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Introduction

The melanocortin-1 receptor (MC1R) loss-of-function (LOF) variant is associated with a consistent clinical finding: individual with red hair require ~20% more anesthesia for adequate sedation. We propose that altered melanocortin–opioid signaling in MC1R variants leads to increased neuronal excitability and modified pain and anesthetic responses. Disruption of downstream pathways may shift the balance of excitatory and inhibitory signaling, reducing sensitivity to general anesthetics. Non-red-haired carriers of MC1R variants (e.g., rs3212361, rs885479) may also exhibit altered anesthetic requirements, highlighting broader neuropharmacogenomic implications.

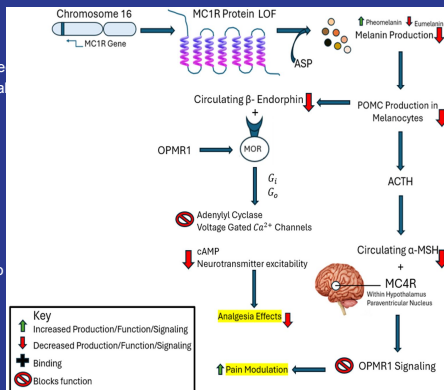
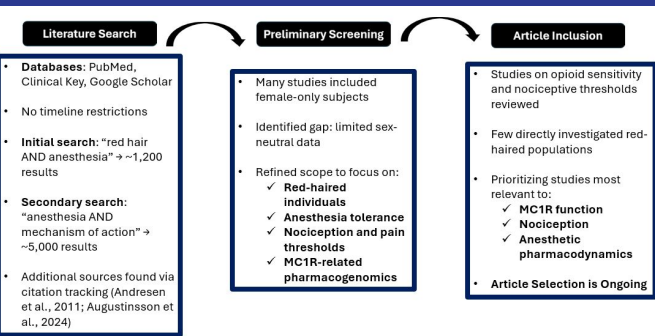


Figure 1. MC1R Signaling Cascade Mechanism – Created By Kassandra Thomazin
 ASP- Agouti Signaling Protein, POMC- Proopiomelanocortin, ACTH- Adrenocorticotrophic Hormone, α - MSH- alpha- Melanocortin
 Stimulating Hormone, OPRM1 – Opioid Receptor Mu 1, AGRP- Agouti-Related Protein. Brain image taken from:
<https://pxls.com/featured/1/anatomy-of-human-brain-side-view-stocktrek-images.html>

Methods



Literature Review Results

MC1R variants impact nociception and anesthetic sensitivity.

Liem et al. compared 20 red-haired females with MC1R loss-of-function variants to 20 dark-haired wild-type controls during sevoflurane induction and desflurane maintenance. Red-haired participants required a significantly higher end-tidal desflurane concentration to suppress movement to electrical stimulation ($p = 0.0004$), representing approximately a 19% increase. They also demonstrated reduced sedation with midazolam (6.2% vs. 5.2%; $p = 0.004$ on OAA/S and $p = 0.034$ on VAS).

Mogil JS et al. assessed objective pain tolerance was assessed by delivering a gradually increasing electrical stimulus (0.5 mA/s) through electrodes placed over the tibia. Individuals carrying two MC1R variant alleles tolerated significantly higher current intensities compared with wild-type and single-allele carriers (n = 47, p < 0.05).

In mouse models, MC1R LOF was linked to elevated nociceptive thresholds ($p = 0.0019$; $p = 0.0038$) and lower α -MSH levels ($p < 0.05$). Murine studies confirm these effects arise from disrupted α -MSH and MC4R signaling, indicating that red hair is not necessary for altered anesthetic physiology.

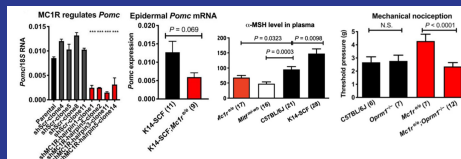


Figure 4. Mc1R regulates Pomc expression, α -MSH levels, and mechanical nociception. A. Cells with Mc1R-targeting shRNAs show significantly lower Pomc mRNA compared to control and parental cells ($***p < 0.001$). B. K14-SCF:Mc1r^{e/e} mice show a trend toward lower Pomc expression compared to K14-SCF controls ($p = 0.069$). C. Mc1r^{e/e} and Mitf^{mi-mi} mice have significantly lower α -MSH levels than C57BL/6J and K14-SCF mice ($p < 0.05$ to $p < 0.001$). D. Mc1r^{e/e} mice have a higher mechanical threshold (less sensitivity), which is reversed in Mc1r^{e/e};Oprm1^{-/-} double mutants ($p < 0.0001$), indicating an Oprm1-dependent effect.

Discussion

MC1R loss-of-function variants define a physiologically distinct group with altered pain perception and anesthetic response. Red-haired individuals consistently require 20% more inhaled anesthetics like desflurane and show less sedation with midazolam. This stems from decreased α -MSH levels, depressing central opioid tone via OPRM1 and MC4R, altering pain thresholds. Crucially, non-red-haired MC1R variant carriers also exhibit altered subjective and objective pain sensitivity, implying increased anesthetic needs and potential intraoperative recall. This "silent" population is often overlooked, with perioperative planning relying on phenotype. Existing research primarily focuses on white, red-haired females, highlighting phenotypic bias and limited inclusivity for high-eumelanin populations or diverse genders. Broader genotyping and phenotypically inclusive trials are essential to personalize anesthetic care and mitigate overlooked clinical risk.

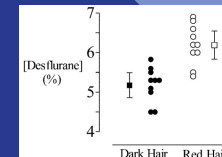


Figure 2. Baseline tolerance of electrical current (10 Hz pulse; 0.1 ms duration, 0.5 mA steps) on non vs variant MC1R carriers.

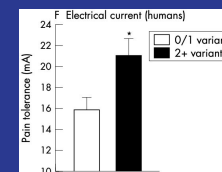


Figure 3. Baseline tolerance of electrical current (10 Hz pulse; 0.1 ms duration, 0.5 mA steps) on MC1R variant carriers and non-carriers [4], (Mogil et al., 2005).

Acknowledgements

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References

