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Global genetic study involving different populations sheds light on glaucoma

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4 Sep 2017

Glaucoma is a group of diseases that damage the eye's optic nerve and results in vision loss and irreversible blindness in some people. The diseases usually occur on their own but when they are caused by other conditions they are known as secondary glaucoma.

The most common cause of secondary glaucoma is exfoliation syndrome – a disease where abnormal protein is deposited throughout the body. When the protein deposits collect in the eye they may cause glaucoma. Exfoliation syndrome – which doesn't always lead to secondary glaucoma – affects between 60 and 70 million people

The syndrome is most common in Greek and Nordic people. And at least 10% of the population of Iceland are affected. Although the syndrome is uncommon in African Americans and virtually non-existent in West Africans, it is the cause of glaucoma in up to 20% of black South Africans.

Exfoliation syndrome has confounded scientists for decades. They have been unable to establish what causes the protein deposits to collect. This has made treating it hard.

The fact that the condition is common in some populations and uncommon in others suggests that it's inherited and comes about as a result of a variation in the genes. If these were identified it could lead to unravelling the mechanisms underlying the disease – and ultimately lead to new treatments.

Early genetic studies – performed on people of European descent – found that people who develop exfoliation syndrome that led to glaucoma had specific variants in the *LOXL1* gene.

We did a follow up study in 2011 on South Africans which found similarities to the first studies as well as some differences, particularly in the way that the gene variants affected particular groups of people. These findings led to a collaborative study across six continents to clarify the gene variants in *LOXL1*. The aim was to identify genetic links that other population groups may have.

Our findings were remarkable. We identified five more genes associated with exfoliation syndrome and established that some Japanese people have a different variant in *LOXL1* gene that in fact protects them from developing exfoliation syndrome.

What our study tells geneticists and ophthalmologists is that the *LOXL1* gene is important in patients with exfoliation syndrome, but there are also other genes and other factors involved in the condition. It has helped geneticists and ophthalmologists understand how complex the disease is and brought scientists closer to understanding an important contribution to blindness as a result of one form of glaucoma.

More importantly it highlights the importance of including different populations in research studies to provide more varied results. But we also know we still don't have all the answers.

An African variant

In our 2011 study we set out to test the variation in the *LOXL1* gene by looking at African populations. The study involved people with and without exfoliation syndrome in Soweto, South Africa. We extracted DNA from blood samples and compared the *LOXL1* variants in the group of exfoliation patients from the variants in the group of control participants.

The study confirmed the findings of the earlier research on people of European descent: that the *LOXL1* variants were different in those who had the condition when compared with those who were unaffected.

But we discovered an important difference: surprisingly one of the variants associated with the disease in Europeans was associated with unaffected individuals in South Africa and vice versa.

Had this study not been done, geneticists would have been convinced that the first variant was the cause of the exfoliation syndrome. In fact, this isn't the case – in South Africans its actually protective.

These findings led to a global study to clarify the association with *LOXL1* and to identify other genetic associations among more varied groups across the world.

The large trans-ethnic study was led by a group from Singapore with collaborators worldwide. It involved close to 14 000 people who had exfoliation syndrome and over 110 000 people without. Participants came from 24 countries across six continents.

Our study identified five new genes linked to exfoliation syndrome. But it also found that some Japanese people had a rare genetic variant in the *LOXL1* gene – not seen in other populations – that protected them from developing exfoliation syndrome.

Detailed cellular experiments showed that this variant led to the formation of strong bonds between cells while the previously identified variants had no effect on these bonds. We believe that these strong bonds may make the cells more resistant to

stress and therefore less likely to produce the exfoliation protein.

This finding may be the first step towards finding a way to stabilise cells. In turn, this could potentially lead the way towards a cure for the disease.

The African and Japanese patients changed the course of the research into exfoliation syndrome and its link to glaucoma. It led researchers to look for answers in different ways. The experiments that were performed suggested that some of the earlier hypotheses were wrong.

The findings have highlighted the value of doing genetic studies on different populations to understand the effect of genetic differences. They could potentially lead the way towards a cure for the disease.

This article was originally published on The Conversation. Read the original article.

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