

Review

# Behind the Scene: Exploiting MC1R in Skin Cancer Risk and Prevention

Michele Manganelli <sup>1,2,†</sup> , Stefania Guida <sup>3,†</sup> , Anna Ferretta <sup>1</sup> , Giovanni Pellacani <sup>4</sup>, Letizia Porcelli <sup>5</sup>, Amalia Azzariti <sup>5</sup>  and Gabriella Guida <sup>1,\*</sup>

- <sup>1</sup> Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari-“Aldo Moro”, 70125 Bari, Italy; m.manganelli@unibs.it (M.M.); anna.ferretta@uniba.it (A.F.)
- <sup>2</sup> DMMT-Department of Molecular and Translational Medicine, University of Brescia, 25123 Brescia, Italy
- <sup>3</sup> Department of Surgical-Medical-Dental and Morphological Science with Interest Transplant-Oncological and Regenerative Medicine, University of Modena and Reggio Emilia, 41124 Modena, Italy; stefania.guida@unimore.it
- <sup>4</sup> Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences, Dermatology Clinic, Sapienza University of Rome, 00161 Rome, Italy; giovanni.pellacani@uniroma1.it
- <sup>5</sup> Laboratory of Experimental Pharmacology, IRCCS Istituto Tumori Giovanni Paolo II, 70124 Bari, Italy; l.porcelli@oncologico.bari.it (L.P.); a.azzariti@oncologico.bari.it (A.A.)
- \* Correspondence: gabriella.guida@uniba.it; Tel.: +39-080-544-8555
- † These authors contributed equally to this work.

**Abstract:** Melanoma and non-melanoma skin cancers (NMSCs) are the most frequent cancers of the skin in white populations. An increased risk in the development of skin cancers has been associated with the combination of several environmental factors (i.e., ultraviolet exposure) and genetic background, including melanocortin-1 receptor (*MC1R*) status. In the last few years, advances in the diagnosis of skin cancers provided a great impact on clinical practice. Despite these advances, NMSCs are still the most common malignancy in humans and melanoma still shows a rising incidence and a poor prognosis when diagnosed at an advanced stage. Efforts are required to underlie the genetic and clinical heterogeneity of melanoma and NMSCs, leading to an optimization of the management of affected patients. The clinical implications of the impact of germline *MC1R* variants in melanoma and NMSCs' risk, together with the additional risk conferred by somatic mutations in other peculiar genes, as well as the role of *MC1R* screening in skin cancers' prevention will be addressed in the current review.

**Keywords:** melanocortin 1 receptor; *MC1R*; melanoma; basal cell carcinoma; squamous cell; skin cancer prevention



**Citation:** Manganelli, M.; Guida, S.; Ferretta, A.; Pellacani, G.; Porcelli, L.; Azzariti, A.; Guida, G. Behind the Scene: Exploiting *MC1R* in Skin Cancer Risk and Prevention. *Genes* **2021**, *12*, 1093. <https://doi.org/10.3390/genes12071093>

Academic Editor: Ignazio Stanganelli

Received: 9 June 2021

Accepted: 16 July 2021

Published: 19 July 2021

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Copyright:** © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

Skin cancers represent the most frequent cancer, with 5 million of new cases each year [1]. The most common skin cancers include melanoma and non-melanoma skin cancers (NMSCs), among which basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). For the last 10 years the incidence of melanoma has been continuously rising, together with that of NMSCs, although a precise estimation of the number of NMSCs is impaired by the fact that their reporting in cancer registries is not mandatory [1,2]. While BCC is usually confined to the skin, SCC and melanoma can be potentially metastatic, being difficult to treat and therefore presenting with a poor prognosis [3,4].

An increased risk of skin cancers has been associated with a combination of environmental agents, such as ultraviolet radiation (UVR), and genetic background. In particular, genes involved in pigmentary regulation, such as melanocortin-1 receptor (*MC1R*), are implicated in skin cancers' development [5,6].

The *MC1R* gene codifies for a G protein-coupled receptor (GPCRs), with a high affinity for  $\alpha$ -melanocyte stimulating hormone ( $\alpha$ -MSH). It is a highly polymorphic gene and it has been related to pigmentary as well as to non-pigmentary functions, including DNA repair.

In the last few years, there has been increasing knowledge about the *MC1R* functions and their clinical impact in dermatology. The aim of this review is to provide an update on the impact of *MC1R* gene in melanoma and NMSCs' risk—together with the additional risk conferred by somatic mutation of other gene—as well as its role in the prevention of skin cancers.

## 2. *MC1R* Structure, Regulation and Functions

### 2.1. *MC1R* Structure and Regulation

The *MC1R* gene (16q24.3, OMIM #155555) codes for seven transmembrane GPCRs of 317 amino acids, evolutionarily conserved [7,8], showing an extracellular N-terminus, with a glycosylation site, seven transmembrane segments, and an intracellular C-terminal extension including a palmitoylation site [9–11]. This receptor was first isolated from melanocytes, where its main physiological role in the skin has been shown [12]. *MC1R* shows a high affinity for the  $\alpha$ -MSH, as well as for adrenocorticotrophic hormone (ACTH) [9,10].

The *MC1R* gene may exhibit splice variants, giving rise to two forms of intergenic splicing, yielding *MC1R-TUBB3* ( $\beta$ -tubulin III) chimera and at least two forms of alternative splicing [13,14]. In all cases, the proteins encoded by the non-canonical mRNAs preserve the general architecture of GPCRs and differ from canonical *MC1R* for a longer C-terminal extension [14,15]. Once *MC1R* mRNA is translated, the receptor undergoes post-translational modifications that include oligomerization, N-glycosylation (Asn15, Asn29), palmitoylation (Cys315) and phosphorylation (Thr157, Thr308, Ser316) [11,16–19], contributing to receptor structure, localization, trafficking, internalization, desensitization.

Human *MC1R* shows a constitutive activation of downstream signaling, independent from the presence of the agonist, which is impaired in presence of *MC1R* variants [20]. Additionally, *MC1R* signaling is induced upon stimulation of human melanocytes with  $\alpha$ -MSH [21], 12-O-tetradecanoylphorbol ester (TPA) [22] and [Nle<sup>4</sup>, DPhe<sup>7</sup>]- $\alpha$ -MSH (NDP-MSH, synthetic analog of  $\alpha$ -MSH) [23]. The induction is also mimicked by the adenylyl-cyclase activator forskolin. Conversely, Agouti Signaling Protein (ASIP) inhibits  $\alpha$ -MSH binding to *MC1R* [24,25]. Human  $\beta$ -defensin 3 (HBD3) prevents the binding of both  $\alpha$ -MSH and ASIP to *MC1R* [26,27], preventing both the increase in cAMP and the upregulation of TYR in melanocytes.

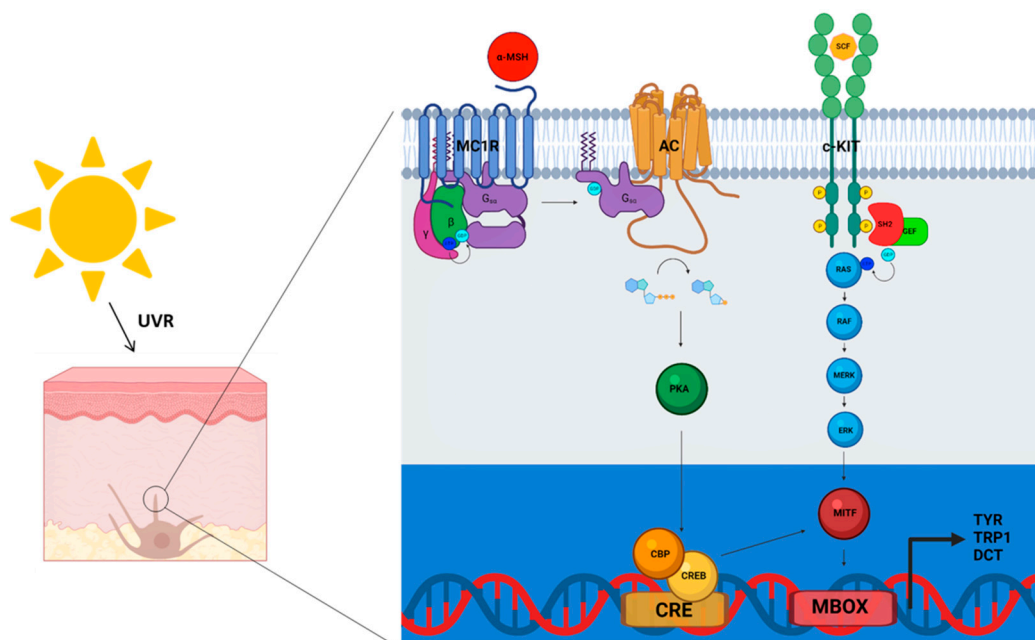
Interestingly, paracrine factors produced by keratinocytes such as endothelin 1 (EDN1) and basic fibroblast growth factor (bFGF), act through their corresponding receptors on the plasma membrane of melanocytes to increase proliferation and differentiation. EDN1 mediates a dose-dependent upregulation of *MC1R* mRNA in normal human melanocytes [28], while the effects of bFGF are less clear, although an upregulation has been reported [28]. Interleukin-1- $\alpha$  (IL-1 $\alpha$ ) and interleukin-1- $\beta$  (IL-1 $\beta$ ) upregulate *MC1R* mRNA in normal human melanocytes [23], while TNF- $\alpha$  [29] and TGF- $\beta$  [30], that potentially repress melanogenesis in melanoma cells, moderately downregulate *MC1R* expression in normal melanocytes [23] and mouse melanoma cells [31].

Additionally, a downregulation of cyclic-adenosine monophosphate (cAMP) signaling has been related to: an increase in phosphodiesterase 4D3 gene (PDE4D), a transcriptional target of cAMP via microphthalmia-associated transcription factor (MITF) [32], limiting cAMP accumulation; the phosphatase and tensin homolog deleted on chromosome 10 (PTEN) [33,34] and the RING Finger domain-containing E3 ubiquitin ligase Mahogunin Ring Finger 1 (MGRN1) [35], inhibiting cAMP signaling, most likely due to a physical interaction of MGRN1 and *MC1R*; activation of ERK signaling, leading to MITF phosphorylation and degradation [36]; prolonged exposure to agonists, such as  $\beta$ -arrestins (ARRB), leading to desensitization or internalization of *MC1R* [17,27,37,38].

## 2.2. MC1R and Pigmentation

MC1R has a pivotal role in pigmentation, although important non-pigmentary functions have also been identified [12].

The pathway leading to pigmentation has been widely characterized. It involves  $\alpha$ -MSH binding to the MC1R, with a consequent increase in adenylyl-cyclase (AC) activity and rising of intracellular cAMP levels. cAMP activates protein kinase A (PKA), leading to the phosphorylation of the cAMP-response element binding protein CREB, which in turn activates the promoter of the *MITF*. The resultant event is the upregulation of tyrosinase (TYR) and Tyr-related proteins (TYRP1 and DCT) (Figure 1), switching pheomelanin to eumelanin synthesis [36,39–47] (Figure 1).



**Figure 1.** Pigmentary pathway of MC1R. Binding of  $\alpha$ -MSH on MC1R receptor activates adenylyl cyclase (AC) and stimulates cAMP production, which in turns induce the activation of several downstream effectors, including MITF transcription factor. MITF binds the MBOX on the promoters of tyrosinase (*TYR*), phosphoribosylanthranilate isomerase (*TRP1*) and dopachrome tautomerase (*DCT*) genes, leading to the expression of different enzymes involved in melanin biosynthesis. Melanin acts as a UV-protective shield in the epidermis. ( $G\alpha$ - $\beta$ - $\gamma$  proteins, CREB (cAMP response element binding protein), CBP (CREB-binding protein), CRE (cAMP response elements), c-KIT (tyrosine-protein kinase KIT), SH2 (Src homology 2), GEF (Guanine nucleotide Exchange Factor), MAPK/ERK (extracellular signal-regulated kinases)). This figure was created with [BioRender.com](https://www.biorender.com).

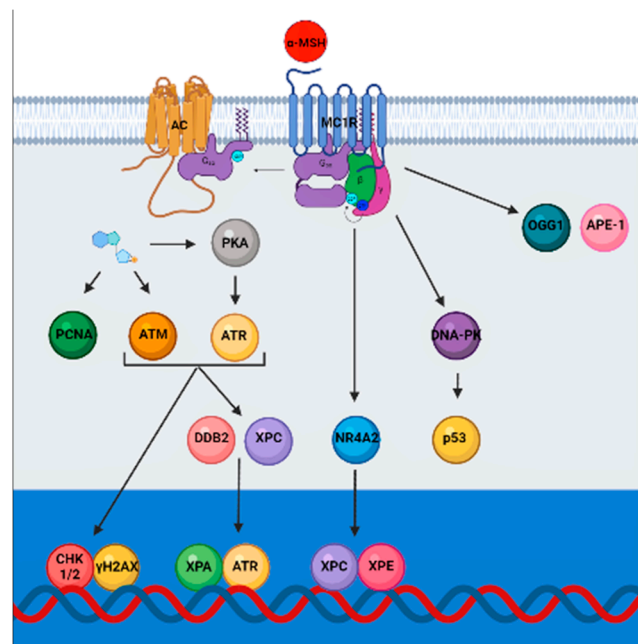
The tyrosine-protein kinase c-KIT also plays a role in pigmentation [48–51]. Binding of the stem cell factor (SCF) to c-KIT induces sequential events [52,53], leading to recruitment of adaptor proteins containing a Src homology 2 (SH2) domain, which will associate with a guanine nucleotide exchange factor (GEF). The SH2/GEF complex activates RAS/RAF/MAPK/ERK cascade which, in turn, activates MITF [54–57] (Figure 1).

Indeed, the functional impairment of MC1R downstream signaling is characterized by prevalent red/yellow pheomelanin. Pheomelanin has weak shielding capacity against UVR relative to eumelanin and has been shown to amplify UVA-induced reactive oxygen species (ROS). Thus, an increased *ratio* of photoprotective eumelanins to pro-oxidant pheomelanins provides an effective shield against mutagenic UVR [58]. Moreover, considering the link existing between  $\alpha$ -MSH and PPAR- $\gamma$  (Peroxisome Proliferator-Activated Receptor  $\gamma$ ), it has been shown that specific PPAR- $\gamma$  modulators provide photoprotective effect in keratinocytes harboring MC1R-inactivating variants [59–61].

### 2.3. MC1R, Non-Pigmentary Functions and DNA Repair

Non-pigmentary functions of MC1R mediated via the  $\alpha$ -MSH/MC1R pathway include modulation of pro-inflammatory cytokines [62], increasing matrix metalloproteases (MMPs), expression of adhesion molecules [63–67], increasing cellular energy production, liver and brown adipose tissue metabolism [67,68] and detoxification of ROS [69–72]. The cAMP pathway, through MITF, also activates the expression of the peroxisome proliferator-activated receptor  $\gamma$  coactivator-1 $\alpha$  (PGC-1 $\alpha$ ), the master regulator of mitochondrial biogenesis [73–75]. Furthermore, MC1R contributes to melanocyte survival through the maintenance of genomic stability [76–78].

UVR includes UVA (320–400 nm) and UVB (290–320 nm), with UVA penetrating deep into the skin, reaching the dermis, inducing pigmentation by oxidation or distribution of pre-existing melanin, and UVB acting at epidermal level, inducing skin pigmentation through increased melanin synthesis [79]. UVR is one of the main DNA-damaging environmental factors [80]. The most predominant damage caused by UVB, eliciting alterations at epidermal level, is covalent linkage between two adjacent pyrimidines, resulting in cyclobutane pyrimidine dimer (CPD) and 6-4 photoproduct (6-4PP). The so-called “UVB signature mutations” are characterized by CT→T and CC→TT transitions [81–85]. UVA, penetrating deeper into the skin, reaching the dermis, induce oxidative stress, producing 7,8-dihydro-8-oxoguanine (8-oxodGuo) DNA damage, resulting in G-C to T-A transversion mutations [86–89]. UVA also efficiently promote photoisomerization of 6-4PPs into Dewar valence isomers [90,91]. Interestingly,  $\alpha$ -MSH levels increase following UVR exposure [23,92–97], therefore contributing to the activation of the downstream signaling, leading to the modulation of the nucleotide excision repair (NER) pathway to enhance genomic stability and melanocytes resistance to UVR-mediated apoptosis [10,98–105]. MC1R activation by  $\alpha$ -MSH triggers cAMP cascade and mediates on one hand the increase in PCNA (proliferating cell nuclear antigen) protein levels and on the other hand the phosphorylation of ATM and ATR (serine/threonine kinases). ATM and ATR, in turns, activate CHK1/2 (checkpoint serine/threonine kinases) [106] and promote the formation of  $\gamma$ H2AX (histone H2Ax) [107,108], leading to the clearance of CPD and 6-4PP photoproducts. Moreover, ATM and ATR mediate the increase in DDB2 (Damage Specific DNA Binding Protein 2) and XPC (xeroderma pigmentosum, complementation group C). Additionally, PKA-dependent ATR phosphorylation, occurring independently from MITF, recruits XPA (xeroderma pigmentosum, complementation group A) to the sites of the photodamage, promoting DNA repair [107–111], together with NR4A2 (Nuclear Receptor Subfamily 4 Group A Member 2), XPC and XPE (xeroderma pigmentosum, complementation group E) [108,112,113] (Figure 2).  $\alpha$ -MSH also enhances the expression of Base excision repair (BER) enzymes OGG1 (8-Oxoguanine DNA Glycosylase) and APE-1 (apurinic/apyrimidinic endonuclease 1) [72], and the phosphorylation of upstream activators of p53, ATR, and DNA-PK (DNA-dependent protein kinase) [72,103]. Activated p53 translocates to the nucleus to induce the expression of *p21* and *GADD45*, contributing to the repair of oxidative DNA damage [103,108,114,115].



**Figure 2.** MC1R signaling promotes genomic stability through NER and BER. MC1R activation induces translocation of NR4A2 to the nucleus where it co-localizes with XPC and XPE at the sites of UV-induced DNA damage. MC1R activation also leads to elevated levels of XPC and  $\gamma$ H2AX, promoting the formation of DNA repair-complexes. Levels of  $\gamma$ H2AX are regulated downstream of ATR and by DNA-PK mediated phosphorylation of p53. In addition, PKA activation promotes the phosphorylation of ATR and ATR complexes with XPA in the nucleus. Following phosphorylation of XPA, the complex translocates to the sites of UV-induced DNA damage.  $\alpha$ -MSH also enhances the expression of OGG1 and APE-1. The cumulative effects is maintenance of genomic stability of melanocytes by activation of nucleotide excision and base excision repair pathways (NER and BER). This figure was created with [BioRender.com](https://www.biorender.com).

### 3. MC1R Polymorphisms

MC1R is a highly polymorphic gene with more than 200 variants described to date [9, 115–117]. Variant alleles including D84E, R142H, R151C, R160W and D294H have been defined as “R” or “RHC” alleles due to their strong association with the red hair color (RHC) phenotype [118]. The V60L, V92M and R163Q variants have a lower association with RHC phenotype and have been therefore designated as “r” alleles [9].

MC1R variants have been associated with a reduced receptor function, impairing the switch of melanin synthesis from eumelanin to the red–yellow pro-oxidant pheomelanin [115,118,119]. MC1R polymorphisms, both RHC and “r”, generate hypomorphic proteins, leading to different degrees of cAMP pathway activation impairment, therefore leading to reduced pigmentary and non-pigmentary MC1R functions, as described in the previous sections [120,121]. Specifically, D84E, R151C and R160W polymorphisms have been related to a decreased cell surface expression [122–124], due to deficient anterograde trafficking or increased desensitization and internalization [18,125,126], while an impaired coupling has been reported for R142H and D294H alleles [122,123,127]. Only a marginal effect of the V92M substitution on cell-surface expression or ability to activate downstream signaling has been reported [122,123].

### 4. Clinical Impact of MC1R Polymorphisms: Hair and Skin Color and Non-Invasive Imaging Features

Considering the pivotal role of MC1R in pigmentation, MC1R status has been proven to have a key role on hair and skin color. Homozygotes, compound heterozygotes as well as heterozygotes for RHC MC1R alleles have been associated with red hair color [128,129]. The V60L variant may act as a partially penetrant recessive allele. However, some indi-

viduals carrying compound heterozygote/homozygote *MC1R* variants do not have red hair. A possible explanation might be that red hair color has also been related to mutations in other genes (i.e., *POMC*) [130]. A dosage effect of *MC1R* variants on hair, as well as skin color, should also be considered, being implicated in different shades of red hair in heterozygotes as compared to homozygotes/compound heterozygotes. There is also evidence for a heterozygote effect on beard hair color, skin type and freckling [128], although an association between *MC1R* RHC polymorphisms and freckles has been demonstrated to be independent of skin and hair color [131]. A dosage effect of *MC1R* variant alleles on sensitivity to UVR has also been described [28]. Accordingly, heterozygotes for one variant allele show an intermediate ability to tan after repeated sun exposure between those with two variant alleles (most likely to be red hair subjects) and those with none of the variants. Therefore, a high frequency of *MC1R* heterozygous allele carriers could influence the skin's response to UVR in most of the population who do not have red hair [132]. As a consequence, those who are homozygous/compound heterozygous for *MC1R* do not only have red hair, but also have pale skin, tan poorly and tend to burn on exposure to UVR, while subjects with pale skin who do not have red hair are more likely to be *MC1R* heterozygotes [128].

Non-invasive skin imaging performed with reflectance confocal microscopy (RCM) and optical coherence tomography (OCT), enabling in vivo evaluation of different layers of the skin, revealed a different dermal microenvironment in photoexposed skin of *MC1R* RHC variants carriers as compared to wild-type (WT) [133], suggesting a correlation between photoaging (aging related to UV exposure) in *MC1R* variant subjects and increased susceptibility to skin cancers [134]. Additionally, as revealed by clinical and daily routine non-invasive dermoscopy of nevi, *MC1R* status has an impact on nevus phenotype and RCM features. In detail, *MC1R* RHC variants carriers have a peculiar nevus phenotype, dermoscopically characterized by reduced structures and lower prevalence of atypical pigment network, visible vessels, dots and globules, and eccentric hyperpigmentation, associated with a high degree of skin freckling [135,136]. In addition, melanoma patients carrying *MC1R* variants as well as *CDKN2A* mutations, show clinically hypopigmented nevi and, at RCM, roundish cells infiltrating the dermo–epidermal junction [137].

## 5. *MC1R* and Skin Cancers Risk

Genome-wide association studies (GWAS) and meta-analyses have widely demonstrated the association of RHC variants with increased risk of melanoma [124,138–141] and NMSCs [71,124,131,142,143]. These associations were initially related to the pigimentary functions of *MC1R*, although many studies confirmed that the increased skin cancer susceptibility in *MC1R* carriers is independent from pigimentary traits [28,71,144–146].

### 5.1. *MC1R* and Melanoma Risk

Darker-pigmented subjects present a significantly higher risk of melanoma associated with *MC1R* variants [71,147–152]. Individuals carrying just one *MC1R* variant have almost 40% increased risk of melanoma, whereas carriers of two or more *MC1R* variants have more than a double risk, as compared to WT subjects [124,153]. In particular, the association of *MC1R* RHC variant alleles D84E, R142H, R151C, R160W and D294H with a direct effect on melanoma risk has been confirmed by several studies and meta-analyses [71,139–141,147,148,154,155]. However, melanoma in RHC individuals shows a significantly higher somatic mutational burden, as compared to melanoma patients without any RHC variants. Intriguingly, C > T and non-C > T were the most common mutations observed across all *MC1R* genotypes [156,157]. This might be related to a decreased protection against UVR damage in RHC carriers, or indicate that other mutational processes occur in melanocytes of these patients. Moreover, the number of *MC1R* variants also correlated positively with increased risk of melanoma development among individuals not showing the RHC phenotype [6,141]. A pooled analysis including 3830 melanoma cases and 2619 controls showed that the presence of any *MC1R* variant had a direct effect on

melanoma, conferring a 60% higher risk to carriers versus non-carriers. Strikingly, considering the pigmentation-mediated effect of *MC1R* on melanoma risk prediction alone, it is smaller with any *MC1R* variant and each of the RHC and r variants [158]. Therefore, *MC1R* variants may partly mediate their effect through biological pathways that are independent of pigmentation and UVR [138–141,151].

A lower incidence and better survival rates for melanoma have been described in female subjects, as compared to males [159]. Interestingly, females carrying an RHC variant tended to exhibit significant lighter phototypes than males with the same *MC1R* genotypes, therefore contributing to different tanning ability between the two sexes.

Furthermore, *MC1R* variants have also been related to melanoma occurring in childhood and adolescents [160–162]. Interestingly, *MC1R* r variants were found to be more prevalent in childhood and adolescent melanoma than in adult ones, especially in patients aged 18 years or younger [163].

### 5.2. *MC1R* and NMSCs Risk

The most common NMSCs in fair-skinned populations are BCC and SCC [164]. UVR is the major environmental risk factor for NMSCs development [165], whereas fair skin and red hair are considered to be the most important phenotype risk factors [166]. Carriers of two *MC1R* variant alleles, mainly RHC variants, have a 2- to 3-fold increased risk of developing NMSCs, as compared to WT [131,153], also independently from phenotype [158].

In a study of 220 individuals (111 at high risk and 109 at low risk of BCC and SCC) in Queensland (area of high UVR), the prevalence of NMSCs was associated with the presence of *MC1R* RHC variant alleles R151C, R160W and D294H, whereas V60L, V92M and R163Q had minimal impact on BCC and SCC risk [167]. These findings were confirmed and extended in a case–control study of Dutch patients, showing the highest relative risks of NMSCs for D84E, H260P carriers, and slightly lower risks for R142H [131]. Data from the M-SKIP Project highlighted the association of *MC1R* variants and NMSCs development risk in populations living in different geographical areas, with a stronger role for darker-pigmented populations [70,124,131,143,168]. Interestingly, subjects with darker skin (skin types III and IV), carrying two *MC1R* variants, showed a lower risk of superficial multifocal BCC compared with *MC1R* variant carriers with lighter skin (skin types I and II), although the number of individuals in the analyzed subgroup was small [131].

The contribution of *MC1R* variants in the pathogenesis of each specific tumor type is not clear yet. Therefore, further investigation in functional studies focused on the carcinogenic mechanisms leading to BCC and SCC is needed [168].

## 6. *MC1R* Association with Melanoma Susceptible Genes

Germline *MC1R* variants may influence the mutational landscape of melanoma [146,156]. Despite the well-established impact of *MC1R* on skin cancer risk and development, the association of *MC1R* variants in combination with mutations in susceptible melanoma genes has not been clarified yet.

### 6.1. *CDKN2A*

An estimated 5–10% of all melanomas are hereditary, and of those, up to 40% are explained by germline mutations in cyclin-dependent kinase inhibitor 2a (*CDKN2A*). *CDKN2A* is the major susceptible gene in multiple primary melanoma patients [146,169]; it acts as a tumor suppressor gene, negatively regulating G1-S cell-cycle progression and promoting cellular senescence. Recently, a role for *CDKN2A* as a negative regulator of cellular oxidative stress has been suggested [170]. The first germline mutations in *CDKN2A* were reported in familial melanoma (V118D, G93W, R79P, N63S, R50Ter, IVS2 + 1 [G–T]) in 1994 [171]. Heterozygous loss of *CDKN2A* is sufficient to confer a 67% lifetime risk of melanoma [172] and it is associated with high inherited risk in melanoma prone families [173–179].

*MC1R* variants have been shown to increase the penetrance of *CDKN2A* mutations (observed risk over time for a mutation carrier), doubling the risk of melanoma development [124,154]. A stratified analysis of transmission of the R151C allele from parents to melanoma-positive offspring suggested that the contribution of the *MC1R* variant to the increased risk is independent of its effect on skin type [180]. Accordingly, a significant joint-effect of RHC variants (R163Q and D294H), considered either alone or in the presence of pigmentation and dysplastic nevi, influenced the penetrance of *CDKN2A* mutations in 20 French melanoma-prone families [181]. Helsing et al. reported that Norwegian melanoma patients showing both *CDKN2A* mutations and *MC1R* variants had an increased risk of melanoma when carrying D84E or R160W variants [182]. Additionally, carriers of A148T mutation of *CDKN2A* in association with non-synonymous *MC1R* variants (V60L, R151C, R160C and R163Q) have a 2- to 6-fold increased risk of melanoma [155,183]. Furthermore, germline carriers of the *CDKN2A p16-Leiden* deletion mutation in a large collection of Dutch families showed an increased risk of melanoma in carriers of *MC1R* variant alleles, with the R151C allele explaining most of this association [184].

In Queensland a *CDKN2A* mutation in association with *MC1R* variants have a raw penetrance of 84%, with a mean age at onset of 37.8 years when compared with family members who carry a *CDKN2A* mutation alone [179]. Accordingly, *CDKN2A* mutation carriers with *MC1R* variants had a significant lower median age at melanoma diagnosis than *CDKN2A* mutation carriers with no *MC1R* variants (37 years versus 47 years) [154,173,185]. Indeed, *CDKN2A* G101W mutation and *MC1R* variants carriers were younger at the first diagnosis with respect to WT multiple melanoma patients, showing hypopigmented nevi and roundish cells infiltrating the junction, suggesting an influence of *CDKN2A* mutation and *MC1R* variants in the development of dysplastic melanocytic lesions [137].

## 6.2. BRAF

Approximately 50% of melanomas harbor *BRAF* mutations. The association of *MC1R* variants with *BRAF* kinase proto-oncogene somatic mutations has been investigated in melanoma, showing different results among several populations.

An association between germline *MC1R* variants and somatic *BRAF* mutations was reported in tumors from United States and Italian populations. Carriers of at least one *MC1R* variant have a 5- to 15-fold increased risk confined only to *BRAF*+ melanomas, regardless the presence of chronic solar damage signs. On the contrary, no association with *BRAF*- melanomas was reported, suggesting that people carrying germline *MC1R* variants have a greater risk of developing a melanoma harboring a *BRAF* mutation without skin photodamage [186,187].

The association of *MC1R* variants (independently from the number of variants [188]) with somatic *BRAF* mutations has not been replicated in Italian [189,190], Spanish [191], German [192], Australian [193] and North Carolina [194] populations. These conflicting findings across different populations have been related to a different distribution of *MC1R* variants among study populations or a risk-modifying effect due to sun exposure.

Interestingly, a negative association between *MC1R* variants and *BRAF* mutations has been described for head/neck melanomas, suggesting a difference in the pathogenesis of melanomas located at different skin sites, head/neck or trunk, which could contribute to their divergent prognoses [195]. Additionally, a low frequency of somatic *BRAF* mutations in RHC and non-RHC *MC1R* carriers was restricted to nodular melanoma [192].

## 6.3. Other Genes

*MC1R* polymorphisms in association with other susceptible genes for melanoma have also been reported. Kosiniak-Kamysz et al. detected significant intermolecular epistasis effects among *MC1R* and *TYR*, *SLC45A2* (solute carrier family 45 member 2) and vitamin D receptor gene (*VDR*), with *MC1R* RHC variants and *TYR* rs1393350 (G > A) showing the highest statistical significance [196]. Only three studies focused on somatic mutations in the *TERT* gene promoter, all of which reported moderate-to-strong positive associations



with *MC1R* variants [189,190,197]. Several genetic interactions of *MC1R* in melanoma also include *ASIP* [198] and X-ray repair cross-complementing protein (*XRCC*) [70].

### 7. *MC1R* Association with NMSCs Susceptible Genes

The association of *MC1R* variants in combination with mutations in susceptible NM-SCs genes has not been investigated so far. The only evidence comes from Liboutet et al. who reported the P1315L mutation frequency in *PTCH* (Protein Patched Homolog 1, component of the hedgehog signaling pathway) not to be significantly different between BCC patients carrying a *MC1R* variant and those that do not carry one, suggesting an independent effect of both genes on BCC risk [199].

Interestingly, interactions between *MC1R* and melanoma susceptibility genes have been investigated, with inconsistent results [199].

However, future studies might be able to find potential correlations between different pathways leading to different great variability in NMSCs' aggressiveness, morphology and response to treatment.

### 8. Epigenetic Regulation of *MC1R*

Epigenetic factors such as DNA-methylation chromatin-remodeling events, as well as gene regulation through non-coding RNAs play an important role in the pathogenesis of skin cancers [200–208]. Interestingly, epigenetic regulation of *MC1R* expression in melanoma has been recently investigated [209]. A methylated CpG-island (CGI) has been identified on a *MC1R* region, proposed as a *MC1R* enhancer. This CGI has been shown to control *MC1R* expression, with a slight trend of increased methylation in melanomas showing homozygous RHC *MC1R*, as compared to WT and heterozygous tumors. Interestingly, unmethylated tumors had a significantly worse prognosis compared to methylated tumors, although the prognostic effect of *MC1R* CGI methylation has not been fully elucidated [209].

Epigenetic interactions have been recently identified in animal studies, showing some biological mechanisms underpinning their induction, such as dietary intake of cysteine, as well as miRNA targeting *MC1R* transcript, which may have an impact on receptor regulation [210,211].

Taken together, these data shed light on the complex regulation of *MC1R* and efforts should be made to fully elucidate epigenetic regulation of the receptor in humans.

### 9. *MC1R* and the Impact of Skin Cancer Genetic Testing

The well-established role of *MC1R* in skin cancer risk, which has been proven to be independent from skin phototype, highlights the importance of this gene in genetic testing and skin cancers' prediction. However, whether the feedback about genetic risk status may contribute to an increased skin cancer awareness, therefore leading to sun avoidance/protection and self-skin examination, and to a reduction of skin cancer risk is currently under debate [212].

A randomized controlled trial enrolling 73 patients with high risk of developing skin cancers was conducted to compare the impact of a strategy of *CDKN2A/MC1R* counseling, giving test results (intervention group), to a strategy of not offering genetic counseling and test results (usual care) on behaviors and skin cancer risk awareness. Patients enrolled were white, mainly females and college-educated. In particular, just one half of the patients were in the interventional group. This study, limited by the number of subjects enrolled and by the fact that just three patients were positive to *CDKN2A/MC1R* mutations/variants, did not show a significant impact of genetic counseling and test results on sun protection behaviors [213]. Another study, a randomized clinical trial by Hay et al., enrolling 499 patients, focused on the interest in and uptake of *MC1R* testing in the general population, after offering information about advantages and disadvantages of the test. Most of the people enrolled were non-Hispanic white, and had a high school diploma or less. Just a few patients were at a high risk for skin cancers, although more than one half of patients experienced sunburns. Interestingly, college-educated non-Hispanic white were significantly

more prone to read information about *MC1R* testing while subjects experiencing sunburns were significantly more likely to request the test [214]. Importantly, a recent study showed that people with lower health literacy skills or education may need support to understand genetic test results, while higher skills were related to reduced distress after receiving the results of *MC1R* testing [215].

This result underlines the importance of personalized education for the correct communication with patients with different skills, in order to avoid the distress that might be related to the knowledge of increased susceptibility to skin cancers based on genetic information. However, the impact of *MC1R* testing on skin cancer awareness and sun avoidance behavior has not been established yet.

Interestingly, previous studies explored the role of *MC1R* as a prognostic marker in metastatic melanoma and as a potential approach for target treatments in skin cancers. A significant correlation between *MC1R* variants and worse outcomes (overall response rate and progression-free survival) in *BRAF*-mutated metastatic melanoma patients treated with target therapy was observed, due to the interactions of *MC1R* with other pathways [216].

Additionally, considering that impaired function of *MC1R* has been related to an increased susceptibility to skin cancers, *MC1R* agonists and antagonists might be employed as a potential therapeutic approach [12,217]. Accordingly, in vitro and animal studies have shown that forskolin, through increasing cAMP levels, induced an improvement in NER function and DNA repair [108,218,219]. Furthermore, regulation of palmitoylation, which has been shown to be reduced in RHC *MC1R*, has been proven to reduce melanoma risk in in vitro and animal models [11,19].

However, *MC1R* has not been employed as a target treatment for skin cancers in humans so far. Currently, an  $\alpha$ -MSH analogue is employed in clinical practice for treating photosensitivity in patients with erythropoietic protoporphyria [220].

Based on the information currently available in the literature, future studies are needed in order to provide data concerning the role of personalized genomic risk, including *MC1R*, with potential clinical impact in terms of early detection, treatment and preventive strategies.

## 10. Conclusions

As knowledge is expanding very rapidly, future directions should be addressed to determine the biological mechanisms underlying non-pigmentary *MC1R* functions, evaluate the gene–gene and gene–environment interactions, and to incorporate *MC1R* variants into melanoma and NMSCs risk prediction models and test their effect on motivating risk-reducing behaviors as a cancer prevention strategy. Additionally, non-invasive skin imaging evaluation, together with genetic studies, might improve the recognition of early skin variations preceding skin tumors' development as well as melanoma and NMSCs' identification and early tumor diagnosis, for a patient-tailored management protocol.

**Author Contributions:** Conceptualization, M.M., S.G. and G.G.; Resources, M.M., S.G. and G.G.; Writing—original draft preparation, M.M., S.G., A.F. and G.G.; Writing—review and editing, M.M., S.G., A.F., L.P., A.A., G.P. and G.G.; Supervision, S.G. and G.G. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. American Cancer Society. *Cancer Facts Figures 2021*; American Cancer Society: Atlanta, GA, USA, 2021.
2. AIOM. *I Numeri del Cancro in Italia*; AIOM: Milan, Italy, 2020.
3. Zanna, P.; Maida, I.; Grieco, C.; Guida, S.; Turpin Sevilla, M.C.; De Summa, S.; Tommasi, S.; Vena, G.A.; Filotico, R.; Guida, G. Three novel human sporadic melanoma cell lines: Signaling pathways controlled by *MC1R*, *BRAF* and  $\beta$ -catenins. *J. Biol. Regul. Homeost. Agents* **2013**, *27*, 131–141. [[PubMed](#)]

4. Guida, S.; De Pace, B.; Ciardo, S.; Farnetani, F.; Pellacani, G. Non-invasive Imaging for Skin Cancers—The European Experience. *Curr. Dermatol. Rep.* **2019**, *8*, 172–181. [[CrossRef](#)]
5. Roberts, M.R.; Asgari, M.M.; Toland, A.E. Genome-wide association studies and polygenic risk scores for skin cancer: Clinically useful yet? *Br. J. Dermatol.* **2019**, *181*, 1146–1155. [[CrossRef](#)]
6. Caini, S.; Gandini, S.; Botta, F.; Tagliabue, E.; Raimondi, S.; Nagore, E.; Zanna, I.; Maisonneuve, P.; Newton-Bishop, J.; Polsky, D.; et al. MC1R variants and cutaneous melanoma risk according to histological type, body site, and Breslow thickness: A pooled analysis from the M-SKIP project. *Melanoma Res.* **2020**, *30*, 500–510. [[CrossRef](#)]
7. Geschwind, I.I. Change in hair color in mice induced by injection of  $\alpha$ -MSH. *Endocrinology* **1966**, *79*, 1165–1167. [[CrossRef](#)]
8. Sawyer, T.K.; Hruby, V.J.; Wilkes, B.C.; Draelos, M.T.; Hadley, M.E.; Bergsneider, M. Comparative Biological Activities of Highly Potent Active-Site Analogues of  $\alpha$ -Melanotropin. *J. Med. Chem.* **1982**, *25*, 1022–1027. [[CrossRef](#)] [[PubMed](#)]
9. García-Borrón, J.C.; Sánchez-Laorden, B.L.; Jiménez-Cervantes, C. Melanocortin-1 receptor structure and functional regulation. *Pigment Cell Res.* **2005**, *18*, 393–410. [[CrossRef](#)] [[PubMed](#)]
10. Wolf Horrell, E.M.; Boulanger, M.C.; D’Orazio, J.A. Melanocortin 1 receptor: Structure, function, and regulation. *Front. Genet.* **2016**, *7*, 95. [[CrossRef](#)]
11. Chen, S.; Zhu, B.; Yin, C.; Liu, W.; Han, C.; Chen, B.; Liu, T.; Li, X.; Chen, X.; Li, C.; et al. Palmitoylation-dependent activation of MC1R prevents melanomagenesis. *Nature* **2017**, *549*, 399–403. [[CrossRef](#)]
12. Guida, S.; Guida, G.; Goding, C.R. MC1R functions, expression and implications for targeted therapy. *J. Investig. Dermatol.* **2021**, in press.
13. Dalziel, M.; Kolesnichenko, M.; Das Neves, R.P.; Iborra, F.; Goding, C.; Furger, A.  $\alpha$ -MSH regulates intergenic splicing of MC1R and TUBB3 in human melanocytes. *Nucleic Acids Res.* **2011**, *39*, 2378–2392. [[CrossRef](#)]
14. Martínez-Vicente, I.; Abrisqueta, M.; Herraiz, C.; Jiménez-Cervantes, C.; García-Borrón, J.C.; Olivares, C. Functional characterization of a C-terminal splice variant of the human melanocortin 1 receptor. *Exp. Dermatol.* **2020**, *29*, 610–615. [[CrossRef](#)]
15. Herraiz, C.; Olivares, C.; Castejón-Griñán, M.; Abrisqueta, M.; Jiménez-Cervantes, C.; García-Borrón, J.C. Functional characterization of MC1R-TUBB3 intergenic splice variants of the human melanocortin 1 receptor. *PLoS ONE* **2015**, *10*, e0144757. [[CrossRef](#)]
16. Herraiz, C.; Sánchez-Laorden, B.L.; Jiménez-Cervantes, C.; García-Borrón, J.C. N-glycosylation of the human melanocortin 1 receptor: Occupancy of glycosylation sequons and functional role. *Pigment Cell Melanoma Res.* **2011**, *24*, 479–489. [[CrossRef](#)] [[PubMed](#)]
17. Sánchez-Laorden, B.L.; Jiménez-Cervantes, C.; García-Borrón, J.C. Regulation of human melanocortin 1 receptor signaling and trafficking by Thr-308 and Ser-316 and its alteration in variant alleles associated with red hair and skin cancer. *J. Biol. Chem.* **2007**, *282*, 3241–3251. [[CrossRef](#)] [[PubMed](#)]
18. Sánchez-Laorden, B.L.; Sánchez-Más, J.; Martínez-Alonso, E.; Martínez-Menárguez, J.A.; García-Borrón, J.C.; Jiménez-Cervantes, C. Dimerization of the human melanocortin 1 receptor: Functional consequences and dominant-negative effects. *J. Investig. Dermatol.* **2006**, *126*, 172–181. [[CrossRef](#)] [[PubMed](#)]
19. Chen, S.; Han, C.; Miao, X.; Li, X.; Yin, C.; Zou, J.; Liu, M.; Li, S.; Stawski, L.; Zhu, B.; et al. Targeting MC1R depalmitoylation to prevent melanomagenesis in redheads. *Nat. Commun.* **2019**, *10*, 877. [[CrossRef](#)] [[PubMed](#)]
20. Sanchez-Más, J.; Hahmann, C.; Gerritsen, I.; Garcia-Borrón, J.C.; Jiménez-Cervantes, C. Agonist-independent, high constitutive activity of the human melanocortin 1 receptor. *Pigment Cell Res.* **2004**, *17*, 386–395. [[CrossRef](#)] [[PubMed](#)]
21. Rouzaud, F.; Annereau, J.P.; Valencia, J.C.; Costin, G.E.; Hearing, V.J. Regulation of melanocortin 1 receptor expression at the mRNA and protein levels by its natural agonist and antagonist. *FASEB J.* **2003**, *17*, 1–21. [[CrossRef](#)]
22. Swope, V.B.; Abdel-Malek, Z.A. Significance of the melanocortin 1 and endothelin B receptors in melanocyte homeostasis and prevention of sun-induced genotoxicity. *Front. Genet.* **2016**, *7*, 146. [[CrossRef](#)] [[PubMed](#)]
23. Funasaka, Y.; Chakraborty, A.K.; Hayashi, Y.; Komoto, M.; Ohashi, A.; Nagahama, M.; Inoue, Y.; Pawelek, J.; Ichihashi, M. Modulation of melanocyte-stimulating hormone receptor expression on normal human melanocytes: Evidence for a regulatory role of ultraviolet B, interleukin-1 $\alpha$ , interleukin-1 $\beta$ , endothelin-1 and tumour necrosis factor- $\alpha$ . *Br. J. Dermatol.* **1998**, *139*, 216–224. [[CrossRef](#)]
24. Scott, M.C.; Suzuki, I.; Abdel-Malek, Z.A. Regulation of the human melanocortin 1 receptor expression in epidermal melanocytes by paracrine and endocrine factors and by ultraviolet radiation. *Pigment Cell Res.* **2002**, *15*, 433–439. [[CrossRef](#)]
25. Aberdam, E.; Bertolotto, C.; Sviderskaya, E.V.; De Thillott, V.; Hemesath, T.J.; Fisher, D.E.; Bennett, D.C.; Ortonne, J.P.; Ballottit, R. Involvement of microphthalmia in the inhibition of melanocyte lineage differentiation and of melanogenesis by agouti signal protein. *J. Biol. Chem.* **1998**, *273*, 19560–19565. [[CrossRef](#)] [[PubMed](#)]
26. Nix, M.A.; Kaelin, C.B.; Ta, T.; Weis, A.; Morton, G.J.; Barsh, G.S.; Millhauser, G.L. Molecular and functional analysis of human  $\beta$ -defensin 3 action at melanocortin receptors. *Chem. Biol.* **2013**, *20*, 784–795. [[CrossRef](#)] [[PubMed](#)]
27. Swope, V.B.; Jameson, J.A.; McFarland, K.L.; Supp, D.M.; Miller, W.E.; McGraw, D.W.; Patel, M.A.; Nix, M.A.; Millhauser, G.L.; Babcock, G.F.; et al. Defining MC1R regulation in human melanocytes by its agonist  $\alpha$ -melanocortin and antagonists agouti signaling protein and B-defensin 3. *J. Investig. Dermatol.* **2012**, *132*, 2255–2262. [[CrossRef](#)] [[PubMed](#)]
28. Scott, M.C.; Wakamatsu, K.; Ito, S.; Kadekaro, A.L.; Kobayashi, N.; Groden, J.; Kavanagh, R.; Takakuwa, T.; Virador, V.; Hearing, V.J.; et al. Human melanocortin 1 receptor variants, receptor function and melanocyte response to UV radiation. *J. Cell Sci.* **2002**, *115*, 2349–2355. [[CrossRef](#)] [[PubMed](#)]

29. Martínez-Esparza, M.; Jimenez-Cervantes, C.; Solano, F.; Lozano, J.A.; Garcia-Borrón, J.C. Mechanisms of melanogenesis inhibition by tumor necrosis factor- $\alpha$  in B16/F10 mouse melanoma cells. *Eur. J. Biochem.* **1998**, *255*, 139–146. [[CrossRef](#)] [[PubMed](#)]
30. Martínez-Esparza, M.; Jiménez-Cervantes, C.; Beermann, F.; Aparicio, P.; Lozano, J.A.; García-Borrón, J.C. Transforming growth factor- $\beta$ 1 inhibits basal melanogenesis in B16/F10 mouse melanoma cells by increasing the rate of degradation of tyrosinase and tyrosinase-related protein-1. *J. Biol. Chem.* **1997**, *272*, 3967–3972. [[CrossRef](#)] [[PubMed](#)]
31. Martínez-Esparza, M.; Solano, F.; García-Borrón, J.C. Independent regulation of tyrosinase by the hypopigmenting cytokines TGF beta1 and TNF  $\alpha$  and the melanogenic hormone  $\alpha$ -MSH in B16 mouse melanocytes. *Cell. Mol. Biol.* **1999**, *45*, 991–1000.
32. Khaled, M.; Levy, C.; Fisher, D.E. Control of melanocyte differentiation by a MITF-PDE4D3 homeostatic circuit. *Genes Dev.* **2010**, *24*, 2276–2281. [[CrossRef](#)]
33. Cao, J.; Wan, L.; Hacker, E.; Dai, X.; Lenna, S.; Jimenez-Cervantes, C.; Wang, Y.; Leslie, N.R.; Xu, G.X.; Widlund, H.R.; et al. MC1R is a potent regulator of PTEN after UV exposure in melanocytes. *Mol. Cell* **2013**, *51*, 409–422. [[CrossRef](#)]
34. Castejón-Griñán, M.; Herraiz, C.; Olivares, C.; Jiménez-Cervantes, C.; García-Borrón, J.C. CAMP-independent non-pigmentary actions of variant melanocortin 1 receptor: AKT-mediated activation of protective responses to oxidative DNA damage. *Oncogene* **2018**, *37*, 3631–3646. [[CrossRef](#)]
35. Pérez-Oliva, A.B.; Olivares, C.; Jiménez-Cervantes, C.; García-Borrón, J. Mahogunin ring finger-1 (MGRN1) E3 ubiquitin ligase inhibits signaling from melanocortin receptor by competition with G $\alpha$ s. *J. Biol. Chem.* **2009**, *284*, 31714–31725. [[CrossRef](#)]
36. Wu, M.; Hemesath, T.J.; Takemoto, C.M.; Horstmann, M.A.; Wells, A.G.; Price, E.R.; Fisher, D.Z.; Fisher, D.E. c-Kit triggers dual phosphorylations, which couple activation and degradation of the essential melanocyte factor Mi. *Genes Dev.* **2000**, *14*, 301–312. [[CrossRef](#)]
37. Sánchez-Más, J.; Guillo, L.A.; Zanna, P.; Jiménez-Cervantes, C.; García-Borrón, J.C. Role of G protein-coupled receptor kinases in the homologous desensitization of the human and mouse melanocortin 1 receptors. *Mol. Endocrinol.* **2005**, *19*, 1035–1048. [[CrossRef](#)]
38. Abrisqueta, M.; Herraiz, C.; Pérez Oliva, A.B.; Sanchez-Laorden, B.L.; Olivares, C.; Jiménez-Cervantes, C.; García-Borrón, J.C. Differential and competitive regulation of human melanocortin 1 receptor signaling by  $\beta$ -arrestin isoforms. *J. Cell Sci.* **2013**, *126*, 3724–3737. [[CrossRef](#)]
39. Levy, C.; Khaled, M.; Fisher, D.E. MITF: Master regulator of melanocyte development and melanoma oncogene. *Trends Mol. Med.* **2006**, *12*, 406–414. [[CrossRef](#)] [[PubMed](#)]
40. Goding, C.R.; Arnheiter, H. Mitf—The first 25 years. *Genes Dev.* **2019**, *33*, 983–1007. [[CrossRef](#)] [[PubMed](#)]
41. Todd, J.R.; Scurr, L.L.; Becker, T.M.; Kefford, R.F.; Rizos, H. The MAPK pathway functions as a redundant survival signal that reinforces the PI3K cascade in c-Kit mutant melanoma. *Oncogene* **2014**, *33*, 236–245. [[CrossRef](#)]
42. Blume-Jensen, P.; Claesson-Welsh, L.; Siegbahn, A.; Zsebo, K.M.; Westermarck Heldin, B.C.H. Activation of the human c-kit product by ligand-induced dimerization mediates circular actin reorganization and chemotaxis. *EMBO J.* **1991**, *10*, 4121–4128. [[CrossRef](#)] [[PubMed](#)]
43. Lev, S.; Yarden, Y.; Givol, D. Dimerization and activation of the kit receptor by monovalent and bivalent binding of the stem cell factor. *J. Biol. Chem.* **1992**, *267*, 15970–15977. [[CrossRef](#)]
44. Luo, D.; Chen, H.; Searles, G.; Jimbow, K. Coordinated mRNA expression of c-kit with tyrosinase and TRP-1 in melanin pigmentation of normal and malignant human melanocytes and transient activation of tyrosinase by kit/SCF-R. *Melanoma Res.* **1995**, *5*, 303–309. [[CrossRef](#)] [[PubMed](#)]
45. Hemesath, T.J.; Price, E.R.; Takemoto, C.; Badalian, T.; Fisher, D.E. MAP kinase links the transcription factor Microphthalmia to c-Kit signalling in melanocytes. *Nature* **1998**, *391*, 298–301. [[CrossRef](#)]
46. Price, E.R.; Ding, H.F.; Badalian, T.; Bhattacharya, S.; Takemoto, C.; Yao, T.P.; Hemesath, T.J.; Fisher, D.E. Lineage-specific signaling in melanocytes. c-Kit stimulation recruits p300/CBP to microphthalmia. *J. Biol. Chem.* **1998**, *273*, 17983–17986. [[CrossRef](#)] [[PubMed](#)]
47. Xu, W.; Gong, L.; Haddad, M.M.; Bischof, O.; Campisi, J.; Yeh, E.T.H.; Medrano, E.E. Regulation of microphthalmia-associated transcription factor MITF protein levels by association with the ubiquitin-conjugating enzyme hUBC9. *Exp. Cell Res.* **2000**, *255*, 135–143. [[CrossRef](#)]
48. Alexeev, V.; Yoon, K. Distinctive role of the cKit receptor tyrosine kinase signaling in mammalian melanocytes. *J. Invest. Dermatol.* **2006**, *126*, 1102–1110. [[CrossRef](#)] [[PubMed](#)]
49. Nishikawa, S.; Kusakabe, M.; Yoshinaga, K.; Ogawa, M.; Hayashi, S.I.; Kunisada, T.; Era, T.; Sakakura, T.; Nishikawa, S.I. In utero manipulation of coat color formation by a monoclonal anti-c-kit antibody: Two distinct waves of c-kit-dependency during melanocyte development. *EMBO J.* **1991**, *10*, 2111–2118. [[CrossRef](#)]
50. Botchkareva, N.V.; Khlgtian, M.; Jack longley, B.; Botchkarev, V.A.; Gilchrest, B.A. SCF/c-kit signaling is required for cyclic regeneration of the hair pigmentation unit. *FASEB J.* **2001**, *15*, 645–658. [[CrossRef](#)]
51. Boissan, M.; Feger, F.; Guillosson, J.J.; Arock, M. c-Kit and c-kit mutations in mastocytosis and other hematological diseases. *J. Leukoc. Biol.* **2000**, *67*, 135–148. [[CrossRef](#)] [[PubMed](#)]
52. Philo, J.S.; Wen, J.; Wypych, J.; Schwartz, M.G.; Mendiaz, E.A.; Langley, K.E. Human stem cell factor dimer forms a complex with two molecules of the extracellular domain of its receptor, Kit. *J. Biol. Chem.* **1996**, *271*, 6895–6902. [[CrossRef](#)]
53. Lemmon, M.A.; Pinchasi, D.; Zhou, M.; Lax, I.; Schlessinger, J. Kit receptor dimerization is driven by bivalent binding of stem cell factor. *J. Biol. Chem.* **1997**, *272*, 6311–6317. [[CrossRef](#)]

54. Kitamura, Y.; Hirota, S. Kit as a human oncogenic tyrosine kinase. *Cell. Mol. Life Sci.* **2004**, *61*, 2924–2931. [[CrossRef](#)]
55. Kuang, D.; Zhao, X.; Xiao, G.; Ni, J.; Feng, Y.; Wu, R.; Wang, G. Stem cell factor/c-kit signaling mediated cardiac stem cell migration via activation of p38 MAPK. *Basic Res. Cardiol.* **2008**, *103*, 265–273. [[CrossRef](#)]
56. Liang, J.; Wu, Y.L.; Chen, B.J.; Zhang, W.; Tanaka, Y.; Sugiyama, H. The C-Kit receptor-mediated signal transduction and tumor-related diseases. *Int. J. Biol. Sci.* **2013**, *9*, 435–443. [[CrossRef](#)] [[PubMed](#)]
57. Herraiz, C.; Journé, F.; Abdel-Malek, Z.; Ghanem, G.; Jiménez-Cervantes, C.; García-Borrón, J.C. Signaling from the human melanocortin 1 receptor to ERK1 and ERK2 mitogen-activated protein kinases involves transactivation of cKIT. *Mol. Endocrinol.* **2011**, *25*, 138–156. [[CrossRef](#)] [[PubMed](#)]
58. Maresca, V.; Flori, E.; Picardo, M. Skin phototype: A new perspective. *Pigment Cell Melanoma Res.* **2015**, *28*, 378–389. [[CrossRef](#)] [[PubMed](#)]
59. Flori, E.; Mastrofrancesco, A.; Kovacs, D.; Bellei, B.; Briganti, S.; Maresca, V.; Cardinali, G.; Picardo, M. The activation of PPAR $\gamma$  by 2,4,6-Octatrienoic acid protects human keratinocytes from UVR-induced damages. *Sci. Rep.* **2017**, *7*, 9241. [[CrossRef](#)]
60. Flori, E.; Rosati, E.; Cardinali, G.; Kovacs, D.; Bellei, B.; Picardo, M.; Maresca, V. The  $\alpha$ -melanocyte stimulating hormone/peroxisome proliferator activated receptor- $\gamma$  pathway down-regulates proliferation in melanoma cell lines. *J. Exp. Clin. Cancer Res.* **2017**, *36*, 142. [[CrossRef](#)]
61. Herraiz, C.; Martínez-Vicente, I.; Maresca, V. The  $\alpha$ -melanocyte-stimulating hormone/melanocortin-1 receptor interaction: A driver of pleiotropic effects beyond pigmentation. *Pigment Cell Melanoma Res.* **2021**, *34*, 748–761. [[CrossRef](#)]
62. Hill, R.P.; MacNeil, S.; Haycock, J.W. Melanocyte stimulating hormone peptides inhibit TNF- $\alpha$  signaling in human dermal fibroblast cells. *Peptides* **2006**, *27*, 421–430. [[CrossRef](#)]
63. Slominski, A.; Wortsman, J. Neuroendocrinology of the skin. *Endocr. Rev.* **2000**, *21*, 457–487. [[CrossRef](#)]
64. Slominski, A.; Fischer, T.W.; Zmijewski, M.A.; Wortsman, J.; Semak, I.; Zbytek, B.; Slominski, R.M.; Tobin, D.J. On the role of melatonin in skin physiology and pathology. *Endocrine* **2005**, *27*, 137–148. [[CrossRef](#)]
65. Carreira, S.; Goodall, J.; Denat, L.; Rodriguez, M.; Nuciforo, P.; Hoek, K.S.; Testori, A.; Larue, L.; Goding, C.R. Mitf regulation of Dia1 controls melanoma proliferation and invasiveness. *Genes Dev.* **2006**, *20*, 3426–3439. [[CrossRef](#)]
66. Giuliano, S.; Cheli, Y.; Ohanna, M.; Bonet, C.; Beuret, L.; Bille, K.; Loubat, A.; Hofman, V.; Hofman, P.; Ponzio, G.; et al. Microphthalmia-associated transcription factor controls the DNA damage response and a lineage-specific senescence program in melanomas. *Cancer Res.* **2010**, *70*, 3813–3822. [[CrossRef](#)] [[PubMed](#)]
67. Vivas-García, Y.; Falletta, P.; Liebing, J.; Louphrasitthiphol, P.; Feng, Y.; Chauhan, J.; Scott, D.A.; Glodde, N.; Chocarro-Calvo, A.; Bonham, S.; et al. Lineage-Restricted Regulation of SCD and Fatty Acid Saturation by MITF Controls Melanoma Phenotypic Plasticity. *Mol. Cell* **2020**, *77*, 120–137.e9. [[CrossRef](#)] [[PubMed](#)]
68. Louphrasitthiphol, P.; Ledaki, I.; Chauhan, J.; Falletta, P.; Siddaway, R.; Buffa, F.M.; Mole, D.R.; Soga, T.; Goding, C.R. MITF controls the TCA cycle to modulate the melanoma hypoxia response. *Pigment Cell Melanoma Res.* **2019**, *32*, 792–808. [[CrossRef](#)]
69. Abdel-Malek, Z.A.; Ruwe, A.; Kavanagh-Starnes, R.; Kadekaro, A.L.; Swope, V.; Haskell-Luevano, C.; Koikov, L.; Knittel, J.J.  $\alpha$ -MSH tripeptide analogs activate the melanocortin 1 receptor and reduce UV-induced DNA damage in human melanocytes. *Pigment Cell Melanoma Res.* **2009**, *22*, 635–644. [[CrossRef](#)]
70. Scherer, D.; Bermejo, J.L.; Rudnai, P.; Gurzau, E.; Koppova, K.; Hemminki, K.; Kumar, R. MC1R variants associated susceptibility to basal cell carcinoma of skin: Interaction with host factors and XRCC3 polymorphism. *Int. J. Cancer* **2008**, *122*, 1787–1793. [[CrossRef](#)] [[PubMed](#)]
71. Kennedy, C.; Ter Huurne, J.; Berkhout, M.; Gruis, N.; Bastiaens, M.; Bergman, W.; Willemze, R.; Bouwes Bavinck, J.N. Melanocortin 1 receptor (MC1R) gene variants are associated with an increased risk for cutaneous melanoma which is largely independent of skin type and hair color. *J. Investig. Dermatol.* **2001**, *117*, 294–300. [[CrossRef](#)]
72. Kadekaro, A.L.; Chen, J.; Yang, J.; Chen, S.; Jameson, J.; Swope, V.B.; Cheng, T.; Kadakia, M.; Abdel-Malek, Z.  $\alpha$ -melanocyte-stimulating hormone suppresses oxidative stress through a p53-mediated signaling pathway in human melanocytes. *Mol. Cancer Res.* **2012**, *10*, 778–786. [[CrossRef](#)]
73. Ferretta, A.; Maida, I.; Guida, S.; Azzariti, A.; Porcelli, L.; Tommasi, S.; Zanna, P.; Cocco, T.; Guida, M.; Guida, G. New insight into the role of metabolic reprogramming in melanoma cells harboring BRAF mutations. *Biochim. Biophys. Acta—Mol. Cell Res.* **2016**, *1863*, 2710–2718. [[CrossRef](#)]
74. Vazquez, F.; Lim, J.H.; Chim, H.; Bhalla, K.; Girnun, G.; Pierce, K.; Clish, C.B.; Granter, S.R.; Widlund, H.R.; Spiegelman, B.M.; et al. PGC1 $\alpha$  Expression Defines a Subset of Human Melanoma Tumors with Increased Mitochondrial Capacity and Resistance to Oxidative Stress. *Cancer Cell* **2013**, *23*, 287–301. [[CrossRef](#)]
75. Haq, R.; Shoag, J.; Andreu-Perez, P.; Yokoyama, S.; Edelman, H.; Rowe, G.C.; Frederick, D.T.; Hurley, A.D.; Nellore, A.; Kung, A.L.; et al. Oncogenic BRAF regulates oxidative metabolism via PGC1 $\alpha$  and MITF. *Cancer Cell* **2013**, *23*, 302–315. [[CrossRef](#)] [[PubMed](#)]
76. Ganesan, A.; Hanawalt, P. Photobiological Origins of the Field of Genomic Maintenance. *Photochem. Photobiol.* **2016**, *92*, 52–60. [[CrossRef](#)] [[PubMed](#)]
77. Mao, P.; Wyrick, J.J.; Roberts, S.A.; Smerdon, M.J. UV-Induced DNA Damage and Mutagenesis in Chromatin. *Photochem. Photobiol.* **2017**, *93*, 216–228. [[CrossRef](#)]
78. Cadet, J.; Douki, T. Formation of UV-induced DNA damage contributing to skin cancer development. *Photochem. Photobiol. Sci.* **2018**, *17*, 1816–1841. [[CrossRef](#)]

79. Wolber, R.; Schlenz, K.; Wakamatsu, K.; Smuda, C.; Nakanishi, Y.; Hearing, V.J.; Ito, S. Pigmentation effects of solar-simulated radiation as compared with UVA and UVB radiation. *Pigment Cell Melanoma Res.* **2008**, *21*, 487–491. [[CrossRef](#)]
80. Strzałka, W.; Zgłobicki, P.; Kowalska, E.; Bažant, A.; Dziga, D.; Banaś, A.K. The dark side of uv-induced DNA lesion repair. *Genes* **2020**, *11*, 1450. [[CrossRef](#)] [[PubMed](#)]
81. Besaratinia, A.; Yoon, J.; Schroeder, C.; Bradforth, S.E.; Cockburn, M.; Pfeifer, G.P. Wavelength dependence of ultraviolet radiation-induced DNA damage as determined by laser irradiation suggests that cyclobutane pyrimidine dimers are the principal DNA lesions produced by terrestrial sunlight. *FASEB J.* **2011**, *25*, 3079–3091. [[CrossRef](#)] [[PubMed](#)]
82. You, Y.H.; Lee, D.H.; Yoon, J.H.; Nakajima, S.; Yasui, A.; Pfeifer, G.P. Cyclobutane Pyrimidine Dimers Are Responsible for the Vast Majority of Mutations Induced by UVB Irradiation in Mammalian Cells. *J. Biol. Chem.* **2001**, *276*, 44688–44694. [[CrossRef](#)] [[PubMed](#)]
83. Jackson, S.P.; Bartek, J. The DNA-damage response in human biology and disease. *Nature* **2009**, *461*, 1071–1078. [[CrossRef](#)] [[PubMed](#)]
84. Wei, X.; Walia, V.; Lin, J.C.; Teer, J.K.; Prickett, T.D.; Gartner, J.; Davis, S.; Stemke-Hale, K.; Davies, M.A.; Gershenwald, J.E.; et al. Exome sequencing identifies GRIN2A as frequently mutated in melanoma. *Nat. Genet.* **2011**, *43*, 442–446. [[CrossRef](#)]
85. Pleasance, E.D.; Cheetham, R.K.; Stephens, P.J.; McBride, D.J.; Humphray, S.J.; Greenman, C.D.; Varela, I.; Lin, M.L.; Ordóñez, G.R.; Bignell, G.R.; et al. A comprehensive catalogue of somatic mutations from a human cancer genome. *Nature* **2010**, *463*, 191–196. [[CrossRef](#)] [[PubMed](#)]
86. Noonan, F.P.; Zaidi, M.R.; Wolnicka-Glubisz, A.; Anver, M.R.; Bahn, J.; Wielgus, A.; Cadet, J.; Douki, T.; Mouret, S.; Tucker, M.A.; et al. Melanoma induction by ultraviolet A but not ultraviolet B radiation requires melanin Pigment. *Nat. Commun.* **2012**, *3*, 884. [[CrossRef](#)]
87. Beani, J.C. Ultraviolet A-induced DNA damage: Role in skin cancer. *Bull. Acad. Natl. Med.* **2014**, *198*, 273–295. [[CrossRef](#)] [[PubMed](#)]
88. Kvam, E.; Tyrrell, R.M. The role of melanin in the induction of oxidative DNA base damage by ultraviolet A irradiation of DNA or melanoma cells. *J. Investig. Dermatol.* **1999**, *113*, 209–213. [[CrossRef](#)]
89. Bachelor, M.A.; Bowden, G.T. UVA-mediated activation of signaling pathways involved in skin tumor promotion and progression. *Semin. Cancer Biol.* **2004**, *14*, 131–138. [[CrossRef](#)]
90. Cadet, J.; Sage, E.; Douki, T. Ultraviolet radiation-mediated damage to cellular DNA. *Mutat. Res./Fundam. Mol. Mech. Mutagen.* **2005**, *571*, 3–17. [[CrossRef](#)]
91. Cadet, J.; Grand, A.; Douki, T. Solar uv radiation-induced DNA bipyrimidine photoproducts: Formation and mechanistic insights. *Top. Curr. Chem.* **2015**, *356*, 249–275. [[CrossRef](#)]
92. Kadekaro, A.L.; Kavanagh, R.; Kanto, H.; Terzieva, S.; Hauser, J.; Kobayashi, N.; Schwemberger, S.; Cornelius, J.; Babcock, G.; Shertzer, H.G.; et al.  $\alpha$ -melanocortin and endothelin-1 activate antiapoptotic pathways and reduce DNA damage in human melanocytes. *Cancer Res.* **2005**, *65*, 4292–4299. [[CrossRef](#)]
93. Chakraborty, A.K.; Funasaka, Y.; Pawelek, J.M.; Nagahama, M.; Ito, A.; Ichihashi, M. Enhanced expression of melanocortin-1 receptor (MC1-R) in normal human keratinocytes during differentiation: Evidence for increased expression of POMC peptides near suprabasal layer of epidermis. *J. Investig. Dermatol.* **1999**, *112*, 853–860. [[CrossRef](#)] [[PubMed](#)]
94. Corre, S.; Primot, A.; Sviderskaya, E.; Bennett, D.C.; Vaulont, S.; Goding, C.R.; Galibert, M.D. UV-induced expression of key component of the tanning process, the POMC and MC1R genes, is dependent on the p-38-activated upstream stimulating factor-1 (USF-1). *J. Biol. Chem.* **2004**, *279*, 51226–51233. [[CrossRef](#)] [[PubMed](#)]
95. Schiller, M.; Brzoska, T.; Böhm, M.; Metz, D.; Scholzen, T.E.; Rougier, A.; Luger, T.A. Solar-Simulated Ultraviolet Radiation-Induced Upregulation of the Melanocortin-1 Receptor, Proopiomelanocortin, and  $\alpha$ -Melanocyte-Stimulating Hormone in Human Epidermis In Vivo. *J. Investig. Dermatol.* **2004**, *122*, 468–476. [[CrossRef](#)]
96. Chakraborty, A.K.; Funasaka, Y.; Slominski, A.; Ermak, G.; Hwang, J.; Pawelek, J.M.; Ichihashi, M. Production and release of proopiomelanocortin (POMC) derived peptides by human melanocytes and keratinocytes in culture: Regulation by ultraviolet B. *Biochim. Biophys. Acta—Mol. Cell Res.* **1996**, *1313*, 130–138. [[CrossRef](#)]
97. Im, S.; Moro, O.; Peng, F.; Medrano, E.E.; Cornelius, J.; Babcock, G.; Nordlund, J.J.; Abdel-Malek, Z.A. Activation of the cyclic AMP pathway by  $\alpha$ -melanotropin mediates the response of human melanocytes to ultraviolet B radiation. *Cancer Res.* **1998**, *58*, 47–54. [[PubMed](#)]
98. Kadekaro, A.L.; Wakamatsu, K.; Ito, S.; Abdel-Malek, Z.A. Cutaneous photoprotection and melanoma susceptibility: Reaching beyond melanin content to the frontiers of DNA repair. *Front. Biosci.* **2006**, *11*, 2157–2173. [[CrossRef](#)] [[PubMed](#)]
99. Schäfer, O.D. Nucleotide excision repair in Eukaryotes. *Cold Spring Harb. Perspect. Biol.* **2013**, *5*, a012609. [[CrossRef](#)]
100. Sugawara, K. Molecular mechanisms of DNA damage recognition for mammalian nucleotide excision repair. *DNA Repair* **2016**, *44*, 110–117. [[CrossRef](#)]
101. Gillet, L.C.J.; Schäfer, O.D. Molecular mechanisms of mammalian global genome nucleotide excision repair. *Chem. Rev.* **2006**, *106*, 253–276. [[CrossRef](#)]
102. Spivak, G. Nucleotide excision repair in humans. *DNA Repair* **2015**, *36*, 13–18. [[CrossRef](#)]
103. Swope, V.; Alexander, C.; Starner, R.; Schwemberger, S.; Babcock, G.; Abdel-Malek, Z.A. Significance of the melanocortin 1 receptor in the DNA damage response of human melanocytes to ultraviolet radiation. *Pigment Cell Melanoma Res.* **2014**, *27*, 601–610. [[CrossRef](#)]

104. Maddodi, N.; Setaluri, V. Role of UV in cutaneous melanoma. *Photochem. Photobiol.* **2008**, *84*, 528–536. [[CrossRef](#)]
105. Li, X.; Mao, W.; Chen, J.; Goding, C.R.; Cui, R.; Xu, Z.X.; Miao, X. The protective role of MC1R in chromosome stability and centromeric integrity in melanocytes. *Cell Death Discov.* **2021**, *7*, 1–9. [[CrossRef](#)] [[PubMed](#)]
106. Smith, H.L.; Southgate, H.; Tweddle, D.A.; Curtin, N.J. DNA damage checkpoint kinases in cancer. *Expert Rev. Mol. Med.* **2020**, *22*, e2. [[CrossRef](#)] [[PubMed](#)]
107. Scully, R.; Xie, A. Double strand break repair functions of histone H2AX. *Mutat. Res./Fundam. Mol. Mech. Mutagen.* **2013**, *750*, 5–14. [[CrossRef](#)]
108. Jarrett, S.G.; Horrell, E.M.W.; Christian, P.A.; Vanover, J.C.; Boulanger, M.C.; Zou, Y.; D'Orazio, J.A. PKA-Mediated Phosphorylation of ATR Promotes Recruitment of XPA to UV-Induced DNA Damage. *Mol. Cell* **2014**, *54*, 999–1011. [[CrossRef](#)] [[PubMed](#)]
109. Matsumoto, S.; Fischer, E.S.; Yasuda, T.; Dohmae, N.; Iwai, S.; Mori, T.; Nishi, R.; Yoshino, K.I.; Sakai, W.; Hanaoka, F.; et al. Functional regulation of the DNA damage-recognition factor DDB2 by ubiquitination and interaction with xeroderma pigmentosum group C protein. *Nucleic Acids Res.* **2015**, *43*, 1700–1713. [[CrossRef](#)] [[PubMed](#)]
110. Cleaver, J.E. Cancer in xeroderma pigmentosum and related disorders of DNA repair. *Nat. Rev. Cancer* **2005**, *5*, 564–573. [[CrossRef](#)]
111. Puumalainen, M.R.; Rùthemann, P.; Min, J.H.; Naegeli, H. Xeroderma pigmentosum group C sensor: Unprecedented recognition strategy and tight spatiotemporal regulation. *Cell. Mol. Life Sci.* **2016**, *73*, 547–566. [[CrossRef](#)]
112. Smith, A.G.; Luk, N.; Newton, R.A.; Roberts, D.W.; Sturm, R.A.; Muscat, G.E.O. Melanocortin-1 receptor signaling markedly induces the expression of the NR4A nuclear receptor subgroup in melanocytic cells. *J. Biol. Chem.* **2008**, *283*, 12564–12570. [[CrossRef](#)]
113. Jagirdar, K.; Yin, K.; Harrison, M.; Lim, W.; Muscat, G.E.O.; Sturm, R.A.; Smith, A.G. The NR4A2 nuclear receptor is recruited to novel nuclear foci in response to UV irradiation and participates in nucleotide excision repair. *PLoS ONE* **2013**, *8*, e78075. [[CrossRef](#)]
114. Abdel-Malek, Z.A.; Swope, V.B.; Starner, R.J.; Koikov, L.; Cassidy, P.; Leachman, S. Melanocortins and the melanocortin 1 receptor, moving translationally towards melanoma prevention. *Arch. Biochem. Biophys.* **2014**, *563*, 4–12. [[CrossRef](#)] [[PubMed](#)]
115. Beaumont, K.A.; Liu, Y.Y.; Sturm, R.A. Chapter 4 The Melanocortin-1 Receptor Gene Polymorphism and Association with Human Skin Cancer. *Prog. Mol. Biol. Transl. Sci.* **2009**, *88*, 85–153. [[CrossRef](#)]
116. Gerstenblith, M.R.; Goldstein, A.M.; Fargnoli, M.C.; Peris, K.; Landi, M.T. Comprehensive evaluation of allele frequency differences of MC1R variants across populations. *Hum. Mutat.* **2007**, *28*, 495–505. [[CrossRef](#)] [[PubMed](#)]
117. Oliva, A.B.P.; Fernández, L.P.; de Torre, C.; Herráiz, C.; Martínez-Escribano, J.A.; Benítez, J.; Teruel, J.A.L.; Garcia-Borrón, J.C.; Jiménez-Cervantes, C.; Ribas, G. Identification and functional analysis of novel variants of the human melanocortin 1 receptor found in melanoma patients. *Hum. Mutat.* **2009**, *30*, 811–822. [[CrossRef](#)] [[PubMed](#)]
118. Valverde, P.; Healy, E.; Jackson, I.J.; Rees, J.L.; Thody, A.J. Variants of the melanocyte-stimulating hormone receptor gene are associated with red hair and fair skin in humans. *Nat. Genet.* **1995**, *11*, 328–330. [[CrossRef](#)] [[PubMed](#)]
119. Box, N.F.; Wyeth, J.R.; O'Gorman, L.E.; Martin, N.G.; Sturm, R.A. Characterization of melanocyte stimulating hormone receptor variant alleles in twins with red hair. *Hum. Mol. Genet.* **1997**, *6*, 1891–1897. [[CrossRef](#)] [[PubMed](#)]
120. Frändberg, P.-A.; Doufexis, M.; Kapas, S.; Chhajlani, V. Human pigmentation phenotype: A point mutation generates nonfunctional MSH receptor. *Biochem. Biophys. Res. Commun.* **1998**, *245*, 490–492. [[CrossRef](#)]
121. Herraiz, C.; Garcia-Borrón, J.C.; Jiménez-Cervantes, C.; Olivares, C. MC1R signaling. Intracellular partners and pathophysiological implications. *Biochim. Biophys. Acta. Mol. Basis Dis.* **2017**, *1863*, 2448–2461. [[CrossRef](#)]
122. Beaumont, K.A.; Shekar, S.L.; Newton, R.A.; James, M.R.; Stow, J.L.; Duffy, D.L.; Sturm, R.A. Receptor function, dominant negative activity and phenotype correlations for MC1R variant alleles. *Hum. Mol. Genet.* **2007**, *16*, 2249–2260. [[CrossRef](#)]
123. Herraiz, C.; Journé, F.; Ghanem, G.; Jiménez-Cervantes, C.; García-Borrón, J.C. Functional status and relationships of melanocortin 1 receptor signaling to the cAMP and extracellular signal-regulated protein kinases 1 and 2 pathways in human melanoma cells. *Int. J. Biochem. Cell Biol.* **2012**, *44*, 2244–2252. [[CrossRef](#)]
124. Pasquali, E.; García-Borrón, J.C.; Fargnoli, M.C.; Gandini, S.; Maisonneuve, P.; Bagnardi, V.; Specchia, C.; Liu, F.; Kayser, M.; Nijsten, T.; et al. MC1R variants increased the risk of sporadic cutaneous melanoma in darker-pigmented Caucasians: A pooled-analysis from the M-SKIP project. *Int. J. Cancer* **2015**, *136*, 618–631. [[CrossRef](#)]
125. Beaumont, K.A.; Newton, R.A.; Smit, D.J.; Leonard, J.H.; Stow, J.L.; Sturm, R.A. Altered cell surface expression of human MC1R variant receptor alleles associated with red hair and skin cancer risk. *Hum. Mol. Genet.* **2005**, *14*, 2145–2154. [[CrossRef](#)]
126. Sánchez-Laorden, B.L.; Sánchez-Más, J.; Turpín, M.C.; García-Borrón, J.C.; Jiménez-Cervantes, C. Variant amino acids in different domains of the human melanocortin 1 receptor impair cell surface expression. *Cell. Mol. Biol.* **2006**, *52*, 39–46. [[CrossRef](#)]
127. Schiöth, H.B.; Phillips, S.R.; Rudzish, R.; Birch-Machin, M.A.; Wikberg, J.E.S.; Rees, J.L. Loss of function mutations of the human melanocortin 1 receptor are common and are associated with red hair. *Biochem. Biophys. Res. Commun.* **1999**, *260*, 488–491. [[CrossRef](#)] [[PubMed](#)]
128. Flanagan, N.; Healy, E.; Ray, A.; Philips, S.; Todd, C.; Jackson, I.J.; Birch-Machin, M.A.; Rees, J.L. Pleiotropic effects of the melanocortin 1 receptor (MC1R) gene on human pigmentation. *Hum. Mol. Genet.* **2000**, *9*, 2531–2537. [[CrossRef](#)]
129. Morgan, M.D.; Pairo-Castineira, E.; Rawlik, K.; Canela-Xandri, O.; Rees, J.; Sims, D.; Tenesa, A.; Jackson, I.J. Genome-wide study of hair colour in UK Biobank explains most of the SNP heritability. *Nat. Commun.* **2018**, *9*, 1–10. [[CrossRef](#)] [[PubMed](#)]
130. Rees, J.L. The melanocortin 1 receptor (MC1R): More than just red hair. *Pigment Cell Res.* **2000**, *13*, 135–140. [[CrossRef](#)]

131. Bastiaens, M.T.; Ter Huurne, J.A.C.; Kielich, C.; Gruis, N.A.; Westendorp, R.G.J.; Vermeer, B.J.; Bavinck, J.N.B.; Van Amsterdam, N.; Bergman, W.; Berkhout, M.; et al. Melanocortin-1 receptor gene variants determine the risk of nonmelanoma skin cancer independently of fair skin and red hair. *Am. J. Hum. Genet.* **2001**, *68*, 884–894. [[CrossRef](#)]
132. Healy, E.; Flannagan, N.; Ray, A.; Todd, C.; Jackson, I.J.; Matthews, J.N.S.; Birch-Machin, M.A.; Rees, J.L. Melanocortin-1-receptor gene and sun sensitivity in individuals without red hair. *Lancet* **2000**, *355*, 1072–1073. [[CrossRef](#)]
133. Guida, S.; Ciardo, S.; De Pace, B.; De Carvalho, N.; Peccerillo, F.; Manfredini, M.; Farnetani, F.; Chester, J.; Kaleci, S.; Manganelli, M.; et al. The influence of MC1R on dermal morphological features of photo-exposed skin in women revealed by reflectance confocal microscopy and optical coherence tomography. *Exp. Dermatol.* **2019**, *28*, 1321–1327. [[CrossRef](#)] [[PubMed](#)]
134. Guida, S.; Ciardo, S.; De Pace, B.; De Carvalho, N.; Farnetani, F.; Pezzini, C.; Chester, J.; Shaniko, K.; Manganelli, M.; Guida, G.; et al. Atrophic and hypertrophic skin photoaging and melanocortin-1 receptor (MC1R): The missing link. *J. Am. Acad. Dermatol.* **2021**, *84*, 187–190. [[CrossRef](#)] [[PubMed](#)]
135. Fargnoli, M.C.; Sera, F.; Suppa, M.; Piccolo, D.; Landi, M.T.; Chiarugi, A.; Pellegrini, C.; Seidenari, S.; Peris, K. Dermoscopic features of cutaneous melanoma are associated with clinical characteristics of patients and tumours and with MC1R genotype. *J. Eur. Acad. Dermatol. Venereol.* **2014**, *28*, 1768–1775. [[CrossRef](#)] [[PubMed](#)]
136. Vallone, M.G.; Tell-Marti, G.; Potrony, M.; Rebollo-Morell, A.; Badenas, C.; Puig-Butille, J.A.; Gimenez-Xavier, P.; Carrera, C.; Malvey, J.; Puig, S. Melanocortin 1 receptor (MC1R) polymorphisms' influence on size and dermoscopic features of nevi. *Pigment Cell Melanoma Res.* **2018**, *31*, 39–50. [[CrossRef](#)]
137. Bassoli, S.; Maurichi, A.; Rodolfo, M.; Casari, A.; Frigerio, S.; Pupelli, G.; Farnetani, F.; Pelosi, G.; Santinami, M.; Pellacani, G. CDKN2A and MC1R variants influence dermoscopic and confocal features of benign melanocytic lesions in multiple melanoma patients. *Exp. Dermatol.* **2013**, *22*, 411–416. [[CrossRef](#)] [[PubMed](#)]
138. Amos, C.I.; Wang, L.-E.; Lee, J.E.; Gershenwald, J.E.; Chen, W.V.; Fang, S.; Kosoy, R.; Zhang, M.; Qureshi, A.A.; Vattathil, S.; et al. Genome-wide association study identifies novel loci predisposing to cutaneous melanoma. *Hum. Mol. Genet.* **2011**, *20*, 5012–5023. [[CrossRef](#)]
139. Chatzinasiou, F.; Lill, C.M.; Kypreou, K.; Stefanaki, I.; Nicolaou, V.; Spyrou, G.; Evangelou, E.; Roehr, J.T.; Kodela, E.; Katsambas, A.; et al. Comprehensive field synopsis and systematic meta-analyses of genetic association studies in cutaneous melanoma. *J. Natl. Cancer Inst.* **2011**, *103*, 1227–1235. [[CrossRef](#)]
140. Raimondi, S.; Sera, F.; Gandini, S.; Iodice, S.; Caini, S.; Maisonneuve, P.; Fargnoli, M.C. MC1R variants, melanoma and red hair color phenotype: A meta-analysis. *Int. J. Cancer* **2008**, *122*, 2753–2760. [[CrossRef](#)]
141. Williams, P.F.; Olsen, C.M.; Hayward, N.K.; Whiteman, D.C. Melanocortin 1 receptor and risk of cutaneous melanoma: A meta-analysis and estimates of population burden. *Int. J. Cancer* **2011**, *129*, 1730–1740. [[CrossRef](#)]
142. Dwyer, T.; Stankovich, J.M.; Blizzard, L.; FitzGerald, L.M.; Dickinson, J.L.; Reilly, A.; Williamson, J.; Ashbolt, R.; Berwick, M.; Sale, M.M. Does the addition of information on genotype improve prediction of the risk of melanoma and nonmelanoma skin cancer beyond that obtained from skin phenotype? *Am. J. Epidemiol.* **2004**, *159*, 826–833. [[CrossRef](#)]
143. Han, J.; Kraft, P.; Colditz, G.A.; Wong, J.; Hunter, D.J. Melanocortin 1 receptor variants and skin cancer risk. *Int. J. Cancer* **2006**, *119*, 1976–1984. [[CrossRef](#)] [[PubMed](#)]
144. Palmer, J.S.; Duffy, D.L.; Box, N.F.; Aitken, J.F.; O’Gorman, L.E.; Green, A.C.; Hayward, N.K.; Martin, N.G.; Sturm, R.A. Melanocortin-1 receptor polymorphisms and risk of melanoma: Is the association explained solely by pigmentation phenotype? *Am. J. Hum. Genet.* **2000**, *66*, 176–186. [[CrossRef](#)] [[PubMed](#)]
145. Mitra, D.; Luo, X.; Morgan, A.; Wang, J.; Hoang, M.P.; Lo, J.; Guerrero, C.R.; Lennerz, J.K.; Mihm, M.C.; Wargo, J.A.; et al. An ultraviolet-radiation-independent pathway to melanoma carcinogenesis in the red hair/fair skin background. *Nature* **2012**, *491*, 449–453. [[CrossRef](#)] [[PubMed](#)]
146. De Summa, S.; Lasorella, A.; Strippoli, S.; Giudice, G.; Guida, G.; Elia, R.; Nacchiero, E.; Azzariti, A.; Silvestris, N.; Guida, M.; et al. The Genetic Germline Background of Single and Multiple Primary Melanomas. *Front. Mol. Biosci.* **2021**, *7*, 555630. [[CrossRef](#)] [[PubMed](#)]
147. Landi, M.T.; Kanetsky, P.A.; Tsang, S.; Gold, B.; Munroe, D.; Rebbeck, T.; Swoyer, J.; Ter-Minassian, M.; Hedayati, M.; Grossman, L.; et al. MC1R, ASIP, and DNA repair in sporadic and familial melanoma in a mediterranean population. *J. Natl. Cancer Inst.* **2005**, *97*, 998–1007. [[CrossRef](#)]
148. Concetta Fargnoli, M.; Altobelli, E.; Keller, G.; Chimenti, S.; Höfler, H.; Peris, K. Contribution of melanocortin-1 receptor gene variants to sporadic cutaneous melanoma risk in a population in central Italy: A case-control study. *Melanoma Res.* **2006**, *16*, 175–182. [[CrossRef](#)]
149. Fernandez, L.P.; Milne, R.L.; Bravo, J.; Lopez, J.M.; Avilés, J.A.; Longo, M.I.; Benítez, J.; Lázaro, P.; Ribas, G. MC1R: Three novel variants identified in a malignant melanoma association study in the Spanish population. *Carcinogenesis* **2007**, *28*, 1659–1664. [[CrossRef](#)]
150. Ghiorzo, P.; Bonelli, L.; Pastorino, L.; Bruno, W.; Barile, M.; Andreotti, V.; Nasti, S.; Battistuzzi, L.; Grosso, M.; Bianchi-Scarrà, G.; et al. MC1R variation and melanoma risk in relation to host/clinical and environmental factors in CDKN2A positive and negative melanoma patients. *Exp. Dermatol.* **2012**, *21*, 718–720. [[CrossRef](#)]
151. Kanetsky, P.A.; Panossian, S.; Elder, D.E.; Guerry, D.P.; Ming, M.E.; Schuchter, L.; Rebbeck, T.R. Does MC1R genotype convey information about melanoma risk beyond risk phenotypes? *Cancer* **2010**, *116*, 2416–2428. [[CrossRef](#)]



152. Guida, S.; Bartolomeo, N.; Zanna, P.T.; Grieco, C.; Maida, I.; De Summa, S.; Tommasi, S.; Guida, M.; Azzariti, A.; Foti, C.; et al. Sporadic melanoma in South-Eastern Italy: The impact of melanocortin 1 receptor (MC1R) polymorphism analysis in low-risk people and report of three novel variants. *Arch. Dermatol. Res.* **2015**, *307*, 495–503. [[CrossRef](#)]
153. Wendt, J.; Rauscher, S.; Burgstaller-Muehlbacher, S.; Fae, I.; Fischer, G.; Pehamberger, H.; Okamoto, I. Human determinants and the role of melanocortin-1 receptor variants in melanoma risk independent of UV Radiation Exposure. *JAMA Dermatol.* **2016**, *152*, 776–782. [[CrossRef](#)]
154. Fargnoli, M.C.; Gandini, S.; Peris, K.; Maisonneuve, P.; Raimondi, S. MC1R variants increase melanoma risk in families with CDKN2A mutations: A meta-analysis. *Eur. J. Cancer* **2010**, *46*, 1413–1420. [[CrossRef](#)] [[PubMed](#)]
155. Dębniak, T.; Scott, R.; Masojc, B.; Serrano-Fernández, P.; Huzarski, T.; Byrski, T.; Dębniak, B.; Górski, B.; Cybulski, C.; Mędrak, K.; et al. MC1R common variants, CDKN2A and their association with melanoma and breast cancer risk. *Int. J. Cancer* **2006**, *119*, 2597–2602. [[CrossRef](#)]
156. Robles-Espinoza, C.D.; Roberts, N.D.; Chen, S.; Leacy, F.P.; Alexandrov, L.B.; Pornputtpong, N.; Halaban, R.; Krauthammer, M.; Cui, R.; Timothy Bishop, D.; et al. Germline MC1R status influences somatic mutation burden in melanoma. *Nat. Commun.* **2016**, *7*, 12064. [[CrossRef](#)]
157. Johansson, P.A.; Pritchard, A.L.; Patch, A.-M.; Wilmott, J.S.; Pearson, J.V.; Waddell, N.; Scolyer, R.A.; Mann, G.J.; Hayward, N.K. Mutation load in melanoma is affected by MC1R genotype. *Pigment Cell Melanoma Res.* **2017**, *30*, 255–258. [[CrossRef](#)]
158. Tagliabue, E.; Gandini, S.; Bellocco, R.; Maisonneuve, P.; Newton-Bishop, J.; Polsky, D.; Lazovich, D.; Kanetsky, P.A.; Ghiorzo, P.; Gruis, N.A.; et al. MC1R variants as melanoma risk factors independent of at-risk phenotypic characteristics: A pooled analysis from the M-SKIP project. *Cancer Manag. Res.* **2018**, *10*, 1143–1154. [[CrossRef](#)] [[PubMed](#)]
159. Roh, M.R.; Eliades, P.; Gupta, S.; Grant-Kels, J.M.; Tsao, H. Cutaneous melanoma in women. *Int. J. Women's Dermatol.* **2017**, *3*, S11–S15. [[CrossRef](#)]
160. Lu, C.; Zhang, J.; Nagahawatte, P.; Easton, J.; Lee, S.; Liu, Z.; Ding, L.; Wyczalkowski, M.A.; Valentine, M.; Navid, F.; et al. The genomic landscape of childhood and adolescent melanoma. *J. Investig. Dermatol.* **2015**, *135*, 816–823. [[CrossRef](#)] [[PubMed](#)]
161. Daniotti, M.; Ferrari, A.; Frigerio, S.; Casieri, P.; Miselli, F.; Zucca, E.; Collini, P.; Della Torre, G.; Manoukian, S.; Peissel, B.; et al. Cutaneous melanoma in childhood and adolescence shows frequent loss of INK4A and gain of KIT. *J. Investig. Dermatol.* **2009**, *129*, 1759–1768. [[CrossRef](#)] [[PubMed](#)]
162. Rabbie, R.; Rashid, M.; Arance, A.M.; Sánchez, M.; Tell-Marti, G.; Potrony, M.; Conill, C.; van Doorn, R.; Dentro, S.; Gruis, N.A.; et al. Genomic analysis and clinical management of adolescent cutaneous melanoma. *Pigment Cell Melanoma Res.* **2017**, *30*, 307–316. [[CrossRef](#)] [[PubMed](#)]
163. Pellegrini, C.; Botta, F.; Massi, D.; Martorelli, C.; Facchetti, F.; Gandini, S.; Maisonneuve, P.; Avril, M.F.; Demenais, F.; Bressac-de Paillerets, B.; et al. MC1R variants in childhood and adolescent melanoma: A retrospective pooled analysis of a multicentre cohort. *Lancet Child. Adolesc. Heal.* **2019**, *3*. [[CrossRef](#)]
164. Preston, D.S.; Stern, R.S. Nonmelanoma Cancers of the Skin. *N. Engl. J. Med.* **1992**, *327*, 332–342. [[CrossRef](#)] [[PubMed](#)]
165. Kricger, A.; Armstrong, B.K.; English, D.R. Sun exposure and non-melanocytic skin cancer. *Cancer Causes Control* **1994**, *5*, 367–392. [[CrossRef](#)] [[PubMed](#)]
166. Kricger, A.; Armstrong, B.K.; English, D.R.; Heenan, P.J. Pigmentary and cutaneous risk factors for non-melanocytic skin cancer—A case-control study. *Int. J. Cancer* **1991**, *48*, 650–662. [[CrossRef](#)] [[PubMed](#)]
167. Tagliabue, E.; Fargnoli, M.C.; Gandini, S.; Maisonneuve, P.; Liu, F.; Kayser, M.; Nijsten, T.; Han, J.; Kumar, R.; Gruis, N.A.; et al. MC1R gene variants and non-melanoma skin cancer: A pooled-analysis from the M-SKIP project. *Br. J. Cancer* **2015**, *113*, 354–363. [[CrossRef](#)]
168. Box, N.F.; Duffy, D.L.; Irving, R.E.; Russell, A.; Chen, W.; Griffyths, L.R.; Parsons, P.G.; Green, A.C.; Sturm, R.A. Melanocortin-1 receptor genotype is a risk factor for basal and squamous cell carcinoma. *J. Investig. Dermatol.* **2001**, *116*, 224–229. [[CrossRef](#)]
169. Puig, S.; Malvehy, J.; Badenas, C.; Ruiz, A.; Jimenez, D.; Cuellar, F.; Azon, A.; González, U.; Castel, T.; Campoy, A.; et al. Role of the CDKN2A locus in patients with multiple primary melanomas. *J. Clin. Oncol.* **2005**, *23*, 3043–3051. [[CrossRef](#)]
170. Liontos, M.; Pateras, I.S.; Evangelou, K.; G. Gorgoulis, V. The Tumor Suppressor Gene ARF as a Sensor of Oxidative Stress. *Curr. Mol. Med.* **2012**, *12*, 704–715. [[CrossRef](#)]
171. Hussussian, C.J.; Struewing, J.P.; Goldstein, A.M.; Higgins, P.A.T.; Ally, D.S.; Sheahan, M.D.; Clark, W.H.; Tucker, M.A.; Dracopoli, N.C. Germline p16 mutations in familial melanoma. *Nat. Genet.* **1994**, *8*, 15–21. [[CrossRef](#)] [[PubMed](#)]
172. Bishop, D.T.; Demenais, F.; Goldstein, A.M.; Bergman, W.; Bishop, J.N.; Bressac-De Paillerets, B.; Chompret, A.; Ghiorzo, P.; Gruis, N.; Hansson, J.; et al. Geographical variation in the penetrance of CDKN2A mutations for melanoma. *J. Natl. Cancer Inst.* **2002**, *94*, 894–903. [[CrossRef](#)] [[PubMed](#)]
173. Goldstein, A.M.; Chan, M.; Harland, M.; Hayward, N.K.; Demenais, F.; Bishop, D.T.; Azizi, E.; Bergman, W.; Bianchi-Scarra, G.; Bruno, W.; et al. Features associated with germline CDKN2A mutations: A GenoMEL study of melanoma-prone families from three continents. *J. Med. Genet.* **2007**, *44*, 99–106. [[CrossRef](#)]
174. Lang, J.; Boxer, M.; MacKie, R.M. CDKN2A mutations in Scottish families with cutaneous melanoma: Results from 32 newly identified families. *Br. J. Dermatol.* **2005**, *153*, 1121–1125. [[CrossRef](#)]
175. Borges, A.L.; Cuéllar, F.; Puig-Butillé, J.A.; Scarone, M.; Delgado, L.; Badenas, C.; Milà, M.; Malvehy, J.; Barquet, V.; Núñez, J.; et al. CDKN2A mutations in melanoma families from Uruguay. *Br. J. Dermatol.* **2009**, *161*, 536–541. [[CrossRef](#)]

176. Yakobson, E.; Eisenberg, S.; Isacson, R.; Halle, D.; Levy-Lahad, E.; Catane, R.; Safro, M.; Sobolev, V.; Huot, T.; Peters, G.; et al. A single Mediterranean, possibly Jewish, origin for the Val59Gly CDKN2A mutation in four melanoma-prone families. *Eur. J. Hum. Genet.* **2003**, *11*, 288–296. [[CrossRef](#)]
177. Majore, S.; De Simone, P.; Crisi, A.; Eibenschutz, L.; Binni, F.; Antignoni, I.; De Bernardo, C.; Catricalà, C.; Grammatico, P. CDKN2A/CDK4 molecular study on 155 Italian subjects with familial and/or primary multiple melanoma. *Pigment Cell Melanoma Res.* **2008**, *21*, 209–211. [[CrossRef](#)]
178. Eliason, M.J.; Larson, A.A.; Florell, S.R.; Zone, J.J.; Cannon-Albright, L.A.; Samlowski, W.E.; Leachman, S.A. Population-based prevalence of CDKN2A mutations in Utah melanoma families. *J. Investig. Dermatol.* **2006**, *126*. [[CrossRef](#)] [[PubMed](#)]
179. Box, N.F.; Duffy, D.L.; Chen, W.; Stark, M.; Martin, N.G.; Sturm, R.A.; Hayward, N.K. MC1R genotype modifies risk of melanoma in families segregating CDKN2A mutations. *Am. J. Hum. Genet.* **2001**, *69*, 660–666. [[CrossRef](#)] [[PubMed](#)]
180. Sturm, R.A. Skin colour and skin cancer-MC1R, the genetic link. *Melanoma Res.* **2002**, *12*, 405–416. [[CrossRef](#)]
181. Chaudru, V.; Laud, K.; Avril, M.F.; Minière, A.; Chompret, A.; Bressac-De Paillerets, B.; Demenais, F. Melanocortin-1 receptor (MC1R) gene variants and dysplastic nevi modify penetrance of CDKN2A mutations in French melanoma-prone pedigrees. *Cancer Epidemiol. Biomarkers Prev.* **2005**, *14*, 2384–2390. [[CrossRef](#)]
182. Helsing, P.; Nymoen, D.A.; Rootwelt, H.; Vårdal, M.; Akslen, L.A.; Molven, A.; Andresen, P.A. MC1R, ASIP, TYR, and TYRP1 gene variants in a population-based series of multiple primary melanomas. *Genes Chromosom. Cancer* **2012**, *51*, 654–661. [[CrossRef](#)] [[PubMed](#)]
183. Demenais, F.; Mohamdi, H.; Chaudru, V.; Goldstein, A.M.; Bishop, J.A.N.; Bishop, D.T.; Kanetsky, P.A.; Hayward, N.K.; Gillanders, E.; Elder, D.E.; et al. Association of MC1R variants and host phenotypes with melanoma risk in CDKN2A mutation carriers: A GenoMEL study. *J. Natl. Cancer Inst.* **2010**, *102*, 1568–1583. [[CrossRef](#)]
184. Van der Velden, P.A.; Sandkuijl, L.A.; Bergman, W.; Pavel, S.; Van Mourik, L.; Frants, R.R.; Gruis, N.A. Melanocortin-1 receptor variant R151C modifies melanoma risk in Dutch families with melanoma. *Am. J. Hum. Genet.* **2001**, *69*, 774–779. [[CrossRef](#)]
185. Aoude, L.G.; Wadt, K.A.W.; Pritchard, A.L.; Hayward, N.K. Genetics of familial melanoma: 20 years after CDKN2A. *Pigment Cell Melanoma Res.* **2015**, *28*, 148–160. [[CrossRef](#)]
186. Fargnoli, M.C.; Pike, K.; Pfeiffer, R.M.; Tsang, S.; Rozenblum, E.; Munroe, D.J.; Golubeva, Y.; Calista, D.; Seidenari, S.; Massi, D.; et al. MC1R variants increase risk of melanomas harboring BRAF mutations. *J. Investig. Dermatol.* **2008**, *128*, 2485–2490. [[CrossRef](#)] [[PubMed](#)]
187. Landi, M.T.; Bauer, J.; Pfeiffer, R.M.; Elder, D.E.; Hulley, B.; Minghetti, P.; Calista, D.; Kanetsky, P.A.; Pinkel, D.; Bastian, B.C. MC1R germline variants confer risk for BRAF-mutant melanoma. *Science* **2006**, *313*, 521–522. [[CrossRef](#)] [[PubMed](#)]
188. Hacker, E.; Olsen, C.M.; Kvaskoff, M.; Pandeya, N.; Yeo, A.; Green, A.C.; Williamson, R.M.; Triscott, J.; Wood, D.; Mortimore, R.; et al. Histologic and Phenotypic Factors and MC1R Status Associated with BRAFV600E, BRAFV600K, and NRAS Mutations in a Community-Based Sample of 414 Cutaneous Melanomas. *J. Investig. Dermatol.* **2016**, *136*, 829–837. [[CrossRef](#)] [[PubMed](#)]
189. Pellegrini, C.; Di Nardo, L.; Cipolloni, G.; Martorelli, C.; De Padova, M.; Antonini, A.; Maturo, M.G.; Del Regno, L.; Strafella, S.; Micantonio, T.; et al. Heterogeneity of BRAF, NRAS, and TERT Promoter Mutational Status in Multiple Melanomas and Association with MC1R Genotype: Findings from Molecular and Immunohistochemical Analysis. *J. Mol. Diagn.* **2018**, *20*, 110–122. [[CrossRef](#)]
190. William, B.; Claudia, M.; Bruna, D.; Virginia, A.; Lorenza, P.; Francesco, C.; Marina, G.; Francesco, S.; Alberto, B.; Paola, Q.; et al. Combining molecular and immunohistochemical analyses of key drivers in primary melanomas: Interplay between germline and somatic variations. *Oncotarget* **2018**, *9*, 5691–5702. [[CrossRef](#)]
191. García-Casado, Z.; Traves, V.; Bañuls, J.; Niveiro, M.; Gimeno-Carpio, E.; Jimenez-Sanchez, A.I.; Moragón, M.; Onrubia, J.A.; Oliver, V.; Kumar, R.; et al. BRAF, NRAS and MC1R status in a prospective series of primary cutaneous melanoma. *Br. J. Dermatol.* **2015**, *172*, 1128–1131. [[CrossRef](#)] [[PubMed](#)]
192. Scherer, D.; Rachakonda, P.S.; Angelini, S.; Mehnert, F.; Sucker, A.; Egberts, F.; Hauschild, A.; Hemminki, K.; Schadendorf, D.; Kumar, R. Association between the germline MC1R variants and somatic BRAF/NRAS mutations in melanoma tumors. *J. Investig. Dermatol.* **2010**, *130*, 2844–2848. [[CrossRef](#)] [[PubMed](#)]
193. Hacker, E.; Hayward, N.K.; Dumenil, T.; James, M.R.; Whiteman, D.C. The association between MC1R genotype and BRAF mutation status in cutaneous melanoma: Findings from an Australian population. *J. Investig. Dermatol.* **2010**, *130*, 241–248. [[CrossRef](#)]
194. Thomas, N.E.; Kanetsky, P.A.; Edmiston, S.N.; Alexander, A.; Begg, C.B.; Groben, P.A.; Hao, H.; Busam, K.; Ollila, D.W.; Berwick, M.; et al. Relationship between germline MC1R variants and BRAF-mutant melanoma in a North Carolina population-based study. *J. Investig. Dermatol.* **2010**, *130*, 1463–1465. [[CrossRef](#)]
195. Hacker, E.; Nagore, E.; Cerroni, L.; Woods, S.L.; Hayward, N.K.; Chapman, B.; Montgomery, G.W.; Soyer, H.P.; Whiteman, D.C. NRAS and BRAF mutations in cutaneous melanoma and the association with MC1R genotype: Findings from Spanish and Austrian populations. *J. Investig. Dermatol.* **2013**, *133*, 1027–1033. [[CrossRef](#)]
196. Kosiniak-Kamysz, A.; Marczakiewicz-Lustig, A.; Marcińska, M.; Skowron, M.; Wojas-Pelc, A.; Pośpiech, E.; Branicki, W. Increased risk of developing cutaneous malignant melanoma is associated with variation in pigmentation genes and VDR, and may involve epistatic effects. *Melanoma Res.* **2014**, *24*, 388–396. [[CrossRef](#)]
197. Nagore, E.; Reyes-Garcia, D.; Heidenreich, B.; Garcia-Casado, Z.; Requena, C.; Kumar, R. TERT promoter mutations associate with MC1R variants in melanoma patients. *Pigment Cell Melanoma Res.* **2017**, *30*, 273–275. [[CrossRef](#)]

198. Duffy, D.L.; Zhao, Z.Z.; Sturm, R.A.; Hayward, N.K.; Martin, N.G.; Montgomery, G.W. Multiple pigmentation gene polymorphisms account for a substantial proportion of risk of cutaneous malignant melanoma. *J. Investig. Dermatol.* **2010**, *130*, 520–528. [[CrossRef](#)] [[PubMed](#)]
199. Liboutet, M.; Portela, M.; Delestaing, G.; Vilmer, C.; Dupin, N.; Gorin, I.; Saiag, P.; Lebbé, C.; Kerob, D.; Dubertret, L.; et al. MC1R and PTCH gene polymorphism in French patients with basal cell carcinomas. *J. Investig. Dermatol.* **2006**, *126*, 1510–1517. [[CrossRef](#)] [[PubMed](#)]
200. Gujar, H.; Weisenberger, D.J.; Liang, G. The roles of human DNA methyltransferases and their isoforms in shaping the epigenome. *Genes* **2019**, *10*, 172. [[CrossRef](#)]
201. Cappetta, M.; Berdasco, M.; Hochmann, J.; Bonilla, C.; Sans, M.; Hidalgo, P.C.; Artagaveytia, N.; Kittles, R.; Martínez, M.; Esteller, M.; et al. Effect of genetic ancestry on leukocyte global DNA methylation in cancer patients. *BMC Cancer* **2015**, *15*, 1–8. [[CrossRef](#)] [[PubMed](#)]
202. Grönniger, E.; Weber, B.; Heil, O.; Peters, N.; Stäb, F.; Wenck, H.; Korn, B.; Winnefeld, M.; Lyko, F. Aging and chronic sun exposure cause distinct epigenetic changes in human skin. *PLoS Genet.* **2010**, *6*, e1000971. [[CrossRef](#)]
203. Holzschek, N.; Söhle, J.; Schläger, T.; Falckenhayn, C.; Grönniger, E.; Kolbe, L.; Wenck, H.; Terstegen, L.; Kaderali, L.; Winnefeld, M.; et al. Concomitant DNA methylation and transcriptome signatures define epidermal responses to acute solar UV radiation. *Sci. Rep.* **2020**, *10*, 12918. [[CrossRef](#)]
204. Vandiver, A.R.; Irizarry, R.A.; Hansen, K.D.; Garza, L.A.; Runarsson, A.; Li, X.; Chien, A.L.; Wang, T.S.; Leung, S.G.; Kang, S.; et al. Age and sun exposure-related widespread genomic blocks of hypomethylation in nonmalignant skin. *Genome Biol.* **2015**, *16*, 1–15. [[CrossRef](#)]
205. Nikolouzakis, T.K.; Falzone, L.; Lasithiotakis, K.; Krüger-Krasagakis, S.; Kalogeraki, A.; Sifaki, M.; Spandidos, D.A.; Chrysos, E.; Tsatsakis, A.; Tsiaoussis, J. Current and Future Trends in Molecular Biomarkers for Diagnostic, Prognostic, and Predictive Purposes in Non-Melanoma Skin Cancer. *J. Clin. Med.* **2020**, *9*, 2868. [[CrossRef](#)]
206. Jones, P.A.; Baylin, S.B. The fundamental role of epigenetic events in cancer. *Nat. Rev. Genet.* **2002**, *3*, 415–428. [[CrossRef](#)]
207. Riefolo, M.; Porcellini, E.; Dika, E.; Broseghini, E.; Ferracin, M. Interplay between small and long non-coding RNAs in cutaneous melanoma: A complex jigsaw puzzle with missing pieces. *Mol. Oncol.* **2019**, *13*, 74–98. [[CrossRef](#)]
208. Sang, Y.; Deng, Y. Current insights into the epigenetic mechanisms of skin cancer. *Dermatol. Ther.* **2019**, *32*, e12964. [[CrossRef](#)]
209. Budden, T.; Bowden, N.A. MC1R CpG island regulates MC1R expression and is methylated in a subset of melanoma tumours. *Pigment Cell Melanoma Res.* **2019**, *32*, 320–325. [[CrossRef](#)] [[PubMed](#)]
210. Rodríguez-Martínez, S.; Márquez, R.; Inácio, Á.; Galván, I. Changes in melanocyte RNA and DNA methylation favour pheomelanin synthesis and may avoid systemic oxidative stress after dietary cysteine supplementation in birds. *Mol. Ecol.* **2019**, *28*, 1030–1042. [[CrossRef](#)] [[PubMed](#)]
211. Dong, Z.; Luo, M.; Wang, L.; Yin, H.; Zhu, W.; Fu, J. MicroRNA-206 Regulation of Skin Pigmentation in Koi Carp (*Cyprinus carpio* L.). *Front. Genet.* **2020**, *11*, 47. [[CrossRef](#)]
212. Aspinwall, L.G.; Leaf, S.L.; Dola, E.R.; Kohlmann, W.; Leachman, S.A. CDKN2A/p16 genetic test reporting improves early detection intentions and practices in high-risk melanoma families. *Cancer Epidemiol. Biomark. Prev.* **2008**, *17*, 1510–1519. [[CrossRef](#)] [[PubMed](#)]
213. Glanz, K.; Volpicelli, K.; Kanetsky, P.A.; Ming, M.E.; Schuchter, L.M.; Jepson, C.; Domchek, S.M.; Armstrong, K. Melanoma genetic testing, counseling, and adherence to skin cancer prevention and detection behaviors. *Cancer Epidemiol. Biomark. Prev.* **2013**, *22*, 607–614. [[CrossRef](#)] [[PubMed](#)]
214. Hay, J.L.; Zielaskowski, K.; White, K.M.; Kaphingst, K.; Robers, E.; Guest, D.; Sussman, A.; Talamantes, Y.; Schwartz, M.; Rodríguez, V.M.; et al. Interest and uptake of MC1R testing for melanoma risk in a diverse primary care population a randomized clinical trial. *JAMA Dermatol.* **2018**, *154*, 684–693. [[CrossRef](#)]
215. Kaphingst, K.A.; Khan, E.; White, K.M.; Sussman, A.; Guest, D.; Schofield, E.; Dailey, Y.T.; Robers, E.; Schwartz, M.R.; Li, Y.; et al. Effects of health literacy skills, educational attainment, and level of melanoma risk on responses to personalized genomic testing. *Patient Educ. Couns.* **2021**, *104*, 12–19. [[CrossRef](#)]
216. Guida, M.; Strippoli, S.; Ferretta, A.; Bartolomeo, N.; Porcelli, L.; Maida, I.; Azzariti, A.; Tommasi, S.; Grieco, C.; Guida, S.; et al. Detrimental effects of melanocortin-1 receptor (MC1R) variants on the clinical outcomes of BRAF V600 metastatic melanoma patients treated with BRAF inhibitors. *Pigment Cell Melanoma Res.* **2016**, *29*, 679–687. [[CrossRef](#)]
217. Koikov, L.; Starner, R.J.; Swope, V.B.; Upadhyay, P.; Hashimoto, Y.; Freeman, K.T.; Knittel, J.J.; Haskell-Luevano, C.; Abdel-Malek, Z.A. Development of hMC1R Selective Small Agonists for Sunless Tanning and Prevention of Genotoxicity of UV in Melanocytes. *J. Investig. Dermatol.* **2021**, *141*, 1819–1829. [[CrossRef](#)] [[PubMed](#)]
218. Bautista, R.M.; Carter, K.M.; Jarrett, S.G.; Napier, D.; Wakamatsu, K.; Ito, S.; D’Orazio, J.A. Cutaneous pharmacologic cAMP induction induces melanization of the skin and improves recovery from ultraviolet injury in melanocortin 1 receptor-intact or heterozygous skin. *Pigment Cell Melanoma Res.* **2020**, *33*, 30–40. [[CrossRef](#)] [[PubMed](#)]
219. D’Orazio, J.A.; Nobuhisa, T.; Cui, R.; Arya, M.; Spry, M.; Wakamatsu, K.; Igras, V.; Kunisada, T.; Granter, S.R.; Nishimura, E.K.; et al. Topical drug rescue strategy and skin protection based on the role of Mc1r in UV-induced tanning. *Nature* **2006**, *443*, 340–344. [[CrossRef](#)]
220. Langendonk, J.G.; Balwani, M.; Anderson, K.E.; Bonkovsky, H.L.; Anstey, A.V.; Bissell, D.M.; Bloomer, J.; Edwards, C.; Neumann, N.J.; Parker, C.; et al. Afamelanotide for Erythropoietic Protoporphyrria. *N. Engl. J. Med.* **2015**, *373*, 48–59. [[CrossRef](#)]