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REVIEW ARTICLE

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Red hair and pain sensitivity: insights into genomics of pain?

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Abstract

Purpose To present a review of insights gained from investigating the question as to whether red haired individuals have altered sensitivity to pain.

Methods A narrative review of the literature.

Results Anecdotal observations from anaesthesiologists have suggested that individuals with red hair require more analgesia on average than members of the general population. This observation has been confirmed and the redheaded phenotype is associated with an altered sensitivity to pain across a wide range of different pain types. Through the use of mouse models, a central mechanism for this altered pain sensitivity has been proposed involving both the melanocortin and opioid receptor systems, despite the causative mutation for this phenotype occurring in melanocortin 1 receptors (MC1Rs) on peripheral melanocytes.

Conclusions Understanding the endocrine imbalance caused by this loss of function mutation helps us to further explore the mechanisms behind pain sensitivity. It also facilitates a discussion about how pharmacogenomics can be exploited to personalise and subsequently optimise treatment.

Keywords Nociception, Red hair, Melanocortins

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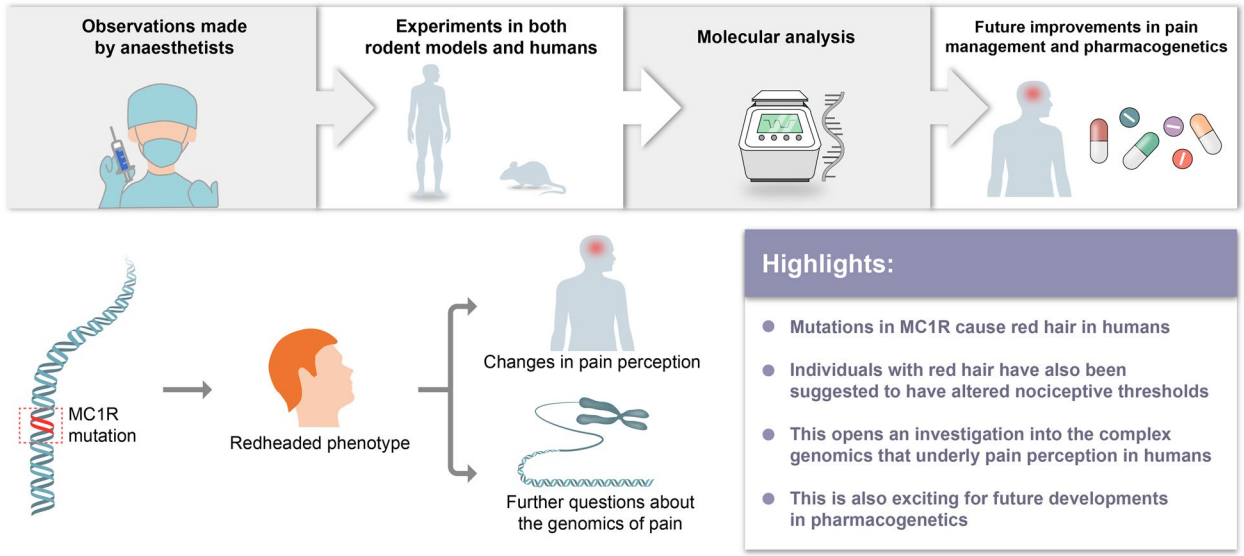
Graphical Abstract



1 Introduction

Anecdotally it has long been noted that individuals with natural red hair often required more anaesthesia than other patients, and this has subsequently been confirmed for inhalational anaesthesia [1]. Since the determination of minimum alveolar concentration (MAC) involves the response to a noxious stimulus [2] this also implies that redheads are more sensitive to pain. This has now been confirmed in several clinical studies, with the proviso that the type of pain stimulus may matter [3–6]. Redheads may be more sensitive to thermal induced pain [3] but have equal sensitivity to ischaemic pain [4]. It is important to note that not all studies agree: Gradwohl et al. were unable to find any differences between anaesthetic or pain sensitivity in a study of patients undergoing surgery [5]. While an advantage of their study was that it was in a clinical rather than experimental setting, one disadvantage was that they used only phenotype and not genotype to identify red-haired patients. Other studies have in fact reported reduced sensitivity to (capsaicin-induced) pain, and the interpretation of these contradictory results will be discussed later [6]. In dental surgery, no difference in response to local anaesthetic has been found [7], but intriguingly the rate of anxiety in the red-haired is higher than others [7, 8]. Thus, clinical studies offer the stimulus to investigate this hypothesis in more detail, but do not offer sufficiently clear information from which to draw robust conclusions. Not including studies that assess potential general anaesthetic sensitivities to red hair (something quite different from, and not necessarily related to, pain sensitivity [9]), there are relatively few human trials examining this specific question. The literature in the animal, genomic and molecular science of red hair and pain appears wider and is the predominant focus of this review. We seek though to link results back to the human condition.

2 Genomics of red hair

The redheaded phenotype arises through a mutation in the melanocortin 1 receptor (MC1R) [10–12] found on epidermal melanocytes, with loss of receptor function causing disrupted pigment production. Instead of the darker eumelanin, a stable molecule that resists photodamage by ultra-violet (UV) radiation [13, 14], sulphated pheomelanin, a red/yellow pigment, is instead produced. The phenotype is a combination of red hair and fair skin. The red-haired phenotype has long been associated with Celtic populations, and is mostly concentrated around North and Northwest Europe, particularly in Iceland, Ireland and Great Britain [15]. The exact number of redheads worldwide is debated, with inconsistent data, but is frequently quoted to be around 2% of the global population.

There are several alleles coding for MC1R, and it is debated whether the existence of these confers any survival advantage. One theory is that these alleles are present in European populations to maximise production of vitamin D from UV light; the disadvantage being an increased risk for developing UV damage-associated skin cancers such as melanoma [16, 17]. However,

distribution of these alleles do not conform to the Hardy-Weinberg equilibrium suggesting that there is a neutral survival advantage [18, 19]. The alleles are virtually absent in African populations, indicating large survival disadvantage to red hair in that environment.

The natural, main ligand of MC1R, α-melanocyte stimulating hormone (α-MSH), is a cleavage product of adrenocorticotrophin hormone (ACTH), which is in turn a product of the prohormone proopiomelanocortin (POMC) within the hypothalamic-pituitary system (Fig. 1) [20]. Additionally, α-MSH is produced in keratinocytes and melanocytes following UV exposure [21], which is clearly an advantage in terms of UV protection. α-MSH therefore can arise from melanotrophs within the pituitary gland or POMC cleavage in the periphery, and has been shown to have a high affinity with the MC1R receptor in human melanocytes [22, 23].

3 Lessons from animal models

One of the main issues within the literature surrounding the study of pain is the significant discrepancy in tests used between human and animal models. Often, little regard is put into the type of pain that is being elicited, and the differences in signalling that will occur as a result — this is a likely cause of the contradictory responses that exist within the literature [3]. It is important to note

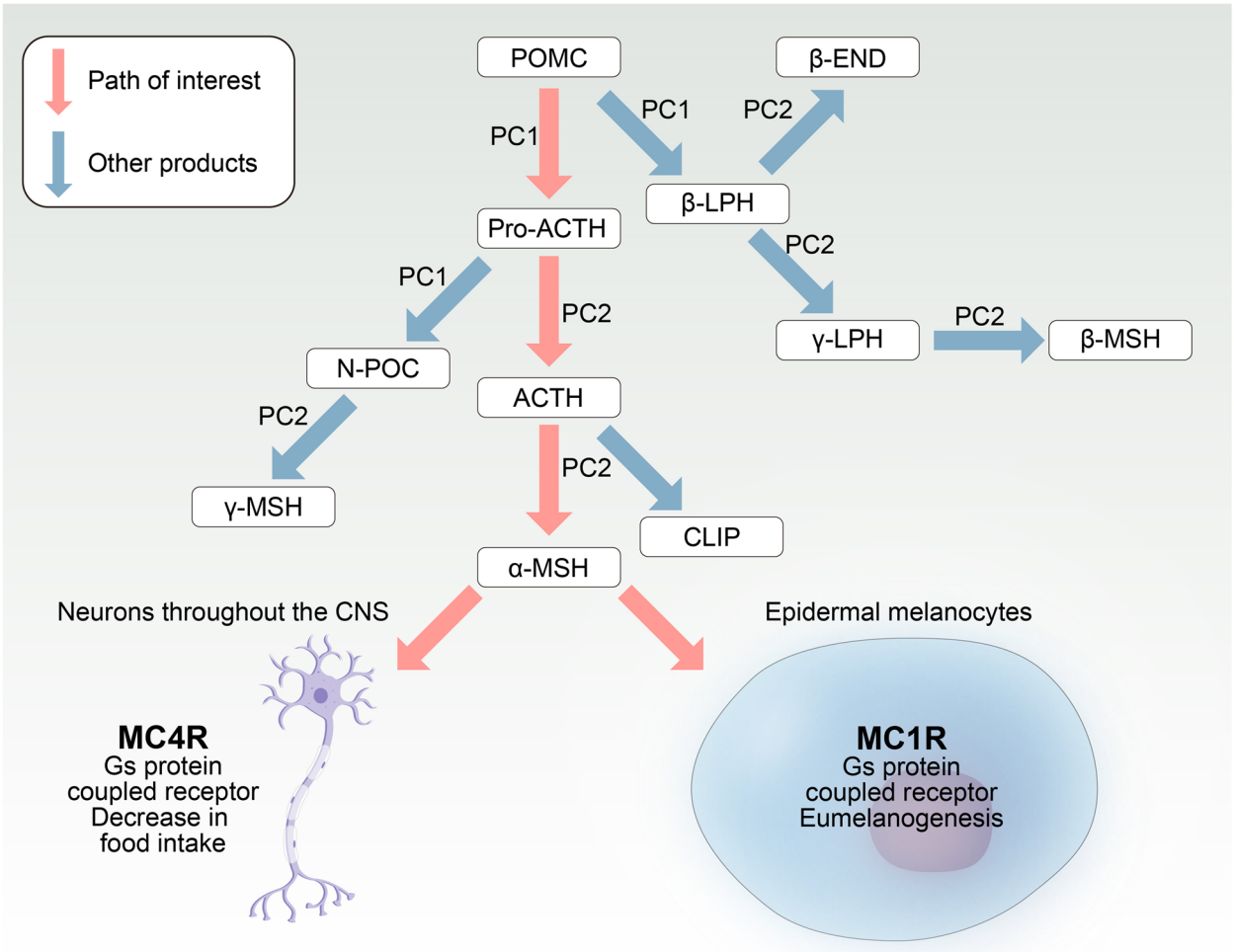


Fig. 1 Metabolic pathways involving α-MSH (alpha-melanocyte stimulating hormone). α-MSH is a major agonist of the melanocortin system including MC1R and MC4R (melanocortin receptors 1 and 4), is a cleavage product of the prohormone POMC (proopiomelanocortin) via another product, ACTH (adrenocorticotrophin hormone). PC (proconvertase) 1 and 2 are the enzymes responsible for peptide cleavage to produce the active products. POMC is the precursor for a range of different products, with a large range of different effects extending from metabolic to pigmentation—some products other than α-MSH have been shown on the diagram below, including N-pro-opiomelanocortin (N-POC (pro- γ-MSH)), γ-MSH (gamma-melanocyte stimulating hormone), CLIP (corticotrophin-like intermediate lobe peptide), β-LPH (beta-lipotropin), β-END (beta-endorphin), γ-LPH (gamma-lipotropin) and β-MSH (beta-melanocyte stimulating hormone)

the differences in assays available between human and animal studies, as the tests available for the latter have more definitive end-points at which results are collated, and are also available to investigate a wider range of different pain types.

Clear types of pain were demonstrated by Mogil et al., who used 11 random mouse strains to investigate differences in response across 12 standardised pain tests [24, 25]. Through genetic analysis, this group was able to organise different pain types into clusters which shared similar modalities [25]. These concepts were built upon to characterise five fundamental types of nociception and hypersensitivity; baseline thermal nociception, spontaneous responses to noxious chemical stimuli, thermal hypersensitivity, mechanical hypersensitivity and afferent input-independent hypersensitivity [26], which can all be investigated using different pain assays. For example, baseline thermal nociception in rodents can be studied using tail withdrawal tests [4, 27], where the latency to remove the tail from a water bath or hot plate at a set 'hot' temperature is measured. For chemical types of pain, 0.9% acetic acid can be injected into the abdomen of mice, and the subsequent number of reflexive abdominal constrictions within a certain timeframe is measured to estimate the spontaneous response to pain [27].

In humans, however, endpoints are more subjective: thermal nociception can be determined by finding a 'nociceptive threshold' using temperature probes in a specific sequence to prevent sensitisation or habituation of cutaneous receptors [3]. This reinforces a key difference in how pain is measured between human and animal models, as the conscious determination of a nociceptive threshold can be influenced by a large number of different factors, including psychological [28] and even placebo [29]. This makes it difficult to compare between individuals or draw objective conclusions from human data.

Nevertheless, animal models have been largely consistent with many human studies, including the variability of response with type of pain stimulus and some inconsistencies in results. Thus, MC1R variants in labrador dogs result in increased sensitivity to thermal (but not mechanical) pain [30]. In both animal and human studies, two findings have emerged that require further exploration. One is that the potential influence of red hair is further modulated by sex; a second is the differential influence of red hair on response to opioids.

Delaney et al. studied mutant mice lacking MC1R (termed *Mc1r*$^{e/e}$) and found an influence as expected, but surprisingly this was an increased tolerance, not sensitivity, to thermal and inflammatory (formalin-induced) pain (but not neuropathic pain following peripheral nerve injury) which was confined to females. Male mutants showed similar responses in all conditions [31]. Note that sex differences in pain sensitivity are well established [32] with females generally displaying greater sensitivity [33, 34], and this is in turn influenced by species strains. Thus, male Sprague Dawley rats are more sensitive than females to thermal pain, while it is the reverse in Long Evans rats [35].

Mogil et al. reported an increased sensitivity to opioid analgesia in red hair in a mouse model. Thus even if pain sensitivity is increased as many studies report, this seems advantageously balanced in therapeutic terms by the increased sensitivity to analgesia [4]. They used quantitative locus mapping to indicate that *Mc1r* allele was associated with the site of action of the broad κ-opioid agonist, U50,488. This association was identified in female mice only. They then elegantly translated this finding to study women with two variant *Mc1r* alleles and confirmed a greater response to κ-opioids, such as pentazocine, than dark-haired controls. This study weaves in the MC1R pathway with opioid response and sex [36, 37]. One limitation of their study is that they did not employ positional cloning to reduce the confidence interval surrounding the quantitative trait locus, eliminating all other genes on distal chromosome 8. Quantitative trait locus (QTL) analysis is a statistical method that links phenotypic (trait measurement) and genotypic data (molecular markers) to explain the genetic basis of variation in complex traits, and Mogil et al. argued that their success in linking their mouse study to human responses superceded the need to undertake more exact positional cloning. A second, perhaps more practical limitation is the κ-opioid system has currently limited therapeutic potential in terms of treating pain, in contrast to the μ-opioid system. Drugs targeting these receptors tend to cause significant dysphoric, rather than euphoric, psychotomimetic side effects, indicating that another major function of this system in mood regulation [38]. There are few specific indications for pentazocine, a κ agonist, and buprenorphine, another commonly used opioid, is in fact a κ antagonist.

However, focus on the endogenous ligand for the κ-opioid receptor, dynorphin, may offer more scientific insight as it also binds with high specificity and antagonises MC1R [39]. Moreover, in addition to their peripheral localization, MC1Rs are expressed in brain glial cells [40] and the ventral periaqueductal gray [41], which are regions putatively relevant to nociception [42].

Mogil et al. later turned attention to the μ-opioid system. They studied spontaneous *Mc1r*$^{e/e}$ mice versus wild-type controls, and in parallel humans with red and dark hair, using a variety of both acute and tonic pain assays to confirm that mice mutants mimicking red-haired humans were less sensitive to pain [27]. They also investigated the response to the morphine metabolite

morphine-8-glucuronide, M6G, as the μ-opioid receptor agonist. Mutants and redheads showed an increased analgesic response, which the authors confirmed was likely a true pharmacodynamic, rather than metabolic/pharmacokinetic effect, as circulating levels of the drug were similar in both groups [27]. Interestingly, Mogil et al. did not find any sex-dependent effects in mice or humans, in contrast to their previous report for the κ-opioid system. However, extending the results of MC1R interaction with both κ- and μ-opioid systems raises the possibility that in dark-haired humans there is an endogenous pain inhibition system resulting from MC1R activation. Reduced or absent in redheads, this results in anti-analgesia.

Mc1r is not the only member of the melanocortin receptor family to be investigated in the context of pain, as there have been explorations into rat models and the involvement of allele for melanocortin 4 receptor (*Mc4r*) in centralised pain phenomena, such as allodynia [43, 44]. Allodynia is the experience of a painful response to a non-nociceptive stimulus and can involve both peripheral sensitisation and central maladaptation, depending on the mode [45]. The co-localisation of μ-opioid and melanocortin receptors in the spinal cord, and their supposed antagonistic relationship, has led to the consideration of melanocortin 4 receptor (MC4R) action in this central sensitisation response. Starowicz et al. compared the anti-allodynic effects of melanocortin receptor antagonist SHU-9119 and μ-opioid receptor agonist morphine, finding that targeting the melanocortin system had a more significant response [43]. This further implicates other members of the melanocortin in the control of pain responses and suggests an important interplay with our endogenous opioid system.

4 Confounders and more complex genomics

When reporting that red-haired women were significantly more sensitive to thermal nociception, Liem et al. also found an increased resistance to subcutaneous lidocaine [3]. This is unexpected as this drug should act primarily on the voltage gated sodium channels of peripheral C fibres. One possibility is that anti-nociceptive actions of lidocaine are recognised via other putative systems [46], although this is at different concentrations from those achieved by subcutaneous injection [46, 47]. It is conceivable that the MC1R system acts in a more complex way in respect of the analgesia conferred by lidocaine block of peripheral nerves (e.g., a modulation of sodium channel sensitivity).

The study of pain has been recognised to be complex [48]. Pain being a subjective sensation is difficult to measure, and as studies cited above show, responses can depend on the stimulus type being used. The stimulus intensity that can be administered in humans is understandably limited, as also it is in animal studies. Pain is ultimately a bio-psycho-social condition where immeasurable factors ideally need to be considered. Acute pain can evolve into chronic pain, which underlines these issues and therefore, pain can exist or continue in the absence of any apparent noxious stimulus. Moreover, the necessary treatment of pain can lead to complexities created by dependence or hyperalgesia [49]. Research has indicated that genotype can at least somewhat determine an individual's response to different types of pain assay [24–26]. Animal studies offer the advantage of creating genomic variants and more invasive techniques, but animals cannot report pain, so all measures are surrogates [50].

Another confounding factor within less genotypically controlled human groups could be the exact mutation in the MC1R gene: within the 'red-haired' human phenotype, there is a wide degree of variation which is understandably reflected by a high degree of polymorphism in this gene [51, 52] and variable expression. This concept was further explored through a retrospective study by Zorina-Lichtenwalter et al. who used the data from an orofacial pain study with full genotyping to investigate the correlation between 17 specific polymorphisms in MC1R and the prevalence of chronic pain conditions. While red hair per se was associated with a greater sensitivity to pain, the association between the polymorphisms and experience of pain was more complex. Individuals with the most common missense variants in alleles for *MC1R* statistically had fewer chronic pain conditions than those with no such mutation [53]. Thus, mutation in the *MC1R* allele is associated with an alteration in pain sensitivity, irrespective of hair colour.

5 Redheads and pain: an imbalance in opioid signalling?

Robinson et al. [54] recently conducted an extensive series of experiments presented within a single paper, and it is worth presenting their results in the logical sequential order they undertook them to unravel the relationships between red hair, MC1R and opioid signalling. For a summary of the different mouse models used by Robinson et al., see Table 1.

They first excluded skin pigment per se as an influence on pain sensitivity in normal and $Mc1r^{e/e}$ mice, by crossing these with albino mice ($Tyr^{c/c}$), in whom melanocyte numbers were unaltered but lacked pigment. Mutant $Mc1r^{e/e}$ always exhibited higher pain tolerance than other types, regardless of the actual skin and coat colour, indicating that melanocytes were important rather than the eumelanin pigment. Next, they assessed whether melanocyte numbers were influential by studying genetically matched (C57BL/6J) mouse models that differed

Table 1 Summary of the different mouse models used to investigate a mechanism for altered pain sensitivity. This is based on Robinson et al.'s paper [54]. 'Pain sensitivity' is synonymous with 'nociceptive threshold' for the purposes of this table. Robinson et al. also used the following cell lines: Melan-C (to investigate the direct effect of melanocortin 1 receptor (MC1R) on proopiomelanocortin (POMC) synthesis, with *Mc1r* activity being shown to be proportional to Pomc mRNA expression) and rat primary hypothalamic neurons (RPHNs, to investigate impact of antagonism between melanocortin and opioid signalling on adenosine 3′,5′-monophosphate (cAMP) production and subsequent opioid modulation, showing that melanocortin agonists increased cAMP content, and this increase could be attenuated by opioid receptor agonists). Cells were also isolated from some of the mouse models for in-depth biochemical analysis

Mouse model	Genotype	Cellular/molecular phenotype	Coat colour	Rationale	Effect
C57BL/6 J	Control	Control	Black	Control, background to cross with other mice	Control/genetically matched background
***Mc1r*$^{e/e}$**	Double KO of *MC1R*	MC1R KO	Red	Investigate effect of *MC1R* KO, background to cross with other mice	Higher nociceptive threshold
Tyr$^{c/c}$	Double KO of tyrosinase gene	Tyrosinase KO/pigmentation	White/albino	Remove the confounding effect of pigment from *Mc1r*$^{e/e}$ and C57BL/6 J mice	No effect on nociception
K14-SCF	Mutant mouse *Kitl* cDNA, TG2 or membrane SCF, otherwise *C57BL/6 J* background	Increased number of melanocytes	Black	Investigate effect of melanocyte number on pain perception	Lower nociceptive threshold
***Mitf*$^{mi-wh/mi-wh}$**	Mutant melanogenesis associated transcription factor, otherwise *C57BL/6 J background*	Decreased number of melanocytes	White/albino	Investigate effect of melanocyte number on pain perception	Higher nociceptive threshold
***Mc1r*$^{e/e}$*;Mitf*$^{mi-wh/mi-wh}$**	Combination of *Mc1r*$^{e/e}$ and *Mitf*$^{mi-wh/mi-wh}$ genotypes	Decreased number of melanocytes, with non-functional MC1R	White/albino (but red-haired phenotype ref. MC1R)	Tests potential for effect of *MC1R* in non-melanocytes	No change in pain threshold to *Mc1r*$^{E/E}$*;Mitf*$^{mi-wh/mi-wh}$
***β-end*$^{-/-}$**	Homozygous mutation in terminal β-endorphin sequence of POMC	β-endorphin KO, unaffected other POMC products	Black or red, crossed with both	Test effect of low β-endorphin levels on nociception thresholds, crossed with both black- and red-haired mice	No significant change from predicted thresholds in either coat colour
***Oprm1*$^{-/-}$**	Double KO of μ-opioid receptor gene	OPRM1 KO	Black or red, crossed with both	Test effect of altered activity at μ-opioid receptors on nociceptive thresholds, cross with both black- and red-haired mice	Abolished nociceptive threshold changes in red-coated mice
***Dyn*$^{-/-}$**	Double KO of dynorphin	Dynorphin KO	Black or red, crossed with both	Investigate effect of endogenous opioids on altered nociceptive thresholds	No significant change from predicted thresholds in either coat colour
***Mc4r*$^{-/-}$**	Double KO of *MC4R* on a *MC1R*$^{E/E}$ background	MC4R KO	Black	Investigate role of MC4R on nociceptive threshold, and balance with OPRM1 signalling, cross with other mice	Higher nociceptive thresholds, sensitive to opioid antagonism

in melanocyte numbers. Mice with increased epidermal melanocytes (K14-SCF) were more sensitive to pain than mice lacking melanocytes (*Mitf* $^{mi-wh/mi-wh}$), who in turn displayed higher pain tolerance than wild type (WT), WT mice (i.e., the pain sensitivity was K14-SCF (most sensitive) > WT > *Mitf* $^{mi-wh/mi-wh}$). This indicates that the number of epidermal melanocytes—independent of MC1R function—modulates pain sensitivity.

Then, they crossed red-haired (*Mc1r*$^{e/e}$) mice with the *Mitf* $^{mi-wh/mi-wh}$ mice lacking melanocytes, to test the potential role of MC1R function in nonmelanocytic cells. Genetic absence of melanocytes now inhibited the ability of MC1R to influence pain sensitivity, suggesting that this is dependent on MC1R function in melanocytes rather than in other cell types.

Robinson et al. then considered β-endorphin as a potential modulator of pain sensitivity. β-endorphin is a posttranslational cleavage product of proopiomelanocortin (POMC), expressed in melanocytes; POMC is induced by adenosine 3′,5′-monophosphate (cAMP) in other cell types and low cAMP levels in red-haired *Mc1r* mutant melanocytes may affect POMC expression and in turn, β-endorphin levels. They confirmed that red-haired mice did indeed exhibit lower plasma levels of β-endorphin. However, this appeared contrary to the higher pain tolerance found in these mice as β-endorphin promotes rather than diminishes analgesia. Moreover, they discovered that β-endorphin levels were also inversely associated with pain thresholds in the other mouse genotypes: K14-SCF mice (more melanocytes; more sensitive to pain) and *Mitf*$^{mi-wh/mi-wh}$ mice (absent melanocytes; more tolerant to pain). Thus, overall, melanocyte numbers and MC1R function were inversely correlated with pain sensitivity, despite themselves being directly related to plasma β-endorphin levels.

Next, to determine whether the reduced pain sensitivity to pain was a result of compensation for—or adaptation to—the lower β-endorphin levels, Robinson et al. employed mice carrying homozygous POMC mutation that expresses all melanocortin peptides except β-endorphin (*β-end*$^{-/-}$), and a strain lacking μ-opioid receptor for β-endorphin (*Oprm1*$^{-/-}$). There was no effect of the knockout on the pain threshold differences in black versus red-haired mice. Lack of μ-receptor had no effect on the pain thresholds in black mice, consistent with previous studies [55]. However, the absence of μ-receptor abolished the elevated nociceptive thresholds in red-haired mice. Separately, opioid receptor antagonists (naloxone and cyprodime) both altered pain sensitivity of red-haired mice to those of black mice.

All these results suggested that pain thresholds in red-haired mice are not dependent on a β-endorphin-opioid receptor signalling pathway. The increased μ-opioid receptor signalling in the context of low plasma β-endorphin levels could be due to (a) increased expression of some other endogenous opioid, (b) μ-receptor adaptation, or (c) reduction of a pathway that is antagonistic to opioid signalling. The first (a) was excluded by a finding of similar dynorphin, enkephalin, and endomorphin levels between red-haired and black mice.

Robinson et al. noted that plasma levels of α-MSH (a melanocortin agonist, like β-endorphin, also encoded within POMC) varied across different-pigmented mice, paralleling β-endorphin levels (i.e., higher α-MSH levels in mice with more melanocytes; lower in red-haired mice). This variation is therefore consistent with the respective changes in pain thresholds, unlike β-endorphin which is inversely related. To test whether the relationship could be causative, Robinson et al. 'rescued' low endogenous α-MSH levels in red-haired mice pharmacologically: melanotan II, (that mimics α-MSH action) increased (i.e., reversed) pain sensitivity in red-haired but not black mice, in a sex-independent manner. Thus, loss of function in MC1R signalling results in increased tolerance to pain, but an MSH receptor other than MC1R is likely involved.

Robinson et al. noted that the different melanocortin receptor, MC4R has been implicated in pain control [56]. The peptide SHU-9119 antagonizes MC4R, despite being an MC1R agonist, and was found to be analgesic in black mice, mimicking the red-haired (*Mc1r*$^{e/e}$) genotype. This was also the case in the cross of K14-SCF with *Mc1r*$^{e/e}$ mice. Since these mice have wild-type pain thresholds, and levels of all POMC products, but lack MC1R function, these results strongly suggest that the analgesic effects of SHU-9119 are MC1R independent and likely due to ligand effects on MC4R (or MC3R, another related receptor). Thus, MC4R signalling may balance opioid signalling in modulating responses to pain.

Robinson et al. undertook a series of experiments to explore the putative MC4R system: (i) *Mc4r* null mice exhibited reduced pain sensitivity; (ii) the absence of MC4R on a genetically black background resulted response to opioid antagonists similar to red-haired mice, suggesting that pain threshold may be a balance between Mu opioid receptor 1 (OPRM1) and MC4R signalling; (iii) naloxonazine, a specific μ-receptor antagonist restores nociceptive thresholds in both *Mc4r* null and red-haired mice; (iv) melanocortin agonist treatment reduced the elevated pain thresholds of red-haired, but not *Mc4r* null mice, suggesting that MC4R is the key melanocortin target for MSH; (v) intraperitoneal administration of naltrexone, an opioid receptor antagonist that crosses the blood–brain barrier (BBB) reduces differences between black and red-haired mice, but administration of methylated naltrexone that does not cross

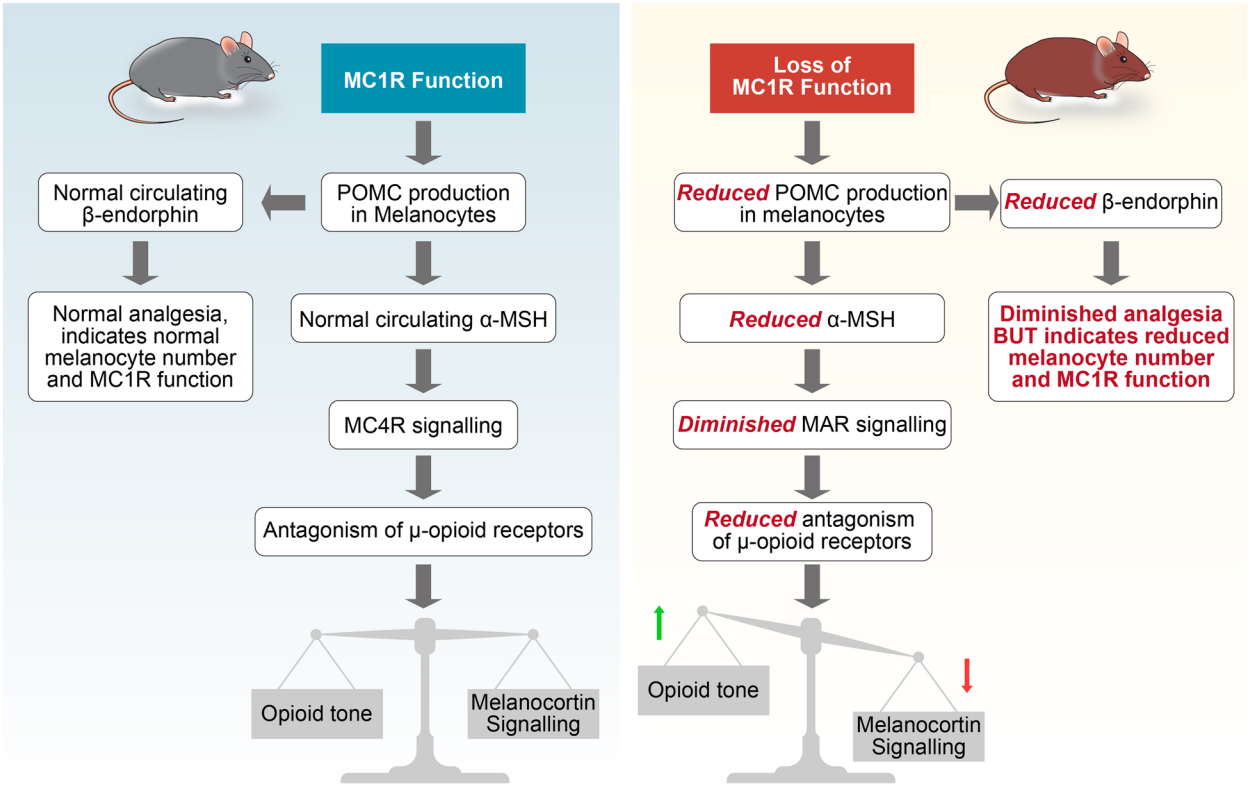


Fig. 2 Diagrammatic summary of the proposed mechanism for altered pain sensitivity in redheads. The details and adaptation is from Robinson et al.'s paper [54], with proposed conclusions considered in the above discussion

the BBB does not, suggesting the influence on opioid signalling in red-haired mice is a central, not peripheral phenomenon – this implicates α-MSH balanced opioid receptor–mediated regulation of central nociception; (vi) in rat primary hypothalamic neurons the melanocortin agonist [Nle4,D-Phe7]-α-MSH increased cAMP content, whereas morphine significantly inhibited this melanocortin-induced cAMP elevation suggesting a mutual antagonistic interaction in these cells.

The detailed work of Robinson et al. suggests that the reduced pain sensitivity in the red-haired arises from reduced α-MSH levels caused by a reduced POMC production in melanocytes, in turn leading to diminished MC4R signalling. The antagonism of opioid signalling within the central nervous system (CNS) is thereby reduced which occurs despite a reduced β-endorphin production consequent on the reduced POMC production. The theory is a 'net melanocortin deficiency', relative to opioid signalling, altering the balance to favour μ-opioid receptor–induced analgesia in the red-haired (Fig. 2). Note that these conclusions are entirely compatible with the suggestions of Zorina-Lichtenwalter et al. that it is the underlying genotype, not the phenotype of red hair, that is the relevant influence and therefore, this work may be revealing of a more generalised mechanism in responses to pain.

6 So, what can we learn from the study of redheads in context of pain?

Understanding how polymorphisms interact with various pharmacological agents is the core concept of pharmacogenomics, with the aim of personalising therapy as mainstream practice. This will make therapy more effective and reduce side-effects. That said, Mogil (whose work has been cited above), writing more than 10 years before the Robinson et al. study, bemoaned the state of genomics in pain [57]. He cited Max and Stewart as writing that 'pain has come late to the genetics party' [58] and observed that transgenic, linkage mapping and microarray studies in rodents might predict the existence of many hundreds of pain-relevant genes, yet focus has been on just a handful: *COMT* (encoding catechol-O-methyltransferase), *GCH1* (encoding guanosine triphosphate (GTP) cyclohydrolase 1), and OPRM1 (discussed above). His summary of the general results applies to the discussion above: poor replicability of genetic association studies, conclusions have become less straightforward

than initially imagined—there is no binary yes/no association or influence on pain—and subsequent studies after the initial have reported no association, or sex-dependent association, or significant associations but of different single nucleotide polymorphisms or haplotypes, and significant associations, but of different phenotypes than those initially suspected. All this is attributed variously to data set heterogeneity, stratification of populations, and genomic statistical underpowering. Both selective publication and at times scientific fraud have had their part to play in pain therapy research [59, 60]. If pointing to one gene as 'responsible for pain' is oversimplistic, then widening to net to include many more—whilst acknowledging the reality that pain is indeed a complex bio-psycho-social phenomenon—then runs the risk that all genes are 'pain genes'. Mogil cites as Goldstein: "in pointing at everything, genetics would point at nothing" [61].

That said, the elegant work of Robinson et al., and others cited, represents an incremental advance and does indeed push forward the genomic understanding of pain, albeit from this limited perspective of the influence of red hair. Examples of the success of genomics include the use of abacavir in HIV treatment, where the presence of a specific human leukocyte antigen (HLA) allele can cause severe side effects [62], preventable by prior genotyping [63, 64]. Particular low-function mutations in the cytochrome P450 2D6 metabolic enzyme (CYP2D6) are thought to limit the metabolic pathway that forms codeine's physiologically active metabolite, morphine [65], resulting in lack of analgesic effect. Because the phenotype associated with MC1R mutation is self-evident, identification of these individuals with potentially altered nociceptive sensitivity, and perhaps anaesthetic efficacy, is easy (at the expense of making blinded trials difficult).

7 Conclusions

Although the model proposed in Fig. 2 represents progress, there remain fundamental questions that require resolution before results can be translated to clinical practice. One is that the direction of influence of red hair/MC1R remains unclear, with some studies reporting increased pain sensitivity and others the reverse (or none). The influence of sex remains unresolved. And of the opioid receptors the δ- or ζ-receptors, or their specific subtypes have not been investigated. Whilst the model presented by Robinson et al. nicely demonstrates the influence of red hair/MC1R on the balance between opioid tone and melatonin signalling, it is possible that other unknown factors may affect input from the opioid system. These other factors may have nothing to do with red hair or the melanocortin system but may lead to confounding results in redhaired individuals. We are a long way off from specific therapies, but the work shows that a simple question about redheads can lead to unravelling of complex pain-relevant pathways within the body.

Abbreviations

ACTH	Adrenocorticotrophin hormone
α-MSH	α-Melanocyte stimulating hormone
BBB	Blood-brain barrier
β-END	Beta-endorphin
β-end$^{-/-}$	Genetic notation for mutation that expresses all melanocortin peptides except β-endorphin
β-LPH	Beta-lipotropin
β-MSH	Beta-melanocyte stimulating hormone
cAMP	Adenosine 3′,5′-monophosphate
C57BL/6J	Species of mouse (wild type)
CLIP	Corticotrophin-like intermediate lobe peptide
CNS	Central nervous system
COMT	Gene encoding catechol-O-methyltransferase)
CYP2D6	Cytochrome P450 2D6 metabolic enzyme
γ-LPH	gamma-lipotropin
GCH1	Gene encoding GTP (guanosine triphosphate) cyclohydrolase 1
GTP	Guanosine triphosphate
HLA	Human leukocyte antigen
K14-SCF	Notation for mice with increased epidermal melanocytes
MAC	Minimum alveolar concentration
MC1R	Melanocortin 1 receptor
Mc1r	Alleles for MC1R
Mc1r$^{e/e}$	Mutant mice lacking MC1R
MC3R	Melanocortin 3 receptor
MC4R	Melanocortin 4 receptors
Mc4r	Allele for MC4R
Mitf$^{mi-wh/mi-wh}$	Allele notation for mice lacking melanocytes
[Nle4,D-Phe7]-α-MSH	Melanocortin agonist
N-POC	N-pro-opiomelanocortin
OPRM1	μ-Opioid receptor for β-endorphin
Oprm1$^{-/-}$	Genetic notation for a strain lacking μ-opioid receptor for β-endorphin
PC	Proconvertase
POMC	Proopiomelanocortin
QTL	Quantitative trait locus
SHU-9119	Melanocortin receptor antagonist
Tyr$^{c/c}$	Genetic notation for albino mice
U50,488	Broad κ-opioid agonist
UV	Ultra-violet
WT	Wild type

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The authors jointly conceived of the project; JJP defined the scope and title; HRW conducted the preliminary literature search and prepared the first draft. Subsequent drafts were prepared by JJP; both authors approved the final version.

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Declarations

Competing interests
The authors declare that they have no competing interests.

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