Scientists solve mystery of how a rare congenital scalp defect forms

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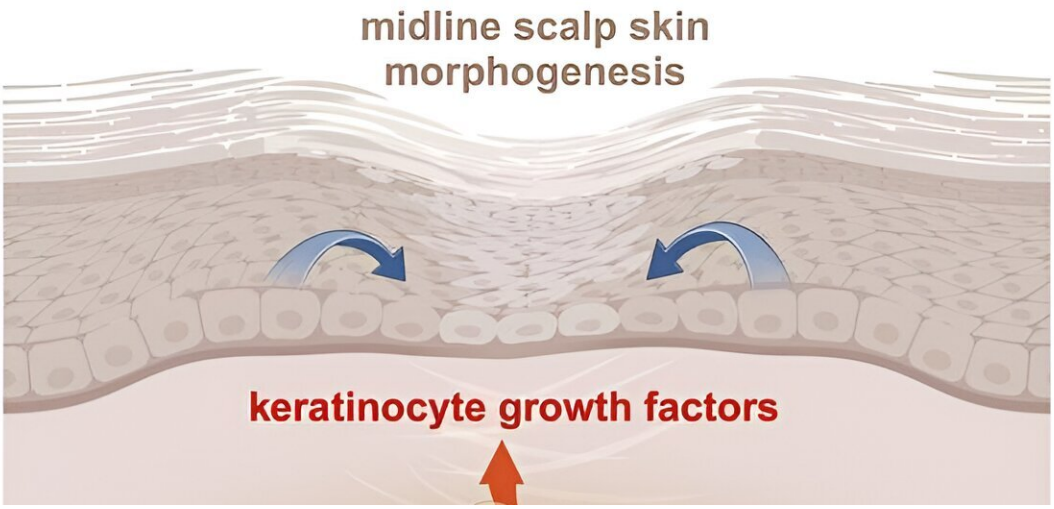

Graphical abstract. Credit: *Journal of Clinical Investigation* (2023). DOI: 10.1172/JCI174138

Children with the condition aplasia cutis congenita (ACC) are born with the absence of skin along the midline of the scalp. Depending on

whether mutations are in the KCTD1 or KCTD15 genes, additional characteristics beyond the scalp—such as kidney or heart problems—are also present.

When investigators led by a team at Massachusetts General Hospital (MGH) modeled these mutations in cells and mice using genetic approaches, they found that the defects lead to the impairment of certain cells that are part of the midline cranial sutures and that these cells normally express growth factors that induce skin formation over the skull.

In a study published in the *Journal of Clinical Investigation*, the scientists learned that the ACC-related KCTD1 and KCTD15 mutations result in a lack of function of the KCTD1 and KCTD15 proteins expressed by these genes.

In mice, ACC occurred when these proteins were inactivated in neural crest cells of the cranial midline sutures—the fibrous joints between bones of a baby's skull that remain flexible during infancy to allow the skull to expand as the brain grows.

Without KCTD1 and KCTD15, which interact with each other to form protein complexes within cells, neural crest cells were impaired, resulting in diminished expression of growth factors that normally stimulate the formation of skin.

These findings reveal a previously unknown role of neural crest cells of midline cranial sutures for the formation of the overlying scalp skin. Experiments also revealed important roles of these proteins for the formation of skin appendages, such as hairs, sweat glands, and sebaceous glands.

"We solved a centuries-old enigma, which allows us now to explain why

this congenital skin disease affects the midline scalp but not other areas of the skin," says senior author Alexander G. Marneros, MD, Ph.D., a principal investigator at the Cutaneous Biology Research Center of MGH and an associate professor of Dermatology at Harvard Medical School. "In the process of this study, we also uncovered fundamental new insights into mechanisms that orchestrate skin and skin appendage formation."

The findings may be used to develop strategies to target the anomalies associated with ACC; however additional questions remain, and more research is needed. "We are now exploring the downstream molecular mechanisms through which KCTD1 and KCTD15 complexes affect the function of cells in and around the skin during development," says Marneros.

More information: Jackelyn R. Raymundo et al, KCTD1/KCTD15 complexes control ectodermal and neural crest cell functions and their impairment causes aplasia cutis, *Journal of Clinical Investigation* (2023). DOI: 10.1172/JCI174138

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