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Information sheet

Genome-wide association meta-analysis of spontaneous coronary artery dissection identifies risk variants and genes related to artery integrity and tissue-mediated coagulation

Beat SCAD summary of the main findings of the above paper, published in Nature Genetics, 29 May 2023

We highly recommend GPs, cardiologists, cardiac rehab staff and other health professionals read the full paper*.

Please note, this information sheet is not intended as medical advice and SCAD patients should always discuss their treatment with a medical professional.

Genetics explainer

Genetics is a complex area so this brief explainer should help you understand the findings of the research paper better.

A **gene** is a segment of DNA that contains instructions for making proteins. Proteins are found in our cells and help create the structure and function of tissues and organs within the body.

A **gene variant**, is a variation in the DNA sequence that makes up a gene. Some variations can either cause disease (single gene disorders) or contribute together with many other variants to the risk of disease (poly genetic disorders). These variants are present throughout a person's life in every cell within their body (although not every cell will use every gene).

Single gene disorders are caused by abnormal genes passed from parent to child which can cause diseases that run in families.

Poly genetic disorders are conditions where small changes in many genes contribute together to increase the risk of a disease. These do not generally run in families.

It is important to say that not all disease is caused by genes. There are also other factors or environmental contributors that have an impact (for example smoking is a common non-genetic risk factor for several diseases).

Understanding the genetics underlying diseases can also help understand the processes in the body which lead to disease and help to develop treatments that work on these processes.

The most common type of genetic variant is called single nucleotide polymorphisms (SNPs- pronounced 'snips'). Every SNP represents a change in one of the building blocks (nucleotide) of our DNA. These are responsible for the physical differences between us including the way we look, our responses to medication and our potential vulnerability to common diseases.

Genome-wide association studies (GWAS) help researchers to find gene variants that are associated with a specific disease. These studies allow scientists to study the entire set of DNA (the genome) from large groups of individuals. This technique allows researchers to search for SNPs in vast numbers at the same time. It is then possible to find SNPs that occur more commonly in people with a certain disease than those without it. This helps to locate genes that may be associated with disease development.

A **locus** (or loci if more than one) tells us the position of a gene on its chromosome. **Chromosomes** are bundles of tightly coiled DNA at the centre of nearly all the cells in our body.

Summary of the research findings

This research involved a genome-wide association meta-analysis (a statistical analysis that combines the results of multiple scientific studies) of 1,917 SCAD cases and 9,292 controls. 16 risk loci for SCAD were identified, 11 of which were described for the first time. A risk locus is a genetic variant that makes someone more susceptible to particular diseases. These 16 risk loci are associated with SCAD, ie they occur more commonly in SCAD patients than in people who haven't had a SCAD, and create an individual risk profile that will affect people differently.

The study found a strong poly genic heritability for SCAD. This means that genes are important determinants of the vulnerability to SCAD but in most patients it is the result of the cumulative effects of many single gene variants, rather than one hereditary gene (which runs in an affected family). These single gene variants are common in the general population.

How these specific combinations and other factors increase the risk of someone having a SCAD and why they have SCAD at a particular point in time, remain areas for further research. However, understanding genetic influences and how they interact with other factors such as vascular conditions and female sex hormones, will help map out overall vulnerabilities to SCAD.

Of the genes identified, some were found to be activated in fibroblasts and vascular smooth muscle cells. These are cell types we know are found in the wall of arteries where SCAD occurs. Many of the genes had roles in linking cells together and maintaining integrity of the connective tissue (the glue that holds our cells together). Again, this makes sense given that we know SCAD is caused by a bruise or bleed tracking and separating the layers of the wall of a coronary artery. One particular gene was identified that has a role in the process of blood clotting within tissues. This gene was found to be specific for SCAD risk. Once again, this fits with our understanding of SCAD as how fast blood clots may affect how the bruise expands or extends within the artery wall.

There is an overlap of genes identified as risk factors for SCAD with other vascular conditions, such as Fibromuscular Dysplasia (FMD), Ehlers-Danlos Syndrome and migraine. Some SCAD patients, but not all, are also diagnosed with some of these conditions.

The research also found several genetic risk loci for SCAD that are shared with conventional coronary artery disease (CAD – atherosclerotic heart disease where there is a build-up of fatty deposits/plaque in the arteries). However, these seem to have opposite associations. This may indicate some kind of protective element and supports clinical observations of lower incidences of CAD in SCAD patients. Although involving different genetic loci, genetically elevated blood pressure (BP) appears to be the only shared genetic risk factor between SCAD and CAD. This supports the rationale for ensuring well controlled BP in SCAD patients.

So, in summary:

- >95% of SCAD is not caused by a variant in a single gene, in the same way that hereditary diseases such as cystic fibrosis or Huntingdon's Disease are. SCAD that runs in families is very uncommon.
- Genetic variants at risk loci (positions) on genes identified in this and previous studies may confer a higher risk of having a SCAD with each gene contributing a small amount of risk.
- Some of the gene variants are related to the integrity of tissues within the arterial wall and to blood clotting.
- There seems to be a genetic risk factor for higher blood pressure in many SCAD patients, so controlling blood pressure is important.
- Gene variants can be likened to a pack of cards we're dealt at birth and each person will have a different pack of cards (combination of variants). It is the combination of many common variants which leads to increased risk. These variants are re-sorted in each generation as we inherit half of our genes from each parent. For this reason, the children of a SCAD patient will have a different combination of variants. This is why SCAD does not usually run in families and why genetic testing is not currently recommended for most SCAD patients.

Useful videos

Watch Dr David Adlam, Associate Professor of Acute and Interventional Cardiology at the University of Leicester, interventional cardiologist at the University Hospitals of Leicester NHS Trust, and lead author of the study, discuss the findings of the paper (https://youtu.be/oU-pziHG7bo).

In January 2019, the first genetics study about SCAD, Association of the PHACTR1/EDN1 genetic locus with spontaneous coronary artery dissection, was published in the Journal of the American College of Cardiology. Watch Dr Adlam discuss the findings (https://tinyurl.com/5n6za9um).

The research was led by the National Institute for Health and Care Research (NIHR) Leicester Biomedical Research Centre (BRC) and Universite Paris Cité, and supported by worldwide partners in Canada, the USA and Australia.

Thanks to Dr David Adlam, UK SCAD research lead, and SCAD patient Ria Griffiths for helping us produce this information sheet.

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David Adlam, Takiy-Eddine Berrandou, Adrien Georges, Christopher P. Nelson, Eleni Giannoulatou, Joséphine Henry, Lijiang Ma, Montgomery Blencowe, Tamiel N. Turley, Min-Lee Yang, Sandesh Chopade, Chris Finan, Peter S. Braund, Ines Sadeg-Sayoud, Siiri E. Iismaa, Matthew L. Kosel, Xiang Zhou, Stephen E. Hamby, Jenny Cheng, Lu Liu, Ingrid Tarr, David W. M. Muller, Valentina d'Escamard, Annette King, Liam R. Brunham, Ania A. Baranowska-Clarke, Stéphanie Debette, Philippe Amouyel, Jeffrey W. Olin, Snehal Patil, Stephanie E. Hesselson, Keerat Junday, Stavroula Kanoni, Krishna G. Aragam, Adam S. Butterworth, CARDIoGRAMPlusC4D, MEGASTROKE, International Stroke Genetics Consortium (ISGC) Intracranial Aneurysm Working Group, Marysia S. Tweet, Rajiv Gulati, Nicolas Combaret, DISCO register, Daniella Kadian-Dodov, Jonathan M. Kalman, Diane Fatkin, Aroon D. Hingorani, Jacqueline Saw, Tom R. Webb, Sharonne N. Hayes, Xia Yang, Santhi K. Ganesh, Timothy M. Olson, Jason C. Kovacic, Robert M. Graham, Nilesh J. Samani & Nabila Bouatia-Naji

Originally published 29 May 2023

https://www.nature.com/articles/s41588-023-01410-1