Researchers find that the genetic underpinnings of a skin disorder at birth indicate future heart problems

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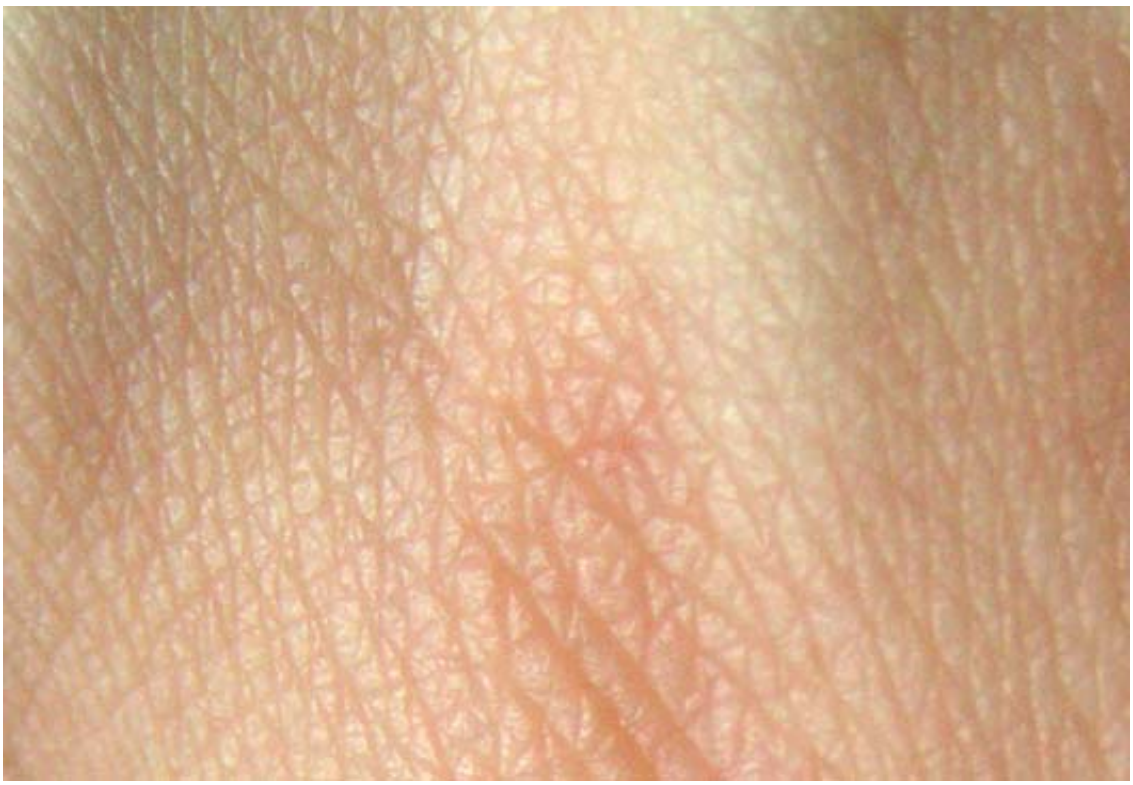

Human skin structure. Credit: Wikipedia

Our skin tells us when we've spent too much time in the sun or when the dry air of winter has sucked away too much moisture. Now Jefferson researchers find that the skin can also foretell issues unrelated to the protective barrier.

An international team of researchers led by Jouni Uitto, MD, Ph.D., a Professor of Dermatology and Cutaneous Biology, report that mutations in a gene known to underlie a rare skin disorder also lead to a serious heart disease. The findings are the latest example from Dr. Uitto's laboratory to show that when combined with genetic analysis, the skin may help to predict future medical conditions.

"By looking into the skin of newborns, we can predict the development of a devastating heart disease later in life," Dr. Uitto says. "This is predictive personalized medicine at its best."

The researchers published the findings December 10th in the journal *Scientific Reports*.

A renowned skin disease expert, Dr. Uitto has been on a global hunt for mutations in families with genetic skin disorders for three decades. Over the last five years, he and his team have analyzed mutations in about 1800 families around the world, searching for the genetic culprits behind skin conditions such as epidermolysis bullosa (EB). EB is a severe disease that makes the skin extraordinarily fragile. Patients with EB can develop blisters and poorly healing wounds from the lightest touch.

In the new publication, co-first authors Hassan Vahidnezhad and Leila Youssefian, and a small cadre of researchers scrutinized the DNA of more than 360 EB patients from around the world. In particular, they analyzed DNA isolated from blood samples for sequence variants in a set of 21 genes known to harbor mutations that cause EB. The analysis revealed that two patients had the exact same mutation in a gene known as JUP.

The patients had shown the same symptoms in early infancy, including very fragile skin, thickened skin on the palms of the hands and soles of the feet, and hair loss that extended to the eyebrows and eyelashes. But

now one patient was a 2.5-year-old boy who only showed skin anomalies, while the other was a 22-year-old woman who also had a heart condition called arrhythmogenic right ventricular cardiomyopathy (ARVC).

"This is a serious disease that can require a heart transplant if the damage is too severe because of heart failure and life threatening fast heart rhythms," says Reginald Ho, MD, a cardiologist in the department of medicine at Sidney Kimmel Medical College, who co-authored the study.

In ARVC, rigid, fibrous tissue displaces healthy heart muscle over time. As a result, the heart develops abnormal rhythms and becomes weak. ARVC patients are vulnerable to heart failure and sudden cardiac death. Indeed, ARVC is responsible for as much as 20 percent of sudden cardiac deaths in those under 30. Many require an implantable defibrillator to manage life-threatening arrhythmias. Mutations in JUP that cause EB can also lead to stiffness of the heart muscle, and ARVC.

Although the young boy did not yet have heart problems, the genetic findings suggest that he will develop them down the road.

"This means that with mutation analysis, you can predict when looking at EB patients at birth, whether they will have this very severe heart condition later in life," Dr. Uitto says.

"These patients need to be monitored carefully for heart problems," he adds.

The findings add to a string of discoveries Dr. Uitto and colleagues have unveiled in recent years in their search for the genes that underlie severe skin conditions. In 2019, for example, the researchers found that patients with a skin condition known as ichthyosis can develop liver problems later in life that are severe enough to require a transplant.

"We are looking to identify new genes behind skin diseases like EB and ichthyosis," Dr. Uitto says. "By looking at patients' symptoms and family history, we have uncovered something completely unexpected."

"Together, these studies show how the skin can help predict severe medical problems," Dr. Uitto says.

More information: "Arrhythmogenic Right Ventricular Cardiomyopathy in Patients with Biallelic JUP-associated Skin Fragility," *Scientific Reports* (2020). DOI: 10.1038/s41598-020-78344-9

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