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Copy number variations in malignant melanoma: genomic regions, biomarkers, and therapeutic targets

Minireview

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Malignant melanoma is a skin tumor arising from melanocytes, occurring mostly in predisposed individuals. Melanomas are frequently present with copy number variations (CNVs), i.e., gains or losses of specific DNA regions that have provided immense potential for disease diagnosis and classification. The methodology of CNV detection has revolutionized in past decades, and current high throughput technologies enable us to analyze the entire spectrum of CNV alterations at the whole genome scale. Thus, identifying novel CNV biomarkers and evaluating their applicability in biomedicine are becoming increasingly important. The aim of this review was to summarize copy number changes occurring in malignant melanomas. We made an overview of specific genes and chromosomal locations affected in sporadic and familial melanoma and also of known germline alterations in melanoma-prone families. We summarized genomic regions aberrant in malignant melanoma and highlighted those frequently discussed in the literature, suggesting 7q, 11q, 12q, 9p, and 1q, but also others, as the most affected ones.

Key words: malignant melanoma; copy number variation; genomic disorder; structural variation

Malignant melanoma (MM) is an aggressive tumor that originates from melanocytes, cells producing pigment melanin [1]. Apart from the skin, melanomas can also arise in the eye, meninges, and mucosal surfaces [2]. It is characterized by heterogeneity and its formation is influenced by the genetic background of the individual in combination with different environmental aspects. There are several risk factors for melanoma development, such as age, presence of an increased number of nevi, clinically atypical nevi, family history, personal history of sunburns, exposure to UV radiation, and having certain physical characteristics (fair skin, light eyes, red or blonde hair) [1, 3]. With the rapid increase of its incidence, together with the high metastatic potential of even small melanomas, it is a leading cause of cancer death [4]. In Europe, the incidence rate is 10–25 new melanoma cases per 100,000 inhabitants, with a recent increase for all age groups [2]. There are several genetic alterations involved in MM development. Pathological changes arise among functionally related molecular pathways such as MAPK, AKT/PI3K, c-KIT, CDK, GNAQ/GNA11, MITF, NRAS (could affect both MAPK and AKT/PI3K pathways), and P53/BCL [5]. It is thought that around 10% of melanoma cases are caused by a family history of the disease [6].

Copy number variations

Copy number variations (CNVs) are unbalanced structural genomic aberrations characterized by deletions, insertions, or amplifications of DNA segments (Figure 1A) ranging from 50 bps up to several Mbs [7, 8]. This molecular phenomenon may vary among individuals and has diverse biological roles, ranging from having no effect on common physiological traits to the development of genetic disorders [9]. Since a variable range is typical for CNVs, depending on

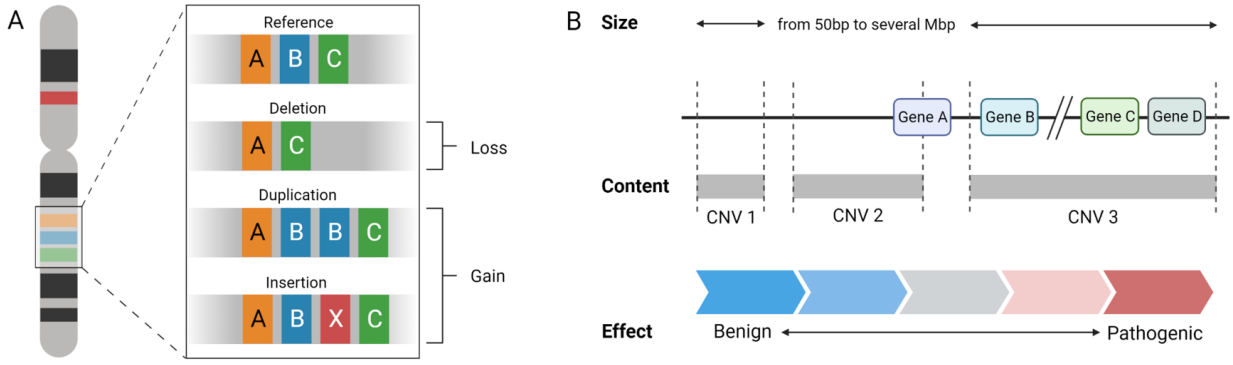

Figure 1. Copy number variation. A) There are three main types of unbalanced structural variability leading to gain (duplications, insertions) or loss (deletions) of genomic material. B) CNVs may span non-coding regions (CNV 1) but may also intersect genes (CNV 2) or encompass several genes and genomic elements (CNV 3). Depending on the affected genomic content, CNVs may lead to phenotypic consequences ranging from benign to pathogenic effects.

their length, they may affect only part or the entire gene, but also a larger genomic segment (Figure 1B) containing several genes, including their regulatory regions [10]. An increase or decrease in the number of copies of a particular gene or genomic region can have a significant impact on the development of various types of disease. To date, there is a long list of diseases associated with CNVs, including cardiovascular [11, 12], neurodegenerative [13], autoimmune diseases [14, 15], and cancer, among others. Even for such a heterogenous disease as cancer, it has been proven that CNVs of certain genes and genome regions are involved in the development and progression of multiple cancer types, including, for example, colorectal cancer [16, 17], lung cancer [18], and last but not least melanoma [19]. Thus, CNVs can serve as a cancer biomarker.

Methods for CNV detection

CNV detection has evolved from conventional cytogenetic techniques to the most recent massively parallel sequencing (MPS). Early techniques relied on visual inspection of chromosomes, improving gradually with the lowering of detection limits from numerical anomalies of whole chromosomes to mega base-scale aberrations. Hybridization-based techniques allowed the detection of mid-sized CNVs. Cytogenetic techniques, along with molecular techniques, have been combined to introduce molecular cytogenetics methods, such as FISH and comparative genomic hybridization (CGH). Additionally, microarray-based methods, specifically aCGH, provided genome-wide coverage at a much higher resolution, becoming the standard in CNV detection. PCR-based methods and their modifications brought the resolution to single nucleotides, with upper detection limits at hundreds of kb or a few Mb. The invention of MPS allowed analyzing the whole size range of CNVs in single runs at scales of whole genomes [20].

CNV and MM

CNVs occur at a frequent rate in MM tumors [21]. MMs with a poor prognosis were associated with a significantly higher incidence of genomic instabilities and contained significantly more copy number changes than MMs associated with a good prognosis [22]. In the late 90s, Bastian and colleagues described, by CGH, the frequent chromosomal copy number changes in melanoma tumor tissue samples. Losses occurred on chromosomes 9, 10, 6q, and 8p and copy number gains on chromosomes 7q, 8q, 6p, 1q, 20, 17, 2, 4q, 5p, and 11q [23]. Since then, numerous scientific groups have devoted their research to the identification of common CNVs in melanomas. Nowadays, lots of whole-genome sequencing datasets of different tumors are available online. For instance, the National Cancer Institute's GDC (Genomic Data Commons) Data portal [24] includes validated datasets of several cancer genome programs such as TCGA, GENIE, and others. When searching for skin cancer, 2,333 cases of nevi and melanoma with 20,658 genes affected are found to this date. According to this database, the most common CNV gain is in genes *KDM7A*, *KIAA1549*, *PARP12*, *HIPK2*, *UBN2*, and *ZC3HAV1L,* while the most frequent loss spans *CDKN2B*, *CDKN2A*, *AL359922.1*, *MTAP*, *DMRTA1,* and different interferon alpha genes. Although, their functions in carcinogenesis are very variable, from downregulation of angiogenesis, inhibition of tumor growth, and DNA repair [25–27] to tumor development and progression [28–30]. When we focus on a subset of the original GDC data including only genes from the COSMIC database [31] v96, the most common CNV gain spans *KIAA1549, TRIM24, BRAF* and the most frequent loss include *CDKN2A, MLLT3, NFIB* genes.

However, the data differ among databases [32], so there is currently no consensus on the most frequently aberrant genes in MM. Moreover, datasets are very extensive and

Table 1. Copy number gain: specific genes/chromosomal regions commonly amplified in malignant melanoma. Copy Number Gain

Gene	Region/Chromosome	Study
Not specified	7q, 8q, 6p, 1q, 20, 17, 2, 4q, 5p, 11q	[23]
BRAF	7q34	[19, 21, 38, 40, 41, 43, 45, 65, 70]
c-KIT	4q12	[38-41, 51, 57, 70]
C-MYC	8q24.21	[21, 39-41, 65, 81]
CCND1	11q13	[19, 21, 38-42, 52, 54-56, 70, 75, 83]
CCND3	6p21.1	[39, 65]
CDK4	12q14.1	[21, 38-41, 52, 54, 55, 65, 70, 75, 83]
CDKN2A (rare)	9p21.3	[66]
EGFR	7p11.2	[41, 65]
EP300	22q13.2	[38, 40, 75]
ERBB3	12q13.2	[39, 65]
E2F1	20q11	[61]
GAB2	11q14.1	[40, 57, 70]
KRAS	12p12.1	[39, 43, 52]
MDM2	12q15	[38-41, 43, 52, 65, 70]
MDM4	1q32.1	[39, 65]
MET	7q31	[39, 41, 62, 65]
MITF	3p13	[19, 38, 41, 46, 70]
NOTCH2	1p12	[40, 41, 70]
NRAS	1p13.2	[19, 38, 52]
PAK1	11q13.5-q14.1	[40, 52]
PDGFRA	4q12	[38, 39, 41]
PD-L1	9p24.1	[38, 48, 49]
SKP2	5p13.2	[40, 64, 75]
TERT	5p15.33	[21, 38, 40, 41, 43, 52, 70]
Not specified	22	[83]
+ *TAOS1, FGF3, FGF19, FGF4, EMS1*	11q13	[42]
+ *KDR, JAK2, AKT3 etc.*	4q12; 9p24.1; 1q43-q44	[38]
+ *MLL3*	7q36.1	[43]
+ *CLPTM1L, SPEF2 etc.*	5p15.33; 5p13.2	[52]
+ *CKS1B, AKT3, MUC1 etc.*	1q21.3; 1q43-q44; 1q22	[65]
+ *RICTOR, AURKA, IGFR1, CCND2*	5p13.1; 20q13.2; 1q21.2; 12p13.32	[39]
+ *RHEB, FGFR3, SMO etc.*	7q36.1; 4p16.3; 7q32.1	[21]
+ *RB1, DAXX, NRAS etc.*	13q14.2; 6p21.32; 1p13.2	[70]
+ *YAP1*	11q22.1	[40]

require additional co-analysis on mRNA and protein levels. Several researchers have been involved in the precise analysis and identification of the specific genes affected by CNV in MM. Studies are either based on the evaluation and analysis of available sequencing datasets [33–37] or performed on MM samples, such as tissue [38–40], cell lines [19, 41, 42], or circulating tumor cells [43]. Due to an extensive number of papers published, we have focused this review on sample studies only (Tables 1–3; Supplementary Table S1).

Copy number gain

The most common mutation found in approximately half of all melanoma patients is *BRAF V600E* (previously reported as V599E). This mutation leads to an alteration in a BRAF protein which results in continuous activation of the MAPK signaling pathway [44]. *BRAF* amplification events may also accompany *BRAF* mutation [45], the same applies to *NRAS* mutation and *NRAS* amplification [38]. *BRAF* can be co-amplified with *MITF*, *NRAS*, *CCND1* [19], and *PD-L1* [38] genes. Genomic amplification of *MITF*, found in approximately 15% of melanomas, correlated with a significantly increased mean MITF protein expression [46]. *PD-L1*, primarily expressed in chronic sun-damaged melanomas [47], is one of the targets of anti-PD therapy. A study focused on copy number changes of *PD-L1* gene has shown that although CNV gain was present in 41.6% of tissue samples, immunohistochemistry was positive in only 8.33% [48]. This fact is supported by a study on rare vaginal melanomas where no *PD-L1* expression was detected despite the *PD-L1* FISH positivity [49]. Another common mutation occurring in MM (mainly in patients with acral lentiginous melanoma)

Table 2. Copy number loss: specific genes/chromosomal regions commonly deleted in malignant melanoma. Copy Number Loss

Gene	Region/Chromosome	Study
Not specified	9p, 10q, 6q, 8p	[23]
ARID1B	6q25.3	[38, 41, 65, 70]
ATM	11q22.3	[65, 70, 75]
CDKN2A/B	9p21.3	[19, 38-41, 43, 52, 55, 65, 66, 70, 75, 81, 83]
NF1	17q11.2	[40, 41, 52, 70]
PD-L1 (rare)	9p24.1	[48]
PTEN	10q23.31	[19, 38-41, 43, 52, 65, 70, 83]
PTPRD	9p24.1-p23	[19, 38]
SPRED1	15q14	[40, 70]
TP53	17p13.1	[39, 41, 65]
Not specified	4q	[83]
+ *HDAC4*	2q37.3	[19]
Not specified	10q23-q26, 11q23-q25	[67]
+PDE4D, LINC00290, RBF0X1 etc.	5q11.2-q12.1; 4q34.3; 16p13.3	[38]
+ ARID2	12q12	[41]
+ ASAH2, TEX15 etc.	10q11.23; 8p12	[52]
+ JAK2, RAD50, APC etc.	9p24.1; 5q31.1; 5q22.2	[65]
+ CHEK2	22q12.1	[39]
+ NF2	22q12.2	[70]
+ CHEK1, RAD51, FANCA	11q24.2; 15q15.1; 16q24.3	[75]

Table 3. Germline CNV. Germline copy number changes (gain, loss) detected in melanoma-prone families.

Gene	Region/Chromosome	Study
Germline CNV Gain		
ANGPT1, IDH1, PDE5A, HIST1H1B, GCNT2, MAD2L1, SFTPD, VLDLR, SFTPA1, TMEM14C	8q23.1, 2q34, 4q26, 6p22-p21.3, 6p24.3-p24.2, 4q27, 10q22.3, 9p24.2, 10q22.3, 6p24.2	[91]
CTNNA2a, mir4264	2p12	[92]
+ GRM6, ADAMTS2, ZNF879, ZNF354C	+ 5q35.3	
E2F1	20q11	[96]
GBE1	3p12.2	[90]
+ CLP-36, SORBS1, PDLIM1, KIAA1296	10q23.33	
IL8, CXCL6, PPBPL1, PF4V1, CXCL1, PF4, PPBP, CXCL5, CXCL3, PPBPL2 + IL8, PPBPL2	4q13	[87]
Germline CNV Loss		
ANGPT1, IDH1, PDE5A, HIST1H1B, GCNT2, MAD2L1, SFTPD, VLDLR, SFTPA1, TMEM14C	8q23.1, 2q34, 4q26, 6p22-p21.3, 6p24.3-p24.2, 4q27, 10q22.3, 9p24.2, 10q22.3, 6p24.2	[91]
BC032899, ACBD3, MIXL1, LIN9, PARP1, AK055856, C1orf95, ITPKB, PSEN2, CABC1, ACDK3, CDC42BPA, BC039356	1q42.12-13	[90]
CDKN2A	9p21.3	[86]
+ ZNF517, region near SPOPL, CXCR4	8q24.3, 2q22.1	[90]

is in gene *c-KIT* (4q12) [50]. Increased copy number of the *c-KIT* gene was found in 27.3% of acral and 26.3% of mucosal melanomas but this amplification was less common among cutaneous 6.7%, conjunctival 7.1%, and choroidal melanomas 0%. Also, *c-KIT* copy number did not necessarily correlate with *c-KIT* mutation status [51]. Genes *PDGFRA* and *KDR* (coding for vascular endothelial growth factor VEGF) can be co-amplified with *c-KIT* [38, 41]. In addition to *KIT* amplification, acral and mucosal melanomas were dominated by CNV gains affecting *PDGFRA*, *CDK4*, *RICTOR,* and *CCND2* [39], while in acral MM only, *TERT* and *PAK1* genes were amplified [52]. Mutations in *PDGFRA*, a target for tyrosine kinase inhibitor (TKI)-based targeted therapy, seem to be mutually exclusive with mutations in *c-KIT* [53]. Amplification of the chromosomal region 11q13 is a common event in primary melanomas [42, 54]. The gain occurs mainly in *CCND1* gene, but several oncogenes and/or cancer-related genes such as *TAOS1, FGF3, FGF4, FGF19,* and *EMS1* can be coamplified [42]. Increased *CCND1* gene copy number has been particularly observed in acral melanoma subtypes [55], occasional amplification has been described in lentigo maligna and superficial spreading melanomas, while only sporadic ampli-

fication was present in nodular melanoma [56]. *GAB2* gene amplifications are associated with MMs arising from unprotected acral and mucosal sites and are independent of genetic alterations in *BRAF*, *NRAS*, and *KIT* genes [57]. Another common amplification is in *MYC* gene [21, 41], found mainly in uveal melanomas [39]. *C-MYC*-expressing melanoma cells were found more frequently at metastatic sites and were associated with increased tumor aggressiveness [58]. *EP300* amplification occurs more often in primary tumors (31%) than in recurrence/metastasis tumors (8%) [40]. Emmons and colleagues studied *EP300* gene expression and its impact on melanoma development. Inhibition of EP300 expression increased the invasion of melanoma cells and their resistance to stress [59]. *E2F1*, an overexpressed gene in melanoma, is another potential target since blocking E2F1 can induce the death of melanoma cells resistant to BRAF inhibitors [60]. Nelson and colleagues showed that an increased copy number of this gene correlated with increased levels of the E2F1 protein [61]. *MET* gene amplification, detected in 11% of melanomas [62], can be another potential target for MET tyrosine kinase inhibitors therapy. SKP2-p27 pathway aberrations have been identified in several solid tumors, including MM [63]. Specifically, copy number gain is a major contributing mechanism of *SKP2* overexpression in metastatic melanoma [64]. Other CNV amplifications were detected in genes *CCND3*, *EGFR*, *ERBB3*, *KRAS,* and others [39, 41, 43, 65] but also in *CDKN2A* and although this gene is mainly deleted in MM, extra 9p21 copies were observed in the advanced stage melanomas [66].

Copy number loss

According to the COSMIC database and GDC Data portal, the most common copy number loss is in genes located on chromosomal region 9p21.3, specifically *CDKN2A* and *CDKN2B*. However, these genes are associated mainly with familial melanomas and are discussed in more detail in the next section. Another common deletion is in the gene *PTEN*, frequently found in BRAF-mutant melanomas [19, 38]. This confirms findings that MMs with the *BRAF* mutation were more likely to show losses on the 10q23-q26 sequence (*PTEN* location) than those with the *NRAS* mutation where losses were mainly localized on the 11q23–q25 sequence [67]. Loss of *PTEN*, a negative regulator of the PI3K-Akt pathway [68], results in melanoma development through the reduction of apoptosis and increasing cell survival [69]. *PTEN* and *TP53* deletion (together with *EGFR* amplifications) was found in MM patients with disease progression while on immune checkpoint inhibitors, PD-1, and CTLA-4 antibodies [39]. Gene *NF1* is significantly mutated in acral melanomas [40, 41]. Region 17q11.2 (*NF1*), together with 9p21.3 (*CDKN2A*), were recurrent locations of focal copy number loss in this melanoma type [40]. *ARID1B*, frequently deleted and mutated in melanoma [41, 65, 70], is one of the genes encoding SWI/SNF (SWItch/Sucrose NonFermentable) subunits. SWI/SNF chromatin remodeling enzymes play important roles in MM development and progression [71]. Copy number losses of genes *PTPRD* and *HDAC4* were also reported in melanoma cell lines [19]. *PTPRD* gene is commonly mutated in MM [72] and although *HDAC4* mutations appear to be rare [73], changes in expression have been detected in a number of tumors [74]. *CHEK2* loss was found mainly in cutaneous and mucosal melanoma [39], deep deletions of *CHEK1* and *ATM* in acral melanomas [75], and *MDM2* gene was amplified mainly in metastasis [52]. Another frequently deleted gene in human cutaneous melanoma is *SPRED1* (Newell et al. 2019; Newell et al. 2020). Copy number loss of this gene can be associated with acquired resistance to MAPK inhibition (Ablain et al. 2021). Additionally, although *PD-L1* is mainly amplified in MM, rare deletion of this gene can be present [48].

Familial melanoma

The term "familial melanoma" refers to a family in which there are at least two first-degree relatives or three or more melanoma patients on the same side of the family [76]. It occurs in families with autosomal dominantly inherited mutations in the *CDKN2A* and *CDK4* genes [77, 78]. The *CDKN2A* gene encodes (together with p14) p16 protein that binds to CDK4 and CDK6 (which phosphorylate *RB* tumor suppressor gene) and negatively regulates cell cycle progression [79]. Mutation in the *CDKN2A* affects the binding of p16 to CDK4 and thus promotes cell proliferation. Furthermore, a rare mutation in *CDK4* causes the expression of proteins able to escape the p16-binding thus allowing continuous phosphorylation of pRB [77]. Deletion of 9p21 region (*CDKN2A*) is present in both early- and late-stage melanomas [66]. Loss of 9p21.3, which includes *CDKN2A* and *CDKN2B* genes, is associated with poor prognosis [80]. Moreover, *CDKN2A* deletions combined with *C-MYC* increased copy number changes seem to be related to a low metastatic potential and better patient outcomes in primary nodular melanoma [81]. Although gene *CDKN2A* is predominantly deleted, rare amplification can occur [66].

CDK4 amplification was detected in different melanoma subtypes [54], mostly gaining 3–4 copies, but in some cases, more than 8 additional copies of this gene were detected [55]. Co-amplification of *CDK4*, together with *MDM2, TERT* [70] as well as *CCND1,* was observed in MM without *BRAF*, *RAS,* or *NF1* mutation [38]. Moreover, *CDK4* and *CCND1* amplifications are mutually exclusive, and the same applies to *CDK4* amplification and *CDKN2A* deletion. It suggests that *CDK4* gain precludes *CDKN2A* loss. As the binding ratio of CDKN2A and CDK4 proteins is 1:1 [82], it seems that a decrease enhances MM development in this ratio resulting in not as strict checkpoint control for S phase entry [83].

Germline CNVs

Whereas it is known that copy number changes play a role in MM, their role in cancer predisposition is still not

fully understood. It is thought that both common and rare CNVs may contribute to cancer susceptibility, but from a population-wide perspective, their impact seems limited. Inconsistent results were shown by previous studies that have investigated the link between CNV burden and familial cancer risk [84, 85]. Identifying germline CNVs in high-risk melanoma-prone families can be used as a search tool for novel cancer-predisposing genes. For instance, large germline deletions of *CDKN2A* have been found in approximately 2% of melanoma-prone families [86]. In 2012, Yang and colleagues identified a duplicated region on chromosome 4q13, in the germline DNA of patients from melanoma-prone family. It includes 10 genes, most of which encode CXC chemokines, *IL8*, *CXCL6*, *PPBPL1*, *PF4V1*, *CXCL1*, *PF4*, *PPBP*, *CXCL5*, *CXCL3*, *PPBPL2*. The *IL8* and *PPBPL2* genes were partially affected, and the remaining eight genes were completely contained in the duplicated region [87]. Additionally, studies have shown, that genes *CXCL1* (melanoma growth-stimulating activity alpha) and *IL8* (interleukin 8) play a role in the stimulation of melanoma growth, both *in vitro* and *in vivo* [88, 89]. Several rare CNVs, either in known melanoma genes (e.g. *CDKN2A* or *PARP1*) or co-segregated with melanoma (deletions on 8q424.3, 2q22.1 and duplications on 10q23.23, 3p12.2), were identified. Some of them were correlated with expression changes in disrupted genes using RNASeq, such as lower expression level of PARP1 in 1q42.12-13 deletion carrier, or low ZNF517 expression in 8q24.3 loss [90]. Fidalgo *et al.* searched for rare CNVs in 41 melanoma-prone patients (negative for *CDKN2A* mutation) who met the criteria for familial or multiple primary melanomas, or both. In nine probands, ten rare CNVs were identified by SNP microarray analysis in genes that play a direct role in melanoma cells *ANGPT1, IDH1, PDE5A, HIST1H1B,* and *GCNT2* and in the genes *MAD2L1, SFTPD, VLDLR, SFTPA1, TMEM14C* which are indirectly related to melanoma by interacting with the major genes of signaling pathways involved in melanin production, angiogenesis, and cell cycle control [91]. Rare germline CNV duplications of regions 2p12 and 5q35.3 were found in a patient who developed both melanoma and intraepithelial neoplasia of the pancreas [92]. This region includes, among others, genes *CTNNA2*, *GRM6,* and *ADAMTS2* which play crucial roles in different tumor types [93–95]. Interestingly, Rocca and colleagues found an increased germline copy number of the *E2F1* gene. They evaluated its mRNA expression in a melanoma cell line, SK MEL 267, and found that heat exposure (39°C) alone can significantly induce E2F1 expression [96].

CNVs, ethnicity, and sun exposure

Melanoma incidence and mortality rates can vary by race and geographic location. According to the GLOBOCAN 2020 database, the incidence rate of MM varies widely by region, with the highest rates reported in Australia and New Zealand, North America, and Europe [97]. CNV profiles of MM tumors can also differ among individual races and ethnicities [21, 70]. For instance, the mutational profiles of MM in China are significantly different from Western countries. Analysis of Chinese melanoma samples showed that CNV amplifications of acral melanoma were significantly fewer than those of cutaneous melanoma [21]. On the other hand, Curtin's and Hayward's findings suggest, that acral and mucosal melanomas show higher copy number variations than cutaneous melanomas, using samples predominantly from North America and Australia [41, 83]. Newell *et al.* determined sample genetic ancestry. CNV gains in the *NOTCH2* gene were found to be associated with European ancestry as 4 out of the 6 aberrations found, were in European tumors [70]. Additionally, increased CNVs were spotted in so-called triple-WT (wild type) MM samples (no *BRAF*/*RAS*/*NF1* mutation present), where only 30% of these melanomas harbored a UV signature [38]. Moreover, events like copy number gain in chromosomes 22 and 11q and CNV losses involving chromosome 4q were more common in the group with chronic sun-induced damage than in the group without such damage [83].

In conclusion, malignant melanoma, one of the most aggressive forms of skin cancer, is caused by the uncontrolled growth of pigment-producing cells melanocytes. Besides a wide range of genetic mutations, copy number variations (CNV) have a significant role in the tumorigenesis of MM. For instance, oncogenes such as *BRAF, c-KIT,* and *MYC* are amplified in melanomas, leading to increased cell proliferation and decreased cell death. On the other hand, deletions of tumor suppressor genes such as *CDKN2A* have also been reported and contribute to the development of the disease by reducing the cell's ability to respond to DNA damage. Important additional information to copy number change is the expression level of a particular amplified/deleted gene. Some of the studies, mentioned in this review, showed a correlation between CNV and the expression level of a particular gene [38, 40, 46, 57, 61, 64, 90], on the other hand, it was also reported that although there was copy number alteration present, the expression level was not affected [48, 49]. CNVs differ among individual melanoma types, UV-related and UV-unrelated MM, and different races and ethnicities [21, 39, 39, 51, 52, 55, 70, 83]. However, further research is needed for a better understanding of the role of somatic and germline CNVs in malignant melanoma and for the development of new treatments targeting these aberrations.

Supplementary information is available in the online version of the paper.

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Copy number variations in malignant melanoma: genomic regions, biomarkers, and therapeutic targets

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Supplementary Information

Supplementary Table S1. Studies focused on CNVs identification in MM.

Sample studies		
Detection methods	**Sample type**	**Study**
CGH	Tissue	[23]
CGH, FISH, IHC	Tissue, cell line	[56]
aCGH, IHC	Tissue	[83]
SNP array, qPCR, FISH, protein analysis	Tissue, cell line	[46]
FISH, Western blot	Tissue, cell line	[61]
FISH	Tissue	[81]
SNP array	Cell line	[45]
SNP array	Cell line	[19]
FISH	Tissue	[66]
qPCR, FISH	Tissue	[51]
aCGH, FISH, IHC	Tissue	[57]
qPCR, FISH	Tissue, cell line	[42]
SNP array, qPCR, IHC, WB	Tissue, cell line	[64]
WGS, SNP arrays, RNASeq	Tissue	[38]
Single-cell sequencing	CTCs	[43]
WGS	Tissue, cell line	[41]
Quantigene assay	Tissue	[55]
WGS, WES, qPCR	Tissue	[52]
FISH, IHC	Tissue	[49]
WES, FISH	Tissue	[54]
Panel sequencing	Tissue	[65]
Panel sequencing	Tissue	[39]
Panel sequencing	Tissue	[21]
WGS, WES	Tissue	[70]
WGS, RNASeq	Tissue	[40]
FISH, IHC	Tissue	[48]
WES	Tissue	[75]
FISH	Tissue	[62]
Germline studies		
Detection methods		**Study**
qPCR, MLPA		[86]
aCGH, qPCR		[87]
SNP arrays, qPCR		[92]
SNP arrays, qPCR		[91]
aCGH, SNP arrays, qPCR, dPCR, RNAseq, high-resolution array-CGH		[90]
qPCR		[96]

Abbreviations: aCGH-array Comparative Genomic Hybridization; CGH-Comparative Genomic Hybridization; FISH-Fluorescence in situ hybridization; IHC-Immunohistochemistry; MLPA-Multiplex Ligation-dependent Probe Amplification; SNP-Single Nucleotide Polymorphism; qPCR-Quantitative PCR; WES-Whole Exome Sequencing; WGS-Whole Genome Sequencing; WB-Western Blot