

This fact sheet describes common blood clotting conditions, also known as thrombophilias, and includes the symptoms, cause and any treatment or testing which is available.

In summary

- Hereditary thrombophilia is a genetic predisposition to developing blood clots
- There are many genes involved in the blood clotting process. A genetic variation within some of these genes may increase the tendency to form blood clots
- Common thrombophilia conditions include antithrombin deficiency, protein C deficiency, protein S deficiency, factor V Leiden and prothrombin thrombophilia.

WHAT IS HEREDITARY THROMBOPHILIA?

Thrombophilia refers to a group of conditions where the blood has an increased tendency to form clots. These conditions can be:

- **Acquired** - associated with some other health or medical problem
- **Inherited** - there is a genetic basis for the condition (hereditary thrombophilia).

This Fact Sheet only discusses hereditary thrombophilias.

The normal process of blood clotting is called **haemostasis**. When a blood vessel is injured the clotting process is triggered, known as the coagulation cascade. The coagulation cascade involves a chain reaction of different chemicals (proteins) in the blood called **clotting factors**, whose primary role is to solidify the blood into a clot using platelets, sticking to the injured part of the blood vessel like a Band-Aid.

Other proteins, known as **anticoagulants**, regulate the clotting process, stopping the blood from clotting too much.

Thrombophilia occurs if the normal balance of the coagulation cascade is disrupted. This may occur due to:

- **Loss of Function:** where too little of a protein that inhibits clotting (anticoagulant) is made
- **Gain of Function:** where too much of a clotting factor is made.

Many people with thrombophilia do not experience any health problems.

The main concern is the increased risk of developing blood clots (**thromboses**), including:

- **Venous thrombosis** – a blood clot within a deep or superficial vein. The most commonly known is a clot in a deep vein in the leg (deep vein thrombosis - DVT). A DVT will cause pain and swelling in the affected area and requires treatment with blood thinning medication.
- **Emboli** – partial blood clots that travel throughout the blood stream. Emboli may lodge within vessels of the lung (called a pulmonary embolism) or in the brain, causing a stroke. Both pulmonary embolism and stroke can be life-threatening.
- **Arterial thrombosis** – a blood clot within the artery that may result in a stroke, heart attack, or pregnancy complications including miscarriage. Rarer than venous thromboses.

WHAT CAUSES HEREDITARY THROMBOPHILIA?

People who have a genetic susceptibility (increased risk) to developing blood clots have a mutation in a thrombophilia gene. Many people who have a mutation in a thrombophilia gene however, will not develop a blood clot over their lifetime. Other environmental factors play an important role in the development of clots.

Hereditary thrombophilias are grouped according to their action (*Table 49.1*):

- **Group 1 conditions:** are caused by mutations that result in “loss of function” of anticoagulants (proteins which normally promote blood thinning)
- **Group 2 conditions:** are caused by mutations that result in ‘gain of function’ of clotting factors that increase the tendency towards clot formation.

Group 2 conditions occur approximately 5 times more frequently than Group 1 conditions. The risk of clots forming, however, is higher for people with Group 1 conditions than Group 2 conditions.

HOW IS THROMBOPHILIA INHERITED?

Hereditary thrombophilias usually follow a pattern of **autosomal dominant inheritance**. Autosomal refers to the fact that the thrombophilia genes are located on a numbered chromosome, and therefore affects males and females equally. Dominant means that only one copy of the gene pair needs to be faulty to have thrombophilia and be at increased risk of developing blood clots.

If one parent has a thrombophilia gene mutation (Figure 49.1) in every pregnancy there is:

- 1 chance in 2 (2 chances in 4 or 50% chance) that they will have a child who inherits both copies of the working gene from his/her parents. In this case, the child will not be any more susceptible to clotting than the average individual
- 1 chance in 2 (2 chances in 4 or 50% chance) that their child will inherit the dominant gene mutation and the working copy of the gene from the parents and he/she will be predisposed to developing blood clots.

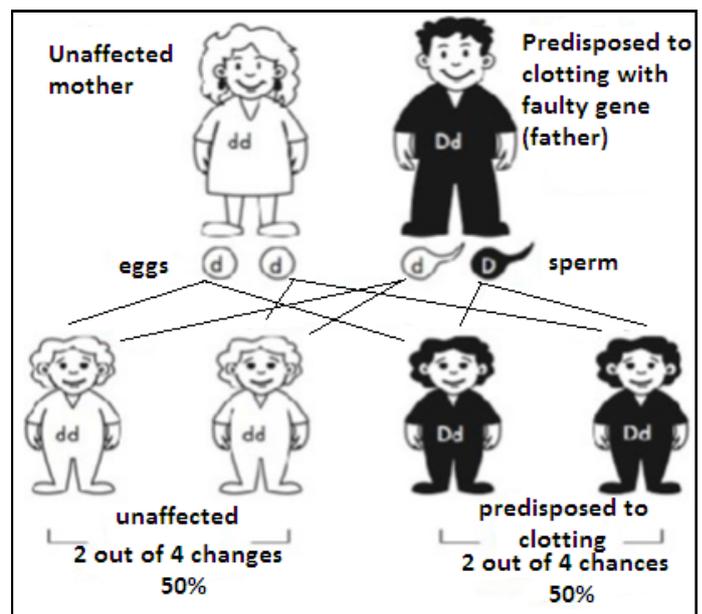


Figure 49.1: Autosomal dominant inheritance when one parent carries the autosomal dominant faulty gene copy of a thrombophilia gene. The autosomal dominant faulty gene copy is represented by 'D'; the working copy of the gene by 'd'.

Our body is made up of millions of cells, and in each cell there are instructions, called genes, that make all the necessary structural components and chemicals for the body to function. These genes are packaged onto little long strands known as chromosomes.

We all have 46 chromosomes arranged into 23 pairs. One copy of each pair is inherited from our mother and the other from our father. The first 22 chromosome pairs are numbered and are known as autosomal chromosomes. The 23rd pair is made up of the sex chromosomes called X and Y. Males have an X and a Y chromosome and females have two copies of the X chromosome.

Since all our chromosomes come in pairs, all our genes also come in pairs. Sometimes, a gene may have a variation in the instruction that causes the gene to no longer function properly. This variation is called a **mutation** or **pathogenic variant**, and means that the product produced by the gene, called a protein, is impaired or even absent.

Gene mutations may be inherited from a parent, or occur for the first time in an individual. Once you have a gene mutation however, it may be passed on to future generations. This is referred to as genetic inheritance.

Hereditary Thrombophilia	Proportion of people who have a genetic mutation	Impact of inheriting one or more genetic mutations
Group 1 conditions		
Antithrombin deficiency (<i>SERPINC1</i> gene)	About 1 in every 500 individuals in the Australian population	About 60% of people with one mutation will develop a VTE by age 60 years. If both antithrombin gene copies have a mutation, in most cases this produces a severe form of the condition and is generally incompatible with life.
Protein C deficiency (<i>PROC</i> gene)	About 1 in 500 individuals in the Australian population	Up to 50% of people with one mutation will develop a VTE by age 60 years. If both protein C gene copies have a mutation, in most cases this produces a severe form of the condition, characterised by a skin condition and illness in newborn babies.
Protein S deficiency (<i>PROS1</i> gene)	3-13 in every 1000 individuals in the Australian population	Up to 30% of people with one mutation will develop a VTE by age 60 years. If both protein S gene copies have a mutation, in most cases this produces a severe form of the condition, characterised by a skin condition and illness in newborn babies.
Group 2 conditions		
Factor V Leiden (<i>F5</i> gene)	About 5 in 100 people of Northern European ancestry Rare in people of Asian or African ancestry	Factor V Leiden describes a specific gene mutation in the factor V gene About 6% of people with one mutation will develop a VTE by age 65 If both Factor V Leiden gene copies have a mutation, in most cases this produces a moderate clotting condition.
Prothrombin gene mutation (<i>F2</i> gene)	2-3 in 100 people of Northern European ancestry Rare in people of Asian or African ancestry	Less than 5% of people with one mutation will develop a VTE by age 60 If both prothrombin gene copies have a mutation, in most cases this produces a moderate clotting condition. If people have one prothrombin gene mutation and one Factor V Leiden mutation, in most cases this produces a moderate clotting condition.

Table 49.1: The major hereditary thrombophilia conditions. The term Venous Thromboembolism (VTE) refers to a deep vein thrombosis with or without a pulmonary embolism and is often used to describe thrombophilia symptoms.

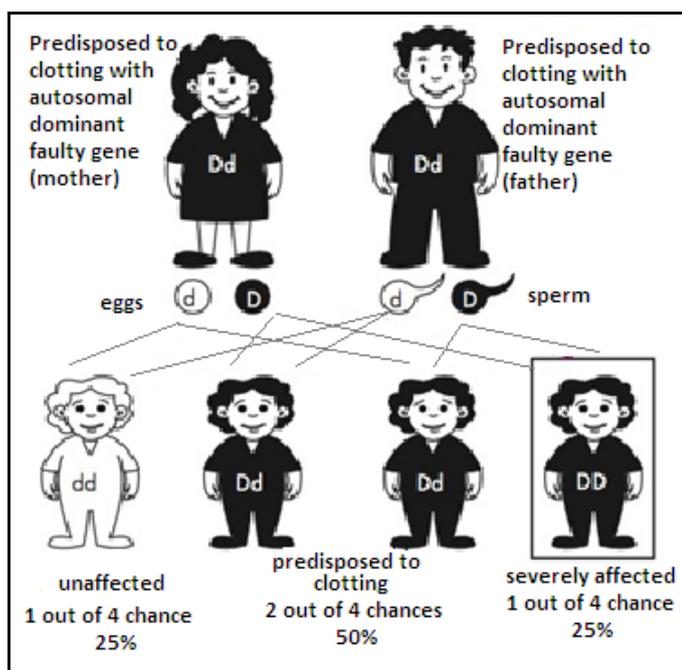


Figure 49.2: Autosomal dominant inheritance when both parents carry the autosomal dominant faulty gene copy of a thrombophilia gene. The autosomal dominant faulty gene copy is represented by 'D'; the working copy of the gene by 'd'.

If both parents have a thrombophilia gene mutation (Figure 49.2) in every pregnancy there is:

- 1 chance in 4 (25% chance) that they will have a child who inherits both copies of the working gene from his/her parents. In this case, the child will not be any more susceptible to clotting than the average individual
- 1 chance in 2 (2 chances in 4 or 50% chance) that their child will inherit the dominant gene mutation and the working copy of the gene from the parents and he/she will be predisposed to developing blood clots, like their parents
- 1 chance in 4 (25% chance) that they will have a child who inherits both copies of the dominant gene mutation from his/her parents. Having two copies of the faulty thrombophilia gene has a much greater impact on the body and usually there is a much higher risk of clotting.

IS THERE ANY TESTING AVAILABLE FOR THROMBOPHILIA?

For people who have experienced an episode of thrombosis your doctor may arrange a thrombophilia screen looking for heritable causes for thrombophilia. This may or may not identify a cause for your clotting as there are many other environmental factors involved.

Testing for genetic carrier status

When a person is identified as having a gene mutation for thrombophilia, their first degree relatives (parents, children, brothers and sisters) all have a 1 chance in 2 (50%) of also having a mutation. Screening may be performed through specialised blood tests through your family doctor, or genetic testing may be offered if the gene mutations have been identified in your family. If you are identified as having a gene mutation but do not have symptoms, usually no treatment is required. Treatment is targeted for people who have had a clotting problem and includes taking anticoagulants to help thin the blood.

Prenatal testing and PGD

Although it may be technically possible to perform genetic testing during pregnancy, it is generally not advised as not all people with a gene mutation for a hereditary thrombophilia will develop significant health problems. These options may be discussed in more detail with your health care practitioner or genetic counsellor.