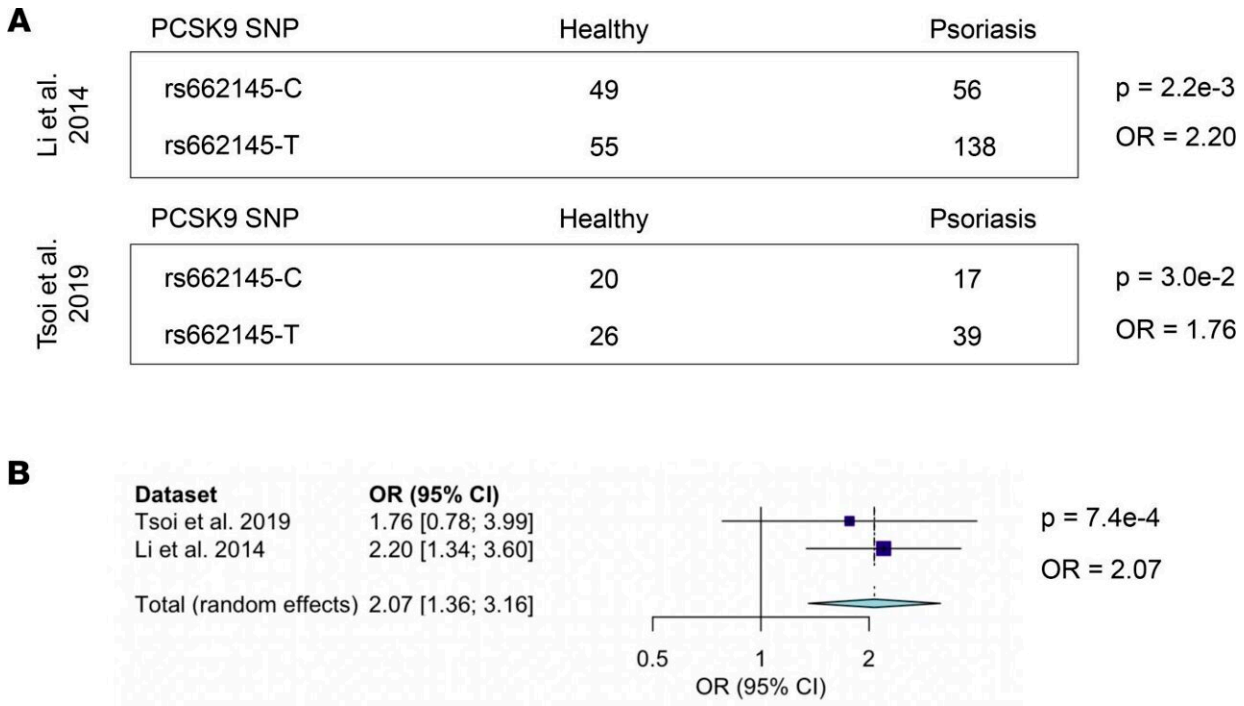
Uncovering the skin's secrets: Studies show how skin forms differently across the body

September 23 2022, by Claudia Coons



RNA-Seq variant calling identified a psoriasis-associated SNP in 3′ UTR of the PCSK9 gene. (A) SNP calling was performed on 2 separate psoriasis RNA-Seq data sets (12, 14), and ORs were calculated using the allele counting method. Fisher's exact test was performed to calculate P values. Names of analyzed data sets are shown on the left with OR and P values on the right. The presence of SNP rs662145 C > T was associated with increased psoriasis risk. SNP rs662145-C constitutes the reference and minor allele, and SNP rs662145-T constitutes the alternative and major allele. (B) Meta-analysis of both RNA-Seq data sets using a random-effects model. Credit: *JCI Insight* (2022). DOI: 10.1172/jci.insight.141193

Why are certain body parts more prone to skin diseases than others?

Two new UC Davis Health studies explored how differences in skin composition may lead to dermatological conditions, such as psoriasis and atopic dermatitis.

"Skin does not have a uniform composition throughout the body," said Emanual Maverakis, professor of dermatology, molecular medical microbiology at UC Davis and senior author on both studies. "Different skin characteristics at different body sites may affect the skin's susceptibility to certain diseases."

Skin diseases affect about 84.5 million Americans. Aging, trauma, and environmental and genetic factors can lead to a wide range of skin conditions.

Body site determines skin structure and function and disease susceptibility

The skin is the largest organ in the body. It has an average area of about 20 square feet—that's the size of a 4' by 5' room. Its outermost layer (epidermis) has a lipid matrix composed of free fatty acids, cholesterol and ceramides (a family of waxy lipid molecules).

This layer must meet the environmental challenges specific to each area of the body. For example, the skin of the face needs to be thin and flexible to accommodate facial expressions. The skin covering the heel of the foot has to be thick and rigid to withstand force and protect it from objects we step on.

Skin composition depends on multiple factors, including the structure of

the skin barrier, the cell types, and the genes they express.

Until recently, little was known about the cellular and molecular processes behind these differences. In the first study, researchers showed the mechanisms that lead to these structural changes in the skin.

The epidermis has a "brick and mortar" structure: molecules like ceramides, cholesterol and fatty acids make up the "mortar," and cells called keratinocytes are the "bricks."

The researchers used single-cell sequencing to characterize how the keratinocytes differ at different body sites. They also used targeted molecular profiling to characterize the molecules that form the "mortar" between the keratinocytes. They then examined how these differences in gene expression matched the compositional differences in the lipid and protein structures across body sites. These experiments explained why the skin looks so different at different body sites.

The compositional differences in the skin's lipids and proteins across different body sites may also explain why different skin diseases are found at different body sites. While characterizing the specific lipid alterations associated with various skin diseases, the researchers discovered that lipids stuck to a piece of tape applied to the skin were sufficient to diagnose a patient with a particular skin disease.

"These discoveries will lead to non-diagnostic tests for common dermatologic disease," said co-lead author, Project Scientist Alexander Merleev.

"These differences are also relevant to the future design of skin care products," said Stephanie Le, dermatology resident and co-lead author of the study. "They demonstrate how skin care products should be specifically formulated to match the particular body site that they will be

applied to."

Psoriasis and the immune system

In the second study, the research team studied how skin cells interact with the immune system.

Previously, it was known that keratinocytes could secrete substances that both increase and decrease inflammation. Using single-cell sequencing to analyze each keratinocyte individually, the researchers observed that these immune-modulating molecules were expressed in certain layers of the epidermis.

Keratinocytes at the lowest layer of the epidermis secrete immune-attracting and immune anti-inflammatory molecules. This is to attract immune cells to the skin and park them in place to wait patiently to fight off any pathogenic microbe or parasite that might break through the physical barrier of the skin. In contrast, they found that the keratinocytes in the outer layer of the epidermis secrete proinflammatory molecules, in particular IL-36.

IL-36 is a main mediator of a subtype of psoriasis, an inflammatory skin disease. The team found that the amount of IL-36 in the skin was regulated by another molecule called PCSK9 and that individuals with variations in their PCSK9 gene were predisposed to developing psoriasis.

"Our discovery that different layers of the skin secrete different immune mediators is an example of how the skin is highly specialized to interact with the immune system. Some people develop skin diseases, such as psoriasis, when there is an imbalance in the molecules secreted by the different layers of the skin," said UC Davis research fellow Antonio Ji-Xu, co-lead author of the study.

Both studies were published in *JCI Insight*.

More information: Alexander A. Merleev et al, Biogeographic and disease-specific alterations in epidermal lipid composition and single-cell analysis of acral keratinocytes, *JCI Insight* (2022). DOI: 10.1172/jci.insight.159762

Alexander Merleev et al, Proprotein convertase subtilisin/kexin type 9 is a psoriasis-susceptibility locus that is negatively related to IL36G, *JCI Insight* (2022). DOI: 10.1172/jci.insight.141193

Provided by UC Davis