Keratin gene study pinpoints mutations associated with 'spindle hair'

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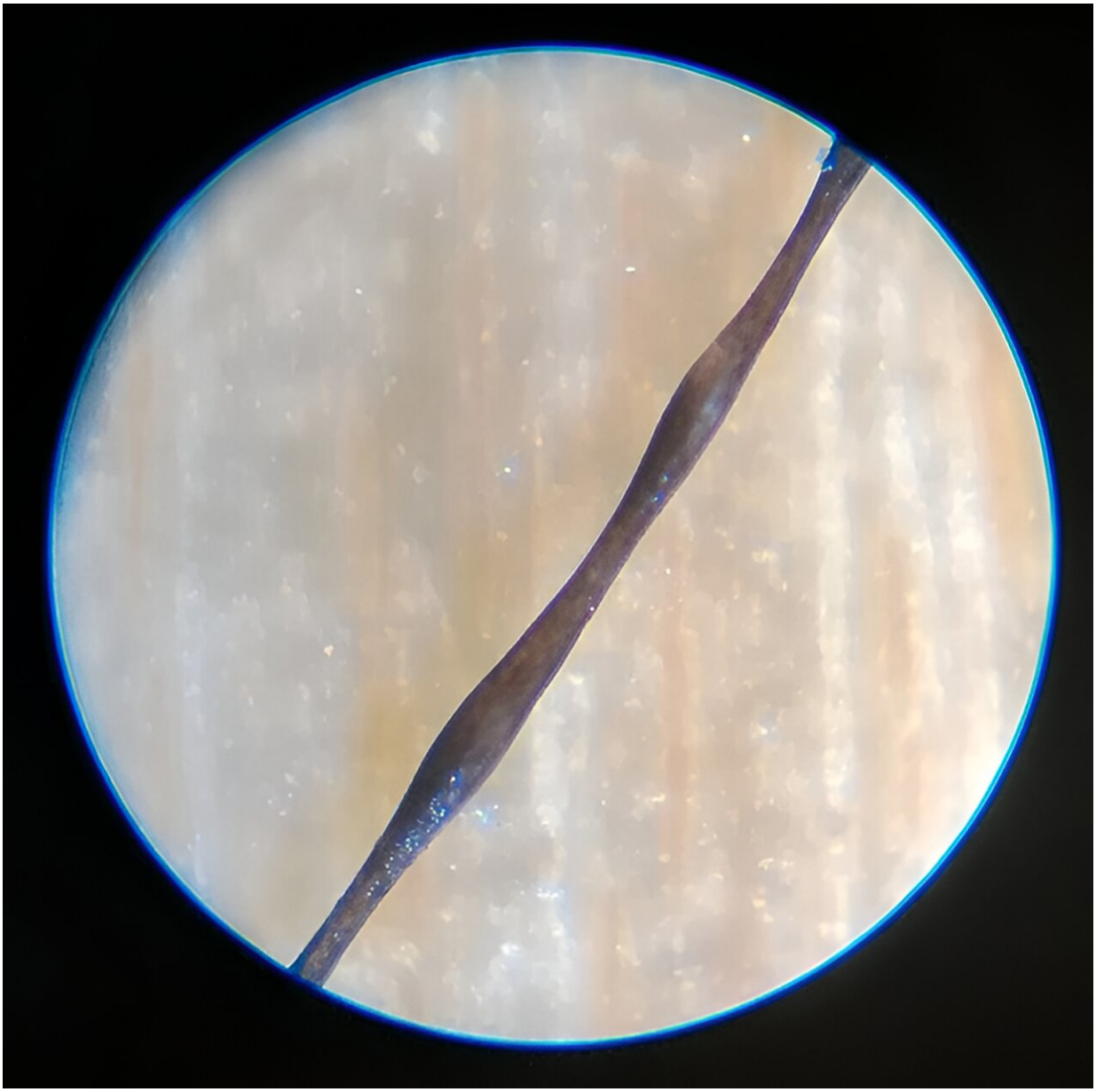

Monilethrix hair. Credit: Clump/Wikimedia Commons, CC0 Public Domain

From infancy and usually for life, some families suffer from broken hair due to a congenital form of hair loss called monilethrix. Researchers at the University Hospital Bonn and the University of Bonn have now identified causative mutations in another keratin gene, KRT31. They hope that this will improve the diagnosis of this rare disease.

Their results have now been published in the *British Journal of Dermatology*.

Monilethrix is a rare congenital form of hairlessness, also known as alopecia, and usually begins in the first few months of life. It mainly affects the area at the back of the head. What is striking is the extreme variability in the degree of hair loss, ranging from little hair loss to complete hairlessness within a family.

Recurring knots of normal thickness give the affected "spindle hair" the appearance of a sheaf of pearls. The constrictions in between break very easily. In dominantly-inherited monilethrix, mutations in the three keratin genes KRT81, KRT83 and KRT86 are known to be responsible for the disrupted keratin network, which plays an important role in building the hair structure.

Nonsense (stop) mutation for 'spindle hair'

A research team led by Prof. Regina Betz from the Institute of Human Genetics at the UKB, who is a member of the Transdisciplinary Research Area (TRA) "Life & Health" and the Cluster of Excellence ImmunoSensation2 at the University of Bonn, investigated four families with suspected monilethrix in which no mutations were found in the

three known genes.

The team carried out exome sequencing on six affected family members, i.e., all protein-coding regions were examined in their genetic material.

The researchers found a so-called nonsense (stop) mutation in the KRT31 gene in all six affected individuals, which leads to premature termination of the synthesis of the protein. With the help of additional sequencing, they were also able to find this mutation in the other affected family members. Prof. Betz's team was thus able to identify a new gene for monilethrix with KRT31.

"Even though the affected families from Germany do not know each other and come from different regions, we were able to show that this mutation most likely originated in a common ancestor and was subsequently passed on over many generations.

"It remains to be seen whether this mutation can also be found across Europe or even worldwide, but it is likely," says first author Xing Xiong, a doctoral student at the University of Bonn's Institute of Human Genetics at the UKB.

Gene localization in the cell determines function

The researchers took a closer look at the function of KRT31. The protein encoded by KRT31, like many other keratins, is involved in the formation of skin cells. These proteins assemble into polymeric fiber proteins and thus form the supporting framework for the cell. If there are defects in these proteins, skin and hair diseases develop.

Investigations under the microscope using immunofluorescence showed that the "normal" KRT31 is localized in the cytoplasm, while the mutated KRT31 is mainly found around the cell membrane. "The

localization of the protein in the cell therefore changes with the mutation. This means that its function will also be impaired," states Prof. Betz.

In cooperation with the team from the Cluster of Excellence ImmunoSenstation2 at the University of Bonn led by Prof. Matthias Geyer, Director of the Institute of Structural Biology at the UKB, Prof. Betz's team also analyzed the structure of the protein and possible effects of the stop mutation.

As a rule, two keratin molecules as heterodimer in a double pack always align their ends with the ends of other heterodimers, and that by forming so-called disulfide bonds.

"We assume that this disulfide bond can no longer be formed due to the stop mutation and that the function of the protein is therefore impaired," says Prof. Betz. She is convinced that the inclusion of KRT31 in diagnostic gene panels for hair, skin and nail diseases will improve diagnostics for those affected by hair loss.

More information: Xing Xiong et al, A nonsense variant in KRT31 is associated with autosomal dominant monilethrix, *British Journal of Dermatology* (2024). DOI: 10.1093/bjd/ljae298

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