

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Prothrombin 20210 Mutation (Factor II Mutation)

Elizabeth A. Varga and Stephan Moll

Circulation 2004;110:e15-e18

DOI: 10.1161/01.CIR.0000135582.53444.87

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

Copyright © 2004 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/cgi/content/full/110/3/e15>

Subscriptions: Information about subscribing to *Circulation* is online at
<http://circ.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>



Prothrombin 20210 Mutation (Factor II Mutation)

Elizabeth A. Varga, MS; Stephan Moll, MD



Testing for the prothrombin 20210 mutation, also called factor II mutation, may have been offered by your doctor because you or someone in your family, has had (1) a blood clot in one of the deep veins of the body (also called deep vein thrombosis or DVT); (2) a blood clot that has traveled to the lung (called a pulmonary embolism or PE); (3) a blood clot in an unusual site (such as the mesenteric or cerebral sinus vein); (4) a heart attack or stroke at a young age; or (5) a history of recurrent pregnancy loss or stillbirth.

A history like this in yourself or a family member may be indicative of an underlying thrombophilia. Thrombophilia is a term that describes a state in which the blood has an increased tendency to clot. People can have this increased tendency because they (1) have one or more inherited (genetic) risk factors, (2) have developed a chronic condition that puts them at increased risk, such as obesity, cancer, inflammatory bowel disease, or the persistence of certain antibodies (antiphospholipid antibodies), or (3) have a temporary condition that leads to an increased clotting tendency, such as recent surgery, trauma, a cast, prolonged immobility, pregnancy, or the use of oral contraceptives or hormone

replacement therapy. The purpose of this Cardiology Patient Page is to provide more information about the prothrombin mutation, which is the second most common cause of hereditary thrombophilia.

Understanding the Blood Clotting Process

Normally, there is a fine balance in the body which ensures that there is not too much bleeding or blood clotting. If this balance is disrupted, a blood clot may occur.

Throughout the course of a normal day, the blood vessels sustain many minor injuries of which you are not aware. In response, the body naturally triggers the “clotting cascade”—a sequence of events that allows the blood cells (platelets) and clotting proteins to respond to the site of the injury to clog up the vessel disruption and stop you from bleeding, and then to repair it. Although the activation of this clotting process occurs normally, a problem may arise in a person with thrombophilia. This is because he or she may possess blood clotting proteins in abnormal amounts, so that the clotting overshoots and a big blood clot may form.

What Is Prothrombin?

Prothrombin is a protein in the blood that is required for the blood to clot. It is also called factor II. Blood clots are composed of a combination of blood platelets and a meshwork of the blood clotting protein fibrin. Prothrombin is a blood clotting protein that is needed to form fibrin. If somebody has too little prothrombin, he or she has a bleeding tendency. If an individual has too much prothrombin, blood clots may form when they shouldn't.

What Does It Mean to Have the Prothrombin 20210 Mutation?

It was discovered in 1996 that a specific change in the genetic code causes the body to produce too much of the prothrombin protein. Having too much prothrombin makes the blood more likely to clot. People with this condition are said to have a prothrombin mutation, also called the prothrombin variant, prothrombin G20210A, or a factor II mutation.

How Did I Get the Prothrombin 20210 Mutation?

You inherit 2 copies of all of your genes from your parents; one from your mother and one from your father.

From the Division of Maternal-Fetal Medicine, University of Kansas Medical Center, Kansas City (E.A.V.); and Carolina Cardiovascular Biology Center, University of North Carolina School of Medicine, Chapel Hill, NC (S.M.).

Correspondence to Stephan Moll, MD, CB 7035, Department of Medicine, Division of Hematology-Oncology, University of North Carolina School of Medicine, Chapel Hill, NC 27599-7035. E-mail smoll@med.unc.edu

(*Circulation*. 2004;110:e15-e18.)

© 2004 American Heart Association, Inc.

Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000135582.53444.87

Therefore, we all have 2 prothrombin genes. It is possible to have a mutation in only 1 of your prothrombin genes. If this is the case, it is said that you are heterozygous for the gene mutation; you inherited the mutation from either your mother or your father. It is rare to have a mutation in both copies of the prothrombin gene, ie, have inherited the mutation from both your mother and your father, but if you do, you are said to be homozygous.

How Is the Diagnosis Made?

The diagnosis of a prothrombin mutation is made by a blood test. The blood is sent to a laboratory for analysis of the DNA (genetic code), and this will reveal if you are homozygous or heterozygous. Even though the prothrombin mutation slightly increases factor II (prothrombin) levels, it is not helpful to determine blood levels of factor II when trying to determine whether a person has the mutation or not.

What Are the Implications of Having a Prothrombin 20210 Mutation?

Heterozygous prothrombin mutations are found in about 2% of the US white population. The mutation is uncommon in African Americans (approximately 0.5%) and is rare in Asians, Africans, and Native Americans. The homozygous form is considered uncommon, with an expected occurrence of approximately 1 in 10 000 individuals. The prothrombin 20210 mutation is equally as common in men and in women. It has nothing to do with blood type.

Having the prothrombin mutation increases the risk of developing a DVT (a blood clot in the deep veins, typically the legs) and/or PE (blood clot that travels to the lungs). DVTs are dangerous because they can damage the veins, leading to pain and swelling, and sometimes to disability. PEs can damage the blood vessels in the lung, leading to chest pain and shortness of breath, and are sometimes life-threatening. Approximately 1 in every 1000 people will develop a DVT or PE

Risk Factors for Blood Clots in Legs and Lungs (DVT and PE)

Congenital and acquired thrombophilias	
Factor V Leiden mutation	
Prothrombin 20210 mutation	
Protein C deficiency	
Protein S deficiency	
Antithrombin III deficiency	
Anticardiolipin antibodies	
Lupus anticoagulant	
Elevated clotting factors VIII, IX, XI	
Elevated fibrinogen	
Elevated homocysteine	
Temporary risk factors	
Immobility	
Surgery	
Trauma	
Hospitalization	
Long-distance air travel	
Oral contraceptives	
Pregnancy	
Hormone replacement therapy	
Chronic conditions	
Obesity	
Cancer	
Inflammatory bowel disease	
Lupus and other rheumatologic diseases	
Congestive heart failure	

each year. The risk of developing a DVT or PE increases with age, with an average risk of 1 in 10 000 for people in their twenties to 1 in 200 for people in their seventies. Having a heterozygous prothrombin mutation increases the risk of developing a first DVT by about 2 to 3 times the background (or 2 to 3 in 1000 people each year). Having homozygous prothrombin mutations increases the risk further, but it is not yet known how much the risk is increased.

It should be noted that many people with the prothrombin mutation will never develop a blood clot in their lifetime. Very often, people who have the prothrombin mutation and develop a blood clot have additional risk factors (see the Table).

Most studies indicate that prothrombin mutations are not a risk factor for

heart attack and stroke in the middle-aged and elderly. However, few studies have shown that the prothrombin mutation may increase risk of heart attacks in young women, particularly those who smoke cigarettes.

Women With Prothrombin 20210 Mutation

There are certain implications of the prothrombin mutation that are specifically relevant for women. For instance, it is well known that using estrogen-containing oral contraceptives and hormones increases the risk of blood clots. It has been shown that women who have the prothrombin mutation increase the risk of developing a DVT by about 16 times by using estrogen-containing oral contraceptives. The risk of developing a blood clot in the brain (cerebral thrombosis, sinus vein thrombosis) is also significantly increased. The first 6 to 12 months of oral contraceptive therapy seem to be the most common time in which clots occur. However, clots can also occur after having taken birth control pills for several years. Although progestin-only contraceptives (tablet, Depo Provera injection, or a slow-release intrauterine device) do not appear to increase the risk for venous blood clots in the majority of women, it is not known whether they are absolutely safe in women with a preexisting clotting disorder, such as the prothrombin mutation. Hormone replacement therapy increases the risk of DVT by 2 to 4 times in those with the prothrombin 20210 mutation. Therefore, women with the prothrombin mutation should discuss the risks and benefits of hormone use with their physician.

There are also implications of the prothrombin mutation for pregnancy. For years, it has been recognized that blood has an increased tendency to clot during pregnancy and in the 6 weeks after delivery. Pregnancy in any woman is thought to increase the risk of a blood clot by approximately 5 times compared with the risk of non-pregnant women; however, in women with a prothrombin mutation, the risk

is further magnified. That being said, it should be noted that mathematically, this calculates to 1 out of 1000 women with the prothrombin mutation developing a DVT during pregnancy. This is not a high risk.

Recently, there has been the suggestion that the prothrombin mutation occurs more commonly among women with certain pregnancy complications. These complications may include stillbirth (pregnancy loss after week 20), second trimester pregnancy loss, placental abruption (where the placenta detaches from the uterus), and preeclampsia (elevated blood pressure that can lead to dangerous consequences). Some studies have also shown a relationship between a mother having the prothrombin mutation and delivering a baby of small size. At this time, it does seem that having the prothrombin mutation may increase the risk of these situations, but it is unclear how strong the association may be.

What Is the Treatment for the Prothrombin 20210 Mutation?

If you have already had a DVT or PE, then you were likely treated with blood thinning medication, also called anticoagulants. Anticoagulants such as warfarin (Coumadin; Bristol-Myers Squibb Company) are given for a variable length of time, depending on your situation. Having a DVT and PE in the past unfortunately increases your risk of developing another one in the future; however, having the prothrombin mutation does not increase the risk of a second clot any further. This reflects the fact that the prothrombin mutation is not a very strong risk factor for blood clots.

Many people have the prothrombin mutation and have not had a blood clot. If you have never had a blood clot, then you will not be routinely treated with blood thinning medication. Instead, you should be counseled about reducing or eliminating other factors that may add to your risk of developing a blood clot in the future.

In addition, you may require treatment with blood thinners during periods of particularly high risk, including surgery.

Who Should Be Tested?

People who develop or have had a DVT or PE may consider testing for the prothrombin mutation. Hereditary risk factors (such as prothrombin mutation) may be more strongly suspected in individuals who:

- had a DVT or PE without the presence of additional risk factors;
- had a clot at a young age (under 50 years of age);
- had a DVT or PE during pregnancy or during oral contraceptive or hormone use;
- developed a blood clot in an unusual site (such as the veins of the brain or abdomen);
- have a history of recurrent pregnancy loss, stillbirth, or certain pregnancy complications;
- have a history of any of these situations in first-degree relatives (parents, siblings, children).

Testing for the prothrombin mutation may be performed in combination with tests for other hereditary risk factors (factor V Leiden, protein C, S, and antithrombin deficiencies), acquired risk factors (antiphospholipid antibodies), or risk factors about which it is not known whether they are inherited or acquired (elevated homocysteine, clotting factors VIII, IX, XI, or fibrinogen).

Family Testing

Individuals who are from a family with a confirmed prothrombin mutation may also consider testing. Testing healthy family members is considered controversial and should be discussed with a family physician, genetic counselor, or hematologist. An advantage to testing is that early identification of the prothrombin mutation may allow for more diligent methods to prevent thrombosis (blood clots); it also may raise the level of suspicion of the patient and the physician that symp-

toms such as leg pain or swelling may be due to a DVT, or that chest pain and shortness of breath may be due to a PE. Individuals at risk can receive counseling about reducing controllable risks and can become informed of signs and symptoms of blood clots, which could aid in early diagnosis and treatment. Women may want to consider testing if they are making decisions about oral contraceptives or hormone replacement therapy. A disadvantage of testing family members is that identification of the gene mutation may lead to unnecessary anxiety, withholding of certain treatments (like oral contraceptives or hormone replacement), and possibly life and disability insurance discrimination. A positive test, therefore, may have unwanted consequences, and a negative test may lead to a false sense of reassurance; therefore, decisions about testing are highly personal.

What Can I Do to Minimize Risks Associated With Having the Prothrombin 20210 Mutation?

The primary risk a person faces related to the prothrombin mutation is the development of a DVT or PE; therefore, reducing or eliminating other risk factors for these conditions is the best way to remain healthy. Some risk factors for DVT and PE, like age and genetics, are not controllable. However, there are several lifestyle modifications that can be made to reduce risk.

Obesity is probably the most common modifiable risk factor, so losing weight (if you are overweight) or maintaining a healthy weight is an important way to reduce your risk of developing a blood clot. Another way to possibly reduce risk is by refraining from (or quitting) smoking, as smoking increases the risk for blood clots. As described above, use of hormones is known to dramatically increase the risk of developing a blood clot. Individuals with the prothrombin mutation should discuss the risks associated with oral contraceptives (birth control)

and hormone replacement therapies with their physician. They may choose contraceptive options that do not increase the risk for blood clots (barrier methods) or have less or no thrombotic risk (progestin-only contraceptives, minipill). Also, non-hormonal treatments without thrombotic risk are available to lessen postmenopausal symptoms or to treat osteoporosis. Long periods of immobility, including times of travel, also increase clotting tendency; therefore, it is important when traveling for 2 hours or more to take the opportunity to stop and walk around for a few minutes to keep blood circulating. When traveling by plane, you may also wish to perform exercises (including calf raises and frequent toe squeezes) and remain hydrated by drinking plenty of water and avoiding caffeine and alcoholic beverages. Wearing compression stockings (20 to 30 mm Hg compression at ankle) can also be considered. If you are sedentary at work, it is recommended that you take periodic breaks to stop and walk around.

Hospitalization and surgery can dramatically increase the likelihood of

developing a blood clot. If you are scheduled to undergo surgery or are hospitalized for some reason, it is important that your doctor know about the prothrombin mutation so that temporary treatments to prevent blood clots can be administered. You may want to be proactive and ask your physician whether you should receive DVT prophylaxis and, if so, for how long.

Lastly, if you have the prothrombin 20210 mutation, you should know the warning signs of DVT and PE so that you can take action immediately if you suspect you have a blood clot. Signs of DVT include pain, swelling, and/or redness of the leg or arm; the area may also feel warm to the touch. Sudden unexplained shortness of breath, which may worsen with exertion, chest pain (which often gets worse on taking deep breaths), and coughing (sometimes with blood) are suggestive of PE. If you observe these signs, it is important to go to the emergency room or consult with your doctor immediately.

Additional Resources

DeStefano V, Martinelli I, Mannucci P, et al. The risk of recurrent deep venous thromboem-

bolism among heterozygous carriers of the G20210A prothrombin gene mutation. *Br J Hematol.* 2001;113:630–635.

Hellmann EA, Leslie N, Moll S. Knowledge and information satisfaction of individuals with factor V Leiden mutation. *J Thromb Hemost.* 2003;1:2335–2339.

Martinelli I, Taioli E, Bucciarelli P, et al. Interaction between the G20210A mutation of the prothrombin gene and oral contraceptive use in deep vein thrombosis. *Arterioscler Thromb Vasc Biol.* 1999;19:700–703.

McGlennen R, Key N. Clinical and laboratory management of the prothrombin G20210A mutation. *Arch Pathol Lab Med.* 2002;126:1219–1325.

Ornstein, D, Cushman M. Factor V Leiden. *Circulation.* 2003;107:e94–e97.

Reich L, Bower M, Key N. Role of the geneticist in testing and counseling for inherited thrombophilia. *Gen Med.* 2003;5:133–143.

Ridker PM, Hennekens C, Miletich J. G20210A mutation in prothrombin gene and risk of myocardial infarction, stroke, and venous thrombosis in a large cohort of US men. *Circulation.* 1999;99:999–1004.

Rosendaal F, Vessey M, Rumley A, et al. Hormonal replacement therapy, prothrombotic mutations and the risk of venous thrombosis. *Br J Hematol.* 2002; 16:851–854.

Vandenbroucke J, Rosing J, Bloemenkamp K, et al. Oral contraceptives and the risk of venous thrombosis. *N Engl J Med.* 2001;344:1527–1535.

Deborah Okner Smith. Factor V Leiden/Thrombophilia Support Page. Available at: <http://www.fvleiden.org>. Accessed May 18, 2004.