INTRODUCTION

This document is your genetic report, which is a straightforward and non-technical presentation of the results from your Dante Labs Genetic Health Risk Test. The insights obtained from learning about your genes may enable you, in partnership with your healthcare provider, to formulate a plan to outsmart your genes and live a longer, more vibrant life. Our reports tell you how specific genetic variants in your DNA can affect your chances of developing certain health conditions. Genetic variants are differences in DNA between people. Some variants may increase the risk of developing certain health conditions. However, not everyone with a risk variant will develop these health conditions. For many of these conditions, people without a risk variant can also develop them. Some variants are more common in certain ethnicities. The effect a variant has on risk for a health condition is often best understood in those ethnicities. Since families share DNA, having a family history of a condition can increase risk. If you have a variant, your family members may also have that variant. For certain conditions, genetics is just one part of a person's total risk. You may be able to manage your risk for some conditions by managing other risk factors. Our tests do not diagnose any health conditions. Talk to your healthcare provider to better understand how to manage your risk. For more information, please visit our website at https://www.dantelabs.com/ and https://www.dantelabs.com/pages/faq

LIMITATIONS AND OTHER IMPORTANT INFORMATION

- This test provides genetic risk information based on assessment of specific genetic variants but does not report on your entire genetic profile. This test does not report all genetic variants related to a given disease or condition, and the absence of a variant tested does not rule out the presence of other genetic variants that may be related to the disease/condition.
- Other genetic risk tests may report different genetic variants for the same disease/condition, so you may get different results using another genetic risk test.
- Other factors such as environmental and lifestyle risk factors may affect your risk of developing a given disease or health condition.
- This test is not a substitute for visits to your doctor or other health care professional. You should consult with your doctor or other health care professional if you have any questions or concerns about the results of your test or your current state of health.
- You may wish to speak to a genetic counselor, board-certified clinical molecular geneticist, or equivalent health care professional about the results of your test and to help answer any questions you may have. You can identify genetic counselors by visiting the National Society of Genetic Counselors website (https://www.nsgc.org).
- This test is not intended to diagnose any disease or condition, tell you anything about your current state of health, or be used to make medical decisions, including whether or not you should take a medication or how much of a medication you should take.
- The laboratory may not have been able to process your saliva sample. In this case Dante Labs will offer to send another kit to you to collect a second sample at no charge. If Dante Labs' attempts to process the second sample are unsuccessful, Dante Labs will not send additional sample collection kits and you or the person who paid for the Service (if that is not you) will be entitled to a complete refund of the amount paid to Dante Labs.
- For full Terms of Services, please visit: https://www.dantelabs.com/pages/terms-of-service
- This is not intended for US people and as such it has not been reviewed and approved by FDA

INFORMATION FOR HEALTH CARE PROFESSIONALS

- This test is not intended to diagnose a disease, determine medical treatment, or tell the user anything about their current state of health.
- This test is intended to provide users with their genetic information to inform lifestyle decisions and conversations with their doctor or other health care professional.
- Any diagnostic or treatment decisions should be based on testing and/or other information that you determine to be appropriate for your patient.

QUICK SUMMARY

NERVOUS SYSTEM DISORDERS		
CONDITION NAME	RESULTS	MAIN MESSAGE
Neurofibromatosis type 2	✓	No variants detected
Canavan disease	✓	No variants detected
D-bifunctional protein deficiency	✓	No variants detected
Familial dysautonomia	✓	No variants detected
Leigh syndrome	✓	No variants detected
Neuronal Ceroid Lipofuscinosis CLN1 Related	✓	No variants detected
Neuronal Ceroid Lipofuscinosis CLN5 Related	✓	No variants detected
Sialic acid storage disease	✓	No variants detected
Tay-Sachs disease	✓	No variants detected

CANCER		
CONDITION NAME	RESULTS	MAIN MESSAGE
Familial adenomatous polyposis	✓	No variants detected
Li-Fraumeni syndrome	✓	No variants detected
Peutz-Jeghers syndrome	✓	No variants detected
Pilomatrixoma	✓	No variants detected
PTEN Hamartoma Tumor Syndrome	✓	No variants detected
Paragangliomas	✓	No variants detected
Tuberous sclerosis	✓	No variants detected
Von Hippel-Lindau syndrome	✓	No variants detected

NEUROMUSCULAR DISORDERS		
CONDITION NAME	RESULTS	MAIN MESSAGE
Andermann syndrome	✓	No variants detected
Limb-girdle muscular dystrophy	✓	No variants detected

RENAL DISORDERS		
CONDITION NAME	RESULTS	MAIN MESSAGE

RENAL DISORDERS

CONDITION NAME	RESULTS	MAIN MESSAGE
Polycystic kidney disease	✓	No variants detected
Primary hyperoxaluria	✓	No variants detected

CARDIAC CONDITIONS

CONDITION NAME	RESULTS	MAIN MESSAGE
Arrhythmogenic right ventricular cardiomyopathy	✓	No variants detected
Catecholaminergic polymorphic ventricular tachycardia	✓	No variants detected
Familial thoracic aortic aneurysm and dissection	✓	No variants detected
Brugada syndrome	✓	No variants detected
Dilated Cardiomyopathy	✓	No variants detected
Familial hypertrophic cardiomyopathy	✓	No variants detected
Left ventricular noncompaction	✓	No variants detected
Long QT Syndrome	✓	No variants detected

CONNECTIVE TISSUE DISORDER

CONDITION NAME	RESULTS	MAIN MESSAGE
Ehlers-Danlos syndrome	✓	No variants detected
Loeys-Dietz syndrome	✓	No variants detected
Marfan syndrome	✓	No variants detected
Rhizomelic chondrodysplasia punctata	✓	No variants detected

BONE MARROW DISEASES

CONDITION NAME	RESULTS	MAIN MESSAGE
Fanconi anemia	✓	No variants detected

METABOLIC DISORDERS

CONDITION NAME	RESULTS	MAIN MESSAGE
Fabry disease	✓	No variants detected
Familial Hypercholesterolemia	✓	No variants detected
Ornithine transcarbamylase deficiency	✓	No variants detected
Wilson Disease	✓	No variants detected
PMM2-congenital disorder of glycosylation	✓	No variants detected
Dihydrolipoamide dehydrogenase deficiency	✓	No variants detected
Familial Hyperinsulinism	✓	No variants detected
Gaucher disease	✓	No variants detected
Glycogen storage disease type I	✓	No variants detected
GRACILE syndrome	✓	No variants detected
Hereditary fructose intolerance	✓	No variants detected
Maple syrup urine disease	✓	No variants detected

METABOLIC DISORDERS

CONDITION NAME	RESULTS	MAIN MESSAGE
Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency	✓	No variants detected
Mucolipidosis type IV	✓	No variants detected
Niemann-Pick Disease Type A	✓	No variants detected
Phenylketonuria	✓	No variants detected
Tyrosinemia	✓	No variants detected
Hereditary Hemochromatosis	✓	No variants detected
Glucose-6-phosphate dehydrogenase deficiency	✓	No variants detected

RESPIRATORY DISEASES

CONDITION NAME	RESULTS	MAIN MESSAGE
Cystic fibrosis	✓	No variants detected

GASTROINTESTINAL TRACT DISORDERS

CONDITION NAME	RESULTS	MAIN MESSAGE
Juvenile polyposis syndrome	✓	No variants detected

BLOOD DISORDERS

CONDITION NAME	RESULTS	MAIN MESSAGE
Beta thalassemia	✓	No variants detected
Sickle cell disease	✓	No variants detected
Factor V Leiden thrombophilia	⛔	We have found a variant associated with Factor V Leiden thrombophilia.
Prothrombin thrombophilia	✓	No variants detected

SKIN DISORDERS

CONDITION NAME	RESULTS	MAIN MESSAGE
Bloom syndrome	✓	No variants detected
Junctional epidermolysis bullosa	✓	No variants detected
Sjögren-Larsson syndrome	✓	No variants detected

SENSORIAL DISORDERS

CONDITION NAME	RESULTS	MAIN MESSAGE
Nonsyndromic Hearing Loss and Deafness GJB2 Related	✓	No variants detected
Pendred syndrome	✓	No variants detected
Age-related macular degeneration	⛔	We have found a variant associated with Age-related macular degeneration.

SYSTEMIC DISORDERS

CONDITION NAME	RESULTS	MAIN MESSAGE
Nijmegen breakage syndrome	✓	No variants detected
Zellweger spectrum disorder	✓	No variants detected
Alpha-1 antitrypsin deficiency	✓	No variants detected

DRUG RESPONSE

DRUG RESPONSE

CONDITION NAME	RESULTS	MAIN MESSAGE
Malignant hyperthermia	✓	No variants detected

KEY SUMMARY

The above Summary provides an overview of the predicted risks for the patient. This information is based solely on genotype information and does not replace a doctor visit or a complete patient profile. Healthcare providers should consider also family history, presenting symptoms, current prescriptions, and other factors before making any clinical or therapeutic decisions.

✓ No negative assertions based on genotype; no increased risk for the evaluated condition.

We have found a variant potentially associated with an increased risk for this condition.

DETAILED INFORMATION

FACTOR V LEIDEN THROMBOPHILIA

Variant found:

- **Gene: F5**
- **Marker: rs6025**
- **Position: chr1:169519049**

We have found a heterozygous variant associated with Factor V Leiden thrombophilia in the F5 gene.

Your genetic make up evidences a nucleotide change from a C to a T in the DNA. This variant is present on one copy of chromosome 1 in position 169519049.

We have found a variant associated with Factor V Leiden thrombophilia.

Description

Factor V Leiden thrombophilia is an inherited disorder of blood clotting. Factor V Leiden is the name of a specific gene mutation that results in thrombophilia, which is an increased tendency to form abnormal blood clots that can block blood vessels.

People with factor V Leiden thrombophilia have a higher than average risk of developing a type of blood clot called a deep venous thrombosis (DVT). DVTs occur most often in the legs, although they can also occur in other parts of the body, including the brain, eyes, liver, and kidneys. Factor V Leiden thrombophilia also increases the risk that clots will break away from their original site and travel through the bloodstream. These clots can lodge in the lungs, where they are known as pulmonary emboli. Although factor V Leiden thrombophilia increases the risk of blood clots, only about 10 percent of individuals with the factor V Leiden mutation ever develop abnormal clots.

The factor V Leiden mutation is associated with a slightly increased risk of pregnancy loss (miscarriage). Women with this mutation are two to three times more likely to have multiple (recurrent) miscarriages or a pregnancy loss during the second or third trimester. Some research suggests that the factor V Leiden mutation may also increase the risk of other complications during pregnancy, including pregnancy-induced high blood pressure (preeclampsia), slow fetal growth, and early separation of the placenta from the uterine wall (placental abruption). However, the association between the factor V Leiden mutation and these complications has not been confirmed. Most women with factor V Leiden thrombophilia have normal pregnancies.

Frequency

Factor V Leiden is the most common inherited form of thrombophilia. Between 3 and 8 percent of people with European ancestry carry one copy of the factor V Leiden mutation in each cell, and about 1 in 5,000 people have two copies of the mutation. The mutation is less common in other populations.

Causes

A particular mutation in the F5 gene causes factor V Leiden thrombophilia. The F5 gene provides instructions for making a protein called coagulation factor V. This protein plays a critical role in the coagulation system, which is a series of chemical reactions that forms blood clots in response to injury.

The coagulation system is controlled by several proteins, including a protein called activated protein C (APC). APC normally inactivates coagulation factor V, which slows down the clotting process and prevents clots from growing too large. However, in people with factor V Leiden thrombophilia, coagulation factor V cannot be inactivated normally by APC. As a result, the clotting process remains active longer than usual, increasing the chance of developing abnormal blood clots.

Other factors also increase the risk of developing blood clots in people with factor V Leiden thrombophilia. These factors include increasing age, obesity, injury, surgery, smoking, pregnancy, and the use of oral contraceptives (birth control pills) or hormone replacement therapy. The risk of abnormal clots is also much higher in people who have a combination of the factor V Leiden mutation and another mutation in the F5 gene. Additionally, the risk is increased in people who have the factor V Leiden mutation together with a mutation in another gene involved in the coagulation system.

Actions and Advice

Your genotype suggests that you might have an increased risk of developing Factor V Leiden thrombophilia. Consider discussing your risk with a healthcare professional, especially if you have a family history or other risk factors for this condition. Lifestyle and other factors can also influence the chances of developing Factor V Leiden thrombophilia. Consult with a healthcare professional before making any major lifestyle changes.

Evaluations Following Initial Diagnosis

To assess the risk for thrombosis in an individual found to have the factor V Leiden variant, the following evaluations are recommended:

- For individuals heterozygous for the Leiden variant: the following testing for other inherited or acquired thrombophilic disorders is recommended by experts (but is not a hard-and-fast rule) given that double heterozygosity for the Leiden variant and *F2* thrombophilia variant 20210G>A occurs more commonly than protein C, S, and AT deficiencies (which are rare and unlikely to be found except in those with "high risk features" such as a strong family history) and antiphospholipid antibody (APLA) syndrome can occur at any age in anyone:
  - DNA testing *F2* thrombophilia variant (c.*97G>A, commonly known as 20210G>A)
  - Multiple phospholipid-dependent coagulation assays for a lupus inhibitor
  - Serologic assays for anticardiolipin antibodies and anti-beta$_2$-glycoprotein 1 antibodies
- For high-risk individuals (i.e., those with a history of recurrent VTE, especially at young age, or those with strong family history of VTE at young age) evaluation should also include assays of:
  - Protein C activity
  - Antithrombin activity
  - Protein S activity or free protein S antigen

Note: Measurement of the following is NOT recommended:

- Plasma concentration of homocysteine since no data support a change in duration of anticoagulation or the use of vitamin supplementation in individuals with hyperhomocysteinemia and a history of VTE
- *MTHFR* variants as no clinical rationale for this testing exists
- Factor VIII and other clotting factor levels

Treatment of Manifestations

Treatment of VTE in Adults

The management of individuals with factor V Leiden thrombophilia depends on the clinical circumstances.

The first acute thrombosis should be treated according to standard guidelines. For initial treatment of VTE, current guidelines suggest a new oral anticoagulant (dabigatran, edoxaban, rivaroxaban, or apixaban) over warfarin because of a lower bleeding risk and greater convenience. Of note, low molecular-weight heparin (LMWH) is given before dabigatran and edoxaban but not before rivaroxaban or apixaban.

For patients not treated with one of the new oral anticoagulants, administration of warfarin is started concurrently with LMWH or fondaparinux (except during pregnancy) and monitored with the international normalized ratio (INR). A target international normalized ratio (INR) of 2.5 (therapeutic range 2.0-3.0) provides effective anticoagulation, even in individuals homozygous for the Leiden variant. LMWH and warfarin therapy should be overlapped for at least five days, and until the INR has been within the therapeutic range on two consecutive measurements over two days.

LMWH and warfarin are both safe in breastfeeding women.

The duration of oral anticoagulation therapy should be based on an assessment of the risks for VTE recurrence and anticoagulant-related bleeding. Recurrence risk is determined by the clinical circumstances of the first event (provoked or unprovoked), adequacy of early treatment, and individual risk factors.

- Heterozygosity for the Leiden variant alone is not an indication for long-term anticoagulation in the absence of other risk factors, according to the American College of Chest Physicians guidelines on antithrombotic therapy and prevention of thrombosis as well as other clinical guidelines and expert opinion.
- Anticoagulation for at least three months is recommended for persons with DVT and/or PE associated with a transient (reversible) risk factor.

Long-term oral anticoagulation is recommended for individuals with a first or recurrent unprovoked (i.e., idiopathic) proximal DVT of the leg or pulmonary embolism (PE) who have a low or moderate bleeding risk. The decision should be based on an assessment of potential risks and benefits regardless of Leiden variant status.

Long-term anticoagulation is occasionally considered in individuals homozygous for the Leiden variant or with multiple thrombophilic disorders, particularly in the presence of additional risk factors (e.g., obesity) as the potential benefits from long-term anticoagulation may outweigh the bleeding risks.

Treatment of VTE in Children

The treatment recommendations for adults (which concluded that presence of a Leiden variant should not influence the intensity or duration of anticoagulation) are generally followed in children as well.

Children with a first VTE should receive initial treatment with either unfractionated heparin (UFH) or LMWH for at least five days. LMWH is favored over warfarin for continued therapy, especially in very young children and those with complex medical problems. Recommendations on the duration of antithrombotic therapy are based on the nature of the thrombotic event (spontaneous or provoked).

Anticoagulation is recommended:

- For at least three months following a VTE provoked by a clinical risk factor that has resolved;
- At least three months and until the risk factor has resolved in children with an ongoing but potentially reversible risk factor;
- For 6-12 months after a first unprovoked VTE.

Expert opinion emphasizes the importance of a careful risk/benefit assessment in each individual.

Prevention of Primary Manifestations

In the absence of a history of thrombosis, long-term anticoagulation is not routinely recommended for asymptomatic individuals who are heterozygous for the Leiden variant because the 1%-3%/year risk for major bleeding from warfarin is greater than the estimated less than 1%/year risk for thrombosis.

Because the initial thrombosis in 50% of Leiden variant heterozygotes occurs in association with other circumstantial risk factors (Table 2), a short course of prophylactic anticoagulation during exposure to hemostatic stresses may prevent some of these episodes. However, currently no evidence confirms the benefit of primary prophylaxis for asymptomatic Leiden variant heterozygotes. Factors that may influence decisions about the indication for and duration of anticoagulation include age, family history, and other coexisting risk factors.

Selected Leiden variant heterozygotes who do not require long-term anticoagulation may benefit from evaluation prior to exposure to circumstantial risk factors such as surgery or pregnancy. Recommendations for prophylaxis at the time of surgery and other high-risk situations are available in consensus guidelines.

Surveillance

Individuals on long-term anticoagulation require periodic reevaluation of their clinical course to confirm that the benefits of anticoagulation continue to outweigh the risk of bleeding.

Agents/Circumstances to Avoid

Women with a history of VTE who are heterozygous for the Leiden variant should avoid estrogen-containing contraception and hormone replacement therapy (HRT).

Women homozygous for the Leiden variant with or without prior VTE should avoid estrogen-containing contraception and HRT.

Asymptomatic women heterozygous for the Leiden variant:

- Should be counseled on the risks of estrogen-containing contraception and HRT use and should be encouraged to consider alternative forms of contraception and control of menopausal symptoms;
- Electing to use oral contraceptives should avoid third-generation and other progestins with a higher thrombotic risk;
- Electing short-term hormone replacement therapy for severe menopausal symptoms should use a low-dose transdermal preparation, which has a lower thrombotic risk than oral formulations.

Evaluation of Relatives at Risk

Although the genetic status of apparently asymptomatic at-risk family members can be established using molecular genetic testing for the Leiden variant, the indications for family testing are unresolved.

- In the absence of evidence that early identification of the Leiden variant leads to interventions that can reduce morbidity or mortality, decisions regarding testing should be made on an individual basis.
- Clarification of Leiden variant status may be considered in at-risk female relatives considering hormonal contraception or pregnancy or in families with a strong history of recurrent venous thrombosis at a young age if the results are likely to affect management.

Pregnancy Management

Prevention of Thrombosis During Pregnancy

No consensus exists on the optimal management of factor V Leiden thrombophilia during pregnancy; guidelines are derived from studies in non-pregnant individuals. All women with inherited thrombophilia should undergo individualized risk assessment in order to base decisions about anticoagulation on the number and type of thrombophilic defects, coexisting risk factors, and personal and family history of thrombosis.

For pregnant women with a prior single episode of VTE provoked by a transient risk factor not related either to pregnancy or to the use of estrogen, clinical vigilance during pregnancy is suggested.

LMWH is the preferred antithrombotic agent for prophylaxis and treatment during pregnancy.

The oral direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors rivaroxaban, apixaban, and edoxaban are contraindicted during pregnancy and breastfeeding because of (1) absence of data on fetal and neonatal safety and (2) animal studies that showed reproductive toxicity.

Prophylactic anticoagulation during pregnancy **is recommended** for all women:

- With a history of unprovoked VTE including those heterozygous for the Leiden variant. LMWH should be given during pregnancy, followed by a six-week course of anticoagulation post partum;
- Heterozygous for the Leiden variant with a prior pregnancy or estrogen-related thrombosis who are also at increased risk for recurrence.

Prophylactic anticoagulation during pregnancy **is suggested** for asymptomatic women who:

- Are homozygous for the Leiden variant;
- Are double heterozygotes for the Leiden variant and the prothrombin 20210G>A variant;
- Have other combined thrombophilic defects;

- Also have a positive family history for VTE.

In the absence of a positive family history for VTE, antepartum clinical vigilance and postpartum prophylaxis with LMWH is suggested as the greatest thrombotic risk is in the initial postpartum period.

Prophylactic anticoagulation during pregnancy **is not routinely recommended** in asymptomatic women heterozygous for the Leiden variant with no history of thrombosis. All women with a Leiden variant should be warned about potential thrombotic complications and counseled regarding the risks and benefits of anticoagulation during pregnancy.

Prevention of Thrombosis During the Postpartum Period

A six-week course of postpartum prophylaxis with LMWH is recommended for:

- All women heterozygous for the Leiden variant with a prior history of VTE;
- Women heterozygous for the Leiden variant and a positive family history of VTE;
- All asymptomatic homozygous women.

Other

Unexplained pregnancy loss. Current consensus guidelines and expert opinion recommend against the use of antithrombotic therapy outside of clinical trials in women with inherited thrombophilia and unexplained pregnancy loss because of the absence of high-quality evidence confirming benefit.

Pregnancy complications. Current guidelines recommend against antithrombotic prophylaxis for women with inherited thrombophilia and a history of other pregnancy complications such as preeclampsia or placental abruption.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

AGE-RELATED MACULAR DEGENERATION

Variant found:

- **Gene: ARMS2**
- **Marker: rs10490924**
- **Position: chr10:124214448**

We have found a heterozygous variant associated with Age-related macular degeneration in the ARMS2 gene.

Your genetic make up evidences a nucleotide change from a G to a T in the DNA. This variant is present on one copy of chromosome 10 in position 124214448.

We have found a variant associated with Age-related macular degeneration.

Description

Age-related macular degeneration is an eye disease that is a leading cause of vision loss in older people in developed countries. The vision loss usually becomes noticeable in a person's sixties or seventies and tends to worsen over time.

Age-related macular degenerationmainly affects central vision, which is needed for detailed tasks such as reading, driving, and recognizing faces. The vision loss in this condition results from a gradual deterioration of light-sensing cells in the tissue at the back of the eye that detects light and color (the retina). Specifically, age-related macular degeneration affects a small area near the center of the retina, called the macula, which is responsible for central vision. Side (peripheral) vision and night vision are generally not affected, but reduced dim light (scotopic) vision often occurs in the early stages of the disease.

Researchers have described two major types of age-related macular degeneration, known as the dry form and the wet form. The dry form is much more common, accounting for 85 to 90 percent of all cases of age-related macular degeneration. It is characterized by a buildup of yellowish deposits called drusen beneath the retina and vision loss that worsens slowly over time. The condition typically affects vision in both eyes, although vision loss often occurs in one eye before the other.

The wet form of age-related macular degeneration is associated with severe vision loss that can worsen rapidly. This form of the condition is characterized by the growth of abnormal, fragile blood vessels underneath the macula. These vessels leak blood and fluid, which damages the macula and makes central vision appear blurry and distorted.

Frequency

Age-related macular degeneration has an estimated prevalence of 1 in 2,000 people in the United States and other developed countries. The condition currently affects several million Americans, and the prevalence is expected to increase over the coming decades as the proportion of older people in the population increases.

For reasons that are unclear, age-related macular degeneration affects individuals of European descent more frequently than African Americans in the United States.

Causes

Age-related macular degeneration results from a combination of genetic and environmental factors. Many of these factors have been identified, but some remain unknown.

Researchers have considered changes in many genes as possible risk factors for age-related macular degeneration. The best-studied of these genes are involved in a part of the body's immune response known as the complement system. This system is a group of proteins that work together to destroy foreign invaders (such as bacteria and viruses), trigger inflammation, and remove debris from cells and tissues. Genetic changes in and around several complement system genes, including the CFH gene, contribute to a person's risk of developing age-related macular degeneration. It is unclear how these genetic changes are related to the retinal damage and vision loss characteristic of this condition.

Changes on the long (q) arm of chromosome 10 in a region known as 10q26 are also associated with an increased risk of age-related macular degeneration. The 10q26 region contains two genes of interest, ARMS2 and HTRA1. Changes in both genes have been studied as possible risk factors for the disease. However, because the two genes are so close together, it is difficult to tell which gene is associated with age-related macular degeneration risk, or whether increased risk results from variations in both genes.

Other genes that are associated with age-related macular degeneration include genes involved in transporting and processing high-density lipoprotein (HDL, also known as "good" cholesterol) and genes that have been associated with other forms of macular disease.

Researchers have also examined nongenetic factors that contribute to the risk of age-related macular degeneration. Age appears to be the most important risk factor; the chance of developing the condition increases significantly as a person gets older. Smoking is another established risk factor for age-related macular degeneration. Other factors that may increase the risk of this condition include high blood pressure, heart disease, a high-fat diet or one that is low in certain nutrients (such as antioxidants and zinc), obesity, and exposure to ultraviolet (UV) rays from sunlight. However, studies of these factors in age-related macular degeneration have had conflicting results

Actions and Advice

Your genotype suggests that you might have an increased risk of developing Age-related macular degeneration. Consider discussing your risk with a healthcare professional, especially if you have a family history or other risk factors for this condition. Lifestyle and other factors can also influence the chances of developing Age-related macular degeneration. Consult with a healthcare professional before making any major lifestyle changes.

Who is at risk?

Age is a major risk factor for AMD. The disease is most likely to occur after age 60, but it can occur earlier. Other risk factors for AMD include:

- **Smoking**. Research shows that smoking doubles the risk of AMD.
- **Race**. AMD is more common among Caucasians than among African-Americans or Hispanics/Latinos.
- **Family history and Genetics**. People with a family history of AMD are at higher risk. At last count, researchers had identified nearly 20 genes that can affect the risk of developing AMD. Many more genetic risk factors are suspected. You may see offers for genetic testing for AMD. Because AMD is influenced by so many genes plus environmental factors such as smoking and nutrition, there are currently no genetic tests that can diagnose AMD, or predict with certainty who will develop it. The American Academy of Ophthalmology currently recommends against routine genetic testing for AMD, and insurance generally does not cover such testing.

Does lifestyle make a difference?

Researchers have found links between AMD and some lifestyle choices, such as smoking. You might be able to reduce your risk of AMD or slow its progression by making these healthy choices:

- Avoid smoking
- Exercise regularly
- Maintain normal blood pressure and cholesterol levels
- Eat a healthy diet rich in green, leafy vegetables and fish

How is AMD detected?

The early and intermediate stages of AMD usually start without symptoms. Only a comprehensive dilated eye exam can detect AMD. The eye exam may include the following:

- **Visual acuity test.** This eye chart measures how well you see at distances.
- **Dilated eye exam.** Your eye care professional places drops in your eyes to widen or dilate the pupils. This provides a better view of the back of your eye. Using a special magnifying lens, he or she then looks at your retina and optic nerve for signs of AMD and other eye problems.
- **Amsler grid.** Your eye care professional also may ask you to look at an Amsler grid. Changes in your central vision may cause the lines in the grid to disappear or appear wavy, a sign of AMD.
- **Fluorescein angiogram.** In this test, which is performed by an ophthalmologist, a fluorescent dye is injected into your arm. Pictures are taken as the dye passes through the blood vessels in your eye. This makes it possible to see leaking blood vessels, which occur in a severe, rapidly progressive type of AMD (see below). In rare cases, complications to the injection can arise, from nausea to more severe allergic reactions.
- **Optical coherence tomography.** You have probably heard of ultrasound, which uses sound waves to capture images of living tissues. OCT is similar except that it uses light waves, and can achieve very high-resolution images of any tissues that can be penetrated by light—such as the eyes. After your eyes are dilated, youll be asked to place your head on a chin rest and hold still for several seconds while the images are obtained. The light beam is painless.

During the exam, your eye care professional will look for *drusen*, which are yellow deposits beneath the retina. Most people develop some very small drusen as a normal part of aging. The presence of medium-to-large drusen may indicate that you have AMD.

Another sign of AMD is the appearance of pigmentary changes under the retina. In addition to the pigmented cells in the iris (the colored part of the eye), there are pigmented cells beneath the retina. As these cells break down and release their pigment, your eye care professional may see dark clumps of released pigment and later, areas that are less pigmented. These changes will not affect your eye color.

Questions to ask your eye care Professional

Below are a few questions you may want to ask your eye care professional to help you understand your diagnosis and treatment. If you do not understand your eye care professional's responses, ask questions until you do understand.

- What is my diagnosis and how do you spell the name of the condition?
- Can my AMD be treated?
- How will this condition affect my vision now and in the future?
- What symptoms should I watch for and how should I notify you if they occur?

- Should I make lifestyle changes?

What are the stages of AMD?

There are three stages of AMD defined in part by the size and number of drusen under the retina. It is possible to have AMD in one eye only, or to have one eye with a later stage of AMD than the other.

- **Early AMD.** Early AMD is diagnosed by the presence of medium-sized drusen, which are about the width of an average human hair. People with early AMD typically do not have vision loss.
- **Intermediate AMD.** People with intermediate AMD typically have large drusen, pigment changes in the retina, or both. Again, these changes can only be detected during an eye exam. Intermediate AMD may cause some vision loss, but most people will not experience any symptoms.
- **Late AMD.** In addition to drusen, people with late AMD have vision loss from damage to the macula. There are two types of late AMD:
  - In geographic atrophy (also called dry AMD), there is a gradual breakdown of the light-sensitive cells in the macula that convey visual information to the brain, and of the supporting tissue beneath the macula. These changes cause vision loss.
  - In neovascular AMD (also called wet AMD), abnormal blood vessels grow underneath the retina. ("Neovascular" literally means "new vessels.") These vessels can leak fluid and blood, which may lead to swelling and damage of the macula. The damage may be rapid and severe, unlike the more gradual course of geographic atrophy. It is possible to have both geographic atrophy and neovascular AMD in the same eye, and either condition can appear first.

AMD has few symptoms in the early stages, so it is important to have your eyes examined regularly. If you are at risk for AMD because of age, family history, lifestyle, or some combination of these factors, you should not wait to experience changes in vision before getting checked for AMD.

Not everyone with early AMD will develop late AMD. For people who have early AMD in one eye and no signs of AMD in the other eye, about five percent will develop advanced AMD after 10 years. For people who have early AMD in both eyes, about 14 percent will develop late AMD in at least one eye after 10 years. With prompt detection of AMD, there are steps you can take to further reduce your risk of vision loss from late AMD.

If you have late AMD in one eye only, you may not notice any changes in your overall vision. With the other eye seeing clearly, you may still be able to drive, read, and see fine details. However, having late AMD in one eye means you are at increased risk for late AMD in your other eye. If you notice distortion or blurred vision, even if it doesnt have much effect on your daily life, consult an eye care professional.

Questions to ask your eye care professional about treatment

- What is the treatment for advanced neovascular AMD?
- When will treatment start and how long will it last?
- What are the benefits of this treatment and how successful is it?
- What are the risks and side effects associated with this treatment and how has this information been gathered?
- Should I avoid certain foods, drugs, or activities while I am undergoing treatment?
- Are other treatments available?
- When should I follow up after treatment?

Loss of Vision

Coping with AMD and vision loss can be a traumatic experience. This is especially true if you have just begun to lose your vision or have low vision. Having low vision means that even with regular glasses, contact lenses, medicine, or surgery, you find everyday tasks difficult to do. Reading the mail, shopping, cooking, and writing can all seem challenging.

However, help is available. You may not be able to restore your vision, but low vision services can help you make the most of what is remaining. You can continue enjoying friends, family, hobbies, and other interests just as you always have. The key is to not delay use of these services.

What is vision rehabilitation?

To cope with vision loss, you must first have an excellent support team. This team should include you, your primary eye care professional, and an optometrist or ophthalmologist specializing in low vision. Occupational therapists, orientation and mobility specialists, certified low vision therapists, counselors, and social workers are also available to help. Together, the low vision team can help you make the most of your remaining vision and maintain your independence.

Second, talk with your eye care professional about your vision problems. Ask about vision rehabilitation, even if your eye care professional says that "nothing more can be done for your vision." Vision rehabilitation programs offer a wide range of services, including training for magnifying and adaptive devices, ways to complete daily living skills safely and independently, guidance on modifying your home, and information on where to locate resources and support to help you cope with your vision loss.

Where to go for services

Low vision services can take place in different locations, including:

- Ophthalmology or optometry offices that specialize in low vision
- Hospital clinics
- State, nonprofit, or for-profit vision rehabilitation organizations
- Independent-living centers

What are some low vision devices?

Because low vision varies from person to person, specialists have different tools to help patients deal with vision loss. They include:

- Reading glasses with high-powered lenses
- Handheld magnifiers
- Video magnifiers
- Computers with large-print and speech-output systems
- Large-print reading materials
- Talking watches, clocks, and calculators
- Computer aids and other technologies, such as a closed-circuit television, which uses a camera and television to enlarge printed text

For some patients with end-stage AMD, an Implantable Miniature Telescope (IMT) may be an option. This FDA-approved device can help restore some lost vision by refocusing images onto a healthier part of the retina. After the surgery to implant the IMT, patients participate in an extensive vision rehabilitation program.

Keep in mind that low vision aids without proper diagnosis, evaluation, and training may not work for you. It is important that you work closely with your low vision team to get the best device or combination of aids to help improve your ability to see.

Questions to ask your eye care professional about low vision

- How can I continue my normal, routine activities?
- Are there resources to help me?
- Will any special devices help me with reading, cooking, or fixing things around the house?
- What training is available to me?
- Where can I find individual or group support to cope with my vision loss?

Coping with AMD

AMD and vision loss can profoundly affect your life. This is especially true if you lose your vision rapidly.

Even if you experience gradual vision loss, you may not be able to live your life the way you used to. You may need to cut back on working, volunteering, and recreational activities. Your relationships may change, and you may need more help from family and friends than you are used to. These changes can lead to feelings of loss, lowered self-esteem, isolation, and depression.

In addition to getting medical treatment for AMD, there are things you can do to cope:

- Learn more about your vision loss.
- Visit a specialist in low vision and get devices and learning skills to help you with the tasks of everyday living.
- Try to stay positive. People who remain hopeful say they are better able to cope with AMD and vision loss.
- Stay engaged with family and friends.

- Seek a professional counselor or support group. Your doctor or eye care professional may be able to refer you to one.

Information for family members

Shock, disbelief, depression, and anger are common reactions among people who are diagnosed with AMD. These feelings can subside after a few days or weeks, or they may last longer. This can be upsetting to family members and caregivers who are trying to be as caring and supportive as possible.

Following are some ideas family members might consider:

- Obtain as much information as possible about AMD and how it affects sight. Share the information with the person who has AMD.
- Find support groups and other resources within the community.
- Encourage family and friends to visit and support the person with AMD.
- Allow for grieving. This is a natural process.
- Lend support by "being there."

What research is being done?

NEI conducts and supports research in labs and clinical centers across the country to better prevent, detect, and treat AMD.

NEI-funded research over the past decade has revealed new insight into the genetics of AMD. By screening the DNA of thousands of people with and without AMD, scientists have identified differences in genes that affect AMD risk. Armed with this knowledge, researchers are identifying key biochemical pathways involved in the disease and are exploring therapies that could interrupt these pathways. It might also be possible to develop drug therapies for AMD that are targeted specifically to a person's unique genetic risk factors.

Scientists are also exploring ways to regenerate tissues destroyed by AMD. One approach is to make stem cells from a patient's own skin or blood. In a lab, these stem cells can be specially treated to form sheets of retinal pigment epithelium (RPE)—the pigmented layer of tissue that supports the light-sensitive cells of the retina. The goal is to generate layers of RPE that can be implanted into the patient's eye to preserve vision.

The NEI Audacious Goals Initiative (AGI) is taking on one of the biggest challenges in medicine: the regeneration of nerve cells in the retina and brain. In humans, once brain and retinal neurons are gone—due to injury or diseases like AMD—they are typically gone for good. However, lessons from nature suggest that it may possible to overcome this limitation. For example, in some fish and amphibians, if the retina is damaged, it can grow back. Through targeted research, the NEI AGI aims to unlock these secrets and utilize them in humans—to develop new therapies to regenerate neurons and neural connections in the eye and visual system.

GLOSSARY

ALLELE	An allele is a variant form of a gene that is located at a specific position, or genetic locus, on a specific chromosome. Humans have two alleles at each genetic locus, with one allele inherited from each parent.
CHROMOSOME	A chromosome is a condensed thread-like structure of DNA that carries hereditary information, or genes. Human cells have 22 chromosome pairs plus two sex chromosomes, giving a total of 46 per cell.
GENOME	A genome is an organism's complete set of DNA, including all of its genes. Each genome contains all of the information needed to build and maintain that organism. In humans, a copy of the entire genome—more than 3 billion DNA base pairs—is contained in all cells that have a nucleus.
GENOTYPE	The genetic makeup of an individual organism. It may also refer to just a particular gene or set of genes carried by an individual. The genotype determines the

	phenotype, or observable traits of the organism.
ODDS RATIO	The odds ratio is a way of comparing whether the odds of a certain outcome is the same for two different groups. In this report, the odds ratio estimates the probability of a condition occurring in a group of people with a certain genetic variant compared to a group of people without that variant. An odds ratio of 1 means that the two groups are equally likely to develop the condition. An odds ratio higher than 1 means that the people with the genetic variant are more likely to develop the condition, while an odds ratio of less than 1 means that the the people with the variant are less likely to develop the condition.
PHENOTYPE	A description of an individual's physical characteristics, including appearance, development and behaviour. The phenotype is determined by the individual's genotype as well as environmental factors.
POPULATION ALLELE FREQUENCY	The allele frequency represents the incidence of a variant in a population. Alleles are variant forms of a gene that are located at the same position, or genetic locus, on a chromosome.
SNP	Single nucleotide polymorphisms, frequently called SNPs, are the most common type of genetic variation among people. A SNP is a variation in a single nucleotide that occurs at a specific position in the genome.