in vivo *37*: 862-867 (2023)
doi:10.21873/invivo.13154

Genetic Characteristics of Primary Cutaneous Malignant Melanoma in Koreans Compared With Western Populations

HYENGUK JANG, HYANG JOO RYU and SANG KYUM KIM

Department of Pathology, Yonsei University College of Medicine, Severance Hospital, Seoul, Republic of Korea

Abstract. *Background/Aim: Cutaneous melanoma, a melanocyte malignancy, can be divided into many clinical subtypes that differ in presentation, demographics, and genetic profile. In this study, we used next-generation sequencing (NGS) analysis to review genetic alterations in 47 primary cutaneous melanomas in the Korean population and compared them to alterations from melanomas in Western populations. Patients and Methods: We retrospectively reviewed clinicopathologic and genetic features of 47 patients diagnosed with cutaneous melanomas between 2019-2021 at Severance Hospital, Yonsei University College of Medicine. NGS analysis was performed at diagnosis to evaluate single nucleotide variations (SNVs), copy number variations (CNVs), and genetic fusions. Genetic features in Western cohorts of melanoma were then compared with previous studies performed in the USA: Cohort 1 (n=556), Cohort 2 (n=79), and Cohort 3 (n=38). Results: The most common histological classification of melanoma was the acral lentiginous type (23/47, 48.9%). BRAF V600 mutation was most frequent (11/47, 23.4%), but was significantly lower compared to Cohort 1 (240/556, 43.2%) and Cohort 2 (34/79, 43.0%) (p=0.0300). CNV analysis identified amplifications in chromosomes 12q14.1-12q15 (11/47, 23.4%) including CDK4 and MDM2 genes and 11q13.3 (9/47, 19.2%) including CND1, FGF19, FGF3, and FGF4 genes more frequently in the present study population than Cohort 1 (p<0.0001). Conclusion: These results clearly demonstrated differences in genetic alterations between melanomas in Asian and Western populations. Therefore, BRAF V600 mutation should be considered a significant signaling pathway explaining melanoma pathogenesis occurrence in both Asian and Western populations, whereas loss of chromosome 9p21.3 is unique to melanomas in Western populations.*

Correspondence to: Sang Kyum Kim, Department of Pathology, Yonsei University College of Medicine, Severance Hospital, Seoul 03722, Republic of Korea. Tel: +82 22286751, Fax: +82 3620860, e-mail: nicekyumi@yuhs.ac

Key Words: Cutaneous malignant melanoma, genetic features, Korean population, Western population.

Cutaneous melanoma is a malignancy associated with melanocytes in the basal layer of the epidermis. Despite comprising only 1% of all skin cancers, melanoma accounts for over 80% of skin cancer-related deaths (1). Traditionally, the primary tool for classification involves histopathological assessment in conjunction with the patient's clinical characteristics (1). However, updated melanoma classifications were suggested based on epidemiologic and genomic findings regarding pathways involved in melanoma development (2-4). Based on these updated classifications, cutaneous malignant melanoma (MM) can be classified into one of two groups: melanomas arising in sun-exposed skin and melanomas arising in sun-shielded sites or sites with unknown etiological associations with sun exposure (1).

The majority of MMs result from solar damage (1-3). Therefore, differential pathways associated with the pathogenesis of low degree of cumulative sun damage (CSD) melanomas and high-degree CSD melanomas are prime targets for explaining differences in cutaneous MM development (5). This idea is also supported by differences in genetic findings between the two types of melanomas (2, 5). High-CSD and low-CSD with a strong ultraviolet (UV) radiation signature melanomas have a high mutation burden and multiple DNA copy-number changes (1, 5). In contrast, melanomas with no consistent relationship to sun exposure have a low mutation burden and variable DNA copy-number changes (2, 5, 6).

According to previous studies, cutaneous MMs in individuals with skin colors darker than Caucasians tend to occur in anatomic locations that are not continuously sun-exposed (7, 8). Based on histological classification, the frequencies of melanoma types also differ between races (7, 9, 10). However, limited studies have been performed comparing clinicopathologic features and genetic alterations of melanomas in Asian populations (11-14). In this study, we reviewed characteristics of cutaneous MMs in Korean individuals that were diagnosed through histopathological

analysis and compared the genetic features of these cutaneous MMs with genetic features of MMs in Western populations.

Patients and Methods

Clinical sample collection and ethical statement. We retrospectively reviewed clinical and pathologic records of 47 Korean patients that had surgical excisions due to clinical suspicion of MM, between 2019-2021 at Severance Hospital, Yonsei University College of Medicine, and subsequently diagnosed as cutaneous melanoma. Two pathologists (HJ and SKK) reviewed the associated clinical presentations, pathological results, and molecular studies results. All methods and experimental protocols using human tissue were carried out in accordance with relevant guidelines and regulations, approved by the Institutional Review Board (IRB) of Severance Hospital, Yonsei University Health System. Formal written informed consent was not required with a waiver by the IRB (IRB No. 4-2022-0912).

Targeted next-generation sequencing (NGS). At diagnosis, NGS analysis was performed to evaluate single nucleotide variations (SNVs), copy number variations (CNVs), and occurrence of genetic fusions. Genomic DNA and RNA were extracted from 10 μm sections cut from Formalin-fixed, Paraffin-embedded (FFPE) tissue blocks, using AllPrep DNA/RNA FFPE Kit (Qiagen, Hilden, Germany) and TruSight™ Oncology 500 kit (Illumina, San Diego, CA, USA). NextSeq 550Dx (Illumina) was used to perform targeted NGS on extracted DNA and RNA. Resulting genetic data was analyzed using TruSight Oncology 500 v2.0 Local App (Ilumina, Workflow Version: Ruo-2.0.0.70). All NGS data were reviewed by two pathologists (HJ and HJR). Genetic information and interpretation were performed using Integrative Genomics Viewer (IGV) 2.10.0 software (Broad Institute, Cambridge, MA, USA) and the following websites: The Single Nucleotide Polymorphism Database (dbSNP; NCBI), Catalogue of Somatic Mutations in Cancer (COSMIC), ClinVar (NCBI), and cBioPortal for Cancer Genomics. Genetic amplification was determined when a relative copy number increased more than 2.0-fold, while homozygous deletion was determined when the change was less than 0.5-fold.

Definition of melanoma Western cohorts. This study utilized genetic data from previous studies to compare genetic findings with those of the Korean study population (n=47) described above. Western melanoma populations included patients in Cohorts 1, 2, and 3.

Cohort 1 comprised MSK-IMPACT assay targeted sequencing data from 696 paired melanoma tumor and normal genomic patient samples. A total of 556 primary cutaneous melanoma out of the 696 cases were included for comparison (15). All patients with primary cutaneous melanomas were sequenced and treated at two centers (Memorial Sloan Kettering Cancer Center, NY, USA and Lehigh Valley Cancer Institute, PA, USA). Cohort 1 included SNV, CNV, and structural variant data.

Cohort 2 data was, in part, based on data classified as "Skin Cutaneous Melanoma", generated by The Cancer Genome Atlas (TCGA) Research Network. Seventy-nine primary cutaneous melanoma cases were selected for inclusion in Cohort 2. Sixty nine out of 79 patients (87.3%) were white, seven (8.9%) were Asian, and three (3.8%) were not identified.

Cohort 3 consisted of genomic analysis of melanomas from 38 acral melanoma patients at Translational Genomics Research Institute, Phoenix, AR, USA (16). Twenty eight out of 38 acral melanoma patients (85.2%) were Caucasian and five were African American (14.7%).

Table I. *Clinicopathologic features of cutaneous melanoma (n=47).*

Parameters	Glabrous (n=28)	Non-glabrous (n=19)	*p*-Value
Age at diagnosis (years±SD)	61.21±2.413	56±3.297	0.1982
Sex			
Male	16	11	>0.9999
Female	12	8	
pT stage	(n=27)	(n=16)	0.4675
pTis	1	0	
pT1a,b	2	0	
pT2a,b	5	1	
pT3a,b	6	5	
pT4a,b	13	10	
Growth phase			0.1668
Horizontal	3/27 (11.1%)	0/16 (0.0%)	
Vertical	24/27 (88.9%)	16/16 (100.0%)	
Mortality rate	12/28 (42.9%)	5/19 (26.3%)	0.1389
Overall survival (days±SD)	1,579±145.7	1,200±202.4	0.1254
Histologic subtype			<0.0001
Acral lentiginous	23 (82.1%)	0 (0.0%)	
Nodular	2 (7.1%)	5 (26.3%)	
Superficial spreading	1 (3.6%)	6 (31.6%)	
Unclassifiable	2 (7.1%)	8 (42.1%)	
Mutation with clinical significance			
SNV	23/28 (82.1%)	18/19 (94.7%)	0.3783
CNV	15/28 (53.6%)	5/19 (26.3%)	0.0789
Genetic fusion	6/28 (21.4%)	1/19 (5.3%)	0.2138

SD: Standard deviation; SNV: single nucleotide variation; CNV: copy number variation.

Statistical analysis. All statistical analyses were performed using SPSS Statistics version 26.0 (IBM, Chicago, IL, USA) and GraphPad Prism version 7.04 (GraphPad Software, San Diego, CA, USA). Categorical data were reported as frequencies and percentages, and continuous data are reported as mean±standard deviation (SD). Differences between groups were compared using Chi-squared test, Fisher's exact test, or unpaired *t*-test. Two-sided *p*-values <0.05 were considered statistically significant. Additionally, *p*-values were indicated as follows: $*p<0.05$; $**p<0.005$; $***p<0.0005$.

Results

Clinicopathologic features of Korean melanoma patients. A total of 47 cases, which were histopathologically diagnosed as primary cutaneous melanoma and analyzed using NGS sequencing at diagnosis were included in this study. The most common histological classification of melanoma was the acral lentiginous type; therefore, the cases were further divided according to the primary tumor sites: glabrous (n=28) and non-glabrous (n=19) (Table I). There were no significant differences in age, sex, pathologic tumor (pT) stage, growth phases at diagnosis, or mortality rate. However, there was a significant difference in histologic

Table II. *Frequent single nucleotide polymorphisms found in the present study compared to those found in other cutaneous melanoma studies.*

Gene	Present study (n=47)	Cohort 1 (n=556)	Cohort 2 (n=79)	*p*-Value
BRAF V600	11, 23.4%	240, 43.2%	34, 43.0%	0.0300
NRAS	7, 14.9%	168, 30.2%	8, 10.1%	0.0001
KIT	6, 12.8%	32, 5.8%	6, 7.6%	0.1648
KMT2A	4, 8.5%	94, 16.9%	5, 6.3%	0.0097
MSH3	4, 8.5%	18, 3.2%	1, 1.3%	0.0857
CTNNB1	2, 4.3%	46,8.3%	2, 2.5%	0.1314
NCOR1	2, 4.3%	41, 7.4%	3, 3.8%	0.3859
TERT	2, 4.3%	467, 84.0%	1, 1.3%	<0.0001
TP53	2, 4.3%	134, 24.1%	4, 5.1%	<0.0001

subtype between groups and the acral lentiginous type was more frequently found in the glabrous sites (23/28, 82.1%) than in the non-glabrous sites (0/19, 0.0%) although the superficial spreading type was the more common subtype of the non-glabrous sites (6/19, 31.6%) than in the glabrous sites (1/28, 3.6%, $p<0.0001$). As expected, the acral lentiginous type was more frequent in glabrous sites (23/28, 82.1%) than in the non-glabrous sites (0/19, 0.0%). There were also genetic differences between groups, including a tendency towards more frequent instances of CNVs in the glabrous melanomas (15/28, 53.6%) than in the non-glabrous melanomas (5/19, 26.3%) ($p=0.0789$).

Comparison of SNVs in melanomas of Korean and Western populations. To further evaluate the findings in the present study population, genetic data were compared with data from previous studies, Cohort 1 (n=556) and Cohort 2 (n=79). The most frequently reported genes with SNVs were determined in Cohort 1 and Cohort 2 (Table II). In the present study, *BRAF V600* mutation was most frequent (11/47, 23.4%), but frequency was significantly lower compared to Cohort 1 (240/556, 43.2%) and Cohort 2 (34/79, 43.0%) ($p=0.0300$). There was a tendency for the present study population to have more frequent *MSH3* mutations (4/47, 8.5%) than either Cohort 1 (18/556, 3.2%) or Cohort 2 (1/79, 1.3%) ($p=0.0857$). As acral lentiginous was the most common histologic type of melanoma in the present study population, instances of SNVs between this study population and Cohort 3 (comprised of 38 acral melanoma patients) were also compared (Table III). Between the two groups, there was no significant difference in SNV occurrence, although the present study population had a tendency towards more frequent *KIT* mutations than Cohort 3 ($p=0.0911$).

Comparison of CNVs in melanomas of Korean and Western populations. The present study population was also analyzed for genetic amplifications and homozygous deletions. When compared with CNVs observed in Cohort 1, amplifications in chromosomes 12q14.1–12q15 (11/47, 23.4%) and 11q13.3 (9/47, 19.2%) were more frequently identified than in Cohort 1 ($p<0.0001$) (Table IV). Additionally, *KIT*, *MYC*, and *PDGFRA* genes were also amplified more frequently in the present study population than in Cohort 1 ($p<0.0001$). Loss of the *RET* gene was observed at similar levels in both study populations (2/47, 4.3%, and 8/556, 1.4%, for present study population and Cohort 1, respectively, $p=0.1465$) (Table V). Frequently observed CNVs in the present study population were detected at much lower rates in Cohort 1.

Table III. *Comparative analysis of frequent single nucleotide polymorphisms found in the present study and those found in the acral melanoma study.*

Gene	Present study (n=47)	Cohort 3 (n=38)	*p*-Value
BRAF V600	11, 23.4%	7, 18.4%	0.5761
NRAS	7, 14.9%	4, 10.5%	0.5509
KIT	6, 12.8%	1, 2.6%	0.0911
KMT2A	4, 8.5%	2, 5.3%	0.5611
MSH3	4, 8.5%	1, 2.6%	0.2521
CTNNB1	2, 4.3%	1, 2.6%	0.6867
NCOR1	2, 4.3%	1, 2.6%	0.6867
TERT	2, 4.3%	1, 2.6%	0.6867
TP53	2, 4.3%	2, 5.3%	0.8273

Comparison of genetic fusions in melanomas in Korean and Western populations. Table VI summarizes the observed genetic fusions that occurred in cutaneous melanomas in the present study population. To compare the frequency of structural variant genes, fusion genes with clinical significance in the Cohort 1 population were also analyzed (Table VII). Results showed that cutaneous melanomas in the present study population had more frequent translocations of the *BRAF* gene than those of Cohort 1 ($p<0.0001$). Notably, however, *BRAF* gene fusion was the most frequent structural variant in both study populations (6/47, 12.8%, and 13/556, 2.3%, for the present study population and Cohort 1, respectively).

Table IV. *Frequent amplifications in the present study compared to those found in Cohort 1.*

Gene	Locus	Present study (n=47)	Cohort 1 (n=556)	*p*-Value
CDK4	12q14.1	11, 23.4%	9, 1.6%	<0.0001
CCND1	11q13.3	9, 19.2%	18, 3.2%	<0.0001
KIT	4q12	8, 17.0%	7, 1.3%	<0.0001
FGF19	11q13.3	7, 14.9%	18, 3.2%	0.0001
FGF3	11q13.3	7, 14.9%	16, 2.9%	<0.0001
FGF4	11q13.3	7, 14.9%	16, 2.9%	<0.0001
MDM2	12q15	6, 12.8%	6, 1.1%	<0.0001
MYC	8q24.21	6, 12.8%	7, 1.3%	<0.0001
PDGFRA	4q12	6, 12.8%	4, 0.7%	<0.0001
MDM4	1q32.1	3, 6.4%	1, 0.2%	<0.0001
RICTOR	5p13.1	3, 6.4%	2, 0.4%	<0.0001
RPS6KB1	17q23.1	3, 6.4%	0, 0.0%	<0.0001
EGFR	7p11.2	2, 4.3%	2, 0.4%	0.0016
ERBB2	17q12	2, 4.3%	0, 0.0%	<0.0001
FGF14	13q33.1	2, 4.3%	0, 0.0%	<0.0001
LAMP1	13q34	2, 4.3%	0, 0.0%	<0.0001

Table V. *Frequent homozygous deletions in the present study compared to those found in Cohort 1.*

Gene	Locus	Present study (n=47)	Cohort 1 (n=556)	*p*-Value
RET	10q11.21	2, 4.3%	8, 1.4%	0.1465
PDGFRB	5q32	2, 4.3%	0, 0.0%	<0.0001
EGFR	7p11.2	1, 2.2%	0, 0.0%	0.0006
FGF8	10q24.32	1, 2.2%	0, 0.0%	0.0006
JAK2	9p24.1	1, 2.2%	2, 0.4%	0.0981
FGF7	15q21.2	1, 2.2%	0, 0.0%	0.0006

Table VI. *Genetic fusions in cutaneous melanomas.*

Clinically significant genetic fusions
KIAA1549-BRAF, TRIM24-BRAF, BRAF-DPP6, ESYT2-BRAF, GOLGA4-BRAF, TPM3-ALK, JMJD1C-FGFR2, FGFR2-REEP3, EWSR1-PARVB
Unknown-significant genetic fusions
DGKG-ETV5, ESR1-ZNF280B, NOTCH2-GOLGA8A, YWHAE-RAF1, KCTD7-BRAF, STYXL1-BRAF, BRAF-HIP, SRP72-KIT, FOXP1-KIT

Discussion

In this study, we analyzed frequent genetic alterations that occurred in melanomas of the Korean population compared to those of the Western population to elucidate the unique features and genetic profile of Asian cutaneous melanoma. The accumulation of genetic alterations leading to melanoma development varies according to both melanoma type and tumor characteristics. Epidemiological, clinicopathological, and genetic features can be explained by common signaling pathways that differ based on the melanoma types: low ultraviolet (UV) radiation exposure/CSD, high UV radiation exposure/CSD, and low-to-no UV radiation exposure/CSD (1, 11).

We found out that the most common histologic type of melanoma in the present study population was the acral lentiginous type, and, as expected, acral lentiginous type was more frequently found in glabrous sites. Compared with populations of Cohort 1 and Cohort 2, NGS analysis showed that *BRAF V600* mutation was the most frequently identified mutation across study groups. However, the frequency was significantly lower in the present study population. Furthermore, mutations in *NRAS*, *KMT2A*, *TERT*, and *TP53* were more frequently observed in Cohort 1 than in the present study population. When we compared the SNVs of the Korean population with those of Cohort 3, which included 38 acral melanoma patients, *KMT2A, TERT,* and *TP53* mutations were

Table VII. *Frequently identified fusion genes in cutaneous melanomas.*

Present study (n=47)		Cohort 1 (n=556)		
Gene	No.	Gene	No.	*p*-Value
BRAF	6, 12.8%	BRAF	13, 2.3%	<0.0001
EWSR1	1, 2.1%	EWSR1	2, 0.4%	0.0981
FGFR2	1, 2.1%	SMARCA4	3, 0.5%	
ALK	1, 2.1%	NTRK1	3, 0.5%	
		SETD2	3, 0.5%	
		ARID1B	2, 0.4%	
		AGK	2, 0.4%	
		CDK5RAP2	2, 0.4%	
		ETV6	2, 0.4%	
		DNMT3A	2, 0.4%	
		APC	2, 0.4%	
		SRP19	2, 0.4%	
		ZFHX3	2, 0.4%	

found although their frequencies were less than 10% in this study population and Cohort 3 (Table III). These results can possibly be explained by the tendency of acral melanoma, the most common histologic subtype in the present study population, to have a lower mutation burden than superficial spreading melanoma which is a representative low-CSD melanoma (1, 11).

Like other eastern Asian countries, acral melanoma is the most common subtype of all cutaneous melanoma cases in Korea (12, 13). Accordingly, whereas UV radiation exposure is the major cause of non-acral melanoma, acral sites are not UV radiation–exposed, therefore, acral melanomas have a low mutation burden, typically without a UV radiation signature (2). In this study, which was performed in Korean patients, acral lentiginous melanoma was the most common type (23/47, 48.9%). To compare the SNVs of Korean melanoma patients with those of Western acral lentiginous melanoma patients, we analyzed the genetic data of Cohort 3. There was no statistically significant difference in SNVs between the population of this study and Cohort 3 although *KIT* mutation was more frequently found in the population of this study. However, large-size comparative studies in Asian melanoma patients are needed because the accumulation of genetic data for acral lentiginous melanoma are still far from satisfactory.

Following analysis for clinically significant CNVs, the most frequently identified mutations in the present study population included amplifications of *CDK4, CCND1, KIT, FGF19, FGF3, FGF4, MDM2, MYC,* and *PDGFRA* genes and homozygous deletions of *RET* and *PDGFRB* genes. It is well documented that melanomas without a UV radiation signature contain numerous DNA copy-number changes (2). This study showed that high-level amplifications in chromosomes 12q14.1–12q15 and 11q13.3 were more readily found than in previous studies of melanomas from Western populations (2, 15, 17, 18). However, loss of chromosome 9p21.3, including *CDKN2A*, *CDKN2B*, and *TEK* genes, was highly detectable in melanomas in Western population studies. Amplifications and homozygous deletions were also detected in several other genes. However, the *p*-value could not be calculated correctly by either Chi-square or Fisher's exact test due to the low number of detected samples (zero or too low for statistical computation) in Cohort 1.

A recent study reported genetic alterations among Korean melanoma patients with a comparison between primary tumors and corresponding metastatic lesions (14). The authors evaluated several well-known genetic alterations of melanoma and demonstrated that the frequent genetic aberrations in the primary melanomas were *BRAF V600* and *NRAS* mutation and *KIT* amplification. However, this previous study analyzed *BRAF, NRAS, GNAQ/11* mutations and *KIT* amplification data, therefore it could not provide the specific features of other genes associated with melanoma. A study showed that *KIT* mutations or amplifications found in 15-40% of acral melanoma and gene amplifications of *CCND1* in 24% of them occur in a mutually exclusive pattern with *BRAF V600* and *NRAS* mutations (5). However, both *NRAS* gene mutation and *CCND1* gene amplification were found in one case in this study population. It was an acral melanoma on the sole with metastasis to the liver. Additional studies are needed to confirm its mutual exclusiveness with *NRAS* gene mutation and *CCND1* gene amplification.

In summary, our results clearly demonstrated the differences in genetic alterations between Asian and Western melanoma cases. We found that *BRAF* V600 gene mutation was the most frequently identified mutation in this study population with relatively lower frequency than in Western populations. In CNVs, amplifications in chromosomes 12q14.1–12q15 including *CDK4* and *MDM2* genes and 11q13.3 including *CND1, FGF19, FGF3*, and *FGF4* genes were more readily found in this study compared to previous studies of melanomas

from Western populations, while loss of chromosome 9p21.3 could be a unique genetic alteration in Western melanomas. In conclusion, these results showed that *BRAF* V600 mutation should be considered a significant signaling pathway explaining melanoma pathogenesis in both Asian and Western populations.

Funding

This research was funded by the Basic Science Research Program through the National Research Foundation of Korea (NRF), grant number 2020R1F1A1076774 (SKK).

Conflicts of Interest

The Authors declare that they have no potential conflicts of interest to disclose in relation to this study.

Authors' Contributions

Conceptualization: SKK; Data curation: HJ, HJR; Formal analysis: HJ; Funding acquisition: SKK; Investigation: HJ; Methodology: HJR; Supervision: SKK; Validation: HJ, SKK; Visualization: SKK; Writing – original draft: HJ, SKK; Writing – review & editing: SKK.

References

1 Elder DE, Massi D, Scolyer RA and Willemze R (eds.): WHO classifcation of skin tumours. 4th edition. Lyon, France, IARC, pp. 66-75, 2018.

2 Curtin JA, Fridlyand J, Kageshita T, Patel HN, Busam KJ, Kutzner H, Cho KH, Aiba S, Bröcker EB, LeBoit PE, Pinkel D and Bastian BC: Distinct sets of genetic alterations in melanoma. N Engl J Med *353(20)*: 2135-2147, 2005. PMID: 16291983. DOI: 10.1056/NEJMoa050092

3 Whiteman DC, Watt P, Purdie DM, Hughes MC, Hayward NK and Green AC: Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. J Natl Cancer Inst *95(11)*: 806-812, 2003. PMID: 12783935. DOI: 10.1093/jnci/95.11.806

4 Lee EY, Williamson R, Watt P, Hughes MC, Green AC and Whiteman DC: Sun exposure and host phenotype as predictors of cutaneous melanoma associated with neval remnants or dermal elastosis. Int J Cancer *119(3)*: 636-642, 2006. PMID: 16572428. DOI: 10.1002/ijc.21907

5 Bastian BC: The molecular pathology of melanoma: an integrated taxonomy of melanocytic neoplasia. Annu Rev Pathol *9*: 239-271, 2014. PMID: 24460190. DOI: 10.1146/annurev-pathol-012513-104658

6 Cancer Genome Atlas Network: Genomic Classification of cutaneous melanoma. Cell *161(7)*: 1681-1696, 2015. PMID: 26091043. DOI: 10.1016/j.cell.2015.05.044

7 Yamaguchi Y, Beer JZ and Hearing VJ: Melanin mediated apoptosis of epidermal cells damaged by ultraviolet radiation: factors influencing the incidence of skin cancer. Arch Dermatol Res *300 Suppl 1*: S43-S50, 2008. PMID: 17985102. DOI: 10.1007/s00403-007-0807-0

8 Bellew S, Del Rosso JQ and Kim GK: Skin cancer in asians: part 2: melanoma. J Clin Aesthet Dermatol *2(10)*: 34-36, 2009. PMID: 20725572.

9 Bradford PT, Goldstein AM, McMaster ML and Tucker MA: Acral lentiginous melanoma: incidence and survival patterns in the United States, 1986-2005. Arch Dermatol *145(4)*: 427-434, 2009. PMID: 19380664. DOI: 10.1001/archdermatol.2008.609

10 Luk NM, Ho LC, Choi CL, Wong KH, Yu KH and Yeung WK: Clinicopathological features and prognostic factors of cutaneous melanoma among Hong Kong Chinese. Clin Exp Dermatol *29(6)*: 600-604, 2004. PMID: 15550131. DOI: 10.1111/j.1365-2230.2004.01644.x

11 Saginala K, Barsouk A, Aluru JS, Rawla P and Barsouk A: Epidemiology of melanoma. Med Sci (Basel) *9(4)*: 63, 2021. PMID: 34698235. DOI: 10.3390/medsci9040063

12 Chang JW: Acral melanoma: a unique disease in Asia. JAMA Dermatol *149(11)*: 1272-1273, 2013. PMID: 24068331. DOI: 10.1001/jamadermatol.2013.5941

13 Jang HS, Kim JH, Park KH, Lee JS, Bae JM, Oh BH, Rha SY, Roh MR and Chung KY: Comparison of melanoma subtypes among Korean patients by morphologic features and ultraviolet exposure. Ann Dermatol *26(4)*: 485-490, 2014. PMID: 25143678. DOI: 10.5021/ad.2014.26.4.485

14 Lee SH, Kim JE, Jang HS, Park KH, Oh BH, Shin SJ, Chung KY, Roh MR and Rha SY: Genetic alterations among Korean melanoma patients showing tumor heterogeneity: a comparison between primary tumors and corresponding metastatic lesions. Cancer Res Treat *50(4)*: 1378-1387, 2018. PMID: 29361821. DOI: 10.4143/crt.2017.535

15 Shoushtari AN, Chatila WK, Arora A, Sanchez-Vega F, Kantheti HS, Rojas Zamalloa JA, Krieger P, Callahan MK, Betof Warner A, Postow MA, Momtaz P, Nair S, Ariyan CE, Barker CA, Brady MS, Coit DG, Rosen N, Chapman PB, Busam KJ, Solit DB, Panageas KS, Wolchok JD and Schultz N: Therapeutic implications of detecting MAPK-activating alterations in cutaneous and unknown primary melanomas. Clin Cancer Res *27(8)*: 2226-2235, 2021. PMID: 33509808. DOI: 10.1158/1078-0432.CCR-20-4189

16 Liang WS, Hendricks W, Kiefer J, Schmidt J, Sekar S, Carpten J, Craig DW, Adkins J, Cuyugan L, Manojlovic Z, Halperin RF, Helland A, Nasser S, Legendre C, Hurley LH, Sivaprakasam K, Johnson DB, Crandall H, Busam KJ, Zismann V, Deluca V, Lee J, Sekulic A, Ariyan CE, Sosman J and Trent J: Integrated genomic analyses reveal frequent TERT aberrations in acral melanoma. Genome Res *27(4)*: 524-532, 2017. PMID: 28373299. DOI: 10.1101/gr.213348.116

17 Potrony M, Badenas C, Aguilera P, Puig-Butille JA, Carrera C, Malvehy J and Puig S: Update in genetic susceptibility in melanoma. Ann Transl Med *3(15)*: 210, 2015. PMID: 26488006. DOI: 10.3978/j.issn.2305-5839.2015.08.11

18 Tovar-Parra D, Gil-Quiñones SR, Nova J and Gutiérrez-Castañeda LD: 3'UTR-CDKN2A and CDK4 germline variants are associated with susceptibility to cutaneous melanoma. In Vivo *35(3)*: 1529-1536, 2021. PMID: 33910831. DOI: 10.21873/invivo.12406

Received December 23, 2022
Revised January 18, 2023
Accepted January 19, 2023