Medical Xpress

Scientists identify mutation that causes skin hyperproliferation

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Scientists have identified a mutation in a gene that causes patches of very thick skin to appear on the palms and soles of affected people. This

skin disorder is related, albeit in a much milder form, to that of the Indonesian 'Tree Man', Dede Koswara. These thick rough skin patches on hands and feet steadily increase in number as a person ages and often coalesce to form larger lesions. In severe cases, these lesions can be painful and debilitating.

The team of scientists from A*STAR's Institute of Medical Biology (IMB), in collaboration with hospitals and research centres from the UK, Japan and Tunisia, found that this skin disorder, called punctate palmoplantar keratoderma (punctate PPK), is caused by mutations in the AAGAB gene. Punctate PPK is a rare subtype of palmoplantar keratoderma (PPK), which appears in subtly different forms and seems to have several possible causes. Several families in Singapore are afflicted by different types of PPKs and scientists at A*STAR have also been working with doctors at the National Skin Centre to understand the different forms of this skin disorder.

The identification of the gene mutation will help scientists to better understand the molecular basis of this disease and potentially lead to a suitable treatment. This discovery will improve the classification and diagnosis of PPKs as well as open the door to novel approaches to treatment of skin disorders. These findings were published in the recent advanced online issue of Nature Genetics on 14th October.

The scientists analyzed DNA samples collected from 18 families from Scotland, Ireland, Japan and Tunisia who had punctate PPK. They showed that the AAGAB gene, which encodes the protein p34, was expressed in skin and had a role in the control of cell division. The depletion in AAGAB led to a deficiency in p34, which resulted in increased cell proliferation in the outer layers of skin, the epidermis, because of an increased growth signal coming through the epidermal growth factor receptor (EGFR). The disruption of EGFR signalling is a feature of abnormal cell proliferation and the discovery suggests that

PPK may be a benign form of hyperproliferation.

Dr Bruno Reversade, Senior Principal Investigator at IMB, who is a member of the team said, "The study of rare genetic disorders can often provide unexpected links; the phenotype seen in punctate PPK patients bears striking resemblance to common warts, and it is tempting to speculate that HPV could also hijack the same pathways to induce skin hyperproliferation. This discovery also demonstrates that EGFR, a hallmark of skin cancer, is part of the molecular explanation of the overproliferation of lesions in PKK patients."

"Every time we find a new genetic mutation that causes a skin disorder, it helps patients and their families to demystify their condition," said Prof Birgitte Lane, Executive Director of IMB. "With scientists and doctors working towards common goals like this, we find better treatments for more and more of these rare conditions."

More information: Pohler, E. et al. Haploinsufficiency for AAGAB causes clinically heterogeneous forms of punctuate palmoplantar keratoderma, *Nature Genetics*. www.nature.com/ng/journal/vaop … nt/full/ng.2444.html

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