

# Researchers identify a novel periodic autoinflammatory syndrome

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A research team from the University of Helsinki, Helsinki University Hospital and Folkhälsan Institute of Genetics in Helsinki, Finland, has identified a new genetic mutation that alters the function of cryopyrin and leads to a life-long periodic inflammation of the cornea, the transparent window of the human eye. Patients who carry the mutation also develop corneal opacities that compromise vision. The study, which broadens the spectrum of cryopyrin-associated periodic syndromes, was published in the *American Journal of Ophthalmology*.

"In 1964, Dr. Olavi Valle, a Finnish ophthalmologist, reported a family in which several members shared a problem—their eyes became irritated for a few days several times a year, and they experienced blurry vision for a few weeks after each attack," said Tero T. Kivelä, professor in Ophthalmology and Chair at the Helsinki University Eye Hospital. "The attacks begin when they are teenagers and continue through middle age. Eventually, patients develop permanent corneal opacities."

Dr. Valle named the disease keratitis fugax hereditaria, which is Latin for "transient inherited corneal inflammation." More than two decades later, a second Finnish family with the same symptoms emerged, and it was found that the inflammation primarily affected the corneal endothelium, a cell layer that covers the back of the cornea, an observation that identified the disease as a keratoendotheliitis.

"Thanks to the discovery by Dr. Valle, we diagnose new patients with keratoendotheliitis fugax hereditaria every year in the Helsinki

University Eye Hospital," said Dr. Joni A. Turunen, the project leader of the research team that discovered the causative mutation. "It is not an uncommon disease, and we have always been intrigued about what is causing it, so we decided to use next-generation sequencing to solve that issue."

## **The fourth cryopyrin-associated periodic syndrome**

Dr. Turunen recruited 30 affected patients from seven families and four additional ones who appeared to have the disease but could not name any affected relative. After first sequencing the protein-coding regions of all chromosomes from 10 patients, he found that all shared an identical point mutation in a gene called Nucleotide-Binding Domain, Leucine-Rich Repeat Family, Pyrin Domain-Containing 3 (NLRP3), which codes cryopyrin.

"Cryopyrin [mutations](#) were known to cause rare periodic autoinflammatory syndromes, diseases in which the white blood cells of the human body become activated without any outside stimulus," said Kivelä. "Corneal opacities have been reported in some patients with the previously known cryopyrin-associated syndromes. Thus, we became confident that the mutation we discovered indeed was disease causing."

The team subsequently confirmed via direct sequencing that the same mutation was present in all other affected family members and absent from those that had healthy eyes.

Keratoendotheliitis fugax hereditaria is the fourth cryopyrin-associated periodic [syndrome](#). The other three—familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and chronic infantile neurological, cutaneous, articular syndrome (also known as neonatal-onset multisystem inflammatory disease)—affect multiple organs and can be debilitating. Like keratoendotheliitis fugax hereditaria, they emerge during

childhood, but their hallmarks are episodic fevers, skin rashes, and inflammation of the joints, gastrointestinal tract and the nervous system rather than ocular irritation.

"Intriguingly, although a relatively minor finding in these syndromes, the patients nevertheless have been reported to show ocular inflammatory signs and some have developed similar corneal opacities than what we see in our patients with keratoendotheliitis fugax hereditaria," said Turunen. "We believe that the mutation that underlies keratoendotheliitis fugax either is a milder form of the spectrum in which only the eye is sensitive enough to become symptomatic, or faulty activation of cryopyrin is entirely restricted to the eye."

## **Up to one in 20,000 Caucasians may be predisposed to develop the syndrome**

So far, keratoendotheliitis fugax hereditaria has only been reported from Finland.

"Now that the gene has been identified, we have reason to believe that the disease actually is more universal. Exome databases show that carriers of this mutation exist in other populations with European ancestry as well, with a frequency comparable to that in Finns," said Anna-Elina Lehesjoki, professor at the Folkhälsan Institute of Genetics, and a senior geneticist in the team that made the discovery.

"The carrier frequency in the ExAC database suggests that up to one in 20,000 Caucasians may be predisposed to develop symptoms of keratoendotheliitis."

In contrast, no carriers of the causative mutation have been reported in African, Asian and Latin American populations with data in ExAC, the

Exome Aggregation Consortium browser hosted at the Broad Institute, Cambridge, Massachusetts.

"Because the symptoms of keratoendotheliitis fugax hereditaria are short lived and unspecific, a family history is seldom volunteered by our patients and also unlikely to be queried by an ophthalmologist unaware of its existence, as almost all ophthalmologists outside Finland have been," said Turunen.

"We expect that [patients](#) begin to emerge more widely now that the diagnosis can be made by genetic testing. We were just the lucky ones to be informed early of the existence of this intriguing corneal [disease](#), thanks to the astute observations by Dr. Valle."

At the moment, no specific treatment for keratoendotheliitis fugax hereditaria is known. The other cryopyrin-associated periodic syndromes have responded to drugs that target interleukin-1-beta, a downstream mediator of the cryopyrin cascade.

**More information:** Joni A. Turunen, Juho Wedenoja, Pauliina Repo, Reetta-Stiina Järvinen, Johannes E. Jääntti, Sanna Mörtenhumer, Antti S. Riikonen, Anna-Elina Lehesjoki, Anna Majander, Tero T. Kivelä. Keratoendotheliitis Fugax Hereditaria: A Novel Cryopyrin-Associated Periodic Syndrome Caused by a Mutation in the Nucleotide-Binding Domain, Leucine-Rich Repeat Family, Pyrin Domain-Containing 3 (NLRP3) Gene. *American Journal of Ophthalmology*. (in press) [DOI: 10.1016/j.ajo.2018.01.017](#)

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