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Research Paper

Genetic polymorphisms may influence the vertical growth rate of melanoma

Mariusz Sikora[1], Lidia Rudnicka[1]✉, Barbara Borkowska[1], Agnieszka Kardynał[2], Monika Słowińska[3], Adriana Rakowska[1], Olga Warszawik-Hendzel[1], Anna Wiergowska[2], Iwona Ługowska[4], Piotr Rutkowski[4], Tadeusz Dębniak[5], Jan Lubiński[5], Małgorzata Olszewska[1]

1. Department of Dermatology, Medical University of Warsaw, 02-008 Warsaw, Poland
2. Department of Dermatology, Central Clinical Hospital MSWiA, 02-507 Warsaw, Poland
3. Department of Dermatology, Military Institute of Medicine, 04-141 Warsaw, Poland
4. Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, 02-781 Warsaw, Poland
5. Department of Genetics and Pathomorphology, Pomeranian Medical University, 70-111 Szczecin, Poland.

✉ Corresponding author: Lidia Rudnicka, MD, PhD, Professor and Chairman, Department of Dermatology, Medical University of Warsaw, Koszykowa 82A, 02-008 Warsaw, Poland. lidia.rudnicka@dermatolodzy.com.pl

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Abstract

Background: Identification of new predictive markers in melanoma is of great clinical importance. This study was aimed to analyze association between selected common variants in the cancer susceptibility genes and melanoma progression at the time of diagnosis.

Material and Method: The study included 243 consecutive patients with melanoma. Genotyping was performed using real-time PCR.

Results: Our data revealed modest association between xeroderma pigmentosum complementation group D (XPD) codon 312 polymorphism and tumor thickness (as defined by Breslow score; XPD D312N CC: 3.00 ± 3.78mm, CT: 1.71 ± 2.48mm, TT: 2,53 ± 3,24mm, P=0.023). The CT genotype in XPD D312N polymorphism was more frequently represented in non-invasive melanomas compared to deeply penetrating tumors. None of the common SNPs in cyclin dependent kinase inhibitor 2A (CDKN2A), vitamin D receptor (VDR), melanocortin 1 receptor (MC1R) were associated with Breslow depth.

Conclusion: These findings suggest that genetic alteration in XPD contributes to melanoma progression and may be a potential diagnostic and molecular prognostic marker.

Key words: CDKN2A, MC1R, cutaneous melanoma, polymorphism, VDR, XPD.

Introduction

Melanoma is considered one of the most aggressive neoplasms with extremely poor prognosis at advanced stages. The worldwide incidence and mortality rates of this tumor have been increasing over the last decades [1]. A combination of clinical criteria and histopathological features are established methods used for melanoma staging and predicting the survival outcome [2]. The most important prognostic factors include tumor thickness, ulceration, Clark level, mitotic rate and status of the sentinel lymph node. However, these markers are limited in their ability to reliably distinguish between low and high-risk melanoma cases [3]. Therefore, there is an urgent need to further sub-classify and identify new prognostic biomarkers to improve prediction and develop new targets for therapy.

Although exposure to ultraviolet (UV) radiation is a major environmental risk factor for melanoma, the genetic factors contribute to the development and progression of the disease. The malignant transformation from melanocytes to melanoma and the progression of primary cutaneous tumors to invasive and metastatic diseases results from a combination of genetic alterations [4].

A number of recent genome wide association studies have confirmed several regions associated with cancer initiation and development [5]. Melanoma risk is attributable to rare germline or somatic mutations in a variety of tumor suppressor genes such as CDKN2A [6], nucleotide excision repair system [7] and many other low-penetrant genetic variants that include melanocortin-1 receptor (MC1R) [8] or vitamin D receptor (VDR) [9]. There is a growing list of candidate genes that have been speculated to be involved in molecular mechanism behind melanoma formation. However, relatively little is known about genetic factors for melanoma progression and metastasis.

Thus, the aim of our study was to evaluate whether polymorphisms in genes previously associated with the increased risk of melanoma play an essential role in tumor progression. Genetic alterations selected for analysis included seven single nucleotide polymorphisms in the common variants of following four genes: CDKN2A (A148T), XPD (D312N, K751Q), VDR (M1T), MC1R (R160W, R151C, R163Q).

Material and Methods

Melanoma patients

We studied a group of 243 consecutive patients with newly diagnosed and histologically confirmed cutaneous melanoma. The study included 135 women and 108 men with a mean age at diagnosis of 49.2 years (age range: 19–83), diagnosed at four major skin cancer centres in Warsaw, Poland.

All participants signed an informed consent document before entering the study. The participation rate was 99,2%. The study was approved by the local ethics committee.

Genotyping

Genotyping was performed in DNA samples isolated from peripheral blood cells of patients with melanoma. Molecular analysis was performed using a combination of real-time PCR (LightCycler 480, Roche, Penzberg, Germany) and MassARRAY MALDI-TOF MS analysis (Sequenom Inc., San Diego, CA, USA). For real-time PCR TaqMan genotyping assays were used (Applied Biosystems, Foster City, CA). MALDI-TOF analysis was based on a primer extension reaction to detect and determine the SNP allele. Reactions were performed according to the manufacturer's instructions.

Sequencing

Random DNA samples were sequenced to verify the results of the MassARRAY genotyping and real-time PCR analysis. Sequencing was conducted using universal primers in combination with the ABI PRISM BigDye Terminator Cycle (Applied Biosystems, Foster City, CA) in the 3130 Genetic Analyzer (Applied Biosystems, Foster City, CA).

SNP selection, experimental conditions to perform RFLP-PCRs, real time PCR and DNA sequencing have been described previously [10-12].

Duration of skin lesion prior to diagnosis

The duration of the lesion diagnosed as melanoma prior to diagnosis was based on detailed anamnesis in all patients.

Statistical methods

Data are presented as mean ± SD. Associations between polymorphisms and clinicopathological features of melanoma patients were analysed by Mann-Whitney U-test for single comparisons and with Kruskal-Wallis test, followed by Dunn's *post hoc* test for multiple comparisons. To determine significant differences of genotype frequencies in patients with tumor Breslow thickness ≤ 1mm or > 1mm two-tailed Fisher exact test was used. All statistical analyses were performed using STATISTICA 12.0 (StatSoft, Krakow, Poland). P-values < 0.05 were considered statistically significant.

Results

Breslow thickness

The comparison of mean tumor Breslow depth between carriers of each analyzed single nucleotide polymorphism (SNP) (Table 1) revealed that the D312N CT genotype was more frequent in patients with thinner tumor thickness (P=0.023) compared to CC and TT genotypes. We further analyzed allele distribution in subgroups of melanoma patients with Breslow thickness ≤ 1mm and > 1mm (Table 2) as well as patients with invasive and in situ cancer (Table 3). The CT genotype in XPD D312N polymorphism was more frequently represented in non-invasive melanomas compared to thicker and more deeply penetrating tumors. Since XPD gene plays an important role in the removal of UV-light-induced DNA damage we investigated correlations between XPD D312N polymorphisms and Fitzpatrick skin phototype, melanoma location (sun-exposed areas vs sun-hidden locations), number of melanocytic nevi or sunburns in anamnesis. However, we did not find any association between this clinical variables and investigated polymorphism (Table 4).

Time of lesion duration before diagnosis

As shown in Table 5, the presence of the A148T CDKN2A polymorphism was more likely to be

diagnosed in patients with pigmented skin lesions that run a shorter course (P=0.012) compared to melanoma patients without this variant. We found no association between common XPD, MC1R, VDR variants and duration of skin lesion prior to diagnosis.

Age at diagnosis and sex

There were no statistically significant differences in the mean age at diagnosis as well as sex between the subjects carrying the examined SNPs (data not shown).

Table 1. Association between gene polymorphisms and Breslow thickness

SNP	Genotype	Mean Breslow thickness	P value
VDR M1T	AA (n=34)	2,78 ± 3,36	-
	GA (n=89)	2,40 ± 3,61	NS
	GG (n=49)	2,25 ± 2,13	NS
XPD D312N	CC (n=54)	3,00 ± 3,78	-
	CT (n=56)	1,71 ± 2,48	**0,023**
	TT (n=51)	2,53 ± 3,24	NS
XPD K751Q	GG (n=23)	2,00 ± 1,90	-
	GT (n=79)	2,32 ± 3,19	NS
	TT (n=68)	2,63 ± 3,59	NS
MC1R R151C rs1805007	CC (n=155)	2,48 ± 3,15	-
	CT (n=14)	2,59 ± 3,96	NS
MC1R V60L rs1805005	GG (n=148)	2,30 ± 2,96	-
	GT (n=21)	2,28 ± 2,01	NS
MC1R R163Q rs885479	GG (n=161)	2,37 ± 3,22	-
	AG (n=11)	3,57 ± 2,83	NS
CDKN2A A148T	Positive (n=8)	2,70 ± 1,68	-
	Negative (n=165)	2,42 ± 3,25	NS

NS - Not Statistically Significant

Table 2. Allele distribution in melanoma patients with Breslow thickness ≤ 1mm and > 1mm

SNP	Genotype	Breslow (≤1mm)	Breslow (>1mm)	P value
VDR M1T	AA (n=34)	15 (44,1%)	19 (55,9%)	-
	GA (n=89)	32 (36%)	57 (64%)	NS
	GG (n=49)	17 (34,7%)	32 (65,3%)	NS
XPD D312N	CC (n=54)	15 (27,8%)	39 (72,2%)	-
	CT (n=56)	26 (46,4%)	30 (53,6%)	-
	TT (n=51)	20 (39,2%)	31 (60,8%)	NS
XPD K751Q	GG (n=23)	9 (39,1%)	14 (60,9%)	-
	GT (n=79)	32 (40,5%)	47 (59,5%)	NS
	TT (n=68)	24 (35,3%)	44 (64,7%)	NS
MC1R R151C rs1805007	CC (n=155)	55 (35,5%)	100 (64,5%)	-
	CT (n=14)	6 (42,9%)	8 (57,1%)	NS
MC1R V60L rs1805005	GG (n=148)	57 (38,5%)	91 (61,5%)	-
	GT (n=21)	6 (28,6%)	15 (71,4%)	NS
MC1R R163Q rs885479	GG (n=161)	59 (36,6%)	102 (63,4%)	-
	AG (n=11)	4 (36,4%)	7 (63,6%)	NS
CDKN2A A148T	Positive (n=8)	1 (12,5%)	7 (87,5%)	-
	Negative (n=165)	58 (35,2%)	107 (64,8%)	NS

NS - Not Statistically Significant

Table 3. Allele distribution in patients with in situ and invasive melanoma.

SNP	Genotype	Tumor in situ	Invasive	P value
VDR M1T	AA (n=30)	3 (10%)	27 (90%)	-
	GA (n=85)	13 (15,3%)	72 (84,3%)	-
	GG (n=46)	6 (13,1%)	40 (86,9%)	NS
XPD D312N	CC (n=48)	4 (8,3%)	44 (91,7%)	-
	CT (n=52)	13 (25%)	39 (75%)	**0,038**
	TT (n=49)	5 (10,2%)	44 (89,8%)	**-**
XPD K751Q	GG (n=21)	2 (9,5%)	19 (90,5%)	-
	GT (n=76)	8 (10,5%)	68 (89,5%)	-
	TT (n=62)	13 (21,0%)	49 (79,0%)	NS
MC1R R151C rs1805007	CC (n=149)	19 (12,8%)	130 (87,2%)	-
	CT (n=12)	3 (25%)	9 (75%)	NS
MC1R V60L rs1805005	GG (n=139)	19 (13,7%)	120 (86,3%)	-
	GT (n=21)	2 (9,5%)	19 (90,5%)	NS
MC1R R163Q rs885479	GG (n=153)	22 (14,4%)	131 (85,6%)	-
	AG (n=10)	1 (10%)	9 (90%)	NS
CDKN2A A148T	Positive (n=8)	1 (14,3%)	7 (83,7%)	-
	Negative (n=157)	25 (15,9%)	132 (84,1%)	NS

NS - Not Statistically Significant

Table 4. Clinical characteristic of patients with XPD D312N polymorphism

Clinical variable		CC (n = 75)	CT (n = 72)	TT (n = 72)
skin phototype	I	11 (14.7%)	10 (13.9%)	10 (13.9%)
	II	44 (58.7%)	43 (59.7%)	41 (56.9%)
	III	16 (21.3%)	15 (20.8%)	18 (25.0%)
	IV	4 (5.3%)	4 (5.6%)	3 (4.2%)
melanoma location	sun-exposed areas	17 (22.6%)	16 (22.2%)	15 (20.8%)
	sun-hidden locations	58 (77.3%)	56 (77.8%)	57 (79.2%)
number of melanocytic nevi	< 10	21 (28.0%)	22 (30.6%)	20 (27.8%)
	10-50	21 (28.0%)	23 (31.9%)	26 (36.1%)
	51-100	14 (18.7%)	11 (15.3%)	10 (13.9%)
	> 100	19 (25.3%)	16 (22.2%)	16 (22.2%)
sunburn in childhood	first-degree	51 (68.0%)	48 (66.7%)	47 (65.3%)
	second-degree	27 (36.0%)	26 (38.2%)	25 (34.7%)

Table 5. Association between gene polymorphisms and time of lesion duration

SNP	Genotype	Time of lesion duration (months)	P value
VDR M1T	AA (n=28)	8,88 ± 17,21	-
	GA (n=84)	6,21 ± 12,01	NS
	GG (n=50)	7,24 ± 14,01	NS
XPD D312N	CC (n=56)	8,52 ± 15,38	-
	CT (n=51)	7,30 ± 13,52	NS
	TT (n=46)	5,26 ± 9,79	NS
XPD K751Q	GG (n=24)	7,46 ± 15,58	-
	GT (n=70)	6,50 ± 12,39	NS
	TT (n=66)	7,48 ± 14,39	NS
MC1R R151C rs1805007	CC (n=143)	7,03 ± 14,04	-
	CT (n=17)	8,03 ± 10,72	NS
MC1R V60L rs1805005	GG (n=138)	6,70 ± 11,88	-
	GT (n=24)	7,35 ± 18,34	NS
MC1R R163Q rs885479	GG (n=151)	7,45 ± 14,03	-
	AG (n=13)	2,85 ± 3,48	NS
CDKN2A A148T	Positive (n=7)	0,79 ± 0,99	-
	Negative (n=157)	7,34 ± 13,79	**0,012**

NS - Not Statistically Significant

Discussion

In the current study molecular analysis of 7 polymorphisms in 4 melanoma susceptibility genes showed a significant association between XPD D312N polymorphism and depth of invasion measured by Breslow thickness. Tumor thickness is considered the most important prognostic factor [13]. Numerous studies demonstrated that Breslow thickness, of all histopathological parameters, presents the strongest correlation with survival rates [14].

One potential mechanism to explain our findings could be that D312N polymorphism may result in protein folding modification and thus affect the protein function [15]. The XPD gene plays an important role in the maintenance of genomic integrity by removing UV-light-induced DNA lesions [16]. The XPD gene product is a DNA helicase involved in transcription, repair of DNA damage, cell cycle regulation and chromosome segregation [17, 18]. Hereditary defects in the XPD gene can result in high susceptibility to carcinogenesis [17]. Individual variations in XPD activity also may be a possible cancer risk factor. Several single nucleotide polymorphisms that induce amino acid changes have been described in XPD including codons 199 (Ile to Met), 201 (His to Tyr), 312 (Asp to Asn) and 751 (Lys to Gln) [19]. The first two are quite rare in most populations, whereas polymorphism in codon 312 and 751 have been associated with p53 gene mutation and cancer risk [20]. The XPD D312N polymorphism may result in the removal of the acidic moiety of aspartic acid, which can alter protein folding and interactions [19]. The amino acid substitution could result in different enzyme activity and repair capacity. Thus, association between the XPD polymorphism and cancer risk as well as progression is biologically plausible.

There are many reports indicating involvement of XPD gene polymorphisms in melanoma risk [7, 21]. However, only two studies have investigated the association of this gene with cancer progression. Kertat et al. examined the codon 751 polymorphism at the XPD gene in 244 melanoma patients in the Swedish population [22]. The authors found that heterozygous form (Lys/Gln) was more frequent in melanomas with Breslow thickness of >1.5 mm and the Clark levels III and IV, thus indicating a predictive role for XPD. The second investigation by Liu et al., conducted in 90 patients with stage IV melanoma failed to find an association between K751Q and prognostic variables and clinical outcomes [23]. No data on XPD D312N polymorphism was provided in these two studies. Similarly to our results, additional investigations showed predictive value of XPD D312N polymorphism in patients with non-small cell lung cancer [24, 25].

Another interesting observation rising from this study is that the presence of a CDKN2A A148T variant was more likely to be diagnosed in patients with shorter history of melanoma development compared to group without this polymorphism. The CDKN2A (OMIM 600160) is a tumor suppressor gene that encodes the p16 protein - a cyclin dependent kinase inhibitor and suppressor of cell proliferation [26]. An alanine to threonine substitution at codon 148 (A148T) is a common variant of CDKN2A, which is present in approximately 3.5% of the general population in Poland and have been shown to predispose to melanoma [10]. Reports assessing the association of A148T CDKN2A polymorphism with the p16 function are inconclusive. Some reports indicate that CDKN2A A148T variant do not alter protein function [27], whereas others studies show that the A148T variant is in strong linkage disequilibrium with a promoter polymorphism P493 and indirectly affects p16 function and reduces its expression [28]. Nevertheless, A148T is considered a molecular risk factor for developing several malignancies such as melanoma, breast or lung cancer [28]. Moreover, the loss of p16 expression in patients with vertical growth phase melanoma is associated with melanoma aggressiveness, increased tumor cell proliferation and reduced patient survival [29]. Our observation that A148T CDKN2A polymorphism is related to shorter clinical onset is also of clinical relevance, particularly for its prognostic implications. However, additional studies are required to determine whether this particular polymorphism can be associated with melanoma progression.

Genetic variants for the melanocortin-1 receptor (MC1R) gene have been found to be associated with the increased risk of melanoma development via pigmentary and non-pigmentary pathways [10, 30]. All SNPs in MC1R that were examined in this study did not appear to correlate significantly with tumor progression markers. Our findings are consistent with a study by Taylor et al., who did not observe any association of MC1R genotypes with Breslow thickness, tumor site and age at first diagnosis [31]. The major limitation in both studies is high polymorphism at the MC1R locus [32].

The role of VDR polymorphisms and melanoma progression remains controversial. In accordance with previous studies [33], no correlation was found between VDR genotype and Breslow thickness. Some reports demonstrate VDR gene polymorphism association with outcome in melanoma patients [34]. However, it remains necessary to determine that observed effects was related to impaired VDR protein

function rather than decreased VDR expression or vitamin D deficiency.

A limitation of our study is the relatively small samples size. Therefore, further studies taking into account heterogeneous nature of melanoma are required to confirm the findings and to better understand the role of genetic factors in cancer progression.

In conclusion, our results suggest that the XPD D312N polymorphism demonstrated a significant association with tumor thickness and may be a prognostic marker.

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Competing Interests

The authors have declared that no competing interest exists.

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