

Melanoma Management

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/immt20

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To cite this article: Oleksandr Dudin, Ozar Mintser, Nazarii Kobyliak, Dmytro Kaminskyi, Roman Shabalkov, Alina Matvieieva, Olga Sukhanova, Antonina Kalmykova, Denys Kozakov, Artem Mashukov & Oksana Sulaieva (2023) Incidence of *BRAF* Mutations in Cutaneous Melanoma: Histopathological and Molecular Analysis of a Ukrainian Population, Melanoma Management, 10:1, MMT64, DOI: 10.2217/mmt-2023-0005

To link to this article: https://doi.org/10.2217/mmt-2023-0005

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Published online: 21 Dec 2023.

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Incidence of *BRAF* mutations in cutaneous melanoma: histopathological and molecular analysis of a Ukrainian population

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Aim: This study aimed to investigate the incidence of *BRAF* mutation in cutaneous melanoma in the Ukrainian population with respect to clinical and histopathological data. **Materials & methods:** This single-center retrospective cohort study enrolled 299 primary CM with known *BRAF* status assessed by RT-PCR. **Results:** The overall *BRAF* mutation rate was 56.5% in CM and demonstrated a link with the younger age ($p < 0.001$), anatomical site ($p < 0.001$) and histological type of CM ($p = 0.022$). *BRAF*-positive CM possessed a slightly higher mitotic rate ($p = 0.015$) and Breslow thickness ($p = 0.028$) but did not relate to tumor-infiltrating lymphocytes. **Conclusion:** The high rate of *BRAF* mutations in CM patients in the Ukrainian cohort was associated with superficial spreading histology, higher depth of invasion and proliferation.

First draft submitted: 30 July 2023; Accepted for publication: 16 November 2023; Published online: 21 December 2023

Keywords: *BRAF*-mutations • cutaneous melanoma • histological subtype • prognosis prediction

Skin malignancies are among the most common groups of tumors diagnosed worldwide. Although cutaneous melanoma (CM) represents less than 5% of skin neoplasms, its incidence worldwide has been continuously growing over the last two decades [1–4]. CM is associated with high lethality (up to 75% of all skin cancer-related deaths), as well as poor prognosis and survival rates [4].

Melanoma development and progression are driven by molecular alterations within specific genes and signaling pathways that regulate the survival and proliferation of melanocytes. These changes can affect various aspects of biological behavior and impact both patient prognosis and sensitivity to various therapeutics [5]. It is recognized that CM displays a high prevalence of somatic mutations, both in primary and metastatic lesions. Among them, *BRAF* mutations were shown to play a pivotal role in melanoma pathogenesis and are undoubtedly integral to predicting the response to targeted treatment [5,6]. Accordingly, from stage III and higher, *BRAF* mutation testing is universally recommended for patients with melanoma [7].

By now, several driver *BRAF* mutations, including the most common codon 600 variants: V600E, V600K and V600D/R have been identified in CM [8]. These codon 600 mutations in *BRAF* oncogene mimic a constantly activated state of *BRAF* kinase resulting in uncontrolled cell proliferation and increased invasiveness [9]. *BRAF* mutation in primary stage III CM was shown to be associated with a worse prognosis, reduced progression-free interval and overall survival [10]. In advanced melanoma stages, the presence of *BRAF* codon 600 mutation constitutes a therapeutic target for *BRAF* inhibitors dabrafenib and vemurafenib, therapeutics that show significant benefits for progression-free survival and overall survival in CM patients [11]. There is, however, little known about the incidence of *BRAF* codon 600 mutations in CM in the Ukrainian population.

Future Medicine

This study aims to investigate the incidence of *BRAF* mutation in cutaneous melanoma in the Ukrainian cohort with respect to clinicopathological data.

Materials & methods

This was a single-center retrospective cohort study that primarily included 1268 melanoma cases with known *BRAF* status, extracted from the database from the period of 2020 to 2022 from various regions of Ukraine. All the data was depersonalized. After the exclusion of uveal melanoma (n = 24), mucosal melanoma (n = 32) and cases with limited available demographic, clinical and pathological data (n = 727), 485 cases remained. They included 299 cases of primary sites melanoma and 186 metastases. Only primary CM cases (n = 299) were kept for further analysis.

Demographic, clinical and pathological data were retrieved, including age, sex, CM location, clinical staging, histological subtype according to WHO classification, pathological stage, Breslow thickness and Clark level, ulceration, mitotic rate and tumor-associated lymphocytes (TILs) were analyzed. Molecular testing for identifying BRAF codon 600 mutation was conducted on tissue samples, using formalin fixed paraffin embedded blocks with verified tumor content. *Ten 10*-μm-thick sections were obtained from each paraffin block containing a representative tumor area (>20% tumor cells, >200 cells in the sample, <20% necrosis area). DNA was extracted using ZYTOVISION VisionArray FFPE DNA Extraction Kit according to the manufacturer's instructions. Detection of *BRAF* mutation was performed using Easy PGX qPCR system: Easy PGX ready *BRAF* (Diatech Pharmacogenetics, Italy) via a real-time polymerase chain reaction. The assay is designed to detect 5 types of *BRAF* mutations in codon 600: V600E (1799T>A), V600E (1799_1800TG>AA), V600K (1798_1799GT>AA), V600D (1799_1800TG>AT), V600R (1798_1799GT>AG). The rates of *BRAF*-mutant (*BRAF*-positive) and *BRAF*-negative (wildtype) melanoma were assessed with respect to sex, age, location, stage, histological type and distinct morphological features. TILs infiltration was evaluated in a dichotomic manner according to the pathology report description (lack of lymphocytes or few tumor-infiltrated lymphocytes were considered as a TILs-low, while moderate or high intensity of lymphocytic infiltrated were recorded as TILs-high.

Statistical analysis was performed using GraphPad Prism (GraphPad Prism Version 10.0.3 (217) GraphPad Software, San Diego, California USA, www.graphpad.com) and involved χ^2 test, *t*-test for comparison of continuous variables between *BRAF*-negative and *BRAF*-mutated groups. For continuous variables the descriptive statistics was provided as Mean ± SEM.

Results

Here a total of 299 cases with primary cutaneous melanoma are reported, including 152 (50.8%) females and 147 (49.2%) males. Among the enrolled cases there were 169 samples of *BRAF*-mutated CM (56.5%), while the rest 130 cases were *BRAF*-wild type. No differences in *BRAF* mutation incidence were observed between male and female groups of patients (Table 1). The average patient age of the observed cases was 55.4 ± 0.48 (95% CI: 53.8–56.9). *BRAF*-mutated CM demonstrated a link with the younger age of onset (52.6 ± 1.01; 95% CI: 50.6–54.6 vs 57.7 ± 0.99; 95% CI: 55.7–59.7 in individuals with *BRAF* wild-type melanoma; $p < 0.001$).

Within the observed cohort, 16 cases (5.4%) were identified as stage I CM, 175 cases (58.5%) – as stage II, 81 (27.1%) – as stage III according to the AJCC tumor staging system, and 27 (9.0%) were recorded as CM with distant metastases (stage IV). Only 5 out of 16 (31.3%) of stage I CM harbored *BRAF* mutation, while II-IV staged CM demonstrated a higher rate of *BRAF* alterations (57.7%; 58.0% and 59.3% respectively), however, there was no statistically significant difference between *BRAF* mutation incidence between early staged and advanced melanoma cases (55.7% vs 58.3%; $p = 0.716$).

Relationship between anatomical site of primary melanoma & *BRAF* mutation status

Most cases with known primary CM origin sites were observed at the skin of the trunk (26.4%) and extremities (9.7% for upper and 17.7% for lower extremities). Less frequently primary melanoma lesions were recorded on the skin of the scalp (4.0%), face (3.7%) and neck (2%). About one-third of all the reported cases (109; 36.5%) were signed without specification on the melanoma site – skin not otherwise specified.

Notably, there was a relationship observed between the anatomical sites of malignant lesions and *BRAF* mutation status of the respective tumor samples (Table 1). Among the observed sites of primary tumor, predominantly, lesions located in the neck and trunk areas were found to harbor a *BRAF* codon 600 mutation. Concurrently, *BRAF* gene

Table 1. Demographics characteristics of cutaneous melanoma cohort.

Characteristics	Total number	*BRAF* status		% of mutated	
		WT	Mutated		
Patients:	299	130	169	56.5%	
– Males	147	65	82	55.8%	p = 0.816
– Females	152	65	87	57.2%	
Stage:					
– I	16	11	5	31.3%	p = 0.219
– II	175	74	101	57.7%	
– III	81	34	47	58.0%	
– IV	27	11	16	59.3%	
Age (years)		57.7 ± 0.99	52.6 ± 1.01		p < 0.001
Anatomical site:					
– Face (and ears)	11	9	2	18.2%	p < 0.001
– Neck	6	0	6	100%	
– Scalp	12	9	3	25.0%	
– Trunk	79	19	60	75.9%	
– Upper limbs	29	17	12	41.4%	
– Lower limbs	53	29	24	45.3%	
– Skin NOS	109	47	62	56.9%	

Data presented as mean ± standard error of the mean or % (n).
NOS: Not otherwise specified; WT: Wild-type.

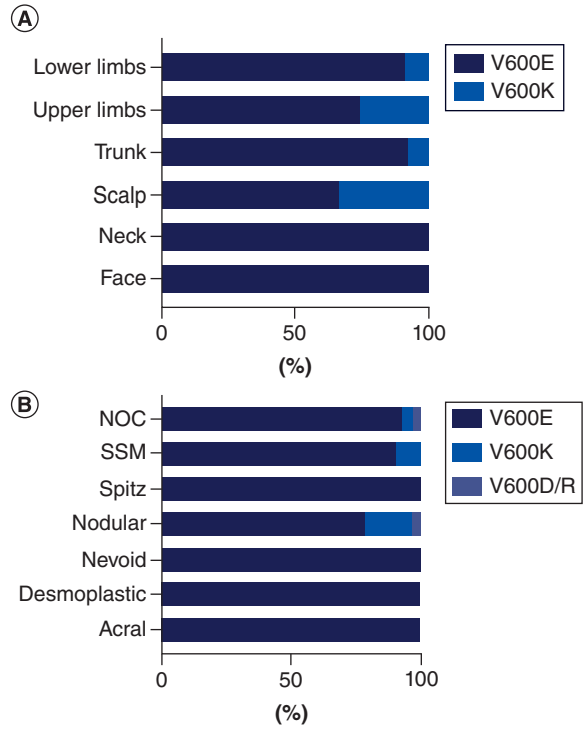


Figure 1. The association of *BRAF* mutation variants with cutaneous melanoma location and histological types. (A) the relationship between *BRAF*-mutation variants with anatomical sites of cutaneous melanoma. The relative frequency (%) of V600E and V600K variants are shown in the chart (as V600D/R mutation was found in cases with no specified location, it is not illustrated). **(B)** the relative rate (%) of *BRAF* mutation variants in cutaneous melanoma of different histological subtypes is shown in the chart. Nodular melanoma cases demonstrated the highest incidence of V600K and V600D/R mutations in the *BRAF* gene.
NOC: Not otherwise classified melanoma; SSM: Superficial spreading melanoma.

mutations in sun-exposed areas of the skin (including extremities and face) were observed at a much lower rate ($p < 0.001$).

Among the studied *BRAF* mutations in codon 600, V600E variant was prevalent (151 out of 169 *BRAF*-mutated cases, 89.3%), while V600K variant was found in 15 CM cases (8.9%), and V600D/R variants were comparatively rare (3; 1.8%). Evaluating the link between different *BRAF* mutation subtypes and CM location, we found that all CM located at the face and neck harbored V600E mutation (Figure 1). Most of CM at the trunk and lower limbs harbored *BRAF* V600E mutation (93 and 92% respectively), while V600K mutation was found in 7 and

Table 2. Histopathological features of cutaneous melanoma with respect to *BRAF*-status.

Characteristics	Total number	*BRAF* status		% of mutated	
		WT	Mutated		
Histological type:					
– Desmoplastic melanoma	3	2	1	33%	$p < 0.022$
– Acral melanoma	10	7	3	30%	
– Melanoma arising in a blue nevus	2	2	0	0%	
– Melanoma arising in a giant congenital nevus	1	1	0	0%	
– Spitz melanoma	5	3	2	40%	
– Nevoid melanoma	2	0	2	100%	
– Nodular melanoma	68	30	38	56%	
– Melanoma, not otherwise classified	98	50	48	49%	
– Superficial spreading melanoma	110	35	75	68%	
Breslow thickness		3.73 ± 0.26	4.70 ± 0.32		p = 0.028
Clark	299	130	169	58.7%	p = 0.742
– I	1	1	0	0	
– II	15	8	7	46.7%	
– III	61	26	35	57.4%	
– IV	198	85	113	57.1%	
– V	24	10	14	58.3%	
Mitosis rate (per 1 mm^2)		7.72 ± 0.67	9.96 ± 0.67		p = 0.0145
Tumor-infiltrating lymphocytes	299	130	169	56.5%	p = 0.117
– Low	164	78	86	52.4%	
– High	135	52	83	61.5%	

Data presented as mean ± standard error of the mean or % (n).

8% of CM at these sites. All three V600D/R mutations were reported in skin not otherwise specified melanoma. However, CM of the scalp had a higher rate of V600K mutation (33.3%).

Relationship between histological features of primary cutaneous melanoma & *BRAF* mutation status

Among 299 cases observed, the predominant histological subtype was superficial spreading melanoma (Table 2). It comprised 110 out of 299 cases (36.8%). 98 cases were represented by not otherwise classified (NOC) melanoma (32.8%) and 68 patients had nodular melanoma (29.7%). The minority of cases were represented by acral melanoma (10/299; 3.3%), Spitz melanoma (5/299; 1.7%), desmoplastic (3/299; 1.0%), nevoid (2/299; 0.7%), melanoma arising in a blue nevus (2/299; 0.7%) and melanoma arising in a giant congenital nevus (1/299; 0.3%).

There was a strong relationship between the histological type of CM and *BRAF*-status (p = 0.022). The highest incidence of *BRAF* codon 600 mutations was found in superficial spreading melanoma (68% of cases). Additionally, the two cases of nevoid melanoma examined were both *BRAF*-positive. Nodular melanoma was found to harbor *BRAF* alterations in 56% of cases, while more than 2/3 of acral and desmoplastic melanoma were identified as *BRAF*-negative. Assessing the link between *BRAF* mutation subtypes and histology of CM, we found that acral, desmoplastic, nevoid and Spitz melanoma harbored exclusively BRAF V600E mutation (Figure 1). Naturally, this type of mutation was predominant in nodular (79%), superficial spreading (91%) and NOC melanoma (94%). However, nodular melanoma cases also harbored V600K (18%) and V600D/R (3%) mutations though the rate of V600K and V600D/R mutations was lower in SMM (8% and 1%) and NOC (4% and 2%) melanomas.

There was no relationship observed between *BRAF* mutation status of CM primary tumor and Clark level, however, Breslow thickness was found to be generally higher in *BRAF*-mutated tumors (4.47 ± 0.29 vs 4.15 ± 0.38 mm in WT melanoma; p = 0.028) (Table 2). At the same time, mitosis rate was shown to be higher in *BRAF*-positive lesions as compared with *BRAF*-negative (9.96 ± 0.67 vs 7.72 ± 0.67; p = 0.0145) (Table 2).

Relationship between *BRAF* mutation status & CM immunogenicity

Assessment of primary sites of melanoma demonstrated presence of *BRAF* mutations in 56.5% of CM primary sites, 83 of which (49.1% of *BRAF*-positive) demonstrated prominent TILs infiltration while the rest of *BRAF* mutated

CM (86 out of 169, 51.9%) was immune "cold". Alternatively, wild-type CM demonstrated a lower prevalence of TILs-high status (52 of 130, 40.0%). There was no significant relationship observed between *BRAF* codon 600 mutation status and TILs ($p = 0.117$) (Table 2).

Discussion

There are only a few data about CM incidence and molecular features in Ukraine [12,13], demonstrating a growing incidence and lower survival as compared with European Union countries [12]. Despite the expansive growth of molecular testing in oncology for the last years, there is no already published data on *BRAF* mutation incidence in melanoma in the Ukrainian population. This study revealed a high rate of *BRAF* mutations in the Ukrainian cohort that accounted for 56.5% of total CM cases.

Mutations in *BRAF* gene in patients with CM range in frequency from 20% to 80% [2,14,15]. The incidence of *BRAF* mutation in Ukraine seems relatively high as compared with the data from some other populations. For instance, the Asian population was reported to have 20–40% rate of *BRAF*-mutant melanoma. In the Japanese study, *BRAF* mutation rate was 41.8% [16], while in Korean and Chinese cohorts *BRAF* mutations were harbored in 26% [17] and 24–25.5% [18] CM cases respectively. In European countries, the rate of *BRAF*-mutated melanoma also varies significantly comprising 40.1% in the German study [19], 38.6% in French research [20] and reached 56.8% in the Latvian study [21], which is comparable to the Ukrainian cohort. It is considered that variations in *BRAF* mutation rate are due to different baseline characteristics of patients, tissues sampled (primary or metastatic melanoma specimens), methods and test-systems used for detecting mutations [22].

Our findings also correlate with the available data regarding the frequencies of different *BRAF* codon 600 genetic variants. *Genetic mutation BRAF* V600E was detected in 89.3% of the Ukrainian CM cohort. This corresponds well to the worldwide statistics that range from 80% to 90% of V600E variants among the whole observed *BRAF* mutation spectrum [14]. The information about *BRAF* variant type is essential for predicting response to targeted treatment in metastatic CM patients as it has shown to vary among different *BRAF* codon 600 variants. The available clinical trial data emphasizes a slightly lower response to targeted treatment in metastatic CM patients with *BRAF* V600K variant as compared with patients with *BRAF* V600E.

In accordance with worldwide statistics, our study reports that the positive *BRAF mutation status of* melanoma tumors has been associated with specific clinicopathological features such as the site of tumor development (trunk and neck) as well as an earlier age of onset. Many studies also highlighted the association between *BRAF* mutations and younger age at first diagnosis and truncal localization of the primary melanoma [14]. The disparity between these features, in fact, highlights the contrast between pathways of probable melanoma development in sun-exposed and non-sun-exposed areas of the skin. Chronic sun-damaged melanoma is characterized by relatively infrequent *BRAF* V600E mutations, increased frequency of *BRAF* V600K and mutations in other genes (NF1, TP53), and high mutational load [23]. Alternatively, melanoma arising from intermittent sun exposure sites is more likely associated with *BRAF*-mutations, suggesting a profound role of MAPK/ERK molecular cascade in the development and progression of pigmented malignant lesions [14].

Additionally, some authors demonstrated the link between *BRAF* mutations and the melanoma stage. For instance, Rubió-Casadevall J. *et al.* reported that *BRAF*-mutations were found in 38.9% of "*in situ*" melanoma and in 53.8% of patients with invasive melanoma [24]. Although we did not reveal the link between *BRAF*-status and melanoma stage among the observed cases, we found that *BRAF*-mutated CM demonstrated higher Breslow thickness reflecting tumor biological behavior during the vertical growth phase of melanoma. These data correlate with the other studies that showed the link between *BRAF* V600 mutational status and Breslow thickness [21].

One more finding of our study was the higher mitotic rate in *BRAF*-mutated melanoma. Activating *BRAF* mutations facilitating constitutive activation of MAPK/ERK signaling have been shown to enhance proliferation and survival of melanoma cells, which may confirm a tendency, nevertheless, the extent of disparity between features reflecting tumor behavior in *BRAF*-positive and negative CM cases remains to be seen [14].

We have also demonstrated the relationship between *BRAF* status and particular histopathological subtypes. The superficial spreading melanoma subtype demonstrated a higher rate of *BRAF* mutation (68%) compared with average incidence (56.5%), nodular melanoma (56%) and melanoma, not otherwise classified (49%). To note Lattanzi M *et al.* showed no significant differences and a relatively low incidence of *BRAF* mutation in SSM and NM (44% and 43%) but found a higher rate of *NRAS* mutation in nodular melanoma. These discrepancies might be connected to different sample group sizes and tumor stages enrolled in the study [25]. The distinctions in *BRAF*

mutation incidence in various histological subtypes of CM may reflect a contribution of this genetic alteration to melanoma progression [25].

One more important issue we addressed in this study was the relationship between *BRAF* status and the immunogenicity of CM. It has been shown, that patients with *BRAF*-positive and wild-type melanoma demonstrate different responses to immunotherapy treatment [26]. Larkin *et al.* reported that the 5-year overall survival under treatment with nivolumab plus ipilimumab was higher in patients with a *BRAF* mutation as compared with patients with *BRAF*-negative CM tumors (60 vs 48%) [27]. The causes of these reported differences in response to therapy, however, are still debatable. Discovery of tumor immune microenvironment in treatment-naive melanoma with respect to *BRAF* status revealed that *BRAF*-mutant melanoma displayed a unique immune contexture with lower $CD8^+$ T cells infiltration but a higher prevalence of B cells, natural killer cells and NKT cells [28]. In our study, we did not find significant links between *BRAF*-status and neither TILs. Further studies are needed to gain a better understanding of the relationship between genetic alterations and immune response in determining tumor-immune interplay and potential benefits from both immune checkpoint blockade and targeted therapy for patients with CM.

Conclusion

In this study we demonstrate a relatively high rate of *BRAF* codon 600 mutation in the Ukrainian population *BRAF* mutations were predominantly associated with cutaneous melanoma affecting skin with low sun exposure (torso, neck) with superficial spreading histology, higher depth of invasion and a higher rate of mitosis.

Summary points

- Overall, 56.5% of primary cutaneous melanoma (CM) cases harbored *BRAF* mutations in the Ukrainian cohort.
- Among the observed cases V600E mutation (89.3%) was the predominating type of *BRAF* alterations, while V600K and V600D/R mutations comprised 8.9% and 1.8% respectively.
- *BRAF*-mutated CM demonstrated a link with the younger age of onset, neck and trunk location.
- There was a strong link between *BRAF* status and the histological subtype of CM with the prevalence of *BRAF* mutations in superficial spreading, nevoid and nodular melanoma.
- *BRAF*-positive CM possessed a higher mitotic rate and Breslow thickness as compared with wild type.
- There was no statistically significant link between *BRAF* status and tumor-infiltrating lymphocytes.

Author contributions

O Dudin, O Mincer and O Sulaieva conceptualized and designed the study; D Kaminskyi, R Shabalkov, A Matvieva retrieved the retrospective data. O Sulaieva, O Skhanova, A Kalmykova and N Kobyliak provided statistical support and data analysis; O Dudin, N Kobyliak, D Kozakov and O Sulaieva wrote the original draft of the manuscript; R Shabalkov, A Matvieieva, O Sukhanova, A Kalmykova, D Kozakov and A Mashukov critically reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Financial disclosure

The authors have no financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

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