

Research reveals why redheads may have different pain thresholds

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New research led by investigators at Massachusetts General Hospital (MGH) provides insights on why people with red hair exhibit altered sensitivity to certain kinds of pain. The findings are published in *Science Advances*.

In people with [red hair](#) (as in numerous other species of animals with red fur), the pigment-producing cells of the skin—called melanocytes—contain a variant form of the melanocortin 1 receptor. This receptor sits on the cell surface, and if it becomes activated by circulating hormones called melanocortins, it causes the melanocyte to switch from generating yellow/red melanin pigment to producing brown/black melanin pigment. Earlier work by David E. Fisher, MD, Ph.D., director of the Mass General Cancer Center's Melanoma Program and director of MGH's Cutaneous Biology Research Center, demonstrated that the inability of red-haired individuals to tan or darken their skin pigment is traced to inactive variants of this receptor.

To investigate the mechanisms behind different

[pain](#) thresholds in red-haired individuals, Fisher and his colleagues studied a strain of red-haired mice that (as in humans) contains a variant that lacks melanocortin 1 receptor function and also exhibits higher pain thresholds.

The team found that loss of melanocortin 1 receptor function in the red-haired mice caused the animals' melanocytes to secrete lower levels of a molecule called POMC (proopiomelanocortin) that is subsequently cut into different hormones including one that sensitizes to pain and one that blocks pain. The presence of these hormones maintains a balance between [opioid receptors](#) that inhibit pain and melanocortin 4 [receptors](#) that enhance perception of pain.

In red-haired mice (and therefore, possibly humans), having both hormones at low levels would seemingly cancel each other out. However, the body also produces additional, non-melanocyte-related factors that activate opioid receptors involved in blocking pain. Therefore, the net effect of lower levels of the melanocyte-related hormones is more opioid signals, which elevates the threshold for pain.

"These findings describe the mechanistic basis behind earlier evidence suggesting varied pain thresholds in different pigmentation backgrounds," says Fisher. "Understanding this mechanism provides validation of this earlier evidence and a valuable recognition for medical personnel when caring for patients whose pain sensitivities may vary."

Fisher adds that the results suggest new ways to manipulate the body's natural processes that control pain perception—for example, by designing new medications that inhibit melanocortin 4 receptors involved in sensing pain.

"Our ongoing work is focused on elucidating how additional skin-derived signals regulate pain and

opioid signaling," adds co-lead author Lajos V. Kemény, MD, Ph.D., a research fellow in Dermatology at MGH. "Understanding these pathways in depth may lead to the identification of novel pain-modulating strategies."

More information: Kathleen C. Robinson et al, Reduced MC4R signaling alters nociceptive thresholds associated with red hair, *Science Advances* (2021). [DOI: 10.1126/sciadv.abd1310](https://doi.org/10.1126/sciadv.abd1310)

Provided by Massachusetts General Hospital

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