

Genome study confirms immune system link to disfiguring leg swelling

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Podoconiosis, a type of elephantiasis (leg swelling) found in farming communities in the tropics, is triggered by an abnormal reaction to irritant mineral particles found in soils of volcanic origins amongst people who cannot afford shoes. Credit: Gail Davey

Genetic variants in a region of the genome linked to our immune response have been linked to increased risk of podoconiosis, a disfiguring and disabling leg swelling caused by an abnormal reaction to the minerals found in soil. An estimated 4 million people worldwide suffer from the condition.

In a study published today in the [New England Journal of Medicine](#), researchers funded by the Wellcome Trust and the Association of Physicians of Great Britain and Ireland compared the genomes of 194 people affected by the disease from southern Ethiopia against 203 people who were unaffected. They identified three genetic variants that

increased the risk of developing the condition.

Podoconiosis, or 'podo', as it is often called, was added to the World Health Organization's list of [neglected tropical diseases](#) in 2011. It is a type of elephantiasis (leg swelling) found in farming communities in the tropics and is triggered by an abnormal reaction to irritant mineral particles found in soils of volcanic origins amongst people who cannot afford shoes.

Many years of walking, ploughing or playing barefoot on these soils appears to trigger inflammatory changes within the lymph system in the legs, which in time can lead to foot swelling and ultimately [elephantiasis](#).

The disease often runs in families, implying that there is a hereditary component to the disease, but until now, no genetic variants had been identified which confer increased risk. The genetic variants discovered in this new study all fall within a region of the genome known as the HLA class II, which is important in controlling immune responses. Combined, the three variants increase the risk of developing podoconiosis by a factor of two to three.

Prof Melanie Newport from Brighton & Sussex Medical School, who led the study, says: "The region where we have found these susceptibility genes for podoconiosis plays an important role in controlling our immune system. It confirms what we had expected, that there is an immunological basis to the disease. Although this is still early days for identifying potential treatments, it suggests that drugs that target immune responses may be useful."

First author Dr Fasil Tekola Ayele from the Armauer Hansen Research Institute, Ethiopia, adds: "Genome wide association studies on African populations are still fairly novel. However, this study highlights the importance of such studies in helping us understand the origins of

diseases that are particularly common on the continent." Dr Ayele is currently on a postdoctoral attachment at the National Human Genome Research Institute, USA.

Dr Abraham Aseffa, also from the Armauer Hansen Research Institute, says: "Our next step is to try to pinpoint exactly which molecules are involved in podoconiosis, and which specific genetic mutations affect the function of these molecules. This will shed a lot more light on potential therapeutic options."

Professor Newport and colleagues have recently launched Footwork, an international initiative to bring together public and private partners to prevent and treat podoconiosis. Footwork aims to integrate podoconiosis control with that of other neglected tropical diseases wherever possible, and to partner with organizations working in foot-related conditions to advocate for shoes as cost-effective interventions to tackle such diseases.

"There are still many places round the world where people cannot afford a pair of shoes," says Dr Gail Davey, co-author on the study and Executive Director of Footwork. "For some people, this means cold, cut or bruised feet, but for others it can lead to podoconiosis, which can have a significant impact on their quality of life. We hope that shoes can become the 'new bed-nets': simple, cost-effective interventions that mean that in future there is no reason for anyone's life to be destroyed for the want of a shoe."

Commenting on the findings, Dr Jimmy Whitworth, Head of International Activities at the Wellcome Trust, adds: "Podoconiosis is finally getting the attention it deserves as a disease that blights the lives of millions of people. The success of this international collaboration is testament to the importance of providing opportunities for training and building capacity for African researchers to take a lead on important work such as this."

More information: Ayele, FT et al. The HLA class II locus confers susceptibility to podoconiosis. *NEJM*; 29 March 2012

Provided by Wellcome Trust

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