromosomes. Telomeres shorten with age and their length is associated with risks for certain age-related diseases such as cardiovascular disease. Telomerase, an enzyme capable of lengthening telomeres, contains a catalytic subunit known as telomerase reverse transcriptase (TERT) and an RNA template (TERC). **This genotype, rs2736100(G;G), has been associated with normal telomere length.** There are common polymorphisms near the *TERT* gene, which codes for the catalytic subunit of the telomerase enzyme. The variant form (**T**) of the rs2736100 polymorphism is located in the intronic region of the gene.

In a genome-wide association study (GWAS) involving 25,842 individuals of European descent, the **T** allele was associated with shorter mean leukocyte telomere length (LTL). Each copy of the **T** allele resulted in a shortening of approximately 94.2 base pairs which the authors report as equivalent to 3.14 years of aging.

Ways to reduce telomere attrition
While telomere length is in part genetically determined, both environmental and lifestyle factors may play a role in delaying telomere shortening or even lengthening them.

Stress reduction
Chronic anxiety and stress have been associated with shorter telomeres and thus stress reducing practices such as meditation, exercise or yoga may be beneficial.

Nutrition
Diet quality may play a role in maintaining telomere length. Reducing added sugar, especially sugar-sweetened beverages, processed foods and processed meats may all be beneficial. Dietary omega-3 fatty acids may also play a role in protecting against cellular aging. One research study demonstrated that individuals adhering more closely to a Mediterranean diet had longer telomeres. Another study showed that individuals experiencing weight loss following a five-year intervention on the Mediterranean diet had longer telomeres.

Other
Try to get adequate sleep. Don't smoke. Avoid being sedentary.

- Read more about rs2736100 on SNPedia
  * These alleles have been adjusted for consistency with SNP orientation. Read more about orientation.

SNPs Involved

rs2736100(G;G)

TERC	rs10936599(C;C)	Normal telomere length

Telomeres are specific repeated nucleotide sequences found at the ends of chromosomes to protect them from degradation and prevent them from fusing to other chromosomes. Telomeres shorten with age and their length is associated with risks for certain age-related diseases such as cardiovascular disease. Telomerase, an enzyme capable of lengthening telomeres, contains a catalytic subunit known as telomerase reverse transcriptase (TERT) and an RNA template (TERC).

This genotype, rs10936599(C;C), has been associated with normal telomere length.

There are common polymorphisms near the *TERC* gene, which codes for the RNA subunit of the telomerase enzyme. This gene is responsible for re-building telomeres and thus stemming some of the natural loss associated with aging. The variant form (**T**) of the rs10936599 polymorphism is located upstream of the gene and may affect telomerase activity.

In a genome-wide association study (GWAS) meta-analysis involving 37,684 individuals of European descent, the **T** allele was associated with shorter mean leukocyte telomere length (LTL). Each copy of the **T** allele resulted in a shortening of approximately 117.3 base pairs, which the authors report as equivalent to 3.91 years of aging.

In a separate cohort, researchers replicated the association between the **T** allele and shorter telomere length. A subsequent case-control study involving 1,628 major depressive disorder (MDD) cases and 1,140 controls showed a correlation between the **T** allele and risk of early-onset MDD. While the authors state that more research is needed, they propose that carriers of the **T** allele with a family history of MDD may benefit from habits that limit telomere attrition. The authors recommend following a healthy diet, engaging in physical activity, and avoiding stress.

Ways to reduce telomere attrition
While telomere length is in part genetically determined, both environmental and lifestyle factors may play a role in delaying telomere shortening or even lengthening them.

Stress reduction
Chronic anxiety and stress have been associated with shorter telomeres and thus stress reducing practices such as meditation, exercise or yoga may be beneficial.

Nutrition
Diet quality may play a role in maintaining telomere length. Reducing added sugar, especially sugar-sweetened beverages, processed foods and processed meats may all be beneficial. Dietary omega-3 fatty acids may also play a role in protecting against cellular aging One research study demonstrated that individuals adhering more closely to a Mediterranean diet had longer telomeres Another study showed that individuals experiencing weight loss following a five-year intervention on the Mediterranean diet had longer telomeres.

Other
Try to get adequate sleep. Don't smoke. Avoid being sedentary.

- Read more about rs10936599 on SNPedia

SNPs Involved

rs10936599(C;C)

Unavailable

Depending on the dataset you provided for report generation, not all possible report entries may be available. *This is normal.* In this case, the following groups were excluded because the data you upload did not contain the requisite SNPs:

TERC, TERC, RTEL1, ACYP2, NAF1

Metabolism Report v5

Source: Cooper_Beaman_23andmenew_v4_Full_20190517100124.zip
Created at February 23 at 4:41 PM PDT

Many different single nucleotide polymorphisms (SNPs) can affect how the body responds to various types of fat (ie. saturated fat, polyunsaturated fat, monounsaturated fat) and carbohydrates (ie. complex carbohydrates, simple carbohydrates).

Learn about polymorphisms that are involved in:

- Elevating blood pressure and blood glucose levels in response to high saturated fat intake
- Increasing fat deposits on the liver (fatty liver) in response to high simple carbohydrate intake
- Increasing LDL cholesterol and triglycerides in response to high in saturated fat intake
- Postprandial blood glucose levels in response to high saturated fat and simple carbohydrate intake
- Increased obesity risk and yet lower risk for cardiovascular disease with high saturated fat intake

Noteworthy

These genotypes are the ones that are potentially worth being aware of.

Gene	SNPs involved	Status	More information
UCP1	rs1800592(A;G)	Reduced resting metabolic rate	Uncoupling protein 1 (UCP1) is a protein found in the inner mitochondrial membrane that is important in thermogenesis. The UCP1 gene is only expressed in brown adipose tissue, resulting in abundant levels of the protein in this tissue which contains numerous mitochondria. UCP1 is thought to play an important role in energy expenditure and disruptions in this process have been reported to be involved in obesity. UCP1 acts by dissipating energy as heat, rather than ATP production, in a process known as non-shivering thermogenesis. This polymorphism, rs1800592 (also known as -3826A/G), is located in the promoter region of the UCP1 gene. The variant form has been reported to result in diminished promoter activity, decreased gene expression, and thus, lower levels of the UCP1 protein. **This genotype, rs1800592(A;G), is associated with reduced resting metabolic rate.** In a study of 82 young females (20-22 years old), individuals with the **(G;G)** and **(A;G)** genotypes were observed to have lower resting energy expenditure (REE), as measured by indirect calorimetry, when compared to **(A;A)** individuals. Brown adipose tissue (BAT) activity has been shown to decrease with age, leading researchers to suggest that this may contribute to the tendency for body fat to accumulate with age. *Cold Exposure* Brown adipose tissue was shown to be activated in a mouse model following short-term cold exposure, resulting in an increased clearance of triglycerides from the blood. For this reason, this mechanism could plausibly be beneficial for the reduction of triglycerides or possibly even the treatment of obesity. In recent human studies, a 10-day cold acclimation protocol was shown to increase BAT volume by 37% while a mild but prolonged cold exposure (5 hours at 16°C) increased BAT activity resulting in a 16% increase in resting energy expenditure. *Fish Oil* In studies using mice, fish oil, which is rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), was reported to induce UCP1 gene expression. Mice fed fish oil gained less weight and had less abdominal fat than those on a control diet. This might suggest that supplementation with fish oil or increasing dietary fish intake could be beneficial for those with the variant form of this polymorphism **(A;G)** or **(G;G)**. • Read more about rs1800592 on SNPedia SNPs Involved rs1800592(A;G)
UCP1	rs6536991(C;T)	Associated with slightly increased bmi	Uncoupling protein 1 (UCP1) is a protein found in the inner mitochondrial membrane that is important in thermogenesis. The UCP1 gene is only expressed in brown adipose tissue, resulting in abundant levels of the protein in this tissue which contains numerous mitochondria. UCP1 is thought to play an important role in energy expenditure and disruptions in this process have been reported to be involved in obesity. UCP1 acts by dissipating energy as heat, rather than ATP production, in a process known as non-shivering thermogenesis. The variant form of this polymorphism rs6536991, found within the intron of the gene, may result in lower levels of the UCP1 protein.

This genotype, rs6536991(C;T), is associated with slightly increased BMI.

In a Brazilian population the **(T;T)** genotype was associated with obesity when compared to those carrying the **C** allele. In a study of 126 obese and 113 non-obese individuals, those with the **(T;T)** genotype had BMIs that were, on average, 3 kg/m2 higher than those with the **(C;C)** genotype. A dose-dependent relationship was observed, whereby those with two copies of the **T** allele **(T;T)** had higher BMIs than those with only one copy **(C;T)**.

Brown adipose tissue (BAT) activity has been shown to decrease with age, leading researchers to suggest that this may contribute to the tendency for body fat to accumulate with age.

Cold Exposure
Brown adipose tissue was shown to be activated in a mouse model following short-term cold exposure, resulting in an increased clearance of triglycerides from the blood. For this reason, this mechanism could plausibly be beneficial for the reduction of triglycerides or possibly even the treatment of obesity.

In recent human studies, a 10-day cold acclimation protocol was shown to increase BAT volume by 37% while a mild but prolonged cold exposure (5 hours at 16°C) increased BAT activity resulting in a 16% increase in resting energy expenditure.

Fish Oil
In studies using mice, fish oil, which is rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), was reported to induce UCP1 gene expression. Mice fed fish oil gained less weight and had less abdominal fat than those on a control diet. This might suggest that supplementation with fish oil or increasing dietary fish intake could be beneficial for those with the variant form of this polymorphism **(C;T)** or **(T;T)**.

- Read more about rs6536991 on SNPedia

SNPs Involved
rs6536991(C;T)

ADIPOQ	rs17300539(G;G)	Lower adiponectin levels and higher risk for obesity	Adiponectin (ADIPOQ) is an anti-inflammatory protein that is secreted by adipose tissue and is thought to be cardioprotective. It plays an important role in glucose and lipid metabolism and has been shown to improve insulin sensitivity. Low levels of adiponectin are associated with obesity and metabolic syndrome.

This genotype, rs17300539(G;G), has been associated with lower adiponectin levels and higher risk for obesity.

There are common polymorphisms in the *ADIPOQ* gene, which codes for the adiponectin protein. The variant form (**A**) of the rs17300539 polymorphism (also known as 11391 G>A), located in the promoter region of the gene, is thought to enhance gene expression resulting in more adiponectin protein being produced.

In a genome-wide association study (GWAS) involving 39,883 individuals, the **A** allele was associated with higher serum adiponectin levels. In the Framingham Offspring Study (n=2,018), **A** allele carriers had higher adiponectin levels than subjects with the (**G;G**) genotype.

In another study (n=1,083), individuals with the **A** allele had higher serum adiponectin levels and lower insulin resistance, BMI, and body weight when compared to subjects with the (**G;G**) genotype. When researchers examined dietary intake, they observed that **A** allele carriers with the highest mono-unsaturated fatty acid (MUFA) intake (≥ median) had lower BMI and obesity risk than (**G;G**) individuals. However, in subjects whose MUFA intake was below the median, **A** allele carriers did not have a reduction in obesity risk compared to individuals with the (**G;G**) genotype.

Maintenance of weight loss
Researchers studying a group of 180 obese Spanish individuals observed that subjects with the (**G;G**) genotype exhibited clinical signs of insulin resistance and metabolic syndrome when compared to (**A;A**) and (**A;G**) subjects. Individuals with the (**G;G**) genotype also had higher HOMA-IR (a biomarker of insulin resistance), insulin and triglyceride levels than carriers of the **A** allele. After following a low-calorie diet for 8 weeks, these unfavorable biomarkers disappeared. However, when reexamined 32 weeks later, the metabolic risk characteristics had returned in the (**G;G**) individuals while those with the **A** allele were protected from weight regain.

Longevity
Researchers measured the serum adiponectin levels of centenarians (n=118), their offspring (n=228) and unrelated controls, <95 years of age (n=78). Investigators observed that long-lived subjects and their offspring had higher adiponectin levels than controls. The **A** allele of this polymorphism is over-represented among exceptionally long-lived male subjects as compared to control individuals. The authors conclude that the **A** allele may contribute to exceptional longevity, particularly in men, possibly due to anti-inflammatory or anti-atherogenic effects.

Weight loss and exercise
Weight loss by lifestyle changes such as diet and exercise are shown to increase adiponectin levels. A sedentary lifestyle tends to be associated with lower adiponectin levels, whereas various types of exercise have been shown to be beneficial towards increasing adiponectin. In one study, increased adiponectin levels were observed after just one week of moderately intense aerobic activity.

Dietary Factors

Adiponectin levels in type 2 diabetics were shown to increase when consuming aMediterranean diet. Increasing dietary intake of monounsaturated fatty acids (MUFAs) such as those found in olive oil, avocados and nuts, as well as, polyunsaturated fatty acids (PUFAs) as found in fatty fish may contribute to increased adiponectin.

There are studies which demonstrate that both fish oil and fiber supplementation are associated with increased adiponectin levels. In addition, there is a positive relationship between caffeinated coffee intake and higher adiponectin levels.

In contrast, smoking may have detrimental effects on adiponectin levels and may negate the positive effects of an improved diet.

Intermittent Fasting
Time-restricted feeding has been shown to increase adiponectin levels in mouse and rat models.

- Read more about rs17300539 on SNPedia

SNPs Involved

rs17300539(G;G)

PNPLA3	rs738409(C;G)	Slight increased risk for fatty liver and alcoholic liver disease	There are common polymorphisms in the patatin-like phospholipase domain-containing protein 3 gene that codes for the PNPLA3 protein also known as adiponutrin. Adiponutrin is thought to have a lipase activity with a role in the hydrolysis of glycerolipids as well as a lipogenic activity. The variant allele appears to disrupt the triglyceride hydrolysis capability. **This genotype, rs738409 (C;G), is associated with an increased risk for fatty liver and alcoholic liver disease.** The variant **C** allele was shown in a meta-analysis to be associated with risk of NAFLD (non-alcoholic fatty liver disease) and the progression to NASH (non-alcoholic steatohepatitis fat) in both adults and children. In a study of 300 obese Hispanic children, **(C;C)** individuals had 2.4 times more liver fat than those with the **(G;G)** genotype and 1.7 times more than **(C;G)** children. In a study of 153 Hispanic children, there was a positive correlation between hepatic fat deposition and both total and added sugar intake in individuals with the **(C;C)** genotype that was not seen in **(C;G)** or **(G;G)** genotypes. These results suggest that **(C;C)** individuals would benefit from reduced dietary sugar intake to prevent excessive liver fat accumulation. Furthermore, a study of 127 children and adolescents, showed that in those with the (**C;C**) genotype, the amount of liver fat was positively correlated with omega-6 to omega-3 fatty acid (FA) intake ratio. This suggests that (**C;C**) individuals may benefit from either decreasing dietary omega-6 or increasing omega-3 rich foods. Supplementing with omega-3 FAs may also be beneficial and studies have also shown that omega-3 FA supplementation can reverse hepatic steatosis. In an intervention study,16 adults (9 **C;C** and 7 **G;G**) were fed a high-carbohydrate diet for 3 weeks, followed by a hypocaloric diet for 6 months. It was found that non-variant individuals showed a positive correlation between fat found in the blood and fat deposited in the liver, whereas, those with the **(C;C)** genotype did not, suggesting that in these **(C;C)** individuals, the fat synthesized from *de novo* lipogenesis (from the high carbohydrate intake) is retained preferentially in the liver. This polymorphism has also been shown to affect the way the body responds to alcohol consumption. In a Mestizo population, the **C** allele was found to be strongly associated with alcoholic cirrhosis and increased susceptibility to hepatic injury. In a study of 384 at-risk alcohol drinkers, it was shown that the risk of cirrhosis was increased three-fold in those with the **C** allele who initiated excessive alcohol consumption prior to the age of 24 as compared to those who started drinking after age 24. In a randomized controlled study of 31 adults with type 2 diabetes and NAFLD, individuals were able to “markedly” reduce hepatic fat content with either aerobic or resistance training over a 4-month period. **Increasing omega-3 fatty acids and decreasing added sugar.** Individuals with this polymorphism may benefit from decreasing dietary carbohydrates, especially added sugars. It may be helpful to consume a balanced intake ratio of omega-6 to omega-3 FAs. Many people eat a diet high in omega-6 FAs, therefore, decreasing omega-6 rich foods and incorporating more omega-3 FAs will address this imbalance. Furthermore, supplementation with omega-3 FAs may be advantageous. Alcohol intake has a more significant deleterious effect on those with this polymorphism, so minimizing alcohol intake may be helpful. It is beneficial to participate in aerobic or resistance training on a regular basis. - Read more about rs738409 on SNPedia.

SNPs Involved

rs738409(C;G)

FGF21	rs838133(C;C)	Preference for salty over sweet foods	Fibroblast Growth Factor 21 (FGF21) is a cytokine hormone involved in glucose and lipid metabolism, as well as energy expenditure. Produced by the liver and adipose tissue, FGF21 has insulin-sensitizing properties, promotes glucose uptake by fat cells and may signal the brain (hypothalamus) to suppress further intake of sugar and alcohol. In adipose tissue FGF21, along with a co-factor βKlotho protein, binds to a receptor on the cell surface and is activated. As a result, GLUT1 transporter expression is increased allowing the cell to take up more glucose. Several conditions, such as NAFLD (non-alcoholic fatty liver disease), obesity, type 2 diabetes, and

metabolic syndrome, are associated with elevated levels of FGF21, leading researchers to speculate that FGF21 resistance may be a problem in these conditions.

Recent research has implicated FGF21 as a stress response hormone that may protect tissues from oxidative stress. Oxidative stress may be either chronic resulting from diseases such as type 2 diabetes, obesity and metabolic syndrome or acute as induced by physical stressors such as exercise, fasting and cold exposure which in turn stimulate antioxidant pathways resulting in a net positive effect. FGF21 may be associated with longevity and healthspan in mammals because of its possible involvement in alleviating many stress and metabolic conditions. The variant form of this polymorphism, rs838133, located in the coding region of the *FGF21* gene, is thought to result in decreased FGF21 function.

This genotype, rs838133(C;C), has been associated with a preference for salty over sweet foods.

In a genome-wide association study (GWAS) of 33,355 individuals of European ancestry, the **T** allele was associated with increased carbohydrate and decreased protein and fat intake, while caloric intake remained the same.

After examining the food intake of 6,134 individuals, the **T** allele was associated with increased sugar intake, as well as, preference for a sweet snack (candy) rather than a fatty-sweet or salty snack. The researchers suggest that because the variant allele carriers preferred candy over fatty-sweets or salty snack foods, FGF21 might be involved in sugar craving. Similarly, in a 23andMe study involving 54,901 individuals, the **C** allele was associated with favoring a salty or savory snack over a sweet snack.

In a clinical study (n = 86), fasting FGF21 plasma levels were 51% higher in individuals who self-reported as being sweet-dislikers as compared to sweet-likers. After a 75g oral sucrose load, FGF21 plasma levels increased 193% above baseline in both groups. The authors speculate that FGF21 may act as a negative regulator of sugar consumption and signal the brain to decrease further intake of sugar. Animal models (mice and non-human primates) illustrate that FGF21, which crosses the blood-brain barrier, regulates sweet preference, possibly via a decrease in dopamine levels (in mice).

- Read more about rs838133 on SNPedia

SNPs Involved

rs838133(C;C)

PGC-1α	rs8192678(A;G)	Slightly reduced cardiorespiratory fitness and slightly increased risk for type 2 diabetes	There are common polymorphisms in the PPAR-gamma-coactivator 1 alpha gene (*PPARGC1A*), also known as *PGC-1α,* which codes for the PGC-1α protein. PGC-1α is a transcriptional cofactor that is involved in mitochondrial biogenesis (production of new mitochondria), as well as modifying the function of existing mitochondria. PGC-1α is also involved in energy metabolism and antioxidant gene expression. The expression of this gene is affected by physiological stimuli such as exercise, fasting and cold exposure. The variant form of this polymorphism, rs8192678, has been reported to decrease gene expression, and thus, yield lower levels of the PGC-1α protein. **This genotype, rs8192678(A;G), may be associated with slightly reduced cardiorespiratory fitness and slightly increased risk for type 2 diabetes.** The A allele is associated with type 2-diabetes in some ethnicities such as Danish, Japanese, South Chinese, and North Indian populations, but not in others, such as Pima Indians, French Caucasians, African Americans, and Haitian Americans. In a study of 565 physically active Mexican-Mestizo adults, carriers of the **A** allele who were obese had an increased risk for pre-diabetes, whereas those with the **A** allele at normal weight showed lower pre-diabetes risk. Therefore, maintaining a healthy weight may diminish the deleterious effects of the variant allele. In a study comparing elite-level Spanish male endurance athletes to unfit male controls, the **A** allele was found in 40% of unfit individuals, 33% of fit individuals and 29% of elite-level endurance athletes. These results suggest that the **A** allele may, in some part, predict aerobic capacity. Carriers of the **A** allele may be predisposed to lower cardiorespiratory fitness which in turn may put them at risk for conditions such as type 2 diabetes. However, exercise can contribute to improved cardiorespiratory fitness and thus, possibly reduce type 2 diabetes risk. Individuals with type 2 diabetes, and even those without the disease but having a family history of diabetes are observed to have reduced expression of PGC-1α. **Increasing PGC-1α expression.** A variety of environmental stimuli have been shown to induce the expression of PGC-1α in various tissues, including exercise (in muscle), cold exposure (in brown fat and muscle) and fasting (in the liver). Individuals with this genotype with the **(A;G)** genotype may benefit from engaging in such activities to increase PGC-1α levels and possibly reduce the risks associated with the genotype. - Read more about rs8192678 on SNPedia SNPs Involved rs8192678(A;G)

MC4R	rs17782313(C;C)	Higher body mass index (bmi), possibly affecting dietary suitability	Melanocortin-4 receptor (MC4R) is a G-protein-coupled receptor expressed in the hypothalamus region of the brain, where it is thought to play a role in appetite control, satiety and regulation of food intake. The *MC4R* gene has rare loss-of-function mutations that are associated with severe early-onset obesity. However, this common polymorphism, rs17782313, is found in an intergenic region near the MC4R gene and is associated with more common forms of obesity. Because of the

location of the SNP and its resulting phenotype, it is thought to result in disrupted transcription of the gene and less MC4R protein.

This genotype, rs17782313(C;C) is associated with a higher body mass index (BMI).

In a genome-wide association study (GWAS) of 77,228 individuals, the **C** allele was associated with higher BMI. Each copy of the **C** allele resulted in a 0.22 kg/m2 increase in BMI, an 8% increase of being overweight (BMI ≥ 25) and a 12% increase of being obese (BMI ≥ 30).

This association was confirmed In a meta-study comprising 80,957 cases and 220,223 controls. The **C** allele was associated with obesity risk in multi-ethnic populations

Potential benefits of a Mediterranean diet.
In a case-control study of 7,052 individuals with risk for cardiovascular disease (3,430 type 2 diabetics, 3,622 non-diabetic controls), dietary intake was assessed for adherence to a Mediterranean diet. When adherence to a Mediterranean diet was low, individuals with the **C** allele had a higher risk for type 2 diabetes as compared to **(T;T)** individuals. However, when adherence to a Mediterranean diet was high, this association was not observed.

- Read more about rs17782313 on SNPedia

SNPs Involved

rs17782313(C;C)

IRS1 | rs2943641(C;C) | Increased risk for type 2 diabetes, alters response to diet

Insulin receptor substrate 1 (IRS1) is a mediator involved in the insulin signaling pathway that is thought to be involved in glucose homeostasis.

This genotype, rs2943641(C;C), has been associated with increased risk for type 2 diabetes (T2DM).

There are common polymorphisms near the *IRS1* gene, which codes for insulin receptor substrate 1. The (**C**) allele of the rs2943641 polymorphism, located in the intergenic region downstream of the *IRS1* gene, has been shown to decrease IRS1 protein production.

In a genome-wide association study (GWAS) involving 14,358 individuals, the **C** allele was associated with insulin resistance (IR), hyperinsulinemia and T2DM as well as lower basal levels of the IRS1 protein.

In the POUNDS LOST trial, a two-year long dietary intervention study, researchers randomly assigned 738 overweight individuals to one of four hypocaloric diets which varied in the amount of carbohydrate, protein, and fat. At baseline, participants with the **C** allele had higher fasting insulin levels and IR. After six months, individuals with the (**C;C**) genotype lost more weight on the diet that had the highest carbohydrate content. At the two year mark, (**C;C**) subjects had greater improvements in IR than carriers of the **T** allele when comparing subjects on the highest carbohydrate diet. The authors are unsure if the weight loss is improving IR or whether improved IR is making weight loss easier. Since calories were held constant, the high carbohydrate diet was also lower in fat, so investigators could not determine whether the higher carbohydrate or lower fat was interacting with this polymorphism. The researchers propose a mechanism linked to lipid-induced IR to explain why subjects with high IR lost more weight on a high-carbohydrate diet. The authors conclude that individuals with the (**C;C**) genotype may benefit from a high-carbohydrate/low-fat diet for improved IR and weight loss. They clarify that participants were encouraged to choose high-quality carbohydrate foods in this study.

In a 4-week dietary intervention trial, researchers fed 59 subjects a high saturated fat, a high mono-unsaturated fat or a high-carbohydrate diet/low-fat diet. Individuals with the risk allele for insulin resistance in a related polymorphism IRS1(rs1801278), became more insulin sensitive after a high-carbohydrate/low-fat diet when compared to the high-fat diet.

In two different populations (GOLDN cohort, n=820 and the BPRHS cohort, n=844) researchers observed that individuals with the **T** allele had lower IR, risk for T2DM and metabolic syndrome when compared to those with the (**C;C**) genotype. However, this relationship was only detected when the dietary saturated fat to carbohydrate ratio was low. The authors state that although more research is needed, diet may influence this polymorphism such that a diet low in fat or high in carbohydrates may benefit those with the **T** allele.

- Read more about rs2943641 on SNPedia

SNPs Involved

rs2943641(C;C)

FADS1 | rs174550(C;T) | Slight increased inflammation in conjunction with a high linoleic acid (omega-6) diet

Fatty acid desaturase 1 (FADS1) is an enzyme involved in the metabolism of polyunsaturated fatty acids (PUFAs). The essential fatty acids, linoleic acid (LA, omega-6) and alpha-linolenic acid (ALA, omega-3) compete for the FADS1 enzyme. The omega-6 pathway leads to arachidonic acid (AA), a precursor of pro-inflammatory compounds, while the omega-3 pathway leads to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) which tend to be anti-inflammatory.

This genotype, rs174550(C,T), has been associated with slightly increased inflammation in conjunction with a high linoleic acid (omega-6) diet.

There are common polymorphisms in the *FADS1* gene, which codes for the fatty acid desaturase 1 enzyme. The variant form (**C**) of the rs174550 polymorphism, located in the intron region of the gene, is thought to be associated with decreased mRNA expression in the liver which may regulate how much of the final enzyme is produced.

In an intervention study, a group of 62 men selected by their FADS1 genotype, followed a linoleic acid-enriched diet (sunflower oil) for four weeks. Researchers measured hsCRP (high sensitivity C-

reactive protein, a marker of low-grade inflammation) before and after the diet intervention. They observed that individuals with the (**T;T**) genotype had decreased hsCRP after the diet while subjects with the (**C;C**) genotype had an increased hsCRP. These results suggest that increasing intake of linoleic acid can result in an enhanced inflammatory response in (**C;C**) individuals and a decreased inflammatory response in those with the (**T;T**) genotype. Low-grade inflammation has been associated with a variety of diseases such as insulin resistance, obesity, cardiovascular disease and non-alcoholic fatty liver disease (NAFLD). The authors advise that while more research is needed, general recommendations for fatty acid intake may not apply to all individuals equally.

The typical western diet has an omega-6 to omega-3 ratio of 15:1 and will likely favor the pro-inflammatory pathway. Consuming more omega-3 and less omega-6 fatty acids may result in less of the FADS1 enzyme being used to produce inflammatory molecules. This may be important for those with the (**C**) allele of the FADS1 gene who appear to have increased inflammation with increased omega-6 fatty acid intake. (**C;C**) individuals may benefit from reducing the omega-6 to omega-3 FA ratio.

- Read more about rs174550 on SNPedia

SNPs Involved

rs174550(C;T)

GIPR	rs2287019(C;C)	Increased risk for obesity	Gastric inhibitory polypeptide (GIP, also known as glucose-dependent insulinotropic peptide) is an incretin hormone which is expressed in the gastrointestinal tract upon eating, particularly following a high-fat or glucose containing meal. By binding to gastric inhibitory polypeptide receptor (GIPR), it is thought to be involved in stimulating the pancreatic beta cells to secrete insulin. GIPR also participates in the uptake of fat and glucose into adipocytes. **This genotype, rs2287019(C;C), has been associated with an increased risk for obesity.** There are common polymorphisms in the *GIPR* gene, which codes for the gastric inhibitory polypeptide receptor. The variant form (**T**) of the rs2287019 polymorphism, located in the intronic region of the gene, is hypothesized to result in a less functional GIPR receptor. In a genome-wide association study (GWAS) involving 249,796 individuals, the **C** allele was associated with increased BMI. The authors speculate that this polymorphism is involved in obesity risk by causing an increase in postprandial (after meals) insulin secretion. Researchers administered an oral glucose tolerance test (OGTT) to 6,039 middle-aged individuals. The results demonstrated that subjects carrying the **C** allele had a higher insulinogenic index (7.4% per copy of the **C** allele) as compared to those without the **C** allele. The insulinogenic index is a ratio of insulin to glucose and measures how much insulin is secreted in response to a glucose challenge. In the POUNDS LOST trial, a two-year long dietary intervention study, researchers randomly assigned 737 overweight individuals to one of four hypocaloric diets which varied in the amount of carbohydrate, protein and fat content. After six months, individuals with the **T** allele lost more weight and had better glucose homeostasis (fasting glucose, fasting insulin, and HOMA-IR) on the low-fat/high-carbohydrate diet than subjects without the **T** allele. Investigators did not observe any genotype interactions with the high-fat/low carbohydrate diet. The authors suggest that individuals with the **T** allele may benefit from a low-fat/high-carbohydrate diet with high-fiber for improved glucose homeostasis and weight loss. The researchers clarify that participants were encouraged to choose high-quality carbohydrate foods in this study. - Read more about rs2287019 on SNPedia SNPs Involved rs2287019(C;C)
PLIN1	rs894160(A;G)	Favorable weight loss and improved biomarkers with a diet high in complex carbohydrates	Perilipin-1 (PLIN1) is a member of a family of proteins involved in the storage and breakdown of lipids in adipocytes (fat cells). **This genotype, rs894160(A;G), has been associated with favorable weight loss and improved biomarkers with a diet high in complex carbohydrates.** There are common polymorphisms in the *PLIN1* gene, which codes for the perilipin-1 protein. The variant form (**A**) of the rs894160 polymorphism (also known as 11482G>A) is located in the intronic region of the gene. Investigators analyzed the dietary intake of 920 individuals of Puerto Rican descent. Researchers observed that amongst subjects who consumed ≥144g/d of complex carbohydrates, individuals carrying the **A** allele had smaller waist circumferences than individuals with the (**G;G**) genotype. However, amongst subjects consuming <144g/d of complex carbohydrates, subjects with the **A** allele had larger waist circumferences than individuals with the (**G;G**) genotype. Researchers did not observe a nutrient-genotype relationship for simple sugars or total carbohydrate content. The authors suggest that **A** allele carriers are somewhat protected from adiposity by a higher complex carbohydrate intake, however, a low complex carbohydrate intake may be less desirable for these individuals. Individuals (n=970) recorded their habitual dietary intake and researchers categorized the data into the following groups, low saturated fat (<11.5%) versus high saturated fat (≥ 11.5%) and low carbohydrate intake (<50.5%) versus high carbohydrate intake (≥50.5%). When carbohydrate intake was low, individuals carrying the **A** allele had higher insulin levels and HOMA-IR (a biomarker of insulin resistance) as compared to subjects with the (**G;G**) genotype, but this was not the case when carbohydrate intake was high. Researchers observed that women with the **A** allele who consumed a high saturated fat to carbohydrate ratio had higher insulin levels and HOMA-IR. However, when saturated fat to carbohydrate ratio was low, this was not observed. There was no interaction

between saturated fat to carbohydrate ratio and the (**G;G**) genotype. The authors speculate that either a high saturated fat intake or a low carbohydrate intake may be detrimental for carriers of the **A** allele of this polymorphism.

In another study, obese individuals consumed a hypocaloric diet (1200 kcal/d) for one year. Researchers observed that participants with the **A** allele had a lower weight and BMI at baseline than subjects with the (**G;G**) genotype. However, after one year on the diet, individuals with the (**G;G**) genotype experienced significant weight loss while individuals carrying the **A** allele did not. The authors theorize that the **A** allele may be associated with difficulty losing weight on a calorie-restricted diet. Moreover, the hypocaloric diet used in this study provided a relatively low percentage of carbohydrates which is in accordance with other studies that propose that individuals with the **A** allele lose weight more readily with higher carbohydrate content.

- Read more about rs894160 on SNPedia

SNPs Involved

rs894160(A;G)

Less noteworthy

These genotypes are normal.

Gene	SNPs involved	Status	More information
PPAR gamma	rs1801282(C;C)	Normal risk for obesity and type 2 diabetes in response to a diet high in saturated fat and low in mono- and polyunsaturated fats	Peroxisome proliferator-activated receptor gamma (PPAR-γ or PPARG) is a master regulator of fatty acid storage and glucose metabolism. PPARG is found in adipose tissue, the colon and in immune cells called macrophages. PPARG serves as a transcription factor and activates a variety of genes that stimulate lipid uptake and adipogenesis by fat cells, insulin sensitivity in muscle tissue and gluconeogenesis in the liver. **This genotype, rs1801282(C;C), has been associated with normal risk for obesity and type 2 diabetes in response to a diet high in saturated fat and low in mono- and polyunsaturated fats.** There are common polymorphisms in the *PPARG* gene, which codes for peroxisome proliferator-activated receptor gamma. The variant form (**G**) of the rs1801282 polymorphism is located in the coding region of the gene. The (**C;C**) genotype is associated with normal fat metabolism, however, individuals with the (**C;G**) or (**G;G**) genotype may be affected by the types of fat they eat. When individuals with the (**C;G**) or (**G;G**) genotype eat a diet high in saturated fat but low in polyunsaturated and monounsaturated fat, their risk for obesity and type 2 diabetes is increased. However, if these individuals consume a diet higher in mono- and polyunsaturated fats and lower in saturated fats, their risk for obesity and type 2 diabetes is normal. - Read more about rs1801282 on SNPedia SNPs Involved rs1801282(C;C)
PPAR alpha	rs1800206(C;C)	Normal risk for altered blood lipids and type 2 diabetes in response to a diet high in saturated fat	Peroxisome proliferator-activated receptor alpha (PPAR-α) is a master regulator of lipid, carbohydrate and amino acid metabolism. PPAR-α is found primarily in brown adipose tissue and the liver, and, to a lesser extent, the kidneys, skeletal muscle, heart and both the small and large intestines. PPAR-α plays an essential role in the process of ketogenesis (the production of ketone bodies from the oxidation of fat, which typically occurs during carbohydrate restriction or fasting). Activation of PPAR-α promotes the uptake, utilization and catabolism of fatty acids by activating genes involved in fatty acid transport, binding, activation and oxidation. PPAR-α is activated primarily through the binding of polyunsaturated fatty acids. **This genotype, rs1800206(C;C), has been associated with normal risk for altered blood lipids and type 2 diabetes in response to a diet high in saturated fat.** There are common polymorphisms in the *PPAR-α* gene, which codes for the peroxisome proliferator-activated receptor alpha. The variant form (**G**) of the rs1800206 polymorphism is located in the exonic region of the gene. The (**C;C**) genotype has been associated with a normal PPAR-α activity, however, the rs1800206(**C;G**) and rs1800206(**G;G**) genotypes have been associated with a lower PPAR-α activity. This reduction in PPAR-α activity may cause these individuals to have a 2-fold higher risk of type 2 diabetes, increased levels of triglycerides, total cholesterol, LDL cholesterol, small-dense LDL particles, apolipoprotein B, and increased risk for non-fatal heart attack particularly when saturated fat intake is higher than polyunsaturated fat (PUFA) intake. The negative effects on triglycerides, lipids, and cholesterol are more pronounced in men compared to women. - Read more about rs1800206 on SNPedia. - Read more about saturated fat and the PPAR-α SNP. - Read more about polyunsaturated fat and the PPAR-α SNP.

			SNPs Involved rs1800206(C;C)
ACE	rs4343(A;A)	Normal sensitivity to saturated fat changes in blood pressure and glucose metabolism	The *ACE* gene codes for the angiotensin-converting enzyme, a regulatory enzyme in the renin-angiotensin system, which plays an important role in the regulation of blood pressure. There is a common insertion/deletion of 287 base pairs in this gene, for which rs4343 serves as a proxy (surrogate marker). Those with the **A** allele have the insertion and those with the **G** allele have the deletion. The deletion (**G**) has been shown to result in higher levels of the ACE enzyme in the serum. **This polymorphism, rs4343(A;A) is associated with normal sensitivity to saturated fat changes in blood pressure and glucose metabolism.** During the NUGAT study of 46 twin-pairs (healthy, non-obese), subjects consumed a low fat diet for 6 weeks followed by a high saturated fat diet for 6 weeks. Following the high fat diet intervention, **(G;G)** individuals had 2-fold higher ACE levels, as well as, higher systolic blood pressure (117 ± 9 mmHg) as compared to **(A;A)** or **(A;G)** individuals (108 ± 12 mmHg). No blood pressure differences were observed among the genotypes during the low fat phase of the study. This led the authors to suggest that **(G;G)** individuals may be at increased risk for cardiovascular disease and may benefit from a lower saturated fat intake. The NUGAT cohort was further studied for glucose tolerance. No differences in glucose tolerance were observed at baseline regardless of genotype. However, after 6 weeks on a high fat diet, **(G;G)** individuals had higher fasting insulin levels and HOMA-IR (biomarker for insulin resistance) as compared to **(A;A)** or **(A;G)** individuals. Biomarkers of insulin resistance did not change in **(A;A)** or **(A;G)** individuals on a high fat diet. Dietary records were examined from a second cohort (n=365) and participants were separated into two groups based on daily fat intake. In the group consuming ≥37% energy from fat, individuals with the **(G;G)** genotype had higher blood pressure and 2.7- fold increased risk for type 2 diabetes (T2D) as compared to **(A;A)** and **(A;G)** individuals. However, among those consuming <37% fat, no differences in blood pressure or increased risk for T2D were observed. In fact, **(G;G)** individuals who ate ≥37% fat had 4.6-fold increased risk for T2D than **(G;G)** individuals who ate <37% fat diet, suggesting that those with the **(G;G)** genotype may benefit from a diet that is lower in fat. • Read more about rs4343 on SNPedia SNPs Involved rs4343(A;A)
FABP2	i6010053(G;G)	Normal sensitivity to saturated fats and refined sugars	There are common polymorphisms in the FABP2 gene that codes for the fatty acid binding protein-2, which is expressed in the small intestine. FABP2 is involved in the uptake and metabolism of long-chain fatty acids. This polymorphism is thought to increase the protein's ability to bind and transport fatty acids into the cell by two-fold. **This genotype, rs1799883(G;G), is associated withnormal sensitivity to saturated fats and refined sugars.** In a meta-analysis of 30 studies with 14,401 subjects, fasting levels of HDL were lower and LDL and total cholesterol levels were higher, in carriers of the **A** allele when compared to those with the (**G;G)** genotype. The CARDIA study: a 20 year-long prospective investigation of 2148 young adults showed that those with the **(A;A)** and **(A;G)** genotypes who ate a diet high in saturated fat (> 53 g/day) had lower HDL cholesterol to total cholesterol ratios, as well as, higher levels of HOMA-IR (a biomarker of insulin resistance) when compared to **(G;G)** individuals. These unfavorable biomarkers were not observed in **(A;A)** or **(A;G)** individuals who ate less than 53g of saturated fat per day. This suggests that carriers of the **A** allele may benefit from a diet that is lower in saturated fat. • Read more about rs1799883 on SNPedia. SNPs Involved rs1799883 i6010053(G;G)
FTO	rs17817449(T;T)	Saturated fat does not have negative effect on blood glucose and insulin levels	The *FTO* gene, the major genetic risk factor for obesity, codes for the fat mass and obesity-associated protein. There is a cluster of polymorphisms in the FTO gene that increase obesity risk. **This genotype, rs17817449(T;T), has been associated with a normal risk for obesity.** There are common polymorphisms in the *FTO* gene, which codes for the fat mass and obesity-associated protein. The rs17817449 polymorphism is located in the intronic region of the *FTO* gene. This particular polymorphism is one of many in this gene that influence genetic obesity risk. The (**T;T**) genotype is not associated with an increased risk of obesity. However, individuals carrying a **G** allele have an increased obesity risk. Having a **G** allele also means that higher saturated fat intake may negatively impact blood glucose and insulin levels and increases type 2 diabetes risk in these individuals. • Read more about rs17817449 on SNPedia. SNPs Involved rs17817449(T;T)

FTO	rs9939609(T;T)	Normal risk for obesity and type 2 diabetes	The *FTO* gene, the major genetic risk factor for obesity, codes for the fat mass and obesity-associated protein. Ghrelin, often called the hunger hormone, is produced when the stomach is empty and is thought to stimulate appetite and desire to eat. **This genotype, rs9939609(T;T), has been associated with a normal risk for obesity and type 2 diabetes**. There are common polymorphisms in the *FTO* gene, which codes for the fat mass and obesity-associated protein. The rs9939609 polymorphism is located in the intronic region of the *FTO* gene. This particular polymorphism is one of many in this gene that influence genetic obesity risk. The **T** allele is associated with normal production of the appetite-stimulating hormone ghrelin. The **A** allele, however, is associated with higher levels of ghrelin, as well as a roughly 60% increased risk of obesity and type-2 diabetes. Higher ghrelin levels are associated with over-eating due to lack of satiation. While this genotype is normal, other polymorphisms in the *FTO* gene have been associated with obesity particularly in the context of high saturated fat and low polyunsaturated fat intake. Saturated fat is found in fatty beef, pork, coconut oil, butter, cheese, and other dairy products, while polyunsaturated fats are found in foods like nuts and fatty fish such as salmon and herring. • Read more about rs9939609 on SNPedia SNPs Involved rs9939609(T;T)
FTO	rs1421085(T;T)	Normal obesity risk and thermogenesis	The *FTO* gene, the major genetic risk factor for obesity, codes for the fat mass and obesity-associated protein. There is a cluster of polymorphisms in the FTO gene that increase obesity risk. **This genotype, rs1421085(T;T), has been associated with a normal obesity risk and thermogenesis.** There are common polymorphisms in the *FTO* gene, which codes for the fat mass and obesity-associated protein. The rs1421085 polymorphism is located in the intronic region of the *FTO* gene. This particular polymorphism is one of many in this gene that influence genetic obesity risk. Approximately 43% of individuals of European ancestry carry one risk allele (**C**), and 20% possess two risk alleles (**C;C**). The (**T;T**) genotype is not associated with an increased risk of obesity. However, individuals carrying the **C** allele have an increased obesity risk, as a result of the body shifting from energy-burning adipocytes (brown adipose tissue) to energy-storing adipocytes (white adipose tissue). Consequently, adipocytes store more lipids, and the individual gains weight. Carrying the **C** allele has also been associated with reduced thermogenesis (the burning of fat to produce heat) in response to cold exposure. • Read more about rs1421085 on SNPedia. • Read more about FTO and fat storage and decreased thermogenesis. SNPs Involved rs1421085(T;T)
FTO	rs1121980(C;C)	Normal obesity risk	The *FTO* gene, the major genetic risk factor for obesity, codes for the fat mass and obesity-associated protein. There is a cluster of polymorphisms in the *FTO* gene that increase obesity risk. **This genotype, rs1121980(C;C), has been associated with a normal obesity risk.** There are common polymorphisms in the *FTO* gene, which codes for the fat mass and obesity-associated protein. The rs1121980 polymorphism is located in the intronic region of the *FTO* gene. This particular polymorphism is one of many in this gene that influence genetic obesity risk. The (**C;C**) genotype has been associated with an average risk for obesity. However, individuals carrying the **T** allele have an increased risk for obesity, particularly in the context of a high saturated fat and low polyunsaturated fat intake. • Read more about rs1121980 on SNPedia. • Read more about the association between this SNP and obesity. SNPs Involved rs1121980(C;C)
FTO	rs1558902(T;T)	Normal obesity risk	The *FTO* gene, the major genetic risk factor for obesity, codes for the fat mass and obesity-associated protein. There is a cluster of polymorphisms in the FTO gene that increase obesity risk. **This genotype, rs1558902(T;T), has been associated with a normal risk of obesity.** There are common polymorphisms in the *FTO* gene, which codes for the fat mass and obesity-associated protein. The rs1558902 polymorphism is located in the intronic region of the *FTO* gene. This particular polymorphism is one of many in this gene that influence genetic obesity risk. The (**T;T**) genotype has been associated with a normal risk of obesity. However, in a genome-wide association study of 249,796 individuals of European descent, the **A** allele was associated with an increased BMI.

			• Read more about rs1558902 on SNPedia. SNPs Involved rs1558902(T;T)
TCF7L2	rs7903146(C;C)	Normal risk for type 2 diabetes in association with saturated and polyunsaturated fat consumption	Transcription factor 7-like 2 (TCF7L2) is a transcription factor that is involved in the regulation of a variety of genes. It is part of the Wnt signaling pathway, which is vital in cellular communication. Not much is known about the mechanism of action of TCF7L2, although it is thought to be involved in lipid metabolism in an insulin-dependent manner. The rs7903146 polymorphism has been suggested to result in increased gene expression and thus decreased insulin secretion and enhanced glucose production in the liver. **This genotype, rs7903146(C;C), has been associated with a normal risk for type 2 diabetes.** In a meta-analysis of 35,843 type 2 diabetics and 39,123 controls, those with the **(T;T)** genotype had a 2-fold increased risk, and those with the **(C;T)** genotype had a 1.4-fold increased risk of developing type 2 diabetes as compared to those with the **(C;C)** genotype. • Read more about rs7903146 on SNPedia SNPs Involved rs7903146(C;C)
TFAP2B	rs987237(A;A)	Normal risk for obesity and waist circumference, alters response to diet	Transcription Factor AP-2 Beta (TFAP2B) is a protein involved in the expression of genes associated with cell division and apoptosis (programmed cell death). TFAP2B functions by activating some genes and repressing other genes. **This genotype, rs987237(A;A), has been associated with normal risk for obesity and waist circumference.** There are common polymorphisms in the *TFAP2B* gene, which codes for transcription factor AP-2 beta. The variant form (**G**) of the rs987237 polymorphism is located in the intronic region of the gene. In a genome-wide association study (GWAS) involving 249,796 individuals, the **G** allele was associated with increased BMI. In a randomized controlled study, 771 obese adults followed a hypocaloric diet containing either low-fat (LF, 20-25%) or high-fat (HF, 40-45%) for ten weeks. Researchers observed that individuals with the **(A;A)** genotype lost more weight on the LF diet while those with the (**G;G**) genotype lost more weight on the HF diet. In a weight maintenance study (n=742) investigators observed that individuals with the **(A;A)** genotype maintain weight better on a high protein diet whereas carriers of the **G** allele regained more weight (1.84kg per **G** allele) on a high protein diet compared to a normal protein diet. Based on these results, researchers reason that this polymorphism interacts with a diet's macronutrient content, but they are uncertain of the mechanism. • Read more about rs987237 on SNPedia SNPs Involved rs987237(A;A)
PPM1K	rs1440581(A;A)	Normal circulating bcaas and normal risk for type 2 diabetes on high fat diet	PP2C domain-containing protein phosphatase 1K (PPM1K) is a mitochondrial enzyme involved in the metabolism of branched-chain amino acids (BCAA). Recent research suggests that high levels of circulating BCAAs may be linked to a future risk of insulin resistance and type 2 diabetes. **This genotype, rs1440581(A;A), has been associated with normal circulating BCAAs and normal risk for type 2 diabetes.** There are common polymorphisms near the *PPM1K* gene, which codes for the PP2C domain-containing protein phosphatase 1K. The variant form (**A**) of the rs1440581 polymorphism, is located in the intronic region of the gene. In a genome-wide association study (GWAS) involving 8,330 individuals, the **G** allele was associated with a higher ratio of branched-chain amino acids (BCAA) to aromatic amino acids (AAA) in the blood. This biomarker, known as Fisher's ratio has been linked to future risk for type 2 diabetes. In the POUNDS LOST trial, a two-year long dietary intervention study, researchers randomly assigned 734 overweight individuals to one of four hypocaloric diets which varied in the amount of carbohydrate, protein and fat content. After six months, individuals with the **G** allele lost less weight and had smaller improvements in insulin resistance when on a high-fat diet as compared to individuals without the **G** allele. Individuals with the **A** allele lost more weight and exhibited improved insulin resistance when on a high-fat diet compared to a low-fat diet. The authors suggest that **G** allele carriers may show fewer benefits from a high-fat diet due to higher circulating levels of BCAAs. While these findings that **G** allele carriers respond differently to a hypocaloric high-fat diet than individuals without the **G** allele are interesting, the authors state that more research is needed to understand the mechanism involved. In a 10-week weight loss study, individuals (n=757) followed a hypocaloric diet which varied in macronutrient content. Participants with the **A** allele on the high-fat diet experienced a greater reduction in insulin, HOMA-IR, and HOMA-B as compared to subjects on a low-fat diet. The authors

suggest that individuals with the (**G;G**) genotype may benefit from a low-fat, high carbohydrate diet while those with the **A** allele may be more suited to a high-fat, low carbohydrate diet for improvements in glucose metabolism.

- Read more about rs1440581 on SNPedia
  * These alleles have been adjusted for consistency with SNP orientation. Read more about orientation.

SNPs Involved

rs1440581(A;A)

MC4R | rs2229616(G;G) | Normal risk for obesity, type 2 diabetes and coronary artery disease

Melanocortin-4 receptor (MC4R) is a G-protein-coupled receptor expressed in the hypothalamus region of the brain, where it is thought to play a role in appetite control, satiety and regulation of food intake. G-protein coupled receptors are important for transmitting signals from outside the cell to inside the cell based on environmental conditions such as nutrient availability. Some researchers believe MC4R is a candidate gene for obesity. Upon eating, leptin levels increase leading to MC4R increases and appetite suppression.

This genotype, rs2229616(G;G), has been associated with normal risk for obesity, type 2 diabetes and coronary artery disease.

The *MC4R* gene contains loss-of-function variants, some of which are associated with severe early-onset obesity, while others are associated with more typical forms of obesity. There are polymorphisms in the MC4R gene, which codes for the melanocortin-4 receptor. The variant form (**A**) of the rs2229616 polymorphism (also known as V103I), is known as a gain-of-function variant, which is thought to result in the production of more MC4R protein and may provide some protection from obesity regardless of lifestyle.

In a recent genetic association meta-analysis involving 452,300 individuals of European descent, the **A** allele was associated with protection against obesity and with a decreased risk of both type 2 diabetes and coronary artery disease. Approximately 6% (n=28,161) of the study population had a gain-of-function polymorphism in the *MC4R* gene. Individuals with two copies of an *MC4R* gain-of-function variant weighed 2.5 kg less and had a 50 percent reduced risk of both coronary artery disease and type 2 diabetes. The authors demonstrated that this polymorphism favored a beta-arrestin signaling pathway rather than a cAMP pathway. They propose a mechanism by which this polymorphism may be involved in protection from obesity and obesity-related diseases. Due to the beneficial aspects of this variant, the MC4R/beta-arrestin signaling pathway is being targeted by pharmaceutical companies for obesity drug development.

- Read more about rs2229616 on SNPedia

SNPs Involved

rs2229616(G;G)

FTO | rs3751812(G;G) | Normal risk of obesity

The *FTO* gene, a major genetic risk factor for obesity, codes for the fat mass and obesity-associated protein. There is a cluster of polymorphisms in the *FTO* gene that increase the risk of obesity.

This genotype, rs3751812(G;G), has been associated with a normal risk of obesity.

There are common polymorphisms in the *FTO* gene, which codes for the fat mass and obesity-associated protein. The variant form (**T**) of the rs3751812 polymorphism is located in the intronic region of the gene. This particular polymorphism is one of many in the *FTO* gene that influences genetic risk of obesity.

The (**G;G**) genotype is not associated with an increased risk of obesity. However, individuals carrying the **T** allele have an increased obesity risk.

In a case-control study, researchers collected and analyzed the dietary intake of obese (n=627) and normal weight (n=627) individuals of Middle Eastern descent. The (**T;T**) genotype of this polymorphism is associated with an increased risk of obesity. However, in this study, individuals with the **T** allele who ate more dietary fiber exhibited less abdominal obesity than individuals with the **T** allele who ate less fiber. Fiber intake did not affect obesity risk in individuals with the (**G;G**) genotype. The authors propose that fiber may activate a transcription factor called PPAR-δ (peroxisome proliferator-activated receptor-δ), which may change the expression of the FTO gene and possibly lessen its obesogenic effects. Based on these observations, the investigators recommend that individuals with the **T** allele may benefit from adequate dietary fiber for reducing the risk of obesity.

- Read more about rs3751812 on SNPedia

SNPs Involved

rs3751812(G;G)

Disclaimer

The results found in this report are NOT FOR MEDICAL PURPOSES and are subject to change in future software updates without notice. Raw data from genetic providers is suitable only for research, educational, and informational use and not for medical or other use.

Micronutrient Report v2

Source: Cooper_Beaman_23andmenew_v4_Full_20190517100124.zip
Created at February 23 at 4:42 PM PDT

This report is focused on SNPs related to the bioavailability and metabolism of micronutrients, which include essential vitamins, minerals, fatty acids, and amino acids that humans must obtain from their diet since they do not produce them. Micronutrients are important for short-term health but have also been shown to be important for the prevention of diseases of aging. Some of the SNPs in this report are involved in vitamins A, C, D, B12, folate, omega-3, iron and more.

Noteworthy

These genotypes are the ones that are potentially worth being aware of.

Gene	SNPs involved	Status	More information
FUT2	rs601338(A;G)	Associated with slightly lower vitamin b12 levels and susceptibility to norovirus infection	Vitamin B12 (cobalamin) status depends on both dietary intake and cellular uptake via the expression of several genes. One of these genes, fucosyltransferase 2 (*FUT2*), encodes a membrane protein that is involved in vitamin B12 absorption. FUT2 is also involved in microbe-host interactions by facilitating bacterial attachment to intestinal cells. FUT2 establishes a symbiotic environment for commensal bacteria and thereby provides protection from some pathogenic microorganisms. **This genotype, rs601338(A;G), has been associated with slightly lower vitamin B12 levels and susceptibility to norovirus infection.** There are common polymorphisms in the *FUT2* gene, which codes for the enzyme fucosyltransferase 2. The variant form, **(A)**, of the rs601338 polymorphism (also known as W143X), is located in the coding region of the gene and results in a premature stop codon and a non-functional enzyme. In a genome-wide association study (GWAS) study (n=1,658 women) and a replication sample (n=1,059 women), individuals with the **(A;A)** genotype had higher vitamin B12 levels as compared to **(A;G)** or **(G;G)** individuals. In a study of 37,283 Icelandic individuals, the **A** allele was again associated with higher vitamin B12 levels. The FUT2 polymorphism is involved in expressing ABO(H) antigens on the surface of cells other than red blood cells, for example, saliva and gastrointestinal cells. Individuals with two copies of the variant form of this polymorphism (about 20% of the population) do not express blood group antigens ABO(H) on cells other than red blood cells and are known as non-secretors. Individuals with the **(A;A)** genotype are referred to as non-secretors whereas **(A;G)** and **(G;G)** genotypes are secretors. In a meta-analysis of 3 GWAS (n=4,763), individuals with the **(A;A)** genotype (non-secretors) were associated with higher levels of plasma vitamin B12 than **(A;G)** or **(G;G)** secretors. *Microbiome* As well as diet, one of the factors that can determine the composition of the microbiome is the host genotype. Non-secretors **(A;A)** do not express histo-blood group antigens in the intestinal mucosa where a microorganism can bind. Certain pathogenic (disease-causing) microorganisms, such as norovirus, cannot attach to the intestinal cells of non-secretors and therefore they are protected from the disease. However, beneficial bacteria may also not be able to attach. Non-secretors had reduced diversity, richness and abundance of bifidobacteria as compared to secretors. Bifidobacteria are thought to be beneficial as they aid in immune response and may guard against pathogenic species. In addition to polymorphisms such as this one, other factors can affect B12 status. Factors known to reduce B12 absorption include age (over 60 years), following a strict vegetarian diet, prolonged use of antacid medications, bariatric surgery, and celiac disease. In some situations, clinical signs of B12 deficiency may take years to develop because vitamin B12 is stored in the body. Poor vitamin B12 absorption can probably be corrected through supplementation. Sublingual vitamin B12, in particular, has been shown to circumvent issues associated with malabsorption. • Read more about rs601338 on SNPedia SNPs Involved rs601338(A;G)
SLC23A1	rs10063949(T;T)	Normal risk of crohn's disease	Vitamin C (or L-ascorbic acid) is an antioxidant that protects cells and DNA from damage caused by free radicals. Vitamin C also participates in several enzymatic reactions in a variety of metabolic pathways. Unlike some animals, humans cannot synthesize vitamin C and therefore it must be obtained from dietary sources. Vitamin C enters the cell in two ways, active transport via sodium-dependent vitamin C transporters SVCT1 and SVCT2 or facilitative diffusion by GLUT transporters. SVCT1, the primary vitamin C transporter in intestinal cells, is encoded for by the SLC23A1 gene. The polymorphism, rs10063949, is located in the promoter region of the SLC23A1 gene. **This genotype, rs10063949(T;T), has been associated with a normal risk of Crohn's disease (CD).** In a study of 311 individuals with inflammatory bowel disease (CD, $n = 162$; ulcerative colitis $n = 149$) and 142 healthy controls, the **C** allele was associated with an increased risk of Crohn's disease but not ulcerative colitis. Individuals with the **(C;T) genotype had a 2.54 increased risk, and those with the (C;C) genotype had a 4.72 increased risk of Crohn's disease** as compared to **(T;T)** individuals.

- Read more about rs10063949 on SNPedia

SNPs Involved

rs10063949(T;T)

MTRR	rs1801394(G;G)	Increased risk for hyperhomocysteinemia and altered choline metabolism	There are common polymorphisms in the MTRR gene that code for the enzymemethionine synthase reductase, which catalyzes the conversion of the inactive form of another enzyme, methionine synthase (MTR), to its active form using riboflavin (vitamin B2) as a cofactor. MTR is involved in the remethylation of homocysteine to methionine with cobalamin (vitamin B12) participating as a cofactor. This reaction is of utmost importance as MTR plays a pivotal role in folate metabolism and methionine cycling. **This genotype, rs1801394(G;G), may be associated with hyperhomocysteinemia and altered choline metabolism.** This polymorphism encodes for an MTRR enzyme with a reduced affinity for MTR resulting in less efficient reactivation of MTR, possibly resulting in elevated homocysteine levels. Some associations have been made between rs1801394 and hyperhomocysteinemia especially in combination with low vitamin B12 levels and the *MTHFR* rs1801133 variant. This polymorphism may be associated with an increased risk for neural tube defects (can be circumvented by folate supplementation), 1.4X risk for meningioma (a form of brain cancer) and altered choline metabolism. This polymorphism has been shown to influence the way choline is partitioned between the Cdp-choline pathway and betaine synthesis. At recommended adequate intake (AI) levels of choline, women with this variant shuttled more choline towards phosphatidylcholine synthesis at the expense of betaine synthesis. However, at levels above the AI, normal partitioning was restored, suggesting that women with this polymorphism may benefit from dietary choline intake above the current AI levels. These recent studies may prompt the Institute of Medicine (IOM) to refine the dietary recommendations to include individuals with increased choline needs. **Dietary choline intake.** Choline is found in foods such as eggs, meat, fish and cruciferous vegetables. Strict vegetarians may need to pay special attention to meeting their choline needs. The Food and Nutrition Board (FNB) of the Institute of Medicine (IOM) has established the Adequate Intake (AI) for choline for men (550 mg) and for women (425 mg) during pregnancy (450 mg) and lactation (550 mg). **Betaine and reductions in homocysteine.** One of the functions of choline is to serve as a precursor of a compound known as betaine or trimethylglycine. Betaine aids in the remethylation of homocysteine to methionine via the enzyme betaine-homocysteine methyltransferase (BHMT), thus serving to lower homocysteine levels in the blood. Multiple studies have now shown that high dose (4-6 grams per day) betaine supplementation can significantly lower plasma homocysteine concentrations by as much as 40% after six weeks, reducing an important risk factor for atherogenesis. High-dose betaine, however, has been associated with a slight *increase* in total and LDL cholesterol by 5 to 10 mg/dL in some studies. Other studies have found that a more conservative and *dietarily* attainable dose of just 1.5 grams per day can also lower homocysteine levels by as much as 23% after six weeks Foods rich in betaine include quinoa, spinach, and beets. **Vitamin B12 and B2.** Cobalamin (vitamin B12) and riboflavin (vitamin B2) balance is thought to be an important factor in people with this polymorphism. When B12 status was low, those with the G allele had higher homocysteine levels than those with the (A;A) genotype. Individuals susceptible to low vitamin B12 status include older adults, those with digestive issues (Crohn's, colitis), post gastric bypass patients and those following vegan diets. *TMAO and choline supplementation* Recent research has suggested that nutrients such as choline, phosphatidylcholine, L-carnitine and betaine are metabolized by gut bacteria to generate trimethylamine (TMA) which is then converted into trimethylene N-oxide (TMAO) by the liver. Elevated plasma levels of TMAO may enhance platelet aggregation (clotting) and increase heart disease risk. However, the metabolism of TMAO is complex and still poorly understood in humans. Furthermore, choline is an essential nutrient in the human diet. - Read more on SNPedia SNPs Involved rs1801394(G;G)
MTHFR	rs1801131(C;C) rs1801133(C;C)	Risk for altered folate metabolism	There are common polymorphisms in the MTHFR gene (5-methylenetetrahydrofolate reductase) that converts 5,10-methylenetetrahydrofolate into 5-methylfolate using riboflavin (vitamin B2) as a cofactor. Folate serves as a precursor in two important pathways: 1. the synthesis of the DNA nucleotide thymine. 2. the generation of methyl groups which are important in epigenetics and also the conversion of homocysteine to methionine, which requires vitamin B12 as a cofactor. MTHFR catalyzes the initial step of this second pathway. **This genotype, rs1801131(C;C) and rs1801133(C;C), has two variant alleles at one polymorphisms and is normal at the other. This genotype may be associated with decreased folate levels.** The rs1801133 polymorphism is in the catalytic domain and encodes for a thermolabile form of the MTHFR enzyme having reduced activity. The rs1801131 polymorphism is in the regulatory domain of the gene and encodes a form of the enzyme that is not thermolabile. This particular polymorphism is thought to be less relevant unless found in combination with the other polymorphism. Even thought decreased enzyme activity may be seen, this genotype has not be shown to increase homocysteine levels in the blood.

Elevated homocysteine levels have previously been associated with a variety of vascular diseases including coronary artery disease, stroke, and dementia. A recent meta-analysis showed that moderate elevation of homocysteine did not significantly increase coronary heart disease.

It should be noted that research concerning the health-related impacts associated with these common MTHFR polymorphisms is still at the investigational stage. This has led 23andMe to release a statement cautioning against such inferences and supporting folate supplementation only for pregnant women.

This genotype complex involves the two most common MTHFR polymorphisms. There are other possible mutations in the MTHFR gene, some of which are thought to lead to serious conditions, such as homocystinuria, which is usually diagnosed in childhood. This is not what this loci refers to.

Supplementation and diet.

5-methylfolate*, methylcobalamin, and riboflavin.*
Supplementing with 5-methylfolate (MTHF), methylcobalamin (vitamin B12), and riboflavin (vitamin B2) may bring down homocysteine levels in these individuals**.** One study showed that **supplementation with 480µg MTHF per day significantly reduced the mean plasma tHcy concentration by 7% after 4 weeks. Despite these results, clinical trials have not been able to show that this decrease was associated with decreased disease risk.**

Betaine and reductions in homocysteine.
Choline is a precursor of betaine. Betaine aids in the remethylation of homocysteine to methionine via the enzyme betaine-homocysteine methyltransferase (BHMT), which serves to lower homocysteine levels in the blood. A meta-analysis showed that betaine supplementation of 4 to 6 g/d lowered plasma homocysteine concentration by 1.23 µmol/L in healthy adults. Reducing plasma homocysteine levels by 5 µmol/L may decrease the risk of cardiovascular disease by 20% to 30% and stroke by 40% to 60%.

Supplementation with betaine was also found to increase total and LDL cholesterol by 5 to 10 mg/dL in some studies. However, for individuals with hyperhomocysteinemia, who may be at increased risk for cardiovascular disease, the beneficial homocysteine lowering effects of betaine supplementation likely outweigh the clinically minor increase in serum lipids.

Blood biomarkers such as plasma homocysteine levels and blood lipids can aid the clinician in determining if betaine supplementation is a beneficial course of action.

TMAO and choline supplementation
Recent research has suggested that nutrients such as choline, phosphatidylcholine, L-carnitine and betaine are metabolized by gut bacteria to generate trimethylamine (TMA), which is then converted into trimethylene N-oxide (TMAO) by the liver. Elevated plasma levels of TMAO may enhance platelet aggregation (clotting) and increase heart disease risk. However, the metabolism of TMAO is complex and still poorly understood in humans. Furthermore, choline is an essential nutrient in the human diet.

- Read more about rs1801131 on SNPedia
- Read more about rs1801133 on SNPedia

SNPs Involved

rs1801131(C;C)

rs1801133(C;C)

PEMT	rs7946(C;T)	Reduced phosphatidylcholine production	Phosphatidylethanolamine-N-methyltransferase (PEMT) is an enzyme that catalyzes the synthesis of phosphatidylcholine and, thus, choline in the liver. Phosphatidylcholine is a fundamental component in all cell membranes and plays an essential role in the structure and function of the cell. **This genotype, rs7946(C;T), has been associated with lower phosphatidylcholine production in the liver.** There are common polymorphisms in the *PEMT* gene, which codes for the phosphatidylethanolamine-N-methyltransferase enzyme. The variant form (**T**) of the rs7946 polymorphism is located in the coding region of the gene and results in an enzyme with partial loss of activity. *Sleep* Phosphatidylcholine is a precursor for the neurotransmitter acetylcholine, which has been shown to play a role in promoting REM sleep. *Memory* Damage to the cholinergic system in the brain has been associated with memory deficits observed with Alzheimer's disease and other neurodegenerative diseases. Acetylcholinesterase inhibitors, which prevent the enzymatic breakdown of acetylcholine, are used as therapeutic targets in the treatment of dementia. *Fatty liver disease* In addition to the essential role that phosphatidylcholine plays in cell membranes (particularly in neurons), it is also necessary in the liver. Phosphatidylcholine is required for the liver to secrete triglycerides into very low-density lipoproteins (VLDL cholesterol). Decreased phosphatidylcholine can lead to reduced fat removal from the liver and, for that reason, may be associated with fatty liver disease. **Lifestyle interactions** *Dietary choline intake* Choline is found in foods such as eggs, meat, fish and cruciferous vegetables. Strict vegetarians may need to pay special attention to meeting their choline needs. The Food and Nutrition Board (FNB) of the Institute of Medicine (IOM) has established the Adequate Intake (AI) for choline for men (550 mg) and for women (425 mg) during pregnancy (450 mg) and lactation (550 mg).

			Phosphatidylcholine is also available in supplement form. *TMAO and choline supplementation* Recent research has suggested that nutrients such as choline, phosphatidylcholine, L-carnitine and betaine are metabolized by gut bacteria to generate trimethylamine (TMA), which is then converted into trimethylene N-oxide (TMAO) by the liver. Elevated plasma levels of TMAO may enhance platelet aggregation (clotting) and increase heart disease risk. However, the metabolism of TMAO is complex and still poorly understood in humans. Furthermore, choline is an essential nutrient in the human diet. • Read more about rs7946 on SNPedia SNPs Involved rs7946(C;T)
FADS1	rs174548(C;G)	Associated with intermediate phosphatidylcholine levels	Phosphatidylcholine is a key component of cell membranes and plays an important role in the structure of the cell. It is also a precursor for the neurotransmitter acetylcholine, which has been shown to play a role in promoting REM sleep. Damage to the cholinergic system in the brain has been shown to be plausibly associated with the memory deficits associated with Alzheimer's disease and possibly other neurodegenerative diseases. For this reason it has been a therapeutic target through the action of acetylcholinesterase inhibitors, which prevent the enzymatic breakdown of acetylcholine. **This genotype, rs174548(C;G), has been associated with having intermediate phosphatidylcholine levels.** There are common polymorphisms in the *FADS1* gene, which codes for the fatty acid delta-5 desaturase enzyme. The variant form (**G**) of the rs174548 polymorphism, located in the intronic region of the gene, is thought to produce an enzyme with reduced efficiency. Study participants (n=1,644) were genotyped and a subset (n=284 males) were tested for various metabolic parameters. Researchers found that individuals carrying the **G** allele had lower phosphatidylcholine levels than individuals with the (**C;C**) genotype. Phosphatidylcholine can be found in supplement form and its precursor choline can be found in dietary sources, such as organ meats and egg yolk. *TMAO and choline supplementation* Recent research has suggested that nutrients such as choline, phosphatidylcholine, L-carnitine and betaine are metabolized by gut bacteria to generate trimethylamine (TMA), which is then converted into trimethylene N-oxide (TMAO) by the liver. Elevated plasma levels of TMAO may enhance platelet aggregation (clotting) and increase heart disease risk. However, the metabolism of TMAO is complex and still poorly understood in humans. Furthermore, choline is an essential nutrient in the human diet. • Read more on SNPedia. SNPs Involved rs174548(C;G)
CYP2R1	rs12794714(A;G)	Genetic risk for vitamin d deficiency	Vitamin D 25-hydroxylase is an enzyme that converts vitamin D3 into 25-hydroxyvitamin D (25(OH)D), the major circulating form of vitamin D that gets converted into the active steroid hormone. **This genotype, rs12794714(A;G), has been associated with a risk for vitamin D deficiency.** There are common polymorphisms in the *CYP2R1* gene, which codes for the vitamin D 25-hydroxylase enzyme. The variant form (**A**) of the rs12794714 polymorphism, located in the exonic region of the gene, is thought to lower the conversion of D3 into 25-hydroxyvitamin D and, thus, is associated with lower circulating levels of 25(OH)D. In a genome-wide association study (GWAS) involving 1,829 women, each copy of the **A** allele was associated with 1.8 ng/mL decrease in 25(OH)D. Carrying the **A** allele has been associated with reduced longevity and higher all-cause mortality. According to the endocrine society, blood levels of 25-hydroxyvitamin D below 20 ng/mL are considered deficient, while levels less than 30 ng/mL are considered inadequate. Individuals having levels between 30-60 ng/mL are considered adequate. Meta-analyses have shown that people with serum levels of 25-hydroxyvitamin D between 40-60 ng/L have the lowest all-cause mortality. Regardless of an individual's genotype for this particular SNP, a 25-hydroxyvitamin D blood test, available from most health care providers, can provide insight into how to optimize vitamin D status. The best way to assess vitamin D levels is to get a blood test. Supplementing with 1,000 IU of vitamin D3 per day generally raises serum 25-hydroxyvitamin D levels by 5-10 ng/mL. However, individuals with the (**A;G**) genotype may require higher vitamin D supplementation doses to achieve the same serum levels as individuals without this polymorphism. A blood test for 25-hydroxyvitamin D levels following supplementation may help to guide optimal dosage. • Read more about rs12794714 on SNPedia SNPs Involved rs12794714(A;G)

GSTP1	rs1695(G;G)	Low dose mixed tocopherol (vitamin e) may benefit	The glutathione S-transferase enzyme plays a significant role in the detoxification of various harmful compounds (either from the environment or generated by normal metabolism and immune function). Glutathione is one of the most potent antioxidant systems that the body possesses and is orders of magnitude more powerful than supplemental vitamin E (alpha-tocopherol). **This genotype, rs1695(G;G), has been associated with possible anti-inflammatory benefit from a low dose (75 IU) supplemental vitamin E**. There are common polymorphisms in the *GSTP1* gene, which codes for the glutathione S-transferase enzyme. The variant form (**G**) of the rs1695 polymorphism, located in the coding region of the gene is thought to alter the activity of the enzyme. Individuals with the (**G;G**) genotype have a version of the glutathione S-transferase enzyme, with reduced activity which is less capable of detoxifying compounds that are harmful to cells. However, those with the (**A;A**) or (**A;G**) genotypes (approximately half of the population), have a form of the glutathione S-transferase enzyme with normal activity. In a study of 160 middle-aged men, subjects with the **A** allele had elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) in the blood when supplementing with vitamin E. However, those with the less active form of the GSTP1 enzyme (**G;G** genotype) had decreased IL-6 levels and thus, may receive an anti-inflammatory benefit from a low dose (75 IU) of supplemental vitamin E. • Read more about rs1695 on SNPedia SNPs Involved rs1695(G;G)

Less noteworthy

These genotypes are normal.

Gene	SNPs involved	Status	More information
FUT2	rs602662(A;A)	Higher vitamin b12 levels	Vitamin B12 (cobalamin) status depends on both dietary intake and cellular uptake via the expression of several genes. One of these genes, fucosyltransferase 2 (*FUT2*), encodes a membrane protein that is involved in vitamin B12 absorption. **This genotype, rs602662(A;A), has been associated with higher vitamin B12 levels.** There are common polymorphisms in the *FUT2* gene, which codes for the enzyme fucosyltransferase 2. The variant form, **(G)**, of the rs602662 polymorphism (also known as G772A), is located in the coding region of the gene and may result in reduced enzyme activity. In a meta-analysis of 3 genome-wide association studies (GWAS) (n=4763) the A allele was associated with higher levels of plasma vitamin B12. In a separate GWAS of three populations (n=2930) carriers of the **A** allele had higher serum levels of vitamin B12 when compared to **(G;G)** individuals. Investigators found that for each copy of the **A** allele there was a 44.2 pg/mL increase in vitamin B12 levels. In a cross-sectional study of 3114 Canadian individuals, investigators confirmed the association of this polymorphism with vitamin B12 status. Participants with the **A** allele had a lower risk of being vitamin B12 deficient (< 148 pmol/L) than those with the **G** allele. In addition to polymorphisms such as this one, other factors can affect B12 status. Factors known to reduce B12 absorption include age (over 60 years), following a strict vegetarian diet, prolonged use of antacid medications, bariatric surgery, and celiac disease. In some situations, clinical signs of B12 deficiency may take years to develop because vitamin B12 is stored in the body. • Read more about rs602662 on SNPedia SNPs Involved rs602662(A;A)
MTHFD1L	rs6922269(G;G)	Normal risk for cardiovascular disease	There are common polymorphisms in the MTHFD1L gene that codes for an enzyme (5,10-methylenetetrahydrofolate dehydrogenase NADP+ dependent 1-like) involved in the synthesis of tetrahydrofolate (THF) in the mitochondria. THF is important in several biosynthetic pathways as well as cellular methylation by aiding in the regeneration of methionine from homocysteine. **This genotype, rs6922269 (G;G), is associated with normal risk for cardiovascular disease (CAD).** The polymorphism occurs within the intronic region of the gene and was associated with increased risk for CAD in two large studies (Samani et al,2007) and (Wellcome Trust Case Control Consortium) in carriers of the **A** allele. In addition, a meta-analysis of 12 studies showed that this risk association was not correlated with conventional biomarkers for CAD such as blood lipids, glucose etc. This polymorphism was found to be associated with early-onset CAD in a study of 1,988 subjects with an MI or vascular surgery before age 66 and with a strong family history of CAD as compared to control subjects. The **A** allele was found in approximately 25% of the study population and the study

showed a 23% increased risk of CAD per copy of the **A** allele. The authors suggest rs6922269 may increase CAD risk by altering plasma homocysteine levels.

- Read more about rs6922269 on SNPedia

SNPs Involved

rs6922269(G;G)

MTHFD1 | rs2236225(C;C) | Normal and not associated with increased risk of choline deficiency at adequate dietary choline intake levels

There are common polymorphisms in the MTHFD1 gene that codes for a trifunctional enzyme (5,10-methylenetetrahydrofolate dehydrogenase) involved in folate metabolism. Folate and choline metabolism are closely linked and changes in folate status can result in changes in choline status and vice versa.

Choline is involved in three major pathways:

1. Phosphatidylcholine synthesis via the CDP-choline pathway
2. Methyl donor to form betaine which facilitates the methylation of homocysteine to methionine, important in DNA synthesis
3. Acetylcholine synthesis

This genotype, rs2236225(C;C), is not associated with an increased risk of choline deficiency at adequate dietary choline intake levels. Individuals with the (C;T) and (T;T) genotype, however, may have increased risks for neural tube defects, cancer, choline deficiency and susceptibility to non alcoholic fatty liver disease (NAFLD) when individuals are deprived of choline.

Lifestyle interactions

Dietary choline intake. Choline is found in foods such as eggs, meat, fish and cruciferous vegetables. Strict vegetarians may need to pay special attention to meeting their choline needs. The Food and Nutrition Board (FNB) of the Institute of Medicine (IOM) has established the Adequate Intake (AI) for choline for men (550 mg) and for women (425 mg) during pregnancy (450 mg) and lactation (550 mg).

TMAO and choline supplementation
Recent research has suggested that nutrients such as choline, phosphatidylcholine, L-carnitine and betaine are metabolized by gut bacteria to generate trimethylamine (TMA), which is then converted into trimethylene N-oxide (TMAO) by the liver. Elevated plasma levels of TMAO may enhance platelet aggregation (clotting) and increase heart disease risk. However, the metabolism of TMAO is complex and still poorly understood in humans. Furthermore, choline is an essential nutrient in the human diet.

- Read more on SNPedia

SNPs Involved

rs2236225(C;C)

COQ2 | rs4693596(C;T) | Normal risk for myopathy with statin use

This gene encodes for coenzyme Q10 (CoQ10), an enzyme produced by every cell in the body. It plays a key role in energy metabolism and is a powerful antioxidant. People who have variants of the gene for CoQ10 (known as COQ2) may be at greater risk for developing statin-related myopathy.

While **this genotype, rs4693596(C;T), is still generally considered normal** the C;C variant has been associated twice the risk of developing statin-related myopathy in a study of nearly 300 people of European ancestry who were taking statins.

- Read more on SNPedia

Statins, myopathy & supplemental CoQ10

Statins are able to reduce cholesterol by inhibiting the action of an enzyme known as HMG-CoA reductase. This inhibition prevents the production of mevalonate, which is a precursor for both cholesterol *and* coenzyme Q10 (CoQ10), a fat-soluble substance found in the mitochondria of respiring cells. CoQ10 is essential for cellular energy production in the form of ATP. It also protects against oxidative stress and helps the body recycle key antioxidants such as vitamin E.

Blood levels of CoQ10 can drop by more than half with statin treatment, and some research suggests that in the setting of CoQ10 deficiency, a concurrent ATP deficiency might induce painful myopathy. In addition, a decrease in CoQ10 levels tends to be accompanied by a higher lactate to pyruvate ratio in the blood, which is commonly seen in myopathy – an indication that the mitochondrial respiratory system is not functioning properly.

Some research suggests that taking CoQ10 supplements may reduce symptoms of myopathy; however, larger randomized controlled trials need to be done to establish definitive conclusions.

In a small, randomized controlled study, 32 adults who had symptoms of myopathy when taking statins were given either CoQ10 or vitamin E for 30 days. Those who took CoQ10 reported having 40% less pain, but those who took vitamin E saw no improvement in their symptoms.

In a randomized, placebo-controlled trial, 51 adults with coronary artery disease who were taking statins were given either a CoQ10 supplement or a placebo for 12 weeks. At the end of the trial, those who were taking the CoQ10 supplement had higher levels of vitamin E and antioxidant enzymes and lower levels of inflammatory markers in their blood compared to those taking the placebo.

An analysis of 5 randomized controlled studies involving more than 250 people taking CoQ10 supplementation for symptoms of statin-induced myopathy concluded that most of the participants experienced some reduction in their myopathy symptoms; however, the findings were not

			statistically significant. • Read more about CoQ10 in *Coenzyme Q10 (CoQ10): In Depth*, an article from the NIH's Office of Dietary Supplements SNPs Involved rs4693596(C;T)
vitamin D binding protein	rs2282679(A;A)	No genetic risk for vitamin d deficiency	GC Vitamin D binding protein is a member of the albumin family involved in the storage and transport of vitamin D throughout the body. The vitamin D binding protein affects the delivery of 25-hydroxyvitamin D (precursor to vitamin D hormone) and activated vitamin D (1,25-dihydroxyvitamin D) to target organs, as well as the clearance of vitamin D metabolites from circulation. **This genotype, rs2282679(A;A), has been associated with no risk for vitamin D deficiency.** There are common polymorphisms in the *GC* gene, which codes for the vitamin D binding protein. The variant form (**C**) of the rs2282679 polymorphism, located in the intronic region of the gene, is thought to result in a protein that binds less efficiently to vitamin D. The (**A;A**) genotype has not been associated with an increased risk of vitamin D deficiency (this does not by itself guarantee optimal blood status of vitamin D). However, in a genome-wide association study (GWAS) involving 4501 individuals, the **C** allele was associated with lower circulating 25-hydroxyvitamin D levels. According to the endocrine society, blood levels of 25-hydroxyvitamin D below 20 ng/mL are considered deficient, while levels less than 30 ng/mL are considered inadequate. Individuals having levels between 30-60 ng/mL are considered adequate. Meta-analyses have shown that people with serum levels of 25-hydroxyvitamin D between 40-60 ng/L have the lowest all-cause mortality. Regardless of an individual's genotype for this particular SNP, a 25-hydroxyvitamin D blood test, available from most health care providers, can provide insight into how to optimize vitamin D status. • Read more about rs2282679 on SNPedia • Read more about 25-hydroxyvitamin D blood levels and all-cause mortality. SNPs Involved rs2282679(A;A)
BCMO1	rs12934922(A;T) rs7501331(C;C)	Normal conversion of beta-carotene into retinal	BCMO1, or beta-carotene 15,15'-monooxygenase, is involved in the metabolism of beta-carotene into retinal, the pro-vitamin A. Provitamin A carotenoids are converted to vitamin A by BCMO1 expressed in enterocytes of the intestinal mucosa. There are a cluster of polymorphisms in the *BCMO1* gene that can affect the efficiency at which beta-carotene can be converted into the active form of Vitamin A known as retinal. This particular combined genotype for the rs12934922 and rs7501331 SNPs, however, is not associated with a severe reduction in conversion of beta-carotene into retinyl esters. • Read more on SNPedia (rs7501331). • Read more on SNPedia (rs12934922). SNPs Involved rs12934922(A;T) rs7501331(C;C)
vitamin D binding protein	rs4588(C;C)	Normal response to high-dose vitamin d supplementation	This gene encodes for the vitamin D binding protein which affects the delivery of 25-hydroxyvitamin D (precursor to vitamin D hormone) and activated vitamin D (1,25-dihydroxyvitamin D) to target organs, as well as clearance of vitamin D metabolites from the circulation. **This genotype (C;C) is associated with a normal response to high-dose vitamin D supplementation**. However, studies have shown that individuals with the (A;C) or (A;A) genotype have a much higher response to high-dose (4,000 IU of vitamin D) than people without the genotype. It is known that supplementing with 1,000 IU of vitamin D3 per day generally raises serum 25-hydroxy vitamin D levels by 5-10 ng/ml. A 25-hydroxy vitamin D blood test after supplementation may help indicate how much to supplement with. According to the endocrine society, blood levels of 25-hyroxyvitamin D below 20 ng/ml are considered deficient, less than 30 ng/ml is inadequate. Individuals with levels between 30-60 ng/ml are considered adequate. Meta-analyses have shown that people with serum levels between 40-60 ng/ml have the lowest all-cause mortality. • Read more on SNPedia. • Read more about genetically low vitamin D and higher all-cause mortality. • Read more about genetic risk for vitamin D deficiency and multiple sclerosis. SNPs Involved rs4588(C;C)
CYP2R1	rs2060793(G;G)	No genetic risk for	This SNP is one of the common polymorphisms in the CYP2R1 gene (called vitamin D 25-

		vitamin d deficiency	hydroxylase) that converts vitamin D3 into 25-hydroxyvitamin D, the major circulating form of vitamin D that gets converted into the active steroid hormone. **This genotype, rs2060793(G;G), is normal** Individuals with the rs2060793(A;A) or (A;G) genotype, however, can have a lower conversion of D3 into 25-hydroxyvitamin D and, thus, this genotype is also associated with lower circulating levels of 25-OHD. Having lower circulating levels of 25-OHD has been associated with reduced longevity and higher all-cause mortality. The best way to assess vitamin D levels is to get a blood test. It is known that supplementing with 1,000 IU of vitamin D3 per day generally raises serum 25-hydroxy vitamin D levels by 5-10 ng/ml. This may not be the case for people with polymorphisms that lower circulating levels of vitamin D and those individuals may require higher vitamin D supplementation doses to achieve the same serum levels as individuals without these polymorphisms. A 25-hydroxy vitamin D blood test after supplementation may help indicate how much to supplement with. According to the endocrine society, blood levels of 25-hyroxyvitamin D below 20 ng/ml are considered deficient, less than 30 ng/ml is inadequate. Individuals with levels between 30-60 ng/ml are considered adequate. Meta-analyses have shown that people with serum levels between 40-60 ng/ml have the lowest all-cause mortality. • Read more on SNPedia. • Read more about other SNPs that are associated with a higher all-cause mortality. • Read more about genetic risk for vitamin D deficiency and multiple sclerosis. SNPs Involved rs2060793(G;G)
vitamin D binding protein	rs7041(G;G)	No genetic risk for vitamin d deficiency	GC Vitamin D binding protein is a member of the albumin family involved in the storage and transport of vitamin D throughout the body. The GC gene encodes for the vitamin D binding protein which affects the delivery of 25-hydroxyvitamin D (precursor to vitamin D hormone) and activated vitamin D (1,25-dihydroxyvitamin D) to target organs, as well as the clearance of vitamin D metabolites from circulation. **This genotype, rs7041(G;G), has been associated with low vitamin D levels.** There are common polymorphisms in the *GC* gene, which codes for the vitamin D binding protein. The variant form (**T**) of the rs7041 polymorphism, located in the coding region of the gene, is thought to result in a protein that binds less efficiently to vitamin D. The (**G;G**) genotype is not associated with an increased risk of vitamin D deficiency. However, individuals with the (**T;T**) or (**G;T**) genotype may have an increased risk of poor vitamin D status. Genetically low vitamin D levels have been associated with reduced longevity and higher all-cause mortality. In addition, people with a genetic predisposition to low vitamin D levels have been shown to have a two-fold increased risk for multiple sclerosis as a consequence of low 25-hydroxyvitamin D levels. According to the endocrine society, blood levels of 25-hydroxyvitamin D below 20 ng/mL are considered deficient, while levels less than 30 ng/mL are considered inadequate. Individuals having levels between 30-60 ng/mL are considered adequate. Meta-analyses have shown that people with serum levels of 25-hydroxyvitamin D between 40-60 ng/L have the lowest all-cause mortality. Regardless of an individual's genotype for this particular SNP, a 25-hydroxyvitamin D blood test, available from most health care providers, can provide insight into how to optimize vitamin D status. • Read more about rs7041 on SNPedia SNPs Involved rs7041(G;G)
CASR	rs1801725(G;G)	Normal serum calcium levels	The calcium-sensing receptor (CaSR) is a protein involved in regulating calcium homeostasis in the body. The majority of the body's calcium is stored in the bones and teeth, with less than one percent in the bloodstream. CaSR participates in a negative feedback pathway that tightly regulates serum calcium levels. CaSR detects when calcium levels are low and signals the parathyroid hormone to resorb calcium from the bones as well as decrease calcium excretion from the kidneys. **This genotype, rs1801725(G;G), has been associated with normal serum calcium levels.** There are common polymorphisms in the *CASR* gene, which codes for the calcium-sensing receptor. The variant form (**T**) of the rs1801725 polymorphism (also known as Ala986Ser), located in the exonic region of the gene, is thought to result in a less active receptor with decreased sensitivity to calcium. The (**G;G**) genotype is not associated with increased serum calcium levels. However, individuals carrying the **T** allele may have increased serum calcium levels, possibly associated with lower bone mineral density. Researchers identified that the rs1801725 polymorphism is involved in determining extracellular calcium concentrations. By studying healthy adult women (n=163), they observed that individuals carrying the **T** allele had higher serum concentrations of calcium than those with the more common (**G;G**) genotype. Researchers contend that this SNP may be related to certain bone disorders. The association of the **T** allele with higher serum calcium levels was confirmed in a study of Italian men and women (n=377) and another study of Finnish adults (n=339). In a meta-analysis of genome-wide association studies (GWAS) involving 12,865 individuals of European and Indian Asian descent, the **T** allele was associated with increased serum calcium

levels. These findings were confirmed in a genome-wide association study (GWAS) involving 36,400 individuals. Investigators observed that carrying the **T** allele was associated with having a lower bone mineral density as measured at the lumbar spine.

- Read more about rs1801725 on SNPedia

SNPs Involved

rs1801725(G;G)

Unavailable

Depending on the dataset you provided for report generation, not all possible report entries may be available. *This is normal.* In this case, the following groups were excluded because the data you upload did not contain the requisite SNPs:

SLC23A2, SLC23A1, PEMT, CYP2R1, NOS3

Viral Report v1

Source: Cooper_Beaman_23andmenew_v4_Full_20190517100124.zip

Created at June 10 at 5:16 PM PST

This report includes some of the SNPs that have been studied in the context of SARS-CoV-2, SARS-CoV-1, ACE2 gene expression, acute respiratory distress syndrome (ARDS), flu risk, and more.

Noteworthy

These genotypes are the ones that are potentially worth being aware of.

Gene	SNPs involved	Status	More information
IL18	rs1946518(G;T)	Associated with slightly increased viral load in sars-cov-1 infection	Interleukin 18 (IL18) is a potent proinflammatory cytokine expressed in the lung. IL18 performs several functions in the immune response, including stimulation of interferon-gamma (IFN-γ) release from natural killer cells and T lymphocytes. Interestingly, IFN-γ has been shown to directly inhibit the replication of certain viruses, including SARS CoV-1. **This genotype, rs1946518(G;T), has been associated with slightly increased viral load in SARS-CoV-1.** There are common polymorphisms in the *IL18* gene, which codes for the interleukin 18 protein. The variant form (**T**) of the rs1946518 polymorphism, located in the promoter region of the gene, is thought to disrupt a transcription factor-binding site and lead to reduced IL18 production. In the SARS-CoV-1 outbreak of 2003, patients experienced inter-individual differences in nasopharyngeal viral loads, with higher viral load predicting poor prognosis. To determine whether host genetic factors accounted for some of these differences, researchers analyzed immunity related genes in 94 SARS CoV-1 patients. Investigators observed that patients with the **T** allele of the rs1946518 polymorphism exhibited increased risk of virus shedding as compared to those with the (**G;G**) genotype. The authors suggest that in a pandemic where no preexisting immunity exists, the host's innate immunity will be important to decrease viral burden and potentially influence the clinical outcome. • Read more about rs1946518 on SNPedia SNPs Involved rs1946518(G;T)
IL1A	rs1800587(C;T)	Associated with slight increased viral load in sars-cov-1 infection	Interleukin 1 alpha (IL1A) is a proinflammatory cytokine located both intracellularly and bound to cell membranes. IL1A performs several roles in the immune response. Functioning as an alarmin, IL1A alerts the host to infection or cell damage and triggers an inflammatory response. While much remains unknown about 1L1A, some research suggests that it gauges the level of infection or damage and signals other immune response molecules to launch the appropriate response. **This genotype, rs1800587(C;T), has been associated with slightly increased viral load in SARS-CoV-1 infection.** There are common polymorphisms in the *IL1A* gene, which codes for the interleukin 1 alpha protein. The variant form (**T**) of the rs1800587 polymorphism (also known as -889 C>T), is located in the 5 prime untranslated region of the gene and may alter the level of gene expression. In the SARS-CoV-1 outbreak of 2003, patients experienced inter-individual differences in nasopharyngeal viral loads, with higher viral load predicting poor prognosis. To determine whether host genetic factors accounted for some of these differences, researchers analyzed immunity related genes in 94 SARS CoV-1 patients. Investigators observed that patients with the **T** allele of the rs1800587 polymorphism exhibited increased risk of virus shedding as compared to those with the (**C;C**) genotype. The authors suggest that in a pandemic where no preexisting immunity exists, the host's innate immunity will be important to decrease viral burden and potentially influence the clinical outcome. • Read more about rs1800587 on SNPedia SNPs Involved rs1800587(C;T)
OAS1	rs2660(A;G)	Associated with a slightly protective role against sars1	Oligoadenylate synthetase 1 (OAS1) is an interferon-induced protein with antiviral properties. OAS1 activates latent RNase L, a ribonuclease enzyme capable of degrading viral RNA and inhibiting replication. **This genotype, rs2660(A;G), has been associated with a slightly protective role against SARS1.** There are common polymorphisms in the *OAS1* gene, which codes for the 2',5'-oligoadenylate synthetase 1 enzyme. The variant form (**G**) of the rs2660 polymorphism (also known as Arg397Gly), located in the exonic region of the gene, is thought to affect a splicing site resulting in an OAS1 enzyme with higher activity.

			In a case-control study of Chinese subjects (n = 66 confirmed SARS1 patients and 64 serologically negative close contacts), this polymorphism was associated with SARS-CoV-1 infection. Carriers of the **G** allele were more likely to be in the control group than the case group, suggesting a possible protective effect of the **G** allele. The authors suggest that among Chinese individuals the **G** allele confers protection against SARS-CoV-1 infection. The estimated frequencies of the **G** allele are 41.7% among European-Americans, 10.9% among African-Americans, 18.2% among Japanese, and 36.4% among Chinese individuals. • Read more about rs2660 on SNPedia SNPs Involved rs2660(A;G)
IL17A	rs2275913(G;G)	Associated with an increased risk of developing acute respiratory distress syndrome	Interleukin 17 (IL17), also known as IL17A is a proinflammatory cytokine produced by activated memory CD4 + and T-cells. Some patients with acute respiratory distress syndrome have elevated levels of IL17. IL17 amplifies the inflammatory response by attracting other immune cells. While IL17 is useful to defend against pathogens, excessive IL17 may pose problems. The cytokine storm, a characteristic feature of severe COVID-19, involves the expression of mass amounts of proinflammatory cytokines like IL17. **This genotype, rs2275913(G;G), has been associated with an increased risk of developing acute respiratory distress syndrome.** There are common polymorphisms in the *IL17A* gene, which codes for the interleukin 17 protein. The variant form (**A**) of the rs2275913 polymorphism (also known as G197A), located in the promoter region of the gene may affect gene expression. Acute respiratory distress syndrome (ARDS) is a serious form of respiratory failure that occurs in some critically ill patients due to uncontrolled inflammation in the lungs. In a study of 210 patients with ARDS and 210 at-risk patients without ARDS, carriers of the **A** allele exhibited a reduced risk of ARDS as compared to patients with the (**G;G**) genotype. Furthermore, patients with the **A** allele had a decreased 30-day mortality risk compared to patients with the (**G;G**) genotype. The authors note that **A** allele carriers had lower IL17 serum levels, which they suggest may provide the patient with some protection from developing ARDS. paper While further studies are needed, the regulation of IL17 might be involved in the initiation and progression of ARDS, and this polymorphism may be a marker to predict the risk of ARDS. • Read more about rs2275913 on SNPedia SNPs Involved rs2275913(G;G)

Less noteworthy

These genotypes are normal.

Gene	SNPs involved	Status	More information
MX1	rs17000900(C;C)	Associated with normal susceptibility to sars-cov-1 infection	Myxovirus resistance A (MxA) is an intracellular protein with antiviral properties. Levels of MxA protein in the cells of healthy individuals are low, however, upon viral infection, these proteins are induced by interferons. **This genotype, rs17000900(C;C), has been associated with normal susceptibility to SARS 1 coronavirus infection.** There are common polymorphisms in the *MX1* gene, which codes for the myxovirus resistance A protein. The variant form (**A**) of the rs17000900 polymorphism (also known as -123 C>A), located in the promoter region of the gene, increases promoter activity leading to higher gene expression and production of the myxovirus resistance A protein. In a case-control genetic-association study (n = 817 SARS1 patients and 422 seronegative household members), researchers observed that carriers of the **A** allele had a lower risk of SARS-CoV-1 infection than those with the (**C;C**) genotype. The authors propose that the **A** allele of this polymorphism enhances the basal expression of the *MX1* gene without requiring induction by interferon, which may be significant in a disease such as SARS1 where the virus suppresses interferons. In this study, **A** allele carriers exhibited a decreased susceptibility to SARS-CoV-1 infection, however the polymorphism was not associated with clinical outcomes. The authors conclude that this SNP may be useful in assessing susceptibility to infectious diseases, particularly those that are similar to SARS CoV-1. • Read more about rs17000900 on SNPedia SNPs Involved rs17000900(C;C)

MBL2	rs1800450(G;G)	Associated with decreased susceptibility to sars-cov-1 infection	Mannose-binding lectin (MBL) is a protein in the blood that plays a critical role in the innate immune response and is considered to be a first-line host defense against pathogens. Repeating mannose and N-acetylglucosamine sugar motifs are found on the surfaces of bacterial and fungal cells and viruses, but not on mammalian cells. The SARS-CoV-1 S protein, believed to play a critical role in infection, also exhibits these repeating mannose units. The MBL protein binds to an invader via these motifs activating the complement system and initiating opsonophagocytosis (a process that signals the immune system to engulf and destroy a pathogen). **This genotype, rs1800450(G;G), has been associated with decreased susceptibility to SARS-CoV-1 infection.** There are common polymorphisms in the *MBL2* gene, which codes for the mannose-binding lectin protein. The variant form (**A**) of the rs1800450 polymorphism (also known as Gly54Asp), located in the exonic region of the gene, leads to an altered protein structure which degrades more rapidly, resulting in lower plasma concentrations of the MBL protein. In a study of 352 SARS1 patients and 392 healthy control subjects, individuals with the **A** allele had a higher risk of becoming infected with the SARS-CoV-1 virus as compared to those with the (**G;G**) genotype. However, researchers did not find an association between the **A** allele and disease severity. The authors suggest that this polymorphism may play a role in activating the innate immune response. Individuals with the (**A;G**) genotype exhibit one-tenth the level of MBL protein as compared to those with the (**G;G**) genotype. Individuals with the (**A;A**) genotype had undetectable MBL plasma levels. A deficient level of MBL protein may be a critical factor in determining the susceptibility to SARS1 during the initial phase of infection before the production of antibodies. Researchers replicated these findings in a study including 4 case-control populations (n = 932 patients with SARS1 and 982 control subjects). Subjects with low serum MBL levels were at greater risk of SARS-CoV-1 infection as compared to individuals with the (**G;G**) genotype. Again, no association was found between this polymorphism and disease severity. The authors suggest that a deficiency in MBL may be a factor influencing the susceptibility to SARS-CoV-1 infection. The adaptive immune response involves pathogen recognition and the production of specific antibodies. However, this process takes time, often several days. The innate immune response is vital during the early phase of infection before the production of sufficient antibodies. The capability of an individual's innate immune response may partly explain the variable response to the SARS-CoV-1 virus. • Read more about rs1800450 on SNPedia SNPs Involved rs1800450(G;G)
AHR	rs2066853(G;G)	Associated with a decreased risk of ards in patients with pneumonia	Aryl hydrocarbon receptor (AhR) is a transcription factor that controls several genes involved in diverse cellular processes, including inflammation, immune regulation, and the detoxification of xenobiotic substances. A mounting body of evidence suggests that AhR plays a critical role in the intersection between the innate and adaptive immune system, helping to maintain immune homeostasis. Furthermore, AhR may be involved in controlling pathways that protect the lungs from oxidative stress. **This genotype, rs2066853(G;G), has been associated with a decreased risk of ARDS in patients with nosocomial pneumonia.** There are common polymorphisms in the *AHR* gene, which codes for the aryl hydrocarbon receptor. The variant form (**A**) of the rs2066853 polymorphism (also known as Arg554Lys) is located in the coding region of the gene and is thought to decrease gene expression. Nosocomial (hospital-acquired) pneumonia is a complication of trauma that can progress to acute respiratory distress syndrome (ARDS), a serious form of respiratory failure due to excessive inflammation in the lungs. Researchers conducted a prospective study to evaluate if host genetic factors affect whether individuals progress from pneumonia to ARDS. They studied 419 hospitalized patients at high risk of critical illness and 331 healthy controls. Of the hospitalized patients, 268 developed pneumonia, and 151 patients did not. Investigators observed that in patients with hospital-acquired pneumonia, carriers of the **A** allele were more likely to develop ARDS than patients with the (**G;G**) genotype. The authors propose that variants in the *AHR* gene may be involved with increasing lung inflammation and the development of ARDS. • Read more about rs2066853 on SNPedia SNPs Involved rs2066853(G;G)
CD55	rs2564978(C;T)	Associated with normal influenza a disease severity	Complement regulatory protein CD55 (CD55), also known as decay accelerating factor (DAF), occurs as both a membrane-bound and soluble protein that is involved in regulating the complement system of the innate immune response. The complement system is a host-defense strategy against invading pathogens. CD55 binds to complement proteins and induces an accelerated decay, thus keeping the complement system in check so that it does not damage host cells. **This genotype, rs2564978(C;T), has been associated with normal influenza A disease severity.** There are common polymorphisms in the *CD55* gene, which codes for the complement regulatory protein CD55. The variant form (**T**) of the rs2564978 polymorphism, located in the intronic region of the gene, decreases gene expression and results in lower CD55 protein synthesis. This SNP serves as a proxy for a 21 base pair insertion/deletion that occurs in the promoter region of the gene.

			Individuals with the **C** allele possess the insertion, and those with the **T** allele carry the deletion. The influenza H1N1 pandemic of 2009 typically produced mild infection, however, some patients developed severe pneumonia. To investigate whether host genetic factors influenced disease severity, researchers performed a small genome-wide association study (GWAS) involving 25 patients with severe H1N1 infection and 26 controls with mild symptoms. They identified polymorphisms in the *CD55* gene that strongly associated with disease severity. In a second study of 425 Chinese patients with severe (n = 177) or mild (n = 248) disease, investigators observed that the (**T;T**) genotype associated with severe disease as compared to carriers of the **C** allele. Moreover, the investigators report that individuals with the (**T;T**) genotype had lower monocyte CD55 levels compared to **C** allele carriers. The authors propose that CD55 plays a role in determining the severity of H1N1 by protecting respiratory epithelial cells from complement damage. Since **T** allele carriers have lower CD55 levels, they are more prone to severe disease. In another gene association study (n = 275 patients with avian H7N9 or pandemic H1N1 influenza) the (**T;T**) genotype was associated with an increased incidence of the need for hospitalization. In a study of European individuals from northern Greece with severe (*n* = 59) or mild (*n* = 51) H1N1 infection, the (**T;T**) genotype was associated with an increased mortality risk as compared to carriers of the **C** allele. CD55 inhibits an overactive complement system. The researchers propose that individuals with the (**T;T**) genotype who have a deletion in the promoter of the *CD55* gene, and thus lower CD55 levels, may generate a stronger complement activation, which may damage respiratory epithelial cells leading to worse outcomes. The authors state that their findings are preliminary and that more research is needed. • Read more about rs2564978 on SNPedia SNPs Involved rs2564978(C;T)
TLR4	rs4986790(A;A)	Associated with normal risk for septic shock	Toll-like receptor 4 (TLR4) is a member of a family of receptors found on the surfaces of macrophages and dendritic cells. As part of the innate immune response, TLRs recognize specific bacterial and viral proteins and target them for destruction. The interaction of TLR4 and a viral protein leads to the production of pro-inflammatory cytokines. Uncontrolled activation of the TLR4 pathway is a feature of sepsis and cytokine storm. **This genotype, rs4986790(A;A), has been associated with normal risk for septic shock.** There are common polymorphisms in the *TLR4* gene, which codes for the toll-like receptor 4 protein. The variant form (**G**) of the rs4986790 polymorphism (also known as Asp299Gly) is located in the coding region of the gene. In a study of 91 patients in the ICU with septic shock as a result of a bacterial infection and 73 healthy controls, the **G** allele of this polymorphism was only observed in septic shock patients The authors propose that individuals with the **G** allele might be predisposed to develop septic shock when infected with gram-negative bacteria. Investigators examined 99 hospitalized infants with severe respiratory syncytial virus (RSV) bronchiolitis, 88 infants with mild RSV bronchiolitis, and 90 healthy adults. They observed that the **G** allele was associated with severe RSV bronchiolitis. Animal studies show that deleting the TLR4 gene in mice renders the animals resistant to a lethal influenza virus. • Read more about rs4986790 on SNPedia SNPs Involved rs4986790(A;A)
TMPRSS2	rs12329760(C;C)	Predicted to have normal susceptibility to the a2a (d614g) strain of sars-cov-2	Transmembrane serine protease 2 (TMPRSS2) is an enzyme expressed in cells of the lung, ileum, and nasal passage, that participates in both physiological and pathological activities. In some viral infections, including influenza and the coronavirus diseases, SARS1 (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome), this protease cleaves a viral protein, facilitating its entry into the host cell. The SARS-CoV-2 spike (S) glycoprotein exploits the ACE2 receptor to gain entry into host cells. For the viral and cell membranes to fuse, a protease, such as TMPRSS2, must cleave the spike (S) protein in a process known as priming. SARS-CoV-2 was recently shown to use the ACE2 receptor for binding and the TMPRSS2 protease for S protein priming. **This genotype, rs12329760(C;C), has been predicted to have normal susceptibility to the A2a (D614G) strain of SARS-CoV-2.** There are common polymorphisms in the TMPRSS2 gene, which codes for the transmembrane serine protease 2 enzyme. The variant form (**T**) of the rs12329760 polymorphism (also known as V160M), located in the coding region of the gene, is thought to disrupt a pathogen interaction site. Viruses are constantly mutating, and only changes that do not affect essential viral functions persist in the population. SARS-CoV-2 has mutated into at least 10 subtypes, with subtype A2a spreading widely across Europe and North America, but not East Asia. Subtype A2a, also known as D614G, has a mutation in the spike protein that creates an additional enzyme site where the S protein can be cut and activated. This mutation may allow the virus to more easily enter host cells. The **T** variant of this polymorphism is predicted to cleave the spike protein of the A2a strain less effectively (than the **C** allele), thus limiting the virus's entry into cells. The **T** allele is negatively correlated (r^2 = -0.4) with the frequency of the A2a viral subtype, suggesting that individuals with

the (**T;T**) genotype might have some protection against this strain of the virus The allele frequencies of this polymorphism differ between populations, with ~19 percent of East Asians having the (**T;T**) genotype, while only ~7 percent of Europeans and ~4 percent of North Americans possess the (**T;T**) genotype. These varying frequencies may partly explain why the A2a strain spread less rapidly in East Asia. Further research is needed to determine if these preliminary findings are validated in other studies.

- Read more about rs12329760 on SNPedia

SNPs Involved

rs12329760(C;C)

Unavailable

Depending on the dataset you provided for report generation, not all possible report entries may be available. *This is normal.* In this case, the following groups were excluded because the data you upload did not contain the requisite SNPs:

IFITM3, ACE2, ACE2, FGL2, TLR1