Explaining the science and genetics behind Familial Aneurysm Syndrome

This guide was prepared by a genetics professional working in the NHS today. This is a guide for your information and consideration and does not constitute medical advice. We always recommend you discuss any concerns or medical worries with your GP and/or relevant consultant.

I've been told I have familial brain aneurysm syndrome. What does this mean?

This means you have at least two or more first-degree relatives, such as a parent, sibling, or child, who have been diagnosed with a brain aneurysm or had a subarachnoid haemorrhage. You may have others in your extended family that also have aneurysms. For example, your mother and aunt or grandmother. This suggests that the condition might run in your family, so you may have a higher probability of developing a brain aneurysm in your lifetime. This doesn't mean you will develop an aneurysm, or impact on your health, but that there is an increased risk due to your family history.

What is the cause of the condition?

Brain aneurysms are known as a 'complex' condition. This means that there isn't one cause. Instead, many factors can increase the risk of developing an aneurysm over a person's lifetime. One factor is that it runs in families - around 1 in 5 people diagnosed with a brain aneurysm have close family members who are affected, suggesting a hereditary risk. Other factors include smoking, excessive drinking and advanced age.

How is familial brain aneurysm syndrome treated?

If you're at greater risk of developing a brain aneurysm because of a strong family history, you could be offered regular brain screening to detect and treat any possible aneurysm early. Some aneurysms are small enough that surgery isn't needed and can be monitored over time as the risk of rupture is very low. Depending on its size and the location, preventative treatment for the aneurysm may be recommended.

There are two main methods for this, coiling and clipping. Coiling is the method of inserting tiny platinum coils into the aneurysm to block the flow of blood or by sealing the aneurysm with metal clips so that the blood vessel will naturally heal around it and prevent it from bursting in the future.

More detailed information can be found here: https://www.brainandspine.org.uk/health-information/fact-sheets/coiling-of-brain-aneurysms/

https://www.nhs.uk/conditions/brain-aneurysm/treatment/

What causes aneurysms to run or cluster in families?

Diseases tend to run in families for two reasons: your genetics and the environment you live in.

Genetics is the branch of biology that looks at inheritance, including how genes, DNA variation and their interactions with environmental factors can increase or decrease your chance of inheriting a condition or disease. You share 50% of your DNA with your first-degree relatives (a parent, child, brother or sister), so if a particular gene in your body causes a condition, it's more likely to be passed down through the same family. Additionally, people in the same family tend to have similar

lifestyles, such as whether they drink alcohol, which can contribute to the risk of developing certain diseases.

Scientific research suggests that brain aneurysms are genetic. Scientists have been studying how genetics influences our health for decades. They have made huge strides in building knowledge, but we still have yet to learn much. Researchers all over the world are still trying to find and confirm the gene/s that could cause the condition, and, the more research we do into the genetics of familial brain aneurysm syndrome, the sooner we will get answers.

Why is it called a rare disease?

In England, 1 in 15,000 people have a subarachnoid haemorrhage as a result of a ruptured brain aneurysm every year (https://www.nhs.uk/conditions/brain-aneurysm/), and around 20% of them will have a family history (Brown et al. 2014).

Rare Disease UK defines a rare disease as a condition affecting fewer than 1 in 2000 people, so familial subarachnoid haemorrhages would be classed as a rare disease (https://www.raredisease.org.uk/what-is-a-rare-disease/).

However, there is very little evidence about the exact number of people with unruptured familial brain aneurysms, so it may be much more common than we think. That's why research into the disease is so important.

What is the difference between a genetic and familial disease/condition?

A genetic disease is where a person inherits variants of a particular gene or genes known to cause a condition. For example, it is now understood that BRCA1 and BRCA2 gene variants can significantly increase the risk of breast cancer.

A familial disease is one that runs in families, but there isn't always a clear reason why or the genetic cause hasn't been found yet.

Is it a genetic disease?

Whilst many cases of brain aneurysms are 'sporadic' - meaning they occur by chance and are one-off events, others run or cluster in families due to a mixture of genetic and environmental factors. This is the same for other diseases, such as heart disease.

A good way to tell if a condition is genetic is to compare disease rates between identical twins (who share 100% of their DNA) and 'fraternal' or non-identical twins (who share 50% of their DNA). If identical twins are more likely to have a particular condition than non-identical twins, the chances of developing it are higher due to genetic factors.

Studies show that identical twins are more likely to both develop an aneurysm and for the aneurysm to be in the same place in the brain than non-identical twins (Mackey et al 2015). This means genes contribute to a person's risk of developing a brain aneurysm.

How do genetic variants cause the condition?

Brain aneurysms are a complex condition, and many genes are probably working together, contributing to each person's risk. Your genome (that's all your 3.2 billion genes together) is like the instruction manual to make and repair you. If there are spelling errors – genetic variants - in that instruction manual, then sometimes it can cause problems. Scientists and researchers are working hard to try and find these specific variants, but they have a lot to go through to find them.

In HBA Support's Targeted Literature review (a report where we brought together global research into this area), there was evidence of an association between the familial condition and variants of 14 genes involved in the development, maintenance, or integrity of blood vessels in the brain. Of these genes, six were reported in two or more studies. You can find out more here: https://www.hbasupport.org/uploads/brain-aneurysms-research/brain-aneurysm-research.pdf

Do other genetic conditions cause brain aneurysms?

People with genetic diseases like Marfan's Syndrome and polycystic kidney syndrome are more likely to be diagnosed with a brain aneurysm. This doesn't mean you have either of these conditions if you've been diagnosed with an aneurysm. But because Marfan's Syndrome and polycystic kidney syndrome are both connective tissue disorders, meaning they affect how your ligaments and tissue work properly, there are clues that the genes involved in familial brain aneurysms are also responsible for making and maintaining connective tissue.

If it's genetic, does it mean all my family may have the condition?

No–- if there is a genetic cause of brain aneurysms, not everyone will inherit the genes that increase risk, and not everyone with the genes will be guaranteed to develop an aneurysm.

You inherit 50% of your DNA from your mum and 50% from your dad. If it does run in your family, you have a heightened risk but may not have the disease. That's why it's important to consider whether screening is right for you. Please see our family guide for more information at http://www.hbasupport.org.

The condition has also been proven to run through the maternal (mother's side of the family) more than the paternal (father's side). Both men and women can be impacted, and your family history should be looked at when considering screening. It's worth noting that a person's environment and lifestyle also play a big part in their risk.

Can I or my family get a genetic screening?

Genetic screening (where your genome is analysed via a blood test) is currently unavailable for this condition. This is because researchers are still looking to confirm the gene/s that increase a person's chance of developing a brain aneurysm. Once we have a confirmed gene list, genetic screening could be considered.

Why haven't researchers found the gene/s yet?

It took decades of research to find the BRCA genes that can cause breast cancer. Because familial brain aneurysms are probably caused by many different genes, it will take a long time to find them and gather enough evidence to prove that they affect a person's risk.

When do you think there will be a genetic answer?

While we don't know when the genetic causes of familial brain aneurysms will be found, HBA Support is pushing to work with others to support more research while sharing the research currently underway. Visit hbasupport.org for news on the latest research related to the condition.

What will it mean when they find the gene/s?

Firstly, familial brain aneurysm syndrome would officially be classified as a genetic disease. Secondly, it will make it much easier to tell who's at risk of developing a brain aneurysm.

This has the potential to significantly improve or even save lives. Finally, although this is a long way off, once scientists know which genes are causing familial brain aneurysm syndrome and how, it

may be possible to develop treatments to reduce a person's risk through cell and gene therapy, called 'precision medicine'.

For example, the drug Orkambi can now be given to people with Cystic Fibrosis after CFTR genes were found to increase the risk of Cystic Fibrosis greatly. This drug now helps people living with Cystic Fibrosis by helping them make more CFTR protein and improving their symptoms and quality of life.

However, this kind of treatment takes decades to test properly and is especially difficult when dealing with multiple genes or genes that have many different roles in the body. Picture an aquarium with thousands of fish: even if you knew which fish needed to get a special type of food, how could you get the food to them and them only? What if they don't get enough to make a difference? What if the food was harmful to the other fish who accidentally ate it? There are many questions that scientists must consider when deciding if gene therapy is safe and effective enough to give to humans, so it's a long and difficult process, but there is hope. The first step is finding the genes.

Hereditary Brain Aneurysm Support would like to sincerely thank Seren Jones-Reddy for her hard work and expertise in preparing this guide for our community on a voluntary basis.

Other useful resources:

More about brain scans

Brain & Spine Foundation: Brain and Spine Scans Fact Sheet**:**
https://www.brainandspine.org.uk/health-information/fact-sheets/brain-and-spine-scans/

Recovery after a haemorrhage

Brain & Spin Foundation: Subarachnoid Haemorrhage Booklet:
https://www.brainandspine.org.uk/health-information/booklets/subarachnoid-haemorrhage/

References

Brown RD Jr, Huston J, Hornung R, Foroud T, Kallmes DF, Kleindorfer D, Meissner I, Woo D, Sauerbeck L, Broderick J. Screening for brain aneurysm in the Familial Intracranial Aneurysm study: frequency and predictors of lesion detection. J Neurosurg. 2008 Jun;108(6):1132-8. doi: 10.3171/JNS/2008/108/6/1132. PMID: 18518716; PMCID: PMC4190025.

HBA Support. 2022. *Familial Intracranial Aneurysm Research: A Targeted Literature Review.* Available at: https://www.hbasupport.org/uploads/brain-aneurysms-research/brain-aneurysm-research.pdf [Accessed July 2023].

Mackey J, Brown RD, Sauerbeck L, Hornung R, Moomaw CJ, Koller DL, Foroud T, Deka R, Woo D, Kleindorfer D, Flaherty ML, Meissner I, Anderson C, Rouleau G, Connolly ES, Huston J, Broderick JP. Affected twins in the familial intracranial aneurysm study. Cerebrovasc Dis. 2015;39(2):82-6. doi: 10.1159/000369961. Epub 2015 Jan 8. PMID: 25571891; PMCID: PMC4348212.

NHS. 2022. *Conditions: Brain Aneurysms*. Available at: https://www.nhs.uk/conditions/brain-aneurysm/ [Accessed July 2023].

Rare Disease UK. 2021. *What is a rare disease?* Available at: https://www.raredisease.org.uk/what-is-a-rare-disease/ [Accessed July 2023].

Explanation on genes and genetics available at: https://www.genome.gov/genetics-glossary/Genetics

This guide has been made possible by a grant from Localgiving and Postcode Places Trust, a grant-giving charity funded by players of People's Postcode Lottery.

MAGIC LITTLE GRANTS

localgiving

hbasupport.org

Supported by players of PEOPLE'S POSTCODE LOTTERY

Awarded funds from POSTCODE PLACES TRUST