

PERSONAL GENETIC REPORT

CARRIER STATUS



Protected Health Information

Hello Timothy

Pathway Genomics is pleased to present your Carrier Status genetic report. This report is based on a DNA test that you recently submitted. We have scanned your DNA for single nucleotide polymorphisms (SNPs) that have known associations with recessive genetic conditions listed on your report.

You'll notice that your report contains a list of all 76 recessive conditions we test for and illustrates if a known marker is present for any of the conditions. If you have a condition that indicates you have a marker present, this means you are simply a carrier for that condition and will not develop the disease. If, however, you are planning to have children, it's a good idea to test your prospective partner as well, to ensure they also don't carry a recessive mutation in the same gene.

In order to develop one of these monogenic (single gene) diseases, a person must have two disease-causing mutations (also known as alleles or variants) — one on each copy of the gene involved in the condition. Because, as humans, we inherit one copy of each gene from our parents, the disease-causing variant(s) must be present in both the mother and father's copy in order to develop the disease.

Page 4 of your report explains what it means to be a carrier and how these recessive diseases (and carrier status) are passed from generation to generation.

It's important to understand that, while Pathway Genomics tests for the most common mutations known today for each condition reported, there always exists the potential for additional rare mutations that could also be associated with any of the conditions tested. Therefore, while Pathway can certainly deliver greater peace of mind before pregnancy, there is no test today that can give 100% assurance that your child will not inherit a potentially debilitating disease.

Our CAP and CLIA accredited and California state-licensed laboratory tested over 75 of your genes to provide you with the latest, most comprehensive, and scientifically-advanced report that associates your specific genotype with genome-wide association studies (GWAS) conducted all over the world for your specific ethnicity.

Pathway is here to help. If you have questions or concerns regarding any aspect of this report, please contact our staff of genetic, medical or nutritional counselors by logging in to your Pathway Genomics account at www.pathway.com, or call us at (877) 505-7374.

We are delighted we can help you plan your pregnancy and future.



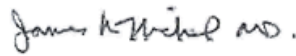
Michael P. Nova, M.D.
Chief Medical Officer

Personal Details**Name:** Timothy Parrett**DOB:** Sep 26, 1967**Gender:** Male**Ethnicity:** Caucasian**Indication:** Population Screening**Report Date:** Dec 12, 2011**Received Date:** Nov 16, 2011**Ordering Healthcare Professional**

Linda Wasserman MD, PHD

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San Diego CA, 92121 US

NPI: 1033265780**Lab Director:** James R. Nickel, M.D.**Test Performed / Method**

Genotyping by array-based evaluation of multiple molecular probes

Laboratory Info**Accession #:** B0002960**Activation Code:** PGKZF-AMUKL**Specimen Source:** Saliva**Collected Date:** Not provided**Carrier Status**

You are a carrier for 4 conditions

Alpha-1 Antitrypsin Deficiency

Ethylmalonic Aciduria

Hemochromatosis

MTHFR Deficiency

We tested your DNA for
76 single gene conditions.

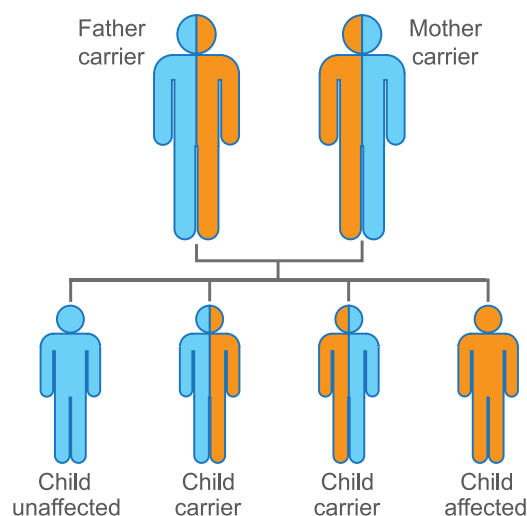
Introduction

Recessive genetic diseases are caused by mutations that can be carried silently in a family for generations, only to be discovered when two carriers have a child with the condition. They are usually single-gene disorders (also known as monogenic disorders), meaning that mutations in a single gene are responsible for the disease.

The most well-known recessive disorders are diseases like cystic fibrosis, nonsyndromic hereditary hearing loss, Tay-Sachs disease, and beta-thalassemia, although there are thousands more. Pathway Genomics tests for hundreds of mutations for recessive genetic diseases. This test can tell you whether you are a carrier of these mutations, which you may pass on to your children. If your partner is also tested, this test will let you know whether your children could inherit a disease-causing mutation from both of you and potentially be affected by the condition.

What it means to be a carrier

Diseases with a recessive inheritance pattern are caused when a person has two disease-causing mutations (also called alleles or variants), one on each copy of the gene involved in the condition. Since we inherit two copies of each gene (one from each of our parents), usually a recessive disease occurs when a person inherits one disease-causing mutation from each parent. In a very small percentage of cases, a person inherits a disease-causing mutation from one parent and has a spontaneous mutation in the normal copy of the gene inherited from the other parent, thus giving rise to two disease-causing mutations.



A person who has only one disease-causing mutation is a carrier, but does not develop the disease. Carriers can pass the disease-causing mutation on to their children, who will also be carriers if they inherit a mutation from only one parent.

If both parents are carriers, then each child of the couple has a 25% chance of inheriting two disease-causing mutations and developing the disease, a 25% chance of inheriting no disease-causing mutations and being free of the disease, and a 50% chance of being an unaffected carrier of the disease. If only one parent is a carrier, then each child has a 50% chance of inheriting one copy of the mutation and being carriers themselves.

People affected with the disease will pass on one of their disease-causing mutations to each child.

This report tells you whether mutations were detected in your DNA for over 70 recessive genetic diseases. If one mutation was detected for any of these diseases, you are a carrier of that disease. If you have two copies of the same mutation, your status as a homozygote means you are likely to be affected by that disease. If two different mutations were detected in the same gene, this is known as compound heterozygote and you could be affected depending on the arrangement of your mutations. If no mutations are detected, then you do not carry the mutations that are included in our test panel.

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Condition Name	Mutations Detected	No Mutations Detected
3-Methylcrotonyl-CoA carboxylase deficiency		✓
Acrodermatitis enteropathica		✓
Alpha-1 antitrypsin deficiency	✓	
Amyotrophic lateral sclerosis		✓
Argininosuccinate lyase deficiency		✓
Autoimmune polyglandular syndrome, type I		✓
Bartter syndrome type 4A		✓
Beta-ketothiolase deficiency		✓
Beta-thalassemia		✓
Biotinidase deficiency		✓
Bloom syndrome		✓
Canavan disease		✓
Carnitine deficiency, primary systemic		✓
Cerebrotendinous xanthomatosis		✓
Citrullinemia type I		✓
Corticosterone methyl oxidase deficiency		✓*
Crigler-Najjar syndrome		✓
Cystic fibrosis		✓
Diabetes, permanent neonatal		✓
Dihydropyrimidine dehydrogenase deficiency		✓
Dubin-Johnson syndrome		✓
Ehlers-Danlos syndrome, dermatosparaxis		✓
Ehlers-Danlos syndrome, hypermobility		✓
Ehlers-Danlos syndrome, kyphoscoliotic		✓
Ethylmalonic aciduria	✓	
Factor XI deficiency		✓
Familial dysautonomia		✓
Familial Mediterranean fever		✓
Fanconi anemia		✓
Galactokinase deficiency		✓
Galactosemia		✓

Condition Name	Mutations Detected	No Mutations Detected
Gaucher disease		✓
Glutaric acidemia, type 1		✓
Glycogen storage disease, type 1A		✓
GM1-gangliosidosis		✓
Hearing loss, DFNB1 and DFNB9 nonsyndromic		✓
Hearing loss, DFNB59 nonsyndromic		✓
Hemochromatosis	✓	
Hemoglobin C		✓
Hemoglobin E		✓
HMG-CoA lyase deficiency		✓
Homocystinuria, cbIE type		✓
Homocystinuria, classic		✓
Hurler syndrome		✓
Krabbe disease		✓
Lipoprotein lipase deficiency, familial		✓
Maple syrup urine disease		✓
Medium-chain acyl-CoA dehydrogenase deficiency		✓
Methylmalonic acidemia		✓
MTHFR deficiency	✓	
Mucopolidosis II		✓
Mucopolidosis III		✓
Mucopolidosis IV		✓
Multiple carboxylase deficiency		✓
Nephrotic syndrome, steroid-resistant		✓
Niemann-Pick disease		✓
Phenylketonuria		✓
Polycystic kidney disease		✓
Pompe disease		✓
Prekallikrein deficiency		✓
Propionic acidemia		✓
Prothrombin deficiency		✓

Condition Name	Mutations Detected	No Mutations Detected
Rh-null syndrome		✓
Rickets, pseudovitamin D-deficiency		✓
Sandhoff disease		✓
Short-chain acyl-CoA dehydrogenase deficiency		✓
Sick sinus syndrome		✓
Sickle cell disease		✓
Spherocytosis, hereditary		✓
Tay-Sachs disease		✓
Tay-Sachs pseudodeficiency		✓
Thrombocytopenia, congenital amegakaryocytic		✓
Tyrosinemia		✓
Very long-chain acyl-CoA dehydrogenase deficiency		✓
Von Willebrand disease type 2 Normandy		✓
Von Willebrand disease type 3		✓

Your carrier status test may have several possible results.

Possible Result	Description
✓	In the "Mutations Detected" column, this means that the patient is a carrier for one or more of the mutations tested for this disease. In the "No Mutations Detected" column, this means that the patient is not a carrier for the mutations that were tested.
✓*	In the "Mutations Detected" column, this means the patient is a carrier for one or more of the mutations tested, but our lab was unable to determine a genotype at another marker. In the "No Mutations Detected" column, this means the patient is not a carrier for the mutations tested, but the lab was unable to determine a genotype at another marker. In both cases, the condition will not be updated.
✓**	The patient is a carrier for one or more of the mutations tested, but there are additional mutations that require further analysis. This report will be updated with the additional information as soon as it is ready.
Pending	The results for this disease are not yet complete. This report will be updated soon.
Unable To Report	After repeated attempts, we are unable to report a result on this disease.

Alpha-1 Antitrypsin Deficiency

Your Results

We scanned your DNA for 2 variants related to alpha-1 antitrypsin deficiency. Your DNA gave positive results for 1:

S allele in SERPINA1

This means that you are a carrier for this condition, but you are not likely to develop the disease yourself. To find out more about carrier status and what this means for your children, please contact our genetic counselors.

Residual risk: Since there are many rare mutations, it is possible to carry a mutation that is not on our test in addition to the variant that we found in your DNA. If you have a family history or are concerned about your status for this disease and wish to find out more, please contact our genetic counselors.

Pathway Genomics has scanned your DNA for markers related to alpha-1 antitrypsin deficiency and found that you carry the following:

S allele

Present

About the Gene

The SERPINA1 gene codes for the alpha-1 antitrypsin protein (AAT), a protease inhibitor that protects the lung from being damaged by neutrophil elastase. Alpha-1 antitrypsin deficiency is caused by mutations in the SERPINA1 gene. More than 120 SERPINA1 mutations have been identified. While some are harmless, others cause a moderate to severe deficiency of AAT in the blood. The two most common disease-causing mutations in SERPINA1 are the Z and S alleles (PMID 20301692).

Disease Description

Alpha-1 antitrypsin (AAT) is a protein in the plasma that helps prevent the lungs from being damaged by a powerful enzyme called neutrophil elastase. Neutrophil elastase functions to help digest bacteria and cell debris. AAT functions to inactivate the enzyme when it is no longer needed. Left unchecked, neutrophil elastase eats away at the inner lining (alveoli) of the lung, leading to emphysema and chronic obstructive pulmonary disease (COPD).

95% of individuals with alpha-1 antitrypsin deficiency (AATD) carry a mutation called the Z allele on both copies of the AAT gene that reduces the level of AAT in the blood. Individuals with AATD may remain healthy throughout their lives. However, AATD leaves the individual at great risk for developing potentially fatal lung and liver disease.

Normally alpha1-antitrypsin is produced in the liver and travels to the lungs to where it is needed. The Z allele produces an altered AAT protein that accumulates in the liver, leaving the lung unprotected and causing liver damage. In rare cases, some AATD individuals develop a skin disease called panniculitis. Smoking is a major contributor to the development of AATD-associated emphysema. Cigarette smoking exaggerates the defect of AAT variants by decreasing the number of functional AAT molecules available to protect the lung. Non-smokers often have a normal life span. However, for AATD patients with emphysema, the 2-year mortality rate is 40% if lung function has deteriorated (PMID 18565211, PMID 20301692).

Mutations Tested

Pathway Genomics tests for the two most common disease-causing variants (Z and S alleles) in the SERPINA1 gene. The genetics of this disease are somewhat complicated by the fact that different combinations of alleles produce a range of possible effects.

There are three main alleles of the SERPINA1 gene, known as M (normal), Z (disease-causing), and S (sometimes disease-causing). The S allele is the most common variant of SERPINA1, found in 1 in 18 people in the US, while the Z allele is present in 1 in 44. However, 95% of alpha-1 antitrypsin deficiency (AATD) results from the presence of two Z alleles - one inherited from each parent.

The ZZ genotype (found in a person homozygous for the Z allele) is associated with liver disease in children and adults, and with emphysema in adults. The onset of lung disease in smokers with AATD is between 40 years and 50 years, and in non-smokers, the onset can be delayed to age 60. Non-smokers often have a normal life span. People with the ZZ genotype will pass on one copy of the Z allele to each of their children.

People who are MZ heterozygotes have one normal copy (the M allele) together with one Z allele, and are carriers who may have an increased risk for developing lung or liver disease. An MZ heterozygote has a 50% chance of passing the Z allele to each child.

ZS heterozygotes are more common than ZZ homozygotes, and probably have some increased risk of lung or liver disease. ZS individuals should not smoke. MS individuals are carriers of S, but do not appear to be at an increased risk for lung or liver disease. Likewise, SS individuals are carriers of 2 copies of S, but do not appear to be at an increased risk for lung or liver disease (PMID 2185272, PMID 2696185, PMID 20301692).

Ethnic Prevalence and Frequency

AATD is one of the most common potentially fatal single-gene diseases in the world. AATD has been identified in virtually all populations and ethnic groups, but is most common in individuals of Northern European (Scandinavian and British) and Iberian (Spanish and Portuguese) descent.

About 100,000 Americans have AAT deficiency. It is estimated that one in every 2,500 U. S. Caucasians has AATD. The overall carrier rate among U. S. Caucasians for AATD is 1/33. It is not a rare disease but it is a disease that has been infrequently diagnosed (PMID 12426287, PMID 14654440, PMID 20301692).

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Ethylmalonic Aciduria

Your Results

We scanned your DNA for 2 variants related to Ethylmalonic aciduria. Your DNA gave positive results for 1:

625G>A in ACADS

This means that you are a carrier for this condition, but you are not likely to develop the disease yourself. To find out more about carrier status and what this means for your children, please contact our genetic counselors.

Residual risk: Since there are many rare mutations, it is possible to carry a mutation that is not on our test in addition to the variant that we found in your DNA. If you have a family history or are concerned about your status for this disease and wish to find out more, please contact our genetic counselors.

Pathway Genomics has scanned your DNA for markers related to Ethylmalonic aciduria and found that you carry the following:

625G>A

Present

About the Gene

Ethylmalonic aciduria can be caused by two common variants, 625G>A and 511C>T, of the ACADS gene. The ACADS gene codes for a mitochondrial enzyme in fatty acid metabolism called short-chain acyl-CoA dehydrogenase (SCAD) (PMID 18977676). The SCAD enzyme helps provide energy, especially for muscles and organs like the heart and liver, by breaking down a group of fats called short-chain fatty acids. When the SCAD enzyme is not working, an unmetabolized byproduct called ethylmalonic acid accumulates in the body and is excreted in the urine. The two variants are inherited in an autosomal recessive manner. Individuals with two copies of a variant, one from the mother and one from the father, often show an increased excretion of ethylmalonic acid in the urine. The copies can be of the same variant (homozygous) or of different variants (compound heterozygous).

Disease Description

Ethylmalonic aciduria (EMA) is the increased excretion of ethylmalonic acid in the urine. We test for the 625G>A and 511C>T variants in the ACADS gene, that are associated with EMA. The majority of people carrying two copies of these variants are healthy and have no visible symptoms.

The reason we report on EMA is that 625G>A and 511C>T are common variants that may make individuals susceptible to a rare inherited fatty acid oxidation disorder called short-chain acyl-CoA dehydrogenase (SCAD) deficiency, but only in the presence of other genetic and environmental factors (PMID 18523805). If you have one of these common variants, please check your short-chain acyl-CoA dehydrogenase deficiency report for disease-causing mutations in the ACADS gene.

Mutations Tested

We test for two common variants, 625G>A and 511C>T, in the ACADS gene that are associated with increased excretion of ethylmalonic acid in the urine. The majority of people carrying two copies of the 625G>A and 511C>T variants are healthy and have no visible symptoms. However, in studies of a rare inherited fatty acid oxidation disorder called short-chain acyl-CoA dehydrogenase (SCAD) deficiency, it was found that 60 out of 67 patients carried two copies of these common variants or one copy of the common variant together with a copy of a rare inactivating mutation in the ACADS gene (PMID 18523805). SCAD deficiency is rare, with an incidence of 1 in 50,000 live births (PMID 16926354). The association of these common variants with a rare, inherited disease suggests that the 625G>A and 511C>T variants may make an individual susceptible to SCAD deficiency, but only in the presence of other genetic or environmental factors (PMID 18523805). Thus, these common variants may be necessary, but not sufficient for the development of SCAD deficiency.

Ethnic Prevalence and Frequency

In a U. S. study with 694 subjects, the carrier rates of 625G>A and 511C>T were 1/5 and 1/33, respectively (PMID 12706374). As much as 14% of the normal population may carry two copies of these variants (PMID 18523805).

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Hemochromatosis

Your Results

We scanned your DNA for 6 variants related to hemochromatosis. Your DNA gave positive results for 1:

H63D in HFE

We found that your DNA contains two copies of this mutation. This means that you may have this condition, and each of your children will inherit one copy of this mutation from you. Your children will be carriers by inheriting one of your mutations. If they also inherit another mutation in this gene from their other parent, they could have this condition.

You should know it is not usually possible to determine disease severity solely from genotype information. There is a great deal of variability in how diseases are expressed among individuals even with the same mutations, which depends on many other factors including environment and lifestyle. To find out more about what your genotype means for your health and for your offspring, please contact our genetic counselors and consult your physician.

Pathway Genomics has scanned your DNA for markers related to hemochromatosis and found that you carry the following:

H63D	Present
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About the Gene

More than one gene has been found to be responsible for hereditary hemochromatosis.

Autosomal recessive mutations in the HFE gene cause HFE-associated hereditary hemochromatosis (HFE-HHC). The age of onset for men is between 40 and 60 years of age and for women is after menopause. The penetrance of this gene is low, meaning that many individuals carrying two HFE variants do not develop clinical symptoms. The HFE protein helps regulate the absorption of iron into the small intestine by interacting with other proteins located on the cell surface and may also help control the levels of another important iron regulatory protein called hepcidin.

Autosomal recessive mutations in the HFE2 gene cause an early onset form of hemochromatosis called juvenile hereditary hemochromatosis (JHHC). The age of onset is usually between 10 and 30 years of age. The HFE2 gene codes for the hemojuvelin protein that appears to regulate the level of the iron-regulatory protein called hepcidin. Most mutations of HFE2 causing JHHC are private, meaning they are carried in individual families or small populations. The only recurrent mutation is G320V.

Autosomal recessive mutations in the TFR2 gene cause TFR2-related hereditary hemochromatosis (TFR2-HHC). The age of onset is in between the age of onset of juvenile and HFE-associated hemochromatosis; symptoms generally begin before age 30. Some individuals carrying two TFR2 variants do not develop clinical symptoms (penetrance is incomplete). The TFR2 gene is a member of the transferrin receptor-like family and codes for a membrane protein that mediates cellular uptake of transferrin-bound iron. Like the HFE and the HFE2 gene product, the TFR2 gene product also appears to regulate the level of iron-regulatory protein hepcidin. 15 diseased-associated mutations of TFR2 have been found, but most of them are rare or private.

Disease Description

Hereditary hemochromatosis is a potentially fatal disorder caused by autosomal recessive mutations in any one of several genes that result in abnormally high absorption of iron into the body. The body normally adjusts levels of iron by regulating the intake of iron from the intestines. Because there is no mechanism for excreting iron, any failure to limit the level of iron intake can lead to a dangerous accumulation of iron in the body. Excess iron can damage many organ systems including the liver, skin, pancreas, endocrine glands, joints, and heart. The only way to remove the excess iron is by bloodletting (therapeutic phlebotomy). If such treatment is started in time, the affected individuals will have a normal lifespan. Therefore, early diagnosis is essential.

Mutations Tested

Pathway Genomics tests for 3 mutations in the HFE gene, 1 mutation in the HFE2 gene and 2 mutations in the TFR2 gene. The C282Y and H63D variants of the HFE gene are the most common cause of hereditary hemochromatosis. The C282Y mutation is thought to have originated by chance in a single Celtic (or Viking) ancestor in northwestern Europe about 2000 years ago. Homozygosity for the C282Y mutation is now found in approximately 5 of every 1000 persons of northern European descent. The carrier rate for C282Y is 1 in 9 for Caucasians, 1 in 33 for Hispanics, 1 in 43 for African-Americans, and 1 in 1000 for Asians. The H63D mutation is an older, more prevalent mutation with a worldwide distribution and a carrier rate of 1 in 4 for Caucasians, 1 in 6 for Hispanics, 1 in 17 for African-Americans, and 1 in 12 for Asians. About 60%-90% of individuals with HFE-HHC carry two copies of C282Y. 87% of individuals of European origin with HFE-HHC either carry two copies of the C282Y variant or carry one copy of the C282Y variant and one copy of the H63D variant. Conventional wisdom as summarized by Beutler (PMID 16409153) in 2006 is that most individuals with two copies of C282Y do not show clinical symptoms (penetrance is low). However, a recent study by Allen et al. (PMID 18199861) in 2008 of 31,192 people in Australia found that, among 203 individuals homozygous for C282Y, 28% of men as compared to 1% of women showed clinical symptoms of hemochromatosis. Thus, men who are homozygous for C282Y should be aware of this possibility. Most individuals with one copy of C282Y and one copy of H63D as well as individuals with two copies of H63D do not show clinical symptoms (penetrance is low). More than 90% of all juvenile hereditary hemochromatosis cases are caused by mutations in the HFE2 gene. G320V is the most prevalent HFE2 mutation reported to date, representing more than 50% of all detected mutations in affected individuals worldwide.

Ethnic Prevalence and Frequency

The prevalence of hereditary hemochromatosis associated with mutations in the HFE gene (HFE-HHC) is 1 in 200 for Caucasians, 1 in 6667 for non-Hispanic blacks and 1 in 3333 for Mexican Americans. Compared to HFE-HHC, hereditary hemochromatosis from mutations in other genes such as HFE2 and TFR2 is rare.

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MTHFR Deficiency

Your Results

We scanned your DNA for 35 variants related to MTHFR deficiency. Your DNA gave positive results for 2:

A1298C (E429A) in MTHFR
C677T (A222V) in MTHFR

Your DNA contains variants at more than one marker. Further testing is required to determine whether these results mean you are likely to develop this disease, and what your carrier status is.

Every person inherits two copies of each of their genes, one from each parent (the exception is in males, who have a single copy of each gene on the X and Y chromosome). In recessive diseases, a person must have two mutations, one in each copy of the gene, in order to get the disease. If one copy of the gene contains both mutations, then the person is a carrier and will not get the disease. However, if both copies of the gene contain a mutation, then the person may develop the disease in question.

The DNA test performed on your sample does not distinguish whether the two mutations we found are in the two copies of this gene on different chromosomes (which would mean you may develop this disease) or in one copy of the gene on the same chromosome (which would mean you are a carrier for this disease). You should know that it is not usually possible to determine health prognosis solely from genotype information. There is a great deal of variability in how diseases are expressed among individuals even with the same mutations, which depends on many other factors including environment and lifestyle.

To obtain more information about these results, your health status and what this means for your offspring, please contact our genetic counselors and consult your physician. Contact us for options for further testing to determine the status of these mutations.

Pathway Genomics has scanned your DNA for markers related to MTHFR deficiency and found that you carry the following:

A1298C (E429A)	Present
C677T (A222V)	Present

About the gene

MTHFR deficiency is caused by defects in the MTHFR gene. The MTHFR gene codes for an enzyme, methylenetetrahydrofolate reductase, involved in the metabolism of amino acids. The MTHFR enzyme makes a compound that is required to convert homocysteine, an amino acid that can be toxic at high levels, to methionine, another amino acid that is non-toxic and essential for a number of functions within the cell. Without proper enzyme function, homocysteine accumulates in the blood and causes a disease state (PMID 12083967). The severity of the condition is dependent on the amount of residual enzyme function in the affected individual. Less than 60% of normal enzyme function is considered a mild MTHFR deficiency, whereas less than 20% of normal enzyme function is defined as a severe MTHFR deficiency and is very rare (Rosenblatt DS (1995) in The Metabolic and Molecular Basis of Inherited Disease, eds Scriver CR, et al. (McGraw-Hill, New York), pp 3111-3128.).

MTHFR deficiency is inherited in an autosomal recessive fashion.

Disease description

Severe methylenetetrahydrofolate reductase (MTHFR) deficiency (less than 20% enzyme activity) leads to developmental delays, mental retardation, seizures, and motor and gait dysfunction often early in life (Rosenblatt DS, loc. cit.). However severe deficiency is very rare and has been documented in fewer than 100 cases worldwide.

Mutations associated with mild MTHFR deficiency are very common in the general population. Mild deficiency that results in increased homocysteine in the blood, such as in C677T homozygotes, has been linked to an increased risk of cardiovascular diseases as well as to congenital abnormalities such as neural tube closure defects. However, the severity or impact of the disease in people with mild enzyme deficiency has been strongly linked to diet, specifically folic acid intake. Sufficient folic acid intake in C677T homozygotes often reduces blood levels of homocysteine to normal (PMID 12083967). It has also been shown that women who have folic acid supplementation around conception reduce the risk of neural tube closure defects by 50-70%, suggesting that folic acid supplementation may decrease the risk for neural tube defects even in carriers of mild MTHFR mutations (PMID 16672082).

Mutations tested

We test for about 40 mutations in the MTHFR gene including the two most common variants (C677T and A1298C) that cause MTHFR deficiency. These two variants are associated with mild deficiency and are found across all ethnicities (PMID 9545406, PMID 9719624).

Ethnic prevalence and frequency

The prevalence of MTHFR carriers varies widely in different populations. The most common variant, known as C677T, leads to mild deficiency and is most prevalent in Mediterranean and Hispanic populations followed by Chinese, Caucasian, other Asian populations and African/African-Americans. In North American populations, the C677T variant is carried by 30% of the population with at least 10% of the population being homozygous, or having two copies of the variant (PMID 12920077, PMID 9545406, PMID 8837319). The second most common mutation known as A1298C is also associated with mild deficiency and is carried by 11-30% of the population with <1%-13% of the population being homozygous (PMID 9719624).

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This section lists the common names of all the individual markers that were tested. Markers are listed by disease, with gene name in parentheses.

Orange: If you carry any of these markers, they will be highlighted in orange and you will have a corresponding Condition Detail page preceding this one that describes the condition and your results.

Black: For markers you do not carry, these are listed below in black.

Strikethrough: We make every effort to provide you with accurate genotypes at all the markers we test. Infrequently, our lab is unable to determine a genotype at a marker. This means that we are not able to determine the status of your DNA for this mutation. Any mutations that give no results are indicated by strike-through of that mutation. If you are concerned about your status for the variant we were unable to determine, other methods are available to test your DNA.

Residual risk: Since there are many rare mutations, it is possible to carry a mutation that is not on our test. If you have a family history or are concerned about your status for this disease and wish to find out more, please contact your physician or a genetic counselor.

You should know that it is not usually possible to determine health prognosis solely from genotype information. There is a great deal of variability in how diseases are expressed among individuals, which depends on many other factors including environment and lifestyle. To find out more about what your genotype means for your health and for your offspring, please contact our genetic counselors and consult your physician.

3-Methylcrotonyl-CoA Carboxylase Deficiency

R193C (MCCC2), V339M (MCCC2), I437V (MCCC2), S173L (MCCC2), E99Q (MCCC2), L437P (MCCC1), R385S (MCCC1), A289V (MCCC1), D532H (MCCC1)

Acrodermatitis Enteropathica (SLC39A4)

1223_1227delCCGGG, L48X

Alpha-1 Antitrypsin Deficiency (SERPINA1)

S allele, Z allele

Amyotrophic Lateral Sclerosis (ALS2)

1867delCT

Argininosuccinate Lyase Deficiency (ASL)

Q354X, V178M, R385C, R193Q, Q116X, IVS5+1G>A, D87G

Autoimmune Polyglandular Syndrome, Type I (AIRE)

R257X, 967-979del13, R139X, Y85C, W78R, Q358X, P370fsX370, IVS8+5G>T, L323fsX372, R303P, C311fsX376, C311Y, M388fsX422, H415fsX422, IVS11+1G>A, A502fsX519, P539L, X546C, C449fsX502, C446G, E298K, L417fsX478, R433/C434fsX, L397fsX478, P252L, F77S, V80L, K83E, L29P, L28P, R15C, T16M, 64-69del6, Y90C, L93R, G218fsX284, G228W, M1L, R203X, IVS3+2T>C, L97P, S135fsX147, IVS3-2A>T, IVS7+1G>A

Bartter Syndrome Type 4A (BSND)

G47R

Beta-ketothiolase Deficiency (ACAT1)

R208X, T297M, IVS11+2T>C, IVS8+1G>T, G183R, 149delC, G152A, Q272X

Beta-thalassemia (HBB)

-29A>G, IVS1+6T>C, IVS1+110G>A, cd39C>T, 17A>T, Hb Malay, cd8/9+G, cd8-AA, 41/42-TTCT, cd44-C, -28A>G, cd24T>A, -88C>T, IVS2+849A>C, IVS2+654C>T, IVS2+849A>G, IVS1+5G>T, IVS2+1G>A, IVS2+745C>G, -87C>G, IVS1+1G>A

Biotinidase Deficiency (BTD)

A171T, D444H, R538C, Q456H, C33FfsX36

Bloom Syndrome (BLM)

blmAsh, R899X, Q975fsX, C1055S, R836fsX, W803fsX, W567X, Q645X, S186X, W428X

Canavan Disease (ASPA)

Y231X, A305E, E285A, 827delGT, F295S, G274R, P280S, M195R, 245insA, Y109X, 433-2A>G, C218X

Carnitine Deficiency, Primary Systemic (SLC22A5)

R254X, W283C, T440M, T468R, T219fsX284, R169W, Y4X, N32S, P46S, Y211C

Cerebrotendinous Xanthomatosis (CYP27A1)

R395C, A216P, T339M, IVS6+1G>A, IVS7+1G>A, R474W, R405W, P401R, IVS6-1G>T, R405Q, E408X, Q461X, P441S, IVS7+5G>T, P384L, G472A, D354G, E195X, R127Q, Q159X, IVS2+1G>A, G145G, R231X, W260X, R127W, K284X, IVS4+1G>A, R270X, R137W

Citrullinemia Type I (ASS1)

G390R, IVS6-2A>G, R304W, V345G, S180N, E191K, Q380X, 952delG, Y190D, R307C, R86H, R95S, V269M, R272C, K310Q

Corticosterone Methyl Oxidase Deficiency (CYP11B2)

R181W, V386A, G435S, 104_108delITGCTG

Crigler-Najjar Syndrome (UGT1A1)

Q357R, A401P, S381R, G377V, P387R, N400D, 1186delG, H376R, I370V, 1043delA, R341X, Q357X, IVS3-2A>G, A368T, S375F, R403C, W483X (TAG), A478D, W483X (TGA), Y486D, G493R, S488F, E463A, L443P, 1223insG, 1220delA, K428E, IVS4+1G>T, K437X, IVS4-1G>A, R336W, W335X, C177R, L175Q, Q185P, Y192X, R209W, M204V, 517delC, F170del, W40R, H39D, Y74X, L131P, V160E, 397_402delCAACAA, 652insT, V225G, 878_890del, A292V, I294T, 973delG, Q331R, Q331X, IVS1+1G>C, Q283X, Q239fsX256, L233R, 801delC, N279Y, C280X, P34Q

Cystic Fibrosis (CFTR)

deltaF508, W1282X, 3849+10kbC>T, N1303K, G551D, 621+1G>T, R553X, R117H, R334W, G85E, R1162X, 1717-1G>A, R347P, 2184delA, A455E, 711+1G>T, 1898+1G>A, 2789+5G>A, 3659delC, R560T, 3120+1G>A, G542X, deltaI507, S1196X, 3667ins4, R1158X, Q1100P, 3272-26A>G, 3171delC, W1089X, 3120G>A, W1204X, D1152H, G1349D, 1949del84, S549R (A>C), V520F/I, I148T, M1101K, S549N, G622D, 3876delA, Q1238X, S1251N, 3905insT, 2869insG, 3791delC, 2108delA, 846delT, V232D, L206W, 935delA, 936delTA, 1078delT, deltaF311, P205S, 712-1G>T, 405+3A>C, 405+1G>A, 394delTT, 444delA, 574delA, G178R, 663delT, G330X, R352Q, 2055del9>A, 2043delG, P574H, 2105del13ins5, R709X, 2307insA, K710X, A561E, 1812-1G>A, Q493X, S364P, Q359K/T360K, 1677delTA, C524X, L558S, S549R (T>G), P750L

Diabetes, Permanent Neonatal

IVS8+2T>G (GCK), R397L (GCK), P45L (ABCC8), N72S (ABCC8), E382K (ABCC8)

[Dihydropyrimidine Dehydrogenase Deficiency \(DPYD\)](#)

IVS14+1G>A, R235W, V335L, M182K, P86L, E386X, IVS11+1G>T, R886H, A777S, I560S, H978R

[Dubin-Johnson Syndrome \(ABCC2\)](#)

I1173F, R1150H

[Ehlers-Danlos Syndrome, Dermatosparaxis \(ADAMTS2\)](#)

Q225X, W795X

[Ehlers-Danlos Syndrome, Hypermobility \(TNXB\)](#)

2116_2117dupGT, 3551_3552delAA

[Ehlers-Danlos Syndrome, Kyphoscoliotic \(PLOD1\)](#)

Y511X, Q327X, 1702insC, W612C, R670X, H706R, G678R, A667T, W446G, Y142X, 153dupC, 467-2delA, R319X, Q49X, 975+2_975+3insTT, 1362delC

[Ethylmalonic Aciduria \(ACADS\)](#)

625G>A, 511C>T

[Factor XI Deficiency \(F11\)](#)

F283L, E117X, IVS14+1G>A, C128X

[Familial Dysautonomia \(IKBKAP\)](#)

R696P, IVS20+6T>C

[Familial Mediterranean Fever \(MEFV\)](#)

M694V, V726A, M680I, R653H, R408Q, M694I, A744S, K695R, R761H

[Fanconi Anemia \(FANCC\)](#)

IVS4+4A>T, 322delG, R548X, Q13X, R185X, L554P

[Galactokinase Deficiency \(GALK1\)](#)

Q382X, R256W, G349S, T344M

[Galactosemia \(GALT\)](#)

Q188R, N314D, L218L (c.652C>T), K285N, Y209C, L195P, S135L, F171S, IVS2-2A>G, E203K

[Gaucher Disease \(GBA\)](#)

N370S, V394L, D409H, R463C, IVS2+1G>A, 84GG

[Glutaric Acidemia, Type 1 \(GCDH\)](#)

A421V, R402W, V400M, A293T, R227P

[Glycogen Storage Disease, Type 1A \(G6PC\)](#)

R83C, Q347X, 378_379dupTA, R83H, deltaF327, G270V, G188R, 79delC, Q242X

[GM1-gangliosidosis \(GLB1\)](#)

R59H

[Hearing Loss, DFNB1 And DFNB9 Nonsyndromic](#)

35delG (GJB2), 167delT (GJB2), 235delC (GJB2), V37I (GJB2), Q829X (OTOF), L90P (GJB2)

[Hearing Loss, DFNB59 Nonsyndromic \(DFNB59\)](#)

L244R, 988delG, 726delT, 509_512delCACT, R167X, 113dupT

[Hemochromatosis](#)

H63D (HFE), C282Y (HFE), G320V (HFE2), M172K (TFR2), S65C (HFE), Y250X (TFR2)

[Hemoglobin C \(HBB\)](#)

Hemoglobin C

[Hemoglobin E \(HBB\)](#)

Hemoglobin E

[HMG-CoA Lyase Deficiency \(HMGCL\)](#)

E37X, R41Q, 504_505delCT

[Homocystinuria, CblE Type \(MTRR\)](#)

1953-6_1953-2del5, 1726delTTG, 1622_1623dupTA, R525X, R3W

[Homocystinuria, Classic \(CBS\)](#)

G307S, I278T, T191M, IVS11-2A>C, A155V, C165Y, G151R, G148R, V168A, P145L, E144K, H232D, E239K, A226T, S217F, IVS8+1G>A, E176K, G139R, P78R, G85R, P88S, R58W, P49L, W43X, D47E, L101P, K102N, M126V, E128D, R121C, G116R, C109R, A114V, T257M, IVS9+1G>T, K384E, I435T, R379W, IVS12+1G>A, V371M, D376N, D444N, S466L, L539S, 1622ins4, 1591delTTTCG, 1566delG, R491C, R369H, R369C, V320A, R336C (C>T), E302K, 298fsX329, R266K, P290L, R336C (delCC/insTT), R336H, V354M, A355P, T353M, S349N, G347S, R266G

[Hurler Syndrome \(IDUA\)](#)

W402X, Q70X, 1814_1815delTT, 1044delCGACAA, 1695del11

[Krabbe Disease \(GALC\)](#)

R168C, G270D, 1424delA, T513M, A625T

[Lipoprotein Lipase Deficiency, Familial \(LPL\)](#)

G188E

[Maple Syrup Urine Disease](#)

R183P (BCKDHB), E372X (BCKDHB), G278S (BCKDHB), Y438N (BCKDHA)

[Medium-chain Acyl-CoA Dehydrogenase Deficiency \(ACADM\)](#)

K304E, Y42H

[Methylmalonic Acidemia](#)

E117X (MUT), R108C (MUT), N219Y (MUT), G717V (MUT), R145X (MMAA), 503delC (MMAA), R369C (MUT)

[MTHFR Deficiency \(MTHFR\)](#)

C677T (A222V), A1298C (E429A), T227M, C193Y, P251L, IVS4-2A>G, L323P, R183X, IVS4+1G>A, I153M, R52Q, R51P, R6X, IVS1-1G>T, A116T, N324S, G149V, R157Q, L333P, P572L, R567X, R535W, K584X, E586K, X657S, R594Q, 1541_1542delAG, E470X, W339G, M338T, R357C, R377C, S440L, G387D, R325C

[Mucopolidosis II \(GNPTAB\)](#)

3503_3504delTC, R1189X, Q104X, 616_619delACAG, Q845X, R1205X, 1581delC

[Mucopolidosis III](#)

IVS17+6T>G (GNPTAB), 499dupC (GNPTG), K4Q (GNPTAB), 347_349_delACA (GNPTG)

[Mucopolidosis IV \(MCOLN1\)](#)

IVS3-2A>G

[Multiple Carboxylase Deficiency \(HLCS\)](#)

780delG, L237P, R508W, V550M, G581S, D571N, R665X

[Nephrotic Syndrome, Steroid-resistant \(NPHS2\)](#)

R138Q, 436delA, 1036delC

Niemann-Pick Disease

deltaR608 (SMPD1), I1061T (NPC1), E20X (NPC2), G992W (NPC1), R496L (SMPD1), P330SfsX382 (SMPD1), H421Y (SMPD1), L302P (SMPD1)

Phenylketonuria (PAH)

R243X, V245A, R158Q, I65T, F39L, L48S, R261Q, E280K, R408W, R408Q, A403V, IVS10-11G>A, P281L, Y414C

Polycystic Kidney Disease (PKHD1)

P805L, R496X, I222V, T36M, I2944fs, I2957T, V3471G, Q3392X, D3230fs, I3177T, R3482C

Pompe Disease (GAA)

2741AG>CAGG, D645E, G309R

Prekallikrein Deficiency (KLKB1)

C529Y, W383X

Propionic Acidemia

T428I (PCCB), R410W (PCCB), 1218del14ins12 (PCCB), 1172_1173insT (PCCB), R399Q (PCCA)

Prothrombin Deficiency (F2)

R457Q, E352K, R538C, R314C, R263C, D161Y, C181Y, R2W

Rh-null Syndrome (Rhag)

V270I

Rickets, Pseudovitamin D-deficiency (CYP27B1)

3398dupCCCACCC, IVS3+1G>A, 958delG, R389H

Sandhoff Disease (HEXB)

IVS2+1G>A, 76delA, S62L

Short-chain Acyl-CoA Dehydrogenase Deficiency (ACADS)

R107C, S353L, W177R, M370V, R380W, I390M, Q365H, A199V, R139C, T169P, R46W

Sick Sinus Syndrome (SCN5A)

T220I, P1298L, G1408R, R1632H

Sickle Cell Disease (HBB)

Hemoglobin S

Spherocytosis, Hereditary

A142T (EPB42), W119X (EPB42), V463I (ANK1), 5703+16C>T (ANK1), D175Y (EPB42), R310Q (EPB42), IVS6+1G>A (EPB42), R317C (EPB42)

Tay-Sachs Disease (HEXA)

1278insTATC, IVS12+1G>C, IVS9+1G>A, IVS5-1G>T, 613delC, G269S, R170Q, R178H/L, R170W, IVS2+1G>C, IVS9-1G>T, V192L, R499H, deltaTTC910-912, W329X, R504C, S210F, C458Y, I335F

Tay-Sachs Pseudodeficiency (HEXA)

R247W, R249W

Thrombocytopenia, Congenital Amegakaryocytic (MPL)

R43X, R102P

Tyrosinemia (FAH)

P261L, G337S, W262X, Q64H

Very Long-chain Acyl-CoA Dehydrogenase Deficiency (ACADVL)

V283A

Von Willebrand Disease Type 2 Normandy (VWF)

R854Q, R816W, T791M, C788R, C788Y, E787K, Y795C, M771V, R782W, G785E, R763G, P812L, Q1053H, C1060R, E1078K, D879N, H817Q, C1225G, R816Q, C804F

Von Willebrand Disease Type 3 (VWF)

R2535X, 4324dupAGTGTGGA, R365X, 1657dupT, W377C, R373X, Q565X, 1384delG, Y610X, 2269_2270delCT, C1071F, 2157delA, 2016_2019delCTCT, E620X, IVS9-1G>A, Y357X, 276delT, 374del14, S71X, 191delG, D47H, Q218X, W222X, R324X, 892dupG, IVS7+1G>A, R273W, 3258_3259insT, L1267X, R2434X, Q2544X, 7172_7173insT, 7139dupT, C2362F, 7674dupC, 7683delT, C2739Y, C2754W, IVS50+3G>T, C2671Y, IVS45+7C>T, IVS40-1G>C, C2174G, Q1346X, 4092_4093delAC, R1315C, V1314F/3940delG, C2804Y, Y1456X, Y1542X, 6182delT, R1853X, IVS29+10C>T, IVS28+1G>A, 3736_3737dupCC

This report has been reviewed and approved for release to authorized persons by Linda Wasserman, MD, PhD.

Glossary

1 - These are the gene and Single Nucleotide Polymorphism (SNP), also referred to as a marker, that were tested for this report. A SNP/Marker is a specific variation in an individual's DNA sequence.

2 - Your Genotype is the allele or base (A, T, G or C) composition found at the SNP/marker in your DNA and may contain the allele associated with the risk of the disease (Associated Allele). Two alleles (e.g. G/G) are shown because you inherit one copy from your mother and one copy from your father.

3 - The odds ratio is a measure of the likelihood that an event will occur in one group as compared to another. In genetics, the odds ratio measures the likelihood or risk that someone will get a disease/condition if they carry a specific genetic change. An odds ratio of 1 means the patient's observed genotype does not contain the risk associated allele. A patient with an odds ratio greater than 1 has a genotype that is associated with an increase in risk, while a patient with an odds ratio less than 1 has a genotype that is associated with a decrease in risk.

4 - Population Frequency is the percentage of people who have been found to have the Associated Allele in the Population Studied (Asian, Caucasian or African).

5 - Validated markers represent the highest quality genetic markers available, while Preliminary markers represent the latest in genetic research and have not met our high standards for validation.

6 - PubMed is a service managed by the National Library of Medicine that tracks more than 19 million citations for biomedical articles and scientific research. The Pubmed ID is used to identify each of those articles, and can be looked up at <http://www.ncbi.nlm.nih.gov/pubmed>.

Risks & Limitations

Risks

Risk of Laboratory Error

Pathway is a certified laboratory under the federal Clinical Laboratory Improvement Amendments of 1988 (CLIA) with standard and effective procedures in place for handling samples. However, laboratory error can occur, which might lead to incorrect results. Examples include, but are not limited to, a sample or DNA mislabeling or contamination, failure to obtain an interpretable report, and any other operational laboratory error. I understand that sometimes Pathway's laboratory may need a second sample to complete my testing.

Risk of laboratory technical problems

Pathway's CLIA-certified laboratory also has standard and effective procedures in place to protect against technical and operational problems. However, such problems may still occur and examples include, but are not limited to, failure to obtain an interpretable result for a particular SNP. Sometimes it is not possible to obtain a testing result for a particular mutation or marker due to circumstances beyond Pathway's control, in which case it may not be possible for Pathway to conclusively report on a genetic change that might cause or be predictive of a condition. This may mean that Pathway cannot report my results for a particular health trait or condition, carrier status result, drug response, or other phenotype. Pathway may re-test my sample in order to obtain these results, but upon re-testing the results may still not be obtained. As with all medical laboratory testing, there is a small chance that the laboratory could report false positive or false negative results. A false positive result means that a genotype is reported as being present when it is actually not present. A false negative result means that a genotype is not reported as being present when it actually is present. A tested individual may wish to pursue further testing to verify any results.

Limitations

The purpose of this test is to provide information about whether or not a tested individual's DNA sequences carry one or more mutations that are associated with or cause certain recessive diseases. Usually, recessive mutations cause disease in an individual only if the individual inherits a mutation from both parents.

While Pathway tests for a large number of genetic diseases, Pathway may not test for all possible mutations for those diseases, and so it is possible for tested individuals to carry a mutation that is not included in the testing conducted by Pathway. Carriers may pass any mutation they carry to their children.

The association between genetic mutations and carrier diseases is an active area of scientific research, and future scientific discoveries might alter our understanding of how this information is related to your carrier status.

Based on test results and other medical knowledge of the tested individual, health care providers might consider additional independent testing, or consult another health care provider or genetic counselor.

Change History

There are three ways in which this genetic report might get modified. A description of those methods is below, followed by a table listing all modifications to this report.

Corrected	A report is annotated as "Corrected" if there was an error in genotypic data or the algorithms for interpretation of genotypic data that changes a patient's result from a previous report. When a correction is issued, we will notate it along with the date on the summary and the details pages, and communicate the correction to the ordering physician via phone or email. Details of the correction will be provided in the Appendix, along with the date that it occurred.
Updated	A report is annotated as "Updated" when or if we make a substantial modification to the descriptive content in one of our reports, which is typically done to improve clarity or precision. Some updates, such as grammatical corrections or typos, may not be annotated at all, and we will not always send out communications about an update. Details of the update will be provided in the Appendix, along with the date that it occurred.
New	A report is annotated as "New" if we add a new condition or significant piece of content to a report. When a report is amended, we will notate it along with the date on the summary and details page, though we may remove the amended annotation after 6 months from the point it was added. Details of the amendment will be provided in the Appendix, along with the date that it occurred.