THE GENETICS OF THROMBOPHILIA

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Thrombophilia is a term used to describe an increased tendency for the blood to clot. There are many reasons **why** the blood can have this increased tendency.

The blood may clot more easily because the **proteins** present in the blood are produced in irregular amounts or the proteins are abnormal in some way.

There are a number of reasons why a blood clotting protein is produced in irregular amounts or is abnormal in some way. One reason is an **inherited** predisposition.
In order to understand how inherited factors influence blood clotting, it is important to understand some basic concepts.

BLOOD CLOTTING (ALSO CALLED COAGULATION)

Normally, a thrombus, or blood clot, develops in response to a trauma. This prevents an individual from bleeding to death. Hundreds of different **proteins** are involved in helping the blood to clot. These proteins each perform a specific function. If a protein is an irregular shape, or is not produced in adequate amounts, this can lead to problems in the blood clotting process.

WHAT ARE PROTEINS?

Proteins perform specific functions in the body. Specific proteins are necessary for the blood to clot. All proteins are created as a chain of **amino acids**.
Amino acids are chemical compounds that contain nitrogen, hydrogen and carbon. Amino acids are present in the body. They are the "building blocks" of proteins.
Proteins are formed by linking together a chain of amino acids.

WHAT DOES GENETICS HAVE TO DO WITH BLOOD CLOTTING?

The genetic information we inherit can directly influence the shape and the amount of protein the body produces. If an individual inherits a specific genetic defect, this can alter the blood clotting proteins that are produced. This may lead to thrombophilia.

To understand how genetics influences blood clotting, it is important to understand how proteins are made:

Blood clotting proteins are formed from a chain of amino acids.
The amino acid chain is determined by our **genetic code**.
The **genetic code** refers to **DNA**. DNA is a large molecule, shaped like a twisted ladder, which is made up of trillions of chemical bases. Our DNA is passed (inherited) from generation to generation from our parents.

The chemical bases in our DNA are "read" much like a sentence. The chemical bases in DNA are "read" in sets of three. Each three letter code represents a specific amino acid.

Just as your brain is able to assign meaning to words, your body is able to assign specific amino acids to each three letter DNA code.

For example:

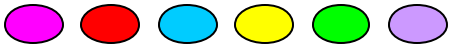
Here is a segment of your DNA code:

AGCCGTACGGTTCAACCG

It is read by the body as:

ACG CGG ACG GTT CAA CCC

Based on this, the amino acids are assigned like this:



Met—Arg—Thr—Val—Gln -- Pro

This chain of amino acids is called a protein. This is how all the proteins in the body are made; by reading the genetic code, and linking together the corresponding amino acids.

However, a problem arises if there is a spelling error (called mutation) in the DNA code. A mutation in the DNA code may result in an incorrect amino acid being assigned.

EXAMPLE: DNA WITH A MUTATION:

ACG CAG ACG GTT CAA CGG

CHANGE IN AMINO ACID ORDER:

Met— Gln— Thr— Val— Gln—Pro

If this occurs, the entire **protein** that is being produced will be **altered**. It will be a different shape, and therefore the function of the protein will be different.

To summarize, if there is a change in a person's DNA, called a mutation, the body may create an irregularly shaped protein. Changes in the DNA may also cause the body to produce too much of a protein.

Inherited thrombophilia occurs when an **inherited DNA mutation** results in:
1) too much or too little of a blood clotting protein being produced or
2) the blood clotting protein that is produced does not function correctly

A person with **inherited thrombophilia** has an increased chance to develop a blood clot, compared to other people in the population.

DNA MUTATIONS THAT LEAD TO INHERITED THROMBOPHILIA

The most common DNA mutations that lead to inherited thrombophilia are called factor V Leiden and prothrombin 20210A.

Factor V (five) Leiden

- Factor V Leiden is the term used to describe the **DNA mutation** in the **gene** used to make the **factor V protein.**
- A **gene** is simply a strip of DNA used to create a specific protein. The **factor V gene** is used to make the **factor V protein**.
- The **factor V** protein is made in all individuals, and **helps the blood to clot.**
- When a person has "factor V Leiden" they have a DNA mutation that results in an abnormal factor V protein. A mutation in the factor V gene is called factor V Leiden, since this mutation was first found in a person from a city called Leiden in the Netherlands.

How does a DNA Mutation in the Factor V Gene Increase the Risk to Develop a Blood Clot?

- Normally the factor V protein is produced to help the blood to clot. It is produced in greater amounts after a trauma.
- The factor V protein is regulated by something called protein C. Protein C breaks up factor V, preventing it from being reused and clotting the blood.
- If there is **a mutation in the factor V gene**, the protein will be abnormally shaped. The abnormal shape prevents it from **being broken down** properly by protein C.
- Because the factor V protein cannot be broken down as quickly, there is more of the factor V protein left in circulation. This leads to an increased tendency for the blood to clot (since the factor V protein helps blood to clot).

TESTING FOR FACTOR V LEIDEN

- Testing for factor V Leiden can either be done using a blood test or a genetic test.
- In the blood test, the lab looks to see if the blood demonstrates resistance to activated protein C (e.g. is preventing protein C from breaking down factor V). If the blood demonstrates resistance to activated protein C, it is likely (90-95%) that the person has a genetic change in the factor V gene (called factor V Leiden).
- A genetic test is usually ordered as a follow-up test to the activated protein C blood test. The genetic test also simply involves a blood draw. The DNA is extracted from blood cells and the lab looks at the factor V gene to see if there is a spelling change (mutation) in the DNA code of that gene only. If there is a specific gene change, the **1691st DNA letter is changed from a G to an A**, the person is said to have **factor V Leiden**.

How common is factor V Leiden (a mutation in the factor V gene)?

A change in the factor V gene (factor V Leiden) is present in about 5% (or 1 out of 20) of Caucasian (white) individuals. It is more common to find this change in individuals of a European background.
In the United States, it has also been found in approximately 1% (1 in 100) of African Americans, Hispanic Americans and Native Americans. Factor V Leiden is rare in Asian populations.

Prothrombin 20210A (also called factor II)

- Prothrombin 20210A (also called the factor II mutation) is the term used to describe the **DNA mutation** in the gene used to make the **prothrombin protein.**
- A **gene** is simply a strip of DNA used to create a specific protein. The **prothrombin gene** is used to make the **prothrombin protein.**
- The **prothrombin** protein is made in all individuals and **helps the blood to clot.**
- When a person has "prothrombin 20210A" they have a DNA mutation that results in abnormal amounts of the prothrombin protein in the body. A mutation in the prothrombin gene occurs at the 20210st letter in the DNA code of the prothrombin gene. This letter is changed from a G to an A.

How does a DNA Mutation in the Prothrombin Gene Increase the Risk to Develop a Blood Clot?

- Normally, the prothrombin protein is produced to help the blood to clot. It is produced in greater amounts after trauma.
- If there is **a mutation in the prothrombin gene**, the body will produce more of the prothrombin protein. Why this occurs is not well understood. Because there is more of the prothrombin protein in circulation, there is an increased tendency for the blood to clot.

TESTING FOR PROTHROMBIN

- Testing for prothrombin 20210A is done using a genetic test.
- The genetic test involves a simple blood draw. The DNA is extracted from blood cells and the lab looks at the prothrombin gene to see if there is a spelling change (mutation) in the DNA code of that gene only. If a specific gene change, the **20210st letter is changed from a G to an A**, the person is said to have a **prothrombin (or factor II) mutation**. Sometimes a positive test is called **Prothrombin G20210A** to represent this change.

How common is the prothrombin mutation?

A change is the prothrombin gene (prothrombin 20210A) is present in 2-4% (or 1 in 50 to one in 25) of Caucasian (white) individuals. It is more common to find this change in individuals of a European background.
In the United States, it has also been found in approximately 0.4% (about 1 in 250) of African Americans. This mutation is rare in other populations.

INHERITANCE OF FACTOR V LEIDEN AND PROTHROMBIN 20210A

As discussed above, genetic mutations are passed from generation to generation. This is because we receive our DNA from our parents.

Our genetic information is inherited in pairs. Every gene (strip of DNA that is used to create a specific protein) has two copies, one from our mothers and one from our fathers.

Different conditions can be inherited in different ways. In terms of thrombophilia, only **one** of a person's **two** copies of a gene must have a mutation in order for that individual to have an increased risk of clotting. This is called **dominant** inheritance.

If a person inherits only one copy of the gene change, they are said to be **heterozygous** ("hetero" means different, "zygous" means bodies). If both copies of a person's genes have a change, they are said to be **homozygous** ("homo" means same, "zygous" means bodies).

If a person is homozygous, (inherits mutations in **both** copies of their gene, one from each parent) they are at a greater risk to develop a blood clot than an individual who is heterozygous.

An individual will also have a greater risk to develop a blood clot if they inherit a mutation in **more than one gene** that leads to thrombophilia. For example, a person has a greater risk to develop a blood clot if they have factor V Leiden and prothrombin 20210A.

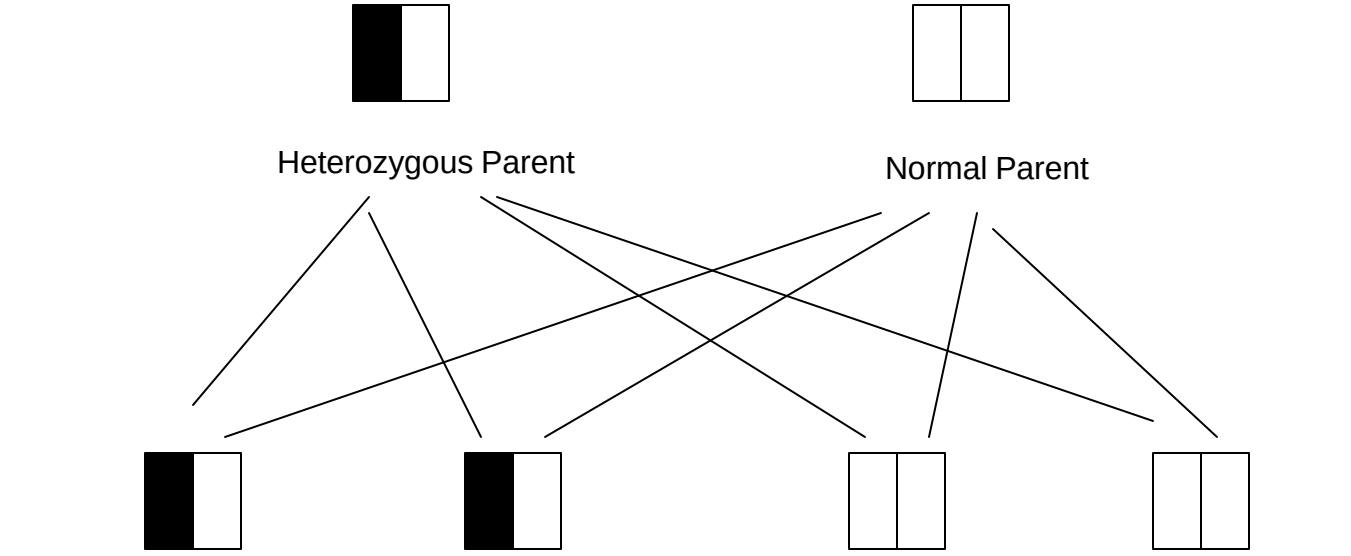
What is the chance that I will pass this on to my children?

As stated above, every individual inherits two copies of each gene. One copy is inherited from the mother, the other copy from the father.

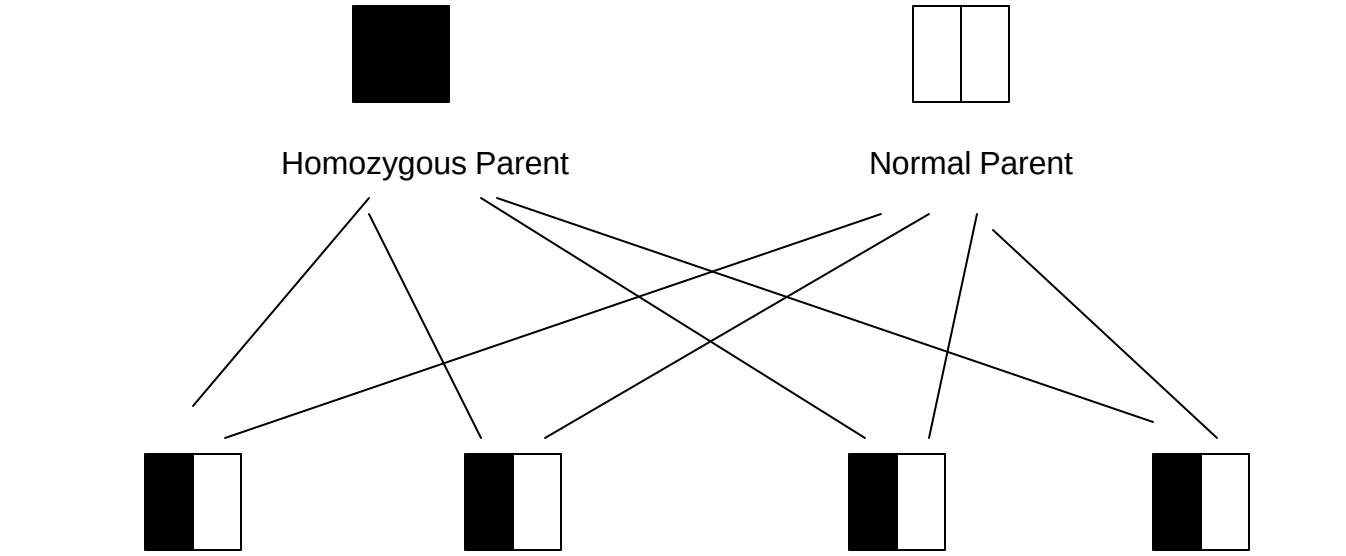
To predict the risk to your children, a few factors must be considered.

The first is whether or not you are heterozygous (only one of your two gene copies contains a mutation) or homozygous (both copies of your two genes contain a mutation) for the gene. A genetic test can tell you whether or not you are heterozygous or homozygous.

If you are heterozygous for the gene mutation, there is a 50:50 (or one half) chance that your child will inherit the gene mutation. This is because there is an equal likelihood that you will pass on the gene copy with the mutation OR the gene copy that is normal. Which copy of the gene your child inherits is a chance event. There is nothing an individual can do to alter this chance. (See diagram below)



If you are homozygous for the gene mutation, your child will definitely inherit it. This is because you do not have a normal copy of the gene, and it is therefore impossible to pass on a normal copy to your child.



100% Chance Child Will Inherit- Heterozygous (1 copy of the gene)
Would have Thrombophilia

A second consideration is whether or not the child's other parent carries a gene mutation that leads to thrombophilia. This would influence the possible outcomes for your child.

Genetic counselors are professionals who can help interpret genetic concepts. If you are interested in learning more about genetic risks, you may want to consult with a genetic counselor in your area, or a health care professional who has specialized training in genetics. To locate a genetic counselor in your area, you may contact the National Society of Genetic Counselors at http://www.nsgc.org.

GENETIC TESTING OF FAMILY MEMBERS

There are many issues surrounding the decision to pursue genetic testing. An individual will want to consider how this information will be used in medical management before having testing done. It is recommended that these issues be discussed with a knowledgeable health care provider or genetics' professional.

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