Int J Mol Epidemiol Genet 2021;12(5):71-89
www.ijmeg.org /ISSN:1948-1756/IJMEG0136390

Review Article

Melanoma susceptibility: an update on genetic and epigenetic findings

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Received June 15, 2021; Accepted September 14, 2021; Epub October 15, 2021; Published October 30, 2021

Abstract: Malignant melanoma is one of the most highly ranked cancers in terms of years of life lost. Hereditary melanoma with its increased familial susceptibility is thought to affect up to 12% of all melanoma patients. In the past, only a few high-penetrance genes associated with familial melanoma, such as *CDKN2A* and *CDK4,* have been clinically tested. However, findings now indicate that melanoma is a cancer most likely to develop not only due to high-penetrance variants but also due to polygenic inheritance patterns, leaving no clear division between the hereditary and sporadic development of malignant melanoma. Various pathogenic low-penetrance variants were recently discovered through genome-wide association studies, and are now translated into polygenic risk scores. These can show superior sensitivity rates for the prediction of melanoma susceptibility and related mixed cancer syndromes than risk scores based on phenotypic traits of the patients, with odds ratios of up to 5.7 for patients in risk groups. In addition to describing genetic findings, we also review the first results of epigenetic research showing constitutional methylation changes that alter the susceptibility to cutaneous melanoma and its risk factors.

Keywords: Melanoma susceptibility, hereditary melanoma, familial melanoma, melanoma genetics, germline mutation, epigenetics, polygenic risk score

Introduction

Malignant melanoma is a type of skin cancer derived from neoplastic melanocytes. Once a rare cancer, incidence numbers have been growing worldwide for decades and are estimated to rise further [1]. Presently, malignant melanoma is one of the most frequent cancers with an estimated lifetime risk of 2% in Western populations. In the United States, it is the fifth most frequent type of cancer in men, and the sixth most frequent in women. Between 1973 and now, the annual number of cases has risen by more than 270%; partially explained by an aging society, imprudent tanning behavior, and loss of the ozone layer [2, 3]. In Europe, incidence rates follow a gradient from the southern Mediterranean with lower, to northern Scandinavian countries with higher malignant melanoma rates [2]. Europe accounts for 45% of all malignant melanoma deaths worldwide [1]. Depending on the geographic region, melanoma can rank as high as third place in a population based on the number of years of life lost (YLL) [4, 5].

However, malignant melanoma is not the most common type of skin cancer, but is the most lethal. This is due to early dissemination and metastasis formation, as well as high resistance to treatment [6]. Currently, the only curative treatment is early detection, followed by tumor excision [7].

Certain somatic mutations driving tumorigenesis have been identified in sporadic cases of malignant melanoma. In contrast, 5-12% of malignant melanoma cases are thought to develop due to genetic germline alterations, referred to as hereditary melanoma [8, 9]. Several genes with pathogenic variants predisposing for a higher risk of developing malignant melanoma have been identified, with *CDKN2A* (cyclin-dependent kinase inhibitor 2A) being the most commonly altered gene, which accounts for an estimated 20-45% of hereditary melanoma cases [8-10]. Genetic alterations can be inherited, as well as constitutional epigenetic modifications. Studies have shown that certain DNA methylation changes increase the susceptibility to melanoma risk factors, such as

dysplastic nevi, or for cutaneous melanoma itself [8, 11, 12].

As most hereditary tumors, also hereditary melanoma presents itself with an earlier age of cancer development onset, as well as familial clustering of specific cancer types [13].

As the available evidence on inherited melanoma susceptibility has advanced rapidly in recent years, the aim of this review was to provide a comprehensive and updated overview of the topic. This includes recent clinical and genome-wide association study (GWAS) findings, as well as a summary of the results from studies investigating the epigenetic factors of malignant melanoma.

Methods

Sources for this review were identified on Medline, UpToDate, and Cochrane Central Register with scientific publications spanning at least a five-year period up until May 17, 2021. Search terms included “melanoma”, “hereditary melanoma” and “familial melanoma”. Peer-reviewed sources were included in this article if they contained specific results on germline mutations and/or constitutional epigenetic alterations. Sources also included a medical textbook and a published doctoral dissertation. We did not include non-English language sources or articles on somatic melanoma driver mutations (exclusion criteria).

Genes with high-penetrance variants

Genes containing pathogenic variants associated with malignant melanoma are usually grouped by penetrance of the variant(s), biological pathomechanism or cumulative number of single nucleotide variants (SNVs) [9, 10].

Penetrance for genes or variants, defined as the ratio of gene expression or susceptibility, can be high, intermediate, or low with respective odds ratios of over 5, 2 to 5, or lower than 2, although slightly varying in the literature. For intermediate-and low-penetrance variants, predicting melanoma occurrence is still very imprecise [9].

CDKN2A (Cyclin-dependent kinase inhibitor 2A): CDKN2A is a gene located on chromosome 9p21. Germline alterations in this gene show an autosomal dominant inheritance pattern, and multiple single-nucleotide variants (SNVs) are associated with a higher risk of malignant melanoma [1, 8, 9].

It is the most common gene with pathogenic variants in hereditary melanoma, with variants varying by geographic region [9, 14-16]. One of the most frequent of these so-called founder mutations is p.G101W, which is mostly detected in French, Spanish and Italian populations [9, 17].

CDKN2A itself consists of four exons containing the genetic code for two unrelated proteins, p16 inhibitor of cyclin-dependent kinase 4 (p16INK4A) and p14 alternate reading frame (p14ARF) [9, 18]. Both protein products act as tumor suppressors. P16INK4A is an inhibitor of CDK4 (cyclin-dependent kinase 4) and CDK6 (cyclin-dependent kinase 6), preventing the cell from entering the S-phase of the cell cycle, whereas p14ARF positively regulates the tumor suppressor p53, thus preventing an excess load of damaged DNA in the cell [9].

CDKN2A mutations increase the risk of malignant melanoma itself, yet certain pathogenic *CDKN2A* variants are associated with other cancer types, such as pancreatic cancer, lung cancer, breast cancer, sarcoma, and, in rare cases, mesothelioma and esophageal squamous cell cancer [13, 18-21].

The most common *CDKN2A* variant-associated melanoma-dominant tumor syndrome is called familial atypical multiple mole-melanoma (FAMMM) and is rarely associated with *CDK4* and *MITF* (microphthalmia-associated transcription factor) alterations [1, 13]. The typical phenotypic manifestations of FAMMM are a high nevi count over 50 and multiple precancerous dysplastic nevi [13]. In this tumor syndrome, affected patients tend to regularly develop melanoma on unaffected and healthy skin tissue, but not from nevi. As with hereditary cancers in general, the onset of disease is also early in FAMMM [1].

Patients with Melanoma-Astrocytoma syndrome have a higher incidence of nervous system tumors (NSTs), such as astrocytoma, which can occur before or after the development of melanoma [1]. Here, the main gene involved is

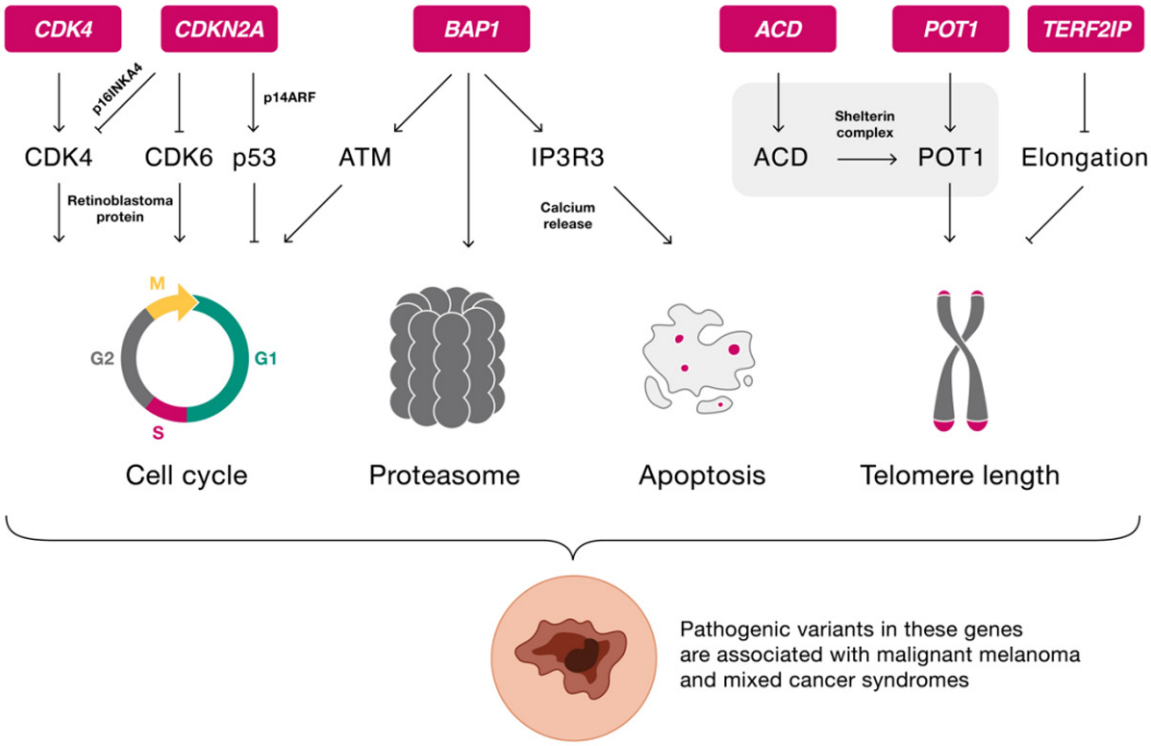

Figure 1. Physiological pathways of genes with possible pathogenic high-penetrance variants associated with hereditary melanoma. *ACD*: adrenocortical dysplasia; ATM: ataxia telangiectasia-mutated signaling pathway; *BAP1*: *BRCA1*-associated protein-1; *CDK4*: cyclin-dependent kinase 4; CDK6: cyclin-dependent kinase 6; *CDKN2A*: cyclin-dependent kinase inhibitor 2 a; IP3R3: receptor for inositol 1,4,5-trisphosphate; p14ARF: p14 alternate reading frame; p16INKA4: p16 inhibitor of cyclin-dependent kinase 4; p53: tumor protein 53; *POT1*: protection of telomeres 1; *TERF2IP*: telomeric repeat binding factor 2 interacting protein.

CDKN2A/ARF, which encodes p14ARF, although there have been rare associations with more comprehensive 9p21 chromosome alterations affecting the genetic cluster of *CDKN2A*, *CDKN2B*, and *CDKN2BAS* until the gene *MLLT3* [1, 22].

For nearly two decades, *CDKN2A* and *CDK4* were the only two genes tested in a clinical context when hereditary melanoma was suspected [23].

Pathways affected by *CDKN2A* and other genes with high-penetrance variants associated with melanoma susceptibility are shown in **Figure 1**, whereas **Figure 2** depicts a gene network analysis based on genes with both high-and medium-penetrance variants.

CDK4 (Cyclin-dependent kinase 4): CDK4 is a gene with rare pathogenic variants found on chromosome 12q4 [8, 9, 23]. Its identically named translational product is part of the same signaling pathway of the cell cycle as the gene products of *CDKN2A* [9]. Pathogenic variants of *CDK4* associated with malignant melanoma are uncommon, and only 18 families have been identified worldwide, as well as a single case of a male patient in Italy, leading to a subsequent need for further studies with more significant populations to solidify the effect of pathogenic variants of *CDK4* on the development of hereditary melanoma [9, 24].

CDK4 and CDK6 are physiologically needed to transition to the S-phase of the cell cycle from the G1-phase by phosphorylating retinoblastoma protein (RB) [9]. To date, only one specific locus with specific pathogenic variants in *CDK4* has been found: Arg24, in exon 2, codon 24 [24]. There, three pathogenic variants were identified. The arginine can be interchanged for either cysteine (Arg24Cys), histidine (Arg24His), or leucine (Arg24Leu with only one described case) [9]. This eliminates the binding domain of p16INKA4, leading to reduced p16INK4A inhibition of CDK4 kinase activity, subsequently

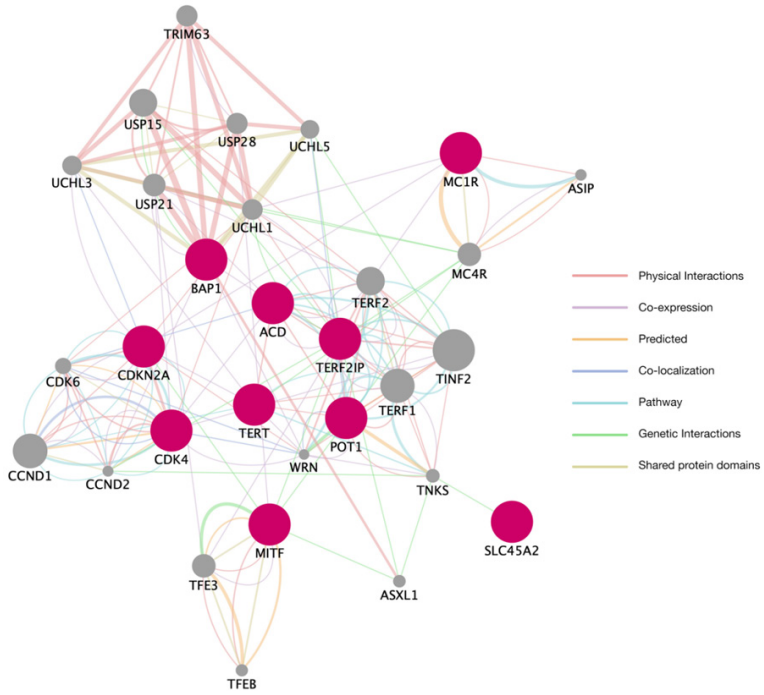

Figure 2. Established melanoma susceptibility genes with high and medium-penetrance variants and their most closely related genes. Utilizing the GeneMania framework (Version 3.5.2) in Cytoscape (Version 3.8.2), we generated a network analysis based on the established hereditary melanoma susceptibility genes, usually bearing high-and medium-penetrance pathogenic variants. These are shown in red. The most closely related genes are shown in gray. Genes were visually grouped according to molecular function. *ACD*: adrenocortical dysplasia; *BAP1*: BRCA1-associated protein-1; *CDK4*: cyclin-dependent kinase 4; *CDKN2A*: cyclin-dependent kinase inhibitor 2 a; *MC1R*: melanocortin 1 receptor gene; *MITF*: microphthalmia-associated transcription factor; *POT1*: protection of telomeres 1; *SLC45A2*: solute carrier family 45 member 2; *TERF2IP*: telomeric repeat binding factor 2 interacting protein; *TERT*: telomerase reverse transcriptase.

deregulating CDK4, resulting in uncontrolled continuation of the cell cycle [18, 24].

As a result, patients carrying pathogenic *CDK4* variants were susceptible to an earlier onset of malignant melanoma with a median age of 39 years at the time of diagnosis, and a lifetime risk of 74% among the studied individuals [9].

The implications of pathogenic *CDK4* variants are, due to the same pathway, similar to the ones of *CDKN2A*. Pathogenic *CDK4* gene variants are associated with a higher risk of cutaneous melanoma, pancreatic cancer, multiple primary melanomas, and atypical nevi [18, 23]. Pathogenic *CDK4* variations are also associated with the development of FAMMM syndrome [13].

BAP1 (BRCA1-associated protein-1): BAP1 is a high-penetrance gene found on chromosome 3p21 [8, 9]. Studies have found that pathogenic variations are responsible for only up to 1% of cutaneous melanoma (CM), but up to 4% of uveal melanoma cases (UM, also known as ocular melanoma) [25].

Its encoded protein is a deubiquitinating enzyme found in the nucleus, mitochondria, and cytosol of the cells [26]. It is mainly a transcription-regulating tumor suppressor—as part of the ubiquitin-proteasome complex. It also participates in regulating the cell cycle, apoptosis, and gluconeogenesis [27].

As a result, pathogenic variants can lead to decreased DNA repair mechanisms via the ataxia telangiectasia-mutated (ATM) signaling pathway, proliferation through uncontrolled cell cycles, and eventually, tumorigenesis [25, 27]. *BAP1* also plays a role in regulating the receptor for inositol 1,4,5-trisphosphate (IP3R3 receptor), which is part of the apoptosis mechanism through intracellular calcium release [25].

Patients harboring pathogenic *BAP1* variants can show specific lesions with distinct morphology, immunohistochemistry, and early onset in young adults [9, 25]. These so-called BAPomas, or melanocytic *BAP1*-mutated atypical intradermal tumors (MBAIT), atypical Spitzoid nevi, or nowadays, *BAP1*-inactivated melanocytic tumors (BIMT) are similar to Spitzoid tumors, yet do not fulfill all given criteria and usually can be seen as skin-colored to pink nodules and papules, varying in size by up to one cm in diameter [9, 25].

BAP1 variants are associated with a tumor syndrome named *BAP1*-tumor predisposition syn-

drome (*BAP1*-TPDS), which is dominated by mesothelioma and uveal melanoma [23, 27]. Other types of cancer are associated with pathogenic *BAP1* variants. These show varying frequencies depending on the cancer subtype, thus concluding that in this case, cancer development might depend on a broader array of genetic or epigenetic factors. These further associated cancers include cutaneous melanoma, basal cell carcinoma, mesothelioma, clear cell renal cell carcinoma, cholangiocarcinoma, and possibly additional unknown tumor types [23, 27].

POT1 (Protection of telomeres 1): POT1 is a high-penetrance gene on chromosome 7 with rare pathogenic variants [8, 28]. The gene itself codes for the POT1 protein, one of six proteins forming the shelterin complex. The complex regulates and protects the single-stranded DNA telomere regions at the end of each chromosome from degradation and chromosomic fusion [29].

Most pathogenic variants have a negative effect on the binding sites—called oligonucleotide/oligosaccharide-binding fold domains (OB fold domains)—needed to adhere the shelterin complex to the single-stranded DNA [9].

Germline *POT1* variants lead to an autosomal dominantly inherited syndrome consisting of several tumor types, predominantly angiosarcoma and superficially spreading melanoma, but also malignant glioma, anaplastic astrocytoma, thyroid cancer, and colorectal cancer [8, 29, 30]. As driver mutations, somatic *POT1* mutations are often found in chronic lymphocytic leukemia (CLL) [29].

TERF2IP (Telomeric repeat binding factor 2 interacting protein) and ACD (Adrenocortical dysplasia): ACD and *TERF2IP*, otherwise known as adrenocortical dysplasia protein homolog, are both classified as genes with rare pathogenic high-penetrance variants. Together with *POT1*, they form a gene group with protein products needed to assemble the shelterin complex, thus regulating the telomeric end of the linear chromosomes [8].

ACD contains a POT1 protein binding domain and is therefore involved in preventing an early degradation of the single-stranded DNA by adhering the shelterin complex to the DNA [9].

TERF2IP has a contrary effect on DNA regulation by preventing excessive elongation of the telomeric region. For pathogenic *TERF2IP* variants, early melanoma onset as young as 15 years of age has been described [9]. Generally, an early onset and multiple primary melanomas, are typical for pathogenic *ACD* and *TERF2IP* variants [8].

Associated cancers, other than superficial spreading melanoma and lentigo maligna melanoma, are breast cancer, ovarian cancer, cervical cancer, uterine cancer, thyroid cancer, colon cancer, lung cancer, renal cancer, urinary cancer, prostate cancer, esophageal cancer, lymphoma, leukemia, and possibly others [8, 30].

Genes with medium-penetrance variants

Historically, there has been a general perception that there is a clear distinction between hereditary tumors with singular high-penetrance pathogenic variants and spontaneous somatic mutations. Several studies, including Lu et al. (2014), have shown that there is an underlying polygenic inheritance even for spontaneous tumors, including non-hereditary melanoma [31]. Genes with medium-penetrance variants might be a part of this polygenic inheritance, not by causing cancer development directly, but in a combination reaching a threshold that could lead to tumorigenesis. Furthermore, medium-and low-penetrance gene variants are much more common than their high-penetrance counterparts [9].

TERT (Telomerase reverse transcriptase): TERT is a medium-penetrance gene on chromosome 5p15 [8, 9, 27]. There have only been a few findings of hereditary pathogenic variants, mainly in the promoter region of *TERT*. In contrast, up to 70% of somatic mutations in this gene lead to tumorigenesis [9, 30].

It is thought that genes protecting and regulating telomeric regions contribute to approximately 1% of hereditary melanoma cases [27]. *TERT* is a part of these genes. The combined protein product of *TERT* and *TERC* (telomerase RNA component) is the telomerase reverse transcriptase as part of the telomerase complex. This complex is needed to manage the length of the telomeric regions at each end of the chromosome to prevent early replicative senescence [9, 30].

Pathogenic variants in *TERT* and *TERC* lead to disproportional elongation of the telomeric region, thus increasing melanoma and various cancer risks. They are also distinctly associated with superficial spreading and nodular melanoma [32].

Other associated cancers include breast, bronchial, ovarian, bladder, and renal cell cancer [30]. In addition to *TERT* and *TERC,* the two genes *OBFC1* and *RTEL1* are also discussed in the spectrum of telomere regulation and increased cancer risk [32].

MC1R (Melanocortin 1 receptor gene): MC1R is a medium-penetrance gene found on chromosome 16. Usually, the inheritance shows an autosomal recessive pattern; however, a dominant-negative effect on wild type alleles has also been described. It has been shown that inheriting any single pathogenic variant in *MC1R* can lead to a 28% higher risk of developing melanoma [9].

A common feature shared by *MC1R*, *MITF* (microphthalmia-associated transcription factor) and *SLC45A2* (solute carrier family 45 member 2) is that they are all part of a wider gene subgroup affecting tanning ability and skin pigmentation [9].

As its name indicates, *MC1R* encodes the melanocortin-1 receptor, which is a G protein-coupled receptor, triggering a signaling cascade when activated through the binding of α-melanocyte stimulating hormone (α-MSH) or UV radiation [9, 30]. This cascade runs via adenylate cyclase, increasing intracellular cAMP levels, microphthalmia-associated transcription factor (MITF), and tyrosinase. At the cellular level, this leads to the growth of melanocytes as well as melanization by shifting the production to darker UVB-ray-protecting eumelanin instead of brighter non-UVB-protecting pheomelanin. Other effects include dendrite formation, the development of the specific dendritic shape of melanocytes, which is needed to distribute melanins to neighboring keratinocytes, and roles in DNA repair [9].

Variants can lead to a reduced receptor density on the cells, thus also leading to a specific phenotype with the traits of red hair, fair skin, freckles, reduced tanning ability, and consequently, an increased risk of melanoma due to UV sensitivity [30]. There are two types of variants. *R* alleles are highly affiliated with the red hair color (RHC) phenotype, with which *r* alleles are less strongly associated [9].

A reduced tanning ability would be the simplest explanation for increased tumor rates. However, Caucasian patients with darker skin pigmentation have a higher melanoma risk when inheriting a pathogenic *MC1R* variant than their red hair colored counterparts. This leads to the conclusion that skin pigmentation processes are not the only drivers in this scenario, but also other regulatory mechanisms in the cell that are mediated by *MC1R* [9].

In addition to the upper body, which is usually a primary site of melanoma, it has been observed that the upper extremities are an affected site if pathogenic *MC1R* variants are present [30]. In addition, pathogenic variants of *MC1R* have been found to predispose to congenital melanocytic nevi, subsequently leading to an increased risk of melanoma as a complication [33].

MITF (Microphthalmia-associated transcription factor): MITF is a gene found on chromosome 3 with a single medium-penetrance pathogenic variant, p.E318K [8, 9]. Approximately 1% of Europeans have inherited this variant, which is believed to increase melanoma susceptibility by 3 to 5-fold or 8 to 31-fold if the family anamnesis is positive for pancreatic or renal cell cancer, respectively [30].

MITF is a part of the Myc proto-oncogene group and a key gene in the regulation and growth of melanocytes. The same-named protein product is believed to be a transcription factor for 37 genes in this cell type [9, 30]. MITF and other transcription factors are regulated by small-ubiquitin-like modifier proteins (SUMO) [9].

Research has shown that a specific pathogenic variant, *MITF* p.E318K, which leads to the substitution of glutamic acid with lysine at position 318, reduces the ability to bind to SUMO proteins, thus increasing cell cycle activities such as differentiation, proliferation, and survival of the melanocytic cells, making it a gain-of-function mutation [30]. The risk of melanoma is increased because the variant has a regulatory effect on 17 of the 37 genes regulated by MITF [9].

Table 1. Melanoma-subordinate syndromes

Syndrome name	Main pathology	Affected genes	Reference
Werner syndrome	Accelerated aging	*WRN*	[57, 58]
BRCA1- and BRCA2-associated hereditary breast and ovarian cancer syndrome (HBOC)	Breast and ovarian cancer	*BRCA1, BRCA2*	[59]
PTEN hamartoma tumor syndrome (PHTS) with its subform Cowden syndrome	Hamartoma, macrocephaly, gastrointestinal polyposis, lipoma, intellectual disabilities, disorders of the autism spectrum and increased cancer risk	*PTEN*	[18, 60]
Lynch syndrome Alternatively, hereditary non-polyposis colorectal cancer syndrome (HNPCC)	Colorectal, endometrial, and ovarian cancer	*MLH1, MSH2, MSH6, PMS2, EPCAM*	[57, 61]
Li-Fraumeni syndrome (LFS) Alternatively, sarcoma, breast, leukemia, and adrenal gland syndrome (SBLA)	Adrenocortical carcinoma, breast cancer, central nervous system tumors, osteosarcoma, soft-tissue sarcoma	*TP53*	[57, 62]
Xeroderma pigmentosum	Non-melanoma skin cancers	*XPA, XPB, XPC, XPD, XPF, XPG, POLH*	[18, 63]

A specific phenotypic observation for the *MITF* p.E318K variant is non-blue eye color, darker hair, yet fair skin [9, 30]. Familial atypical multiple mole-melanoma (FAMMM) and an elevated number of nevi are also associated with this variant [13].

Next to malignant melanoma, which may be nodular, amelanotic, and more thickened than usual, the pathogenic *MITF* variant is also associated with renal cell cancer, as MITF also activates hypoxia-inducible factor 1A (HIF1A) [30].

SLC45A2 (Solute carrier family 45, member 2): SLC45A2 is a gene found on chromosome 5 with medium-penetrance variants linked to cutaneous melanoma (CM) [9].

With seven exons, the gene codes for a 530 amino acid protein membrane-associated transporter of the melanosome—cellular organelles for the production of melanins [3, 34]. This transporter is thought to regulate, process, and transport proteins needed in the melanosome, for example, tyrosinase [9].

In addition to findings in regards to hereditary melanoma, *SLC45A2* variants also frequently undergo research in terms of general skin pigmentation and oculocutaneous albinism [35].

In various cases, the cutaneous melanoma-associated variant rs16891982 (p.L374F) has been associated with a protective role against the disease. Furthermore, the variant is associated with a phenotype of olive up to darker skin color, yet it also maintains its protective role for persons with fair skin coloration. The variant is found mostly in Southern Europe, with a decreasing gradient towards Northern Europe [9]. This finding is in discussion as other *SLC45A2* variants have been proposed as melanoma risk factors [34, 36, 37].

Affected genes in melanoma-subordinate syndromes

Pathogenic variants in melanoma-associated genes can predispose not only to melanoma, but also to a variety of specific cancers, which often derive from a specific tumor cluster and thus can be defined as a mixed cancer syndrome (MCS) or melanoma tumor syndrome [1]. These syndromes can manifest themselves as melanoma-dominant, with pathogenic variants in *CDKN2A*, *CDK4*, *BAP1*, *MITF*, and *POT1*, or as melanoma-subordinate syndromes. **Table 1** provides a summary of the latter [18].

Candidate genes

Only a few genes with high-penetrance variants associated with malignant melanoma have been identified, leading to the presumption that most cases of hereditary melanoma carry various low-risk gene alterations and other genetic modifiers [9].

Aside from the high-and medium-penetrance variants in the established genes described above, several genome-wide association studies (GWAS), for example mentioned in the study of Landi et al. (2020), have found a high number of loci associated with melanoma and its phenotypic associations such as pigmentation, tanning ability, and nevus count [9, 38]. Affected genes can also participate in DNA repair or regulation of the telomeric regions [38, 39]. **Table 2** provides an overview of candidate

Table 2. Melanoma susceptibility candidate genes

Affected mechanism or pathology	Candidate genes	Reference
Pigmentation and tanning ability	*ADAM15, AGR3, ASIP, CDKAL1, CYP1B1, DSTYK, FOXD3, GBA, GPR98, HDGFL1, IRF4, KIAA0930, MAFF, MCF2L, MED13L, MFSD12, MSC, MX2, OCA2, HERC2, PLA2G6, PPARGC1B, RP11-383H13.1, SOX6, TYR, TYRP1, ZBTB7B*	[8, 9, 38, 39, 42]
Nevus count	*AGR3, AKAP12, ASAP1, ATM, CASP8, CBWD1, CDH1, CYP1B1, DTNB, DTNBP1, FNM1, FTO, GDI2, HDAC4, HDGFL1, IRF4, IRX6, KIAA0930, KIAA1239, KLF4, MAFF, MFSD12, MKLN1, MSC, MTAP, OBFC1, PARP1, PLA2G6, PPARGC1B, RAPGEF1, RP11-383H13.1, SOX6, SYNE2, TFAP2B, TMEM38B* (intergenic), *TP53, ZFP36L1*	[9, 38, 39]
Dysplastic nevi	*CDK6, XRCC1*	[64]
Epidermal development	*CASP8*	[42]
DNA repair	*ATM, ERCC2, ERCC4, PARP1*	[9, 39, 42, 65]
Telomere length and maintenance	*CLMPT1L, MPHOSPH6, OBFC1, RETL1, TERT, TINF2*	[38, 42, 66]
Cell-cycle progression	*ATM, CCND1, CDK10*	[42]
Uveal melanoma	*ATM, BRCA1, BRCA2, CHEK2, CLPTM1L, CTNNA1, MDB4, MLH1, MSH3, MSH6, PALB2, PMS1, SMARCE1, TDP1, TP53*	[26, 67-71]
Single primary melanomas (SPM)	*CYP1B1*	[72]
Multiple primary melanomas (MPM)	*MGMT* (protective), *PIK3CA, SPI1* (protective)	[72-74]
Melanoma (not further specified)	*ACD, ACTRT3, ADTRP, AHNAK, AKAP12, APOBEC3A/3B, ARHGEF40, ARNT/SETDB1, ATM, BACH2, BRCA2, BRD9, BRIP1, CASP8, CBWD1, CCND1, CDC91L1, CDH23, CDKAL1, CDKN2B, CTSK, DLG2, DNAJB4, DOT1L, EBF3, EZH2, FABP2, FAM160B2, FAT3, FTO, FZD4, GATA2, GNA11, GOLM1, HAL, HERC2, HLA-DQB2, IKZF2, IL1RN, IRF/EXOC2, LASS2ANXA9, LMO3, LMO7, MAP3K1, MARK3, MCL1, MET, MGMT, MSH2, MTAP, MTH7B, MX2, MXI1, NEK11, NGLY1, NIPAL3, OCA2, PAH, PALB2, PARP1, PIGU, PLA2G6, POLE, PPFIBP2, PRKDC, PROSER2, PRSS23, PTPN14, RAD50, RAD51B, RAPGEF5, RASA3, RB1, RP11-256L6.3, RREB1, SDHA, SLC24A5, SLCO4C1, STK11, TMEM135, TMEM136, TMEM163, TYR, TYRP1, WRN, XRCC3*	[8, 9, 36, 39, 42, 54, 65, 72, 75-97]
	Copy number variation (CNV)-associated susceptibility: *ACBD3, ACDK3, AK055856, ANGPT1, BC032899, BC039356, CABC1, CDC42BPA, CDKN2A, CLP-36, CXCR4, E2F1, GBE1, GCNT2, IDH1, ITPKB, HIST1H1B, KIAA1296, LIN9, MIXL1, PARP1, PDE5A, PDLIM1, PSEN2, SORBS1, SPOPL, STUM, ZNF517*	[98-100]

genes that can harbor single or multiple low-penetrance germline variants associated with melanoma and its risk factors. These candidate genes were also visually displayed as a gene network analysis in **Figure 3**.

Polygenic risk scores (PRS)

Several genome-wide association studies (GWAS) have identified thousands of possible pathogenic loci with low susceptibility to melanoma. This can lead to possible embedding of polygenic risk scores with their weighted sum of low-risk variants into clinical application to improve risk prediction [40, 41]. Several polygenic risk scores have been developed for melanoma, which show increased sensitivity compared to regular phenotypic risk scores comprising of skin, eye and hair color, freckle and nevi number, environmental factors, and monogenetic predisposition. So far, these proposed polygenic risk scores are made up of 11-204 SNVs, with most of the scores containing between 11 and 45 examined SNV locations [42].

Noteworthy PRS findings due to their high odds ratios (OR) for high-risk groups were published by Potjer et al. (2021) and Bakshi et al. (2021), with maximum OR values of 5.70 and 3.66, respectively [43, 44]. The PRS was significantly higher in patients with multiple primary melanomas (MPM) than in those with single primary melanomas (SPM). However, PRS values were slightly, although not significantly lower in families with a higher than average cancer burden, probably due to the possible presence of a more dominant, still unidentified, family-specific single pathogenic variant [44]. Graff et al. (2021) also found a link between melanoma and cancer of the oral cavity and pharynx, while analyzing several cancer PRS and their possible pleiotropy [45].

PRS for skin cancers are not currently in clinical use, although some show equally good sensitivity rates as polygenic risk scores for prostate, lung, or breast cancer, which are commonly included in regular gene panel testing [40, 42]. It has to be mentioned that until now, GWAS for melanoma have only been conducted in

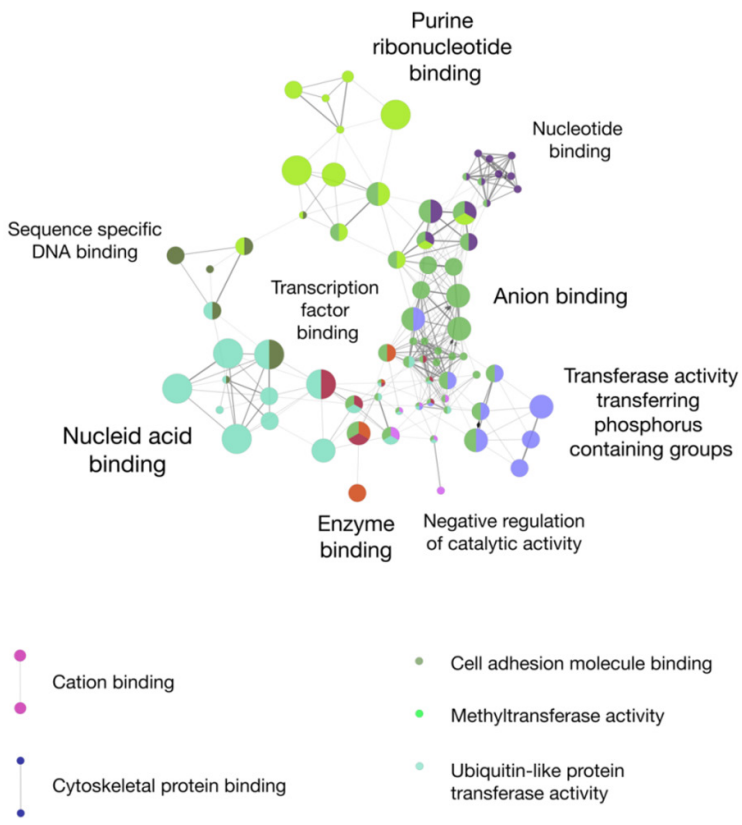

Figure 3. Melanoma susceptibility candidate genes grouped by molecular function. We used the ClueGO framework (Version 2.5.8) in Cytoscape (Version 3.8.2) to visualize a gene network analysis of melanoma susceptibility candidate genes [101, 102]. Colors represent affiliations to gene groups with similar molecular functions. The node size and leading GO term were based on the gene quantity per term. GO term fusion was applied.

Western populations and that participating patient numbers were limited [42]. In this context, Zhang et al. (2020) predicted that considerably increasing sample numbers could lead to a 40% reduction in missing hereditability of GWAS and at the same time, improve PRS quality [41]. Another effort to advance research in the field of low-penetrance variant risk prediction is found in the "Cancer PRSweb" project, a database systematically collecting publicly available PRS data and currently evaluating it against the biobanks of Michigan Genomics Initiative and UK Biobank [46].

Gene interactions

The epistasis of gene variants can affect melanoma susceptibility. It has been found that pathogenic *MC1R* variants have a direct positive effect on the penetrance of pathogenic *CDK2NA* variants. There have been other results on epistatic interactions between *SLC45A2* and *VDR* (vitamin D receptor), *MC1R* and *TYR* (tyrosinase), as well as *TERF1* (telomeric repeat binding factor 1) and *AFAP1L2* (actin filament associated protein 1 like 2), with the last-mentioned pair further confirming a connection between telomere length and melanoma risk [9, 39]. Sangalli et al. (2017) discovered a sex-specific genetic interaction. Men who carry the *RNASEL* rs486907 A allele, as well as the C allele of miR-146a rs2910164, have a higher risk of developing malignant melanoma [47]. Wu et al. (2018) suggested two clusters with five and 17 genes, respectively, leading to an increased melanoma risk due to their epistatic interactions although their findings need further statistical validation [48]. Furthermore, while doing a study on a polygenic risk score (PRS) for a Dutch population, Potjer et al. (2020) discovered, that in order to develop melanoma, carriers of the MITF p. E318K variant require additional genetic risk factors and a high PRS may represent these. They hypothesized that this might also be true for other medium-penetrance variants [44].

Constitutional epigenetics

As a newer field in genetics, epigenetic alterations have been widely researched with regard to somatic melanoma mutations. In the last few years, there has also been an effort to prove a statistical association between constitutional epigenetic changes associated with hereditary melanoma, either with or without present pathogenic DNA variants [49]. The focus of these studies was mostly on hypo- and hypermethylation. Other mechanisms of epigenetic change may include chromatin remodeling, histone modifications and regulation by non-coding RNAs [12, 50-52].

Table 3. Constitutional epigenetic changes of specific genes and melanoma susceptibility

Study	Gene methylation associated with melanoma risk factors	Gene methylation associated with cutaneous melanoma	Reference
Pergoli et al. (2014)	DYSPLASTIC NEVI Positive: *ALU* Negative (protective): *hTERT, TNF-α*	Positive: *CDKN2A/p16, MLH1, TNF-α* and with lower nevi count *(<20), ICAM-1* and *ALU* can also be associated with cutaneous melanoma Negative (protective): *CDK4*, yet positively associated with higher nevi count (>20)	[12]
Hyland et al. (2014)	-	Hypomethylation of *TNFRSF10C* (occurred only in probands without *CDKN2A* pathogenic variants)	[11]
Cappetta et al. (2015)	-	Widespread non-gene specific DNA hypomethylation in leukocytes (also valid for breast cancer)	[53]
Roos et al. (2017)	HIGH NEVUS COUNT Hypermethylation: *ARRDC1, FAM107B, KCNN4* Hypomethylation: *CTC1, GABRB3* Unspecified DNA methylation changes*: NID1, PLA2G6, RAF1, STUM, ZSWIM2*	DNA methylation changes in *ACTRT3, ANXA9, ARNT, ASIP, ATM, CASP8, CDC91L1, DKN2A, CLPTM1L, CTSK, DOCK3, EYS, FTO, LASS2, MC1R, MCL1, MX2, NR, PARP1, PLA2G6, SETDB1, SLC45A2, TERT, TET2, TYR*	[54]

The most recent genome-wide association study (GWAS) by Salgado et al. (2020) did not find any support for heritable epimutations as a cause of familial melanoma. However, they studied a small group, which spanned only five families from the Netherlands where melanoma occurred throughout the ancestral tree [52]. In addition, no specific promoter methylation events were found by Boru et al. (2019) regarding uveal melanoma in melanoma-prone families or by Hyland et al. (2013) for the promoter region of *LINE-1* (long interspersed nuclear element-1) in cutaneous melanoma [49, 50].

In contrast, several other studies have shown significant changes in methylation patterns in peripheral blood cells, as surrogate cells, and subsequently proposed a possible link between epigenetic alterations and the risk of melanoma [11, 12]. Pergoli et al. (2014) studied peripheral blood mononuclear cells (PBMCs) as non-tumor substitution cells. They suggested a possible link between germline (constitutional) epimutations and the risk of cutaneous melanoma, although they could not exclude the roles of environmental factors and somatic epimutations. They observed that controls carrying dysplastic nevi were more likely to show decreased methylation levels of *TNF-α* and *hTERT*. Cutaneous melanoma itself was associated with increased methylation of the *TNF-α* promoter and the transposable element *ALU*. Increased methylation of *CDKN2A/p16* and MLH1 in PBMCs was found to be associated with cutaneous melanoma [12]. Cappetta et al. (2015) discovered a statistically viable link between DNA hypomethylation in leukocytes, melanoma, and breast cancer [53]. Hyland et al. (2014) found statistical evidence that constitutional hypomethylation and increased expression of *TNFRSF10C* in blood DNA might be associated with cutaneous melanoma. Their study included *CDKN2A* variant positive and negative cases [11]. In contrast to Pergoli et al., there was no evidence that constitutional epigenetic changes in *CDKN2A* might play a role in cutaneous melanoma susceptibility, however, interestingly *TNFRSF10C* hypomethylation only occurred in *CDKN2A* pathogenic variant-free probands [11]. The first epigenome-wide association study (EWAS) related to melanoma risk factors was performed by Roos et al. (2017), who showed that several differentially methylated regions are associated with a higher nevus count and melanoma risk. The top-ranked regions involved strong enhancers in melanocyte biology such as *RAF1* and *CTC1*. In *cis*, differentially methylated regions in known GWAS SNVs, for example, in *PLA2G6* and *NID1* were associated with increased nevus count, and in *MC1R*, *MX2*, and *TERT/CLPTM1L* with melanoma risk [54]. The epigenetic findings from the studies mentioned above are shown in **Table 3** and **Figure 4**.

Overall epigenetic research in melanoma has advanced more towards markers for detection and management of malignant melanoma. However, for treatment prognosis, Cortellini et al. (2018) showed that patients with a variety of hereditary cancers, including melanoma, had a significantly better response to treatment, an increased time to treatment failure, and a better overall survival rate [55].

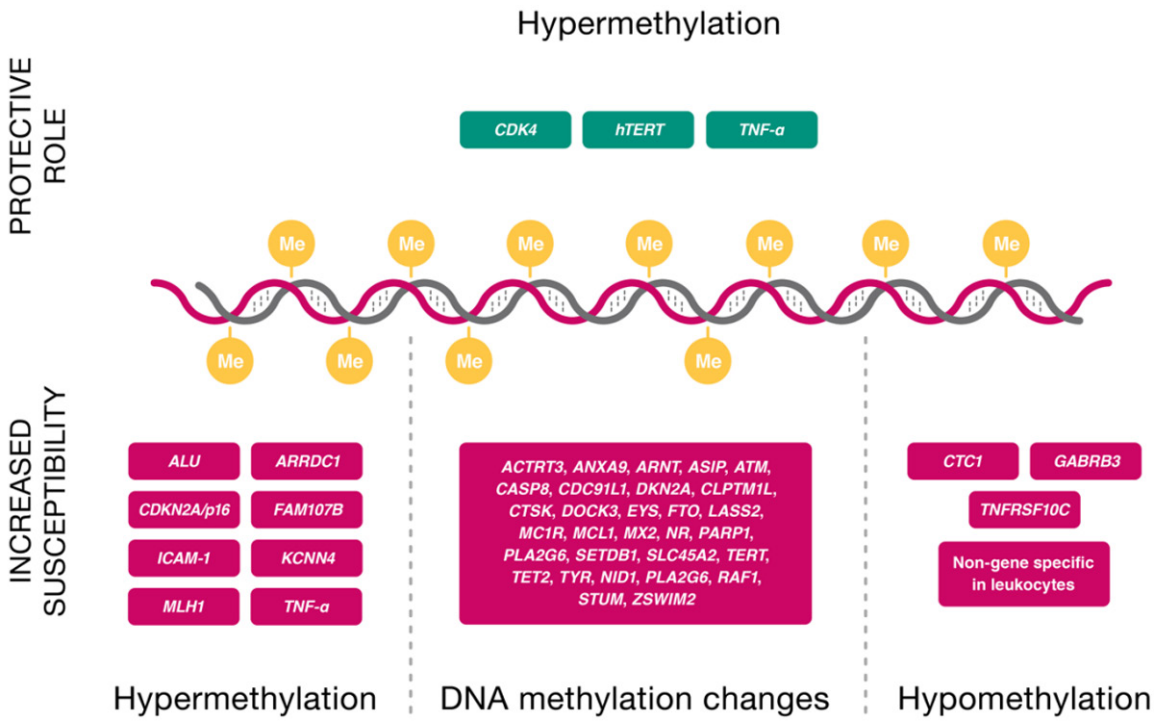

Figure 4. Constitutional epigenetic changes of specific genes associated with melanoma and its risk factors. Me: methyl group.

Discussion

In analyzing scientific work, mostly from the last five years, this review aimed to collect and summarize all available up-to-date knowledge on genetic and epigenetic pathomechanisms of melanoma susceptibility.

Findings and recommendations indicate that the scientific achievements of the previous years can be used in two ways; either to reduce mortality rates through better genetic and thus clinical screening for this cancer type, or, second, to increase chances of better treatment outcome through personalized medicine, relying on genetic and epigenetic markers.

We expected to find genome-wide association studies resulting in the discovery of several high-or medium-penetrance germline variants. However, research has shown that malignant melanoma is a cancer that is most likely to develop not only due to high-penetrance variants but also due to polygenic inheritance patterns, leaving no clear division between the hereditary and sporadic development of tumors [9, 31]. As a result, there were noticeable early changes in genetic testing. Previously, only a few single genes were tested clinically. Today, polygenic risk scores (PRS) for malignant melanoma are in development, showing equally good sensitivity rates to those for prostate, lung, or breast cancer, which are commonly included in regular gene panel testing. These polygenic risk scores contain, in addition to high-penetrance variants, a wide array of pathogenic low-and medium-penetrance germline variants that are being tested [31, 40, 42]. To make polygenic risk scores for melanoma viable for clinical use, larger biobanking, studies on wider and higher variety of populations, and validation of risk prediction reliability are necessary [42].

Genetic testing for melanoma risk could be especially beneficial to teenagers and young adults, as intensified screening can detect lesions early [7, 56]. In addition, a negative test result after genetic testing can provide partial relief to especially anxious family members [1].

Unsurprisingly, several pathogenic variants increase susceptibility to melanoma in fair-skinned patients. Despite this, specific germline variants, which are associated with increased melanoma risk, have been found in patients

with a darker skin type [9]. Generally, risk group patients harboring pathogenic germline alterations should undergo more frequent dermatological check-ups, as better treatment outcomes often follow early lesion detection. It is a common motivation to support intensified genetic testing, as this could be a method to increase the productive years of affected individuals and possibly lower the financial burden on healthcare systems.

Limitations to findings in studies on melanoma susceptibility are the few studies, small population sizes, and the lack of ethnic diversity. Studies are mostly undertaken in Western countries of the Northern Hemisphere, as well as in Australia.

In conclusion, further studies with larger populations and a wider variety of ethnicities and diverse geographical areas are recommended. It would also be advisable to endeavor this in the form of partnerships between several institutions to create bigger datasets, thus hopefully finding additional genetic patterns with increased accuracy. As previously mentioned, this could lead to improved prediction of melanoma susceptibility, which is most likely applicable through advanced polygenic risk scores. The use of advanced risk scores, consisting of PRS, genetic, epigenetic, and phenotypic risk factors, could be favorable, especially for countries that lack infrastructure for satisfactory melanoma screening programs [40].

Disclosure of conflict of interest

None.

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