

The genetics of brain cavernomas

Information leaflet for people concerned about genetic causes of brain cavernomas



Helping the Cavernoma Community

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Registered charity number: 1114145

Who is this leaflet for?

This leaflet is for people affected by a brain cavernoma, which is also known as a 'cavernous angioma', 'cavernous haemangioma', or 'cavernous malformation'.

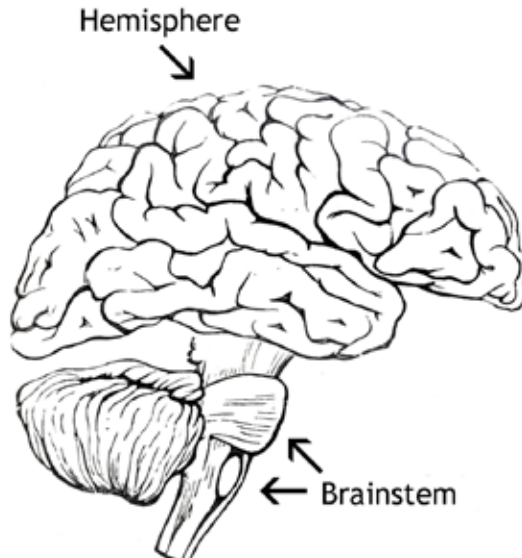
In particular, this leaflet is for patients and their families if they are concerned that brain cavernomas might run in the family.

There are other leaflets in the Cavernoma Alliance UK series:

- one for people who have symptoms due to their brain cavernoma; and
- another for people who do not have symptoms from their brain cavernoma.

What are brain cavernomas?

Cavernomas are clusters of abnormal blood vessels. Cavernomas are found in the brain, brainstem, spinal cord and, rarely, in other areas of the body.



Picture of the lobes and hemispheres of the brain, and the brainstem (labelled).

Cavernomas look like raspberries. They are made up of abnormal blood vessels through which blood flows slowly - these are the caverns that give the condition its name. The cells that line these caverns sometimes ooze small amounts of blood into surrounding brain tissue, which sometimes results in symptoms. Cavernomas can get bigger, but this growth is not cancerous, and they do not spread to other areas of the body.



Cavernomas look like raspberries.

Magnetic resonance imaging (MRI) is the most accurate test and provides pictures of brain cavernomas. Sometimes, small cavernomas can only be found by using a specialised MRI setting, known as 'gradient-recalled echo MRI'. This type of MRI is the only way of being sure about whether someone has just one, or many, cavernomas.

Cavernomas are sometimes found when experts are looking at brain tissue under the microscope.

What is meant by genetic causes?

Genes are made of a material called DNA. Genes make up the code that determines how someone's body is put together. Very rarely, errors in the code can cause brain cavernomas - this is known as a genetic cause. Most cavernomas do not have a genetic cause.



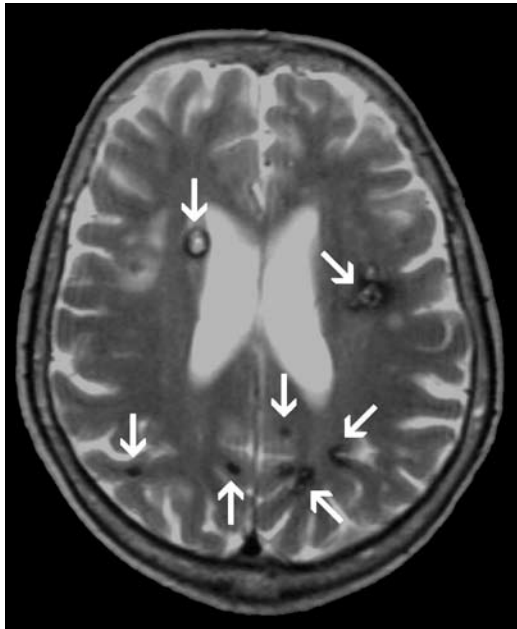
Diagram of DNA.

What is the chance of having a genetic cause?

Your brain scan (MRI) might show clues to an underlying genetic cause.

If an MRI scan which includes gradient-recalled echo sequences shows that you have a **single** brain cavernoma, a genetic cause is very unlikely to affect you and your immediate relatives (parents, brothers, sisters, and children).

If your MRI scan shows that you have **more than one** brain cavernoma, a genetic cause might run in your family. However, it can be difficult to tell if a relative also has a brain cavernoma, because many brain cavernomas never cause any symptoms at all. So, if you have several brain cavernomas, and none of your relatives appear to have one, you still might have a genetic cause.



MRI of the brain with arrows showing many cavernomas.

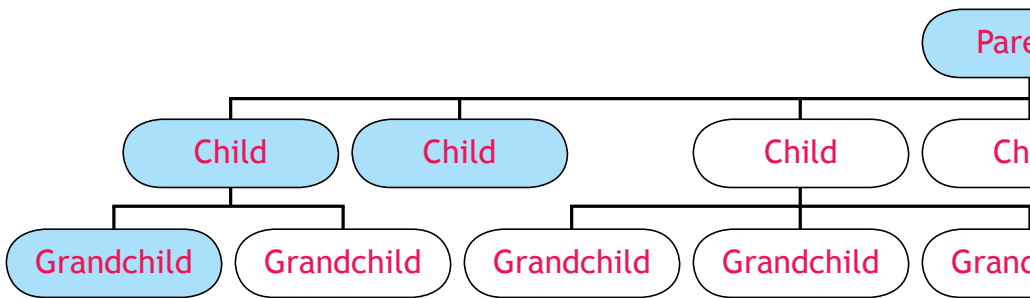
How is a gene cause inherited?

Everyone has two sets of genes, one from their mother and one from their father. Genes are the instructions that decide how your body works. Someone who has a genetic cause of brain cavernomas has a change in one copy of the cavernoma gene. One of the two copies of each gene is passed to a child. So there is a 50% chance that someone with a genetic cause might pass the gene change on to their child. This is called 'autosomal dominant inheritance'.

In the family tree below:

- the box at the top represents parents, one of whom has brain cavernomas;
- the boxes in the middle row represent their children, and those shaded blue have brain cavernomas;
- the boxes on the bottom row represent the grandchildren, and those shaded blue have brain cavernomas.

It may be obvious that brain cavernomas are inherited in a family if several relatives have problems such as epilepsy and brain haemorrhage. Very occasionally, members of families with a genetic form of brain



This family shows autosom

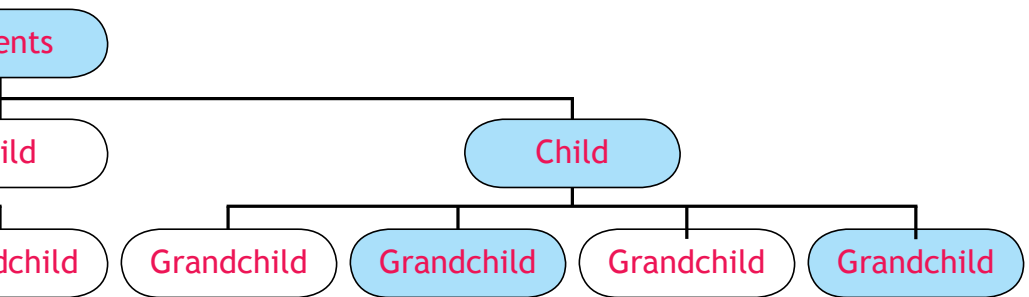
cavernomas have abnormal collections of blood vessels under their skin or on their retina (at the back of the eyeball). However, many brain cavernomas never cause symptoms, so it is usually not obvious that brain cavernomas run in a family.

When is there likely to be genetic cause?

As described in the last section, apart from your family history, the only other clue to a genetic cause is whether your MRI scan shows that you have more than one brain cavernoma.

However, there are a few exceptions to the rule. Many people with more than one cavernoma do not have a known genetic cause. **Very** occasionally, people with a genetic cause have an MRI scan that only shows up one brain cavernoma, or none at all. Not all of the genetic causes of brain cavernomas are known, so a genetic test that gives normal results does not always mean that there is not a genetic cause.

These complicating factors mean that you must think very carefully about having a genetic test and recommending that other members of your family have a genetic test. Ideally, a doctor called a 'clinical geneticist' should help you to make your decision.



autosomal dominant inheritance.

Who can have a genetic test?

If your MRI scan shows that you have more than one brain cavernoma, you could have a genetic test, if you want one. If you only have one cavernoma, a specialist would not usually offer you a genetic test unless you have a relative who you know has brain cavernomas.

What are the advantages and drawbacks of genetic testing for me?

There are many issues to consider. Deciding whether or not to have a genetic test can be difficult, but the decision is rarely urgent, so you can take time to decide. You might want to involve your partner, other members of your family, and a specialist clinical geneticist.

The main advantage of genetic testing to you personally is to know whether or not you have a condition that can be inherited (passed on to your children). Most people are mainly concerned about whether their children are at risk, but this information can be important for other relatives as well. For example, if you have inherited brain cavernomas from your parents, your brothers and sisters may also have them.

There are disadvantages of genetic testing. Being officially sure that you have a genetic condition can make it more difficult or expensive to get health or life insurance. If you are thinking about having children, knowing that your condition could be inherited, could be both informative and worrying.

Should my relatives be tested?

There are good and bad things about genetic testing for your immediate relatives. Whether or not they want to be tested is a very personal choice for them. Ideally, any concerned relative should talk to a clinical geneticist before making their decision. The decision is especially difficult when considering whether children might be affected. In

general, a child would not have the genetic test unless they had symptoms likely to be caused by a brain cavernoma.

Which genetic test should be done?

All that is needed for the genetic test is a blood sample. Specialists will test for three different genes which are known to cause brain cavernomas. These genes are called:

- CCM1 (or KRIT1);
- CCM2 (or MGC4607); and
- CCM3 (or PDCD10).

What is still not known about the genetics of brain cavernomas?

- In some families, inherited brain cavernomas are not caused by any of the three known genes. Researchers are still trying to work out whether there are other genes, or other causes, responsible for why brain cavernomas appear to be inherited in these families.
- Researchers are also interested in the differences between brain cavernomas. They are particularly interested in whether genes influence the type of symptoms and how bad they are.
- Understanding the genetic causes of brain cavernomas could help to find new treatments in the future.

This leaflet

This leaflet was written by Rustam Al-Shahi Salman, and reviewed by Neil Kitchen, Jonathan Berg, and members of Cavernoma Alliance UK.

How Cavernoma Alliance UK can help

We, Cavernoma Alliance UK, were set up by people affected by brain cavernomas to support sufferers and their families. Our website, www.cavernoma.org.uk, provides information about brain cavernomas, our current members and information about how you can become a member. Along with our parent organisation, Angioma Alliance, based in Virginia, USA, we also provide updates on research.

Mission statement

- To make sure that every person with a brain cavernoma, and their family, has access to clear information about the illness.
- To provide information, through our website, about others affected by brain cavernomas and to provide support.
- To increase awareness of brain cavernomas so that those affected by the condition receive understanding and support.

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