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MC1R Common Variants and the 10-Year Survival after Melanoma in Polish Population

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Abstract

Melanoma represents a significant health care burden. The Melanocortin-1-Receptor (MC1R) gene is highly polymorphic, it's pigmentary and non-pigmentary biological functions may be important for survival. Herein we report the 10-year survival of our cohort of 1032 melanoma patients depending on their MC1R status. The p.D84E, p.R142H, p.R151C, p.I155T, p.R160W and p.D294H MC1R variants were evaluated. All study participants were followed-up since the date of diagnosis to 2022 or until death. Statistical analyses included univariable and multivariable COX regression models. In the entire cohort no significant differences of overall survival were observed in relation to the MC1R status. In subgroup of men patients carrying any of the MC1R variant have worse survival than subjects with wild type (HR=2.04; 95% CI=1.04-3.98; p=0.037 and HR=2.05; 95% CI=1.05-4.01; p=0.035 for univariable and multivariable models respectively). Hazard ratios were significantly higher among older (≥ 50) patients (HR=4.14; 95% CI=2.20-7.80; p<0.001). Men compared to women have worse survival (HR 1.65; 95% CI=1.08-2.52; p=0.021). In conclusion- any possible MC1R effect on disease course is not strong, may differ among populations and may lead to worse prognosis among men. Due to a paucity of literature data additional prospective studies focused on possible association of *MC1R* mutations and melanoma prognosis are needed.

Keywords: Melanoma; MC1R; Survival; Genetics

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Introduction

Melanoma is one of the most lethal human malignancies thus representing a significant health care burden. Over 320,000 new cases were diagnosed worldwide in 2020, with 57,000 deaths. According to Global Cancer Observatory over the last ten years the incidence rates of malignant melanoma of the skin have raised by almost 50%, with deaths increasing by 32%. Data from the WHO suggest that the number of deaths related to melanoma will grow by 20% in 2025, rising to 74% in 2040 [1]. Based upon the SEER database, maintained by the National Cancer Institute (NCI), the American Cancer Society estimates the 5-year survival outcome to be 99% in localized, 66% in regional and 23% in distant melanoma stages. The TNM (Tumor Node and Metastasis) staging, Clark staging and Breslow thickness are the most often used clinical parameters for melanoma prognosis prediction, there is a need however for more factors in order to get a precise prognosis of outcome within the same staging groups. AJCC staging is of strong prognostic value for melanoma patients but only explains a proportion of the variance in survival. The evaluation of prognostic biomarkers is crucial for the early detection of recurrence and for selection of different treatment protocols [2].

The Melanocortin-1-Receptor (MC1R) gene codes protein affecting human pigmentation and is highly polymorphic in European populations. Germline variants of the MC1R gene have been reported to increase melanoma risk in populations of European ancestry [3].

MC1R has pigmentary and non-pigmentary biological functions [4,5] and they can be important for survival. It has been suggested that MC1R variants confer less resistance to apoptosis and mitigate cell proliferation, thereby improving overall survival [6]. Recently MC1R expression has been

described as a marker of progression in melanoma and colorectal cancer [7,8]. MC1R had also been reported as an intervention target for melanoma [9,10]. The correlation between MC1R and melanoma risk has been studied extensively, but the value of MC1R in the prognosis or therapeutic potential of Malignant Melanoma (MM) has been investigated to a much lesser extent. Herein we report the 10-year survival of our cohort of 1032 melanoma patients depending on their MC1R status.

Materials and Methods

Study participants

A total of 1032 melanoma patients with complete MC1R status were enrolled into the study after providing written informed consent. They were selected from a registry of ~1500 MM cases with histopathologically confirmed disease, housed at the Hereditary Cancer Center in Szczecin and diagnosed between January 01st, 2006 and December 31st, 2016 in Polish cities (Szczecin, Gorzow Wielkopolski, Opole, Bialystok, Zielona Gora). All newly diagnosed melanoma cases with secured biobank were enrolled in the study. The study was conducted in accordance with the Declaration of Helsinki and all participants signed a written informed consent document prior to donating a blood sample for analysis. The study was approved by the Ethics Committee of the Pomeranian Medical University in Szczecin (number BN-001/33/04). All patient blood samples were collected at the time of melanoma diagnosis, but before the commencement of any treatment other than surgical removal of skin lesion. From the date the patient signed the consent for scientific research, the samples are available for scientific research projects.

Methods

Genomic DNA was extracted from peripheral blood lymphocytes by standard methods. The whole coding region of MC1R was sequenced as reported elsewhere [11]. The MC1R common variants detected in Polish population were genotyped using a TaqMan assay (Applied Biosystems/Life Technologies) and the LightCycler Real-Time PCR 480 system (Roche Life Science). The primer and probe sequences were available upon request. Laboratory technicians were blinded to case control status. The overall genotyping call rate was 99.3%. Nonsynonymous MC1R variants were classified as RHC ('R') or non-RHC ('r') according to previously reported criteria [11,12]. Therefore, the p.D84E, p.R142H, p.R151C, p.I155T, p.R160W and p.D294H MC1R variants were classified as 'R', while all the other nonsynonymous MC1R variants were classified as 'r'. Synonymous variants were considered as Wild-Type (WT) MC1R alleles ('w'). According to this classification we determined the following genotypes: R/R, R/r, R/w, r/r, r/w, w/w.

Statistical analysis

All study participants were followed up since the date of diagnosis to 2020 or until death. Subjects with observation time longer than 10 years were considered as 10-year observations. In order to calculate hazard ratios univariable and multivariable COX regression models were performed. The multivariable models taking account the following variables: Each MC1R status (negative/positive) separately and: Clark (II, III, IV/V), sex (male/female) and age of diagnosis (<50/≥ 50). Due to relatively small number of cases with Clark V Authors decided to merge those patients with Clark IV category. According to the fact that melanoma classified as Clark I does not have impact on mortality such cases were excluded from the study. Kaplan-Meier curves were used to present results for univariable survival analysis. All calculations were performed using: "R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria" (R version 4.2.2 (2022-10-31).

Results

Mean age of diagnosis in whole study group (n=1032) was: 53.67 years. Most of patients were females (62%), 40% were diagnosed with Clark IV/V disease (Table 1). In the entire cohort 720 patients (70%) after 10 years of observation were still alive.

No statistically significant differences of overall survival of MM patients were observed in relation to their MC1R status in both univariable and multivariable models (Table 2). In subgroup of men (n=397) – patients carrying any of the MC1R variant have worse survival in relation to the subjects with wild type MC1R (HR=2.04; 95% CI=1.04-3.98; p=0.037 and HR=2.05; 95% CI=1.05-4.01; p=0.035 for univariable and multivariable models respectively).

The Kaplan-Meier survival curves of male patients in relation to their MC1R status are presented in Figure 1. The difference in survival in subgroup of females (n=635) in relation to carrying any of the MC1R variant was not statistically significant (HR=0.91; 95% CI=0.50-1.66; p=0.8).

Men compared to women have worse survival (HR 1.65; 95% CI=1.08-2.52 p=0.021). Hazard ratios were also significantly higher among older (≥ 50) patients (HR=4.14; 95% CI=2.20-7.80; p<0.001).

No significant survival differences in relation to the analyzed MC1R variants, Clark and Breslow parameters were observed using the multivariable analysis in subgroup with complete Breslow and Clark records (n=480).

Discussion

Only few studies of the survival of the MM patients depending on their MC1R status have been published to date. The BioGenomel consortium data indicated a survival benefit for inherited MC1R variants in melanoma patients. In the analyses adjusted for age and sex only, there was some support to the thesis that carriers of germline MC1R variants had better survival (HR: 0.82; 95% CI, 0.66–1.02; P=0.08 for no consensus alleles versus at least one consensus

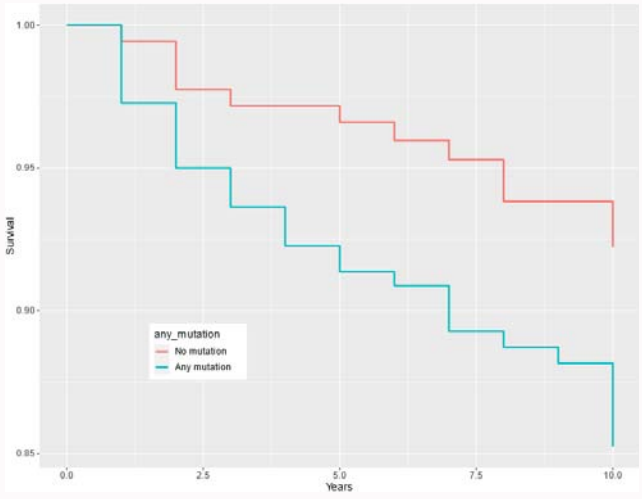

Figure 1: Melanoma male patients' survival in relation to presence any analyzed MC1R variant.

Table 1: Characteristics of study group (n=1032).

Variable	Overall, N=1032	Alive, N=947	Deceased, N=85
R160W			
(-)	814 (79%)	747 (79%)	67 (79%)
(+)	218 (21%)	200 (21%)	18 (21%)
R151C			
(-)	879 (85%)	809 (85%)	70 (82%)
(+)	153 (15%)	138 (15%)	15 (18%)
V60L			
(-)	843 (82%)	776 (82%)	67 (79%)
(+)	189 (18%)	171 (18%)	18 (21%)
R163Q			
(-)	950 (92%)	873 (92%)	77 (91%)
(+)	82 (7.9%)	74 (7.8%)	8 (9.4%)
6122			
(-)	1,030 (100%)	945 (100%)	85 (100%)
(+)	2 (0.2%)	2 (0.2%)	0 (0%)
5751			
(-)	1,026 (99%)	942 (99%)	84 (99%)
(+)	6 (0.6%)	5 (0.5%)	1 (1.2%)
RR			
w/w	460 (45%)	428 (45%)	32 (38%)
r/r	5 (0.5%)	4 (0.4%)	1 (1.2%)
R/r	50 (4.8%)	46 (4.9%)	4 (4.7%)
R/R	24 (2.3%)	22 (2.3%)	2 (2.4%)
r/w	213 (21%)	193 (20%)	20 (24%)
R/w	280 (27%)	254 (27%)	26 (31%)
Number of mutations			
0	460 (45%)	428 (45%)	32 (38%)
1	494 (48%)	448 (47%)	46 (54%)
2	78 (7.6%)	71 (7.5%)	7 (8.2%)
Any mutation			
No mutation	460 (45%)	428 (45%)	32 (38%)
Any mutation	572 (55%)	519 (55%)	53 (62%)
Sex			
Female	635 (62%)	592 (63%)	43 (51%)
Male	397 (38%)	355 (37%)	42 (49%)
Age of diagnosis	15.00 92.00 (53.67)	15.00 92.00 (52.85)	24.00 86.00 (62.81)
<50	383 (37%)	372 (39%)	11 (13%)
≥ 50	649 (63%)	575 (61%)	74 (87%)
Clark			
II	111 (18%)	109 (19%)	2 (5.0%)
III	254 (42%)	234 (41%)	20 (50%)
IV/V	243 (40%)	225 (40%)	18 (45%)
Unknown	424	379	45

alleles). The results were statistically insignificant without the supply of the Leeds cohort data (HR: 0.77, 95% CI 0.64–0.93; P=0.005) [6].

In another study variations at MC1R were evaluated for

Table 2: Univariable and multivariable COX regression models in relation to analyzed MC1R variants.

	Univariable COX Regression			Multivariable COX Regression		
Variable	**HR**	**95% CI**	***p***	**HR²**	**95% CI**	***p***
R160W						
(-)	-	-		-	-	
(+)	1.02	0.60, 1.71	>0.9	0.97	0.57, 1.62	0.9
R151C						
(-)	-			-		
(+)	1.24	0.71, 2.17	0.4	1.30	0.74, 2.27	0.4
V60L						
(-)	-			-	-	
(+)	1.19	0.70, 1.99	0.5	1.30	0.77, 2.19	0.3
R163Q						
(-)	-	-		-	-	
(+)	1.16	0.56, 2.41	0.7	1.20	0.58, 2.48	0.6
6122						
(-)	-			-		
(+)	0.00	0.00, Inf	>0.9	0.00	0.00, Inf	>0.9
5751						
(-)	-			-	-	
(+)	2.02	0.28, 14.5	0.5	4.04	0.55, 29.5	0.2
RR						
w/w	-	-		-	-	
r/r	2.82	0.38, 20.6	0.3	2.74	0.37, 20.1	0.3
R/r	1.15	0.41, 3.26	0.8	1.26	0.45, 3.56	0.7
R/R	1.22	0.29, 5.10	0.8	1.35	0.32, 5.64	0.7
r/w	1.32	0.76, 2.31	0.3	1.43	0.82, 2.51	0.2
R/w	1.34	0.80, 2.25	0.3	1.33	0.79, 2.24	0.3
Number of mutations						
None	-			-		
1	1.33	0.85, 2.09	0.2	1.37	0.87, 2.15	0.2
2	1.30	0.57, 2.95	0.5	1.42	0.63, 3.22	0.4
Any mutation						
No mutation	-			-		
Any mutation	1.33	0.85, 2.06	0.2	1.38	0.89, 2.14	0.2

HR, HR²: Hazard Ratio; CI: Confidence Interval

associations with melanoma-specific survival in a large population-based study. Authors found that melanoma-specific survival was inversely associated with carriage of MC1R variants in the absence of wild-type alleles com-pared to carriage of at least one wild-type allele (HR=0.60; 95% CI=0.40–0.90;). MC1R results for overall survival were consistent with no association [13].

In a Spanish study of 1341 MM patients inherited MC1R variants have been reported to be associated with improved overall and melanoma-specific survival in women with melanoma but not in men [14].

In theory MC1R variants may influence a disease course due to their effect on repair of DNA and apoptosis. Overexpression of DNA repair pathways has been suggested to be associated with metastases and worse melanoma patient's outcome [15,16]. Signaling through

MC1R regulates expression of the MITF transcription factor which has been suggested to affect DNA repair (APEX1) [17], the cell cycle (CDKN2A, CDK2) [18,19], apoptosis (BCL2) [20] and invasion (DIA1) [21]. The APEX1 is important in DNA repair responses to Reactive Oxygen Species (ROS) and oxidative DNA base damage [5]. Liu et al. reported that MITF-positive MM cell lines had high levels of APEX1 [17], and in another study, down-regulation of APEX1 resulted in apoptosis of melanoma cells in culture [22].

These literature data suggest indirectly that melanoma cells carrying MC1R variants might be characterized by altered DNA repair, resistance to apoptosis and increased proliferation. The data need however to be verified by additional studies since the evidence supporting this thesis is not sufficient so far.

Somatic differences between the melanoma tumors might also suggest the possible differences in disease outcome associated with constitutional MC1R status. Inherited MC1R variants have been suggested to increase the likelihood of somatic BRAF mutant tumors [23,24], however the data were not confirmed by others [25,26]. Up to now there is no clear evidence to support the thesis that MC1R has an effect on somatic tumor variation.

Herein in our entire cohort of MM patients from Polish population we observed no significant impact of common MC1R variants on overall survival. We found that MC1R variants might be associated with worse overall survival in men using both univariable and multivariable models. Despite the relatively large nominal size of the group (n=1032), the observed effect size is probably too small to detect significant differences in survival considering each of analyzed MC1R variants in the entire cohort, which is consistent with data presented by Taylor et al. [13].

Conclusion

We can conclude that if there is any possible MC1R effect on disease course, it is not strong, may differ among various populations and may lead to worse prognosis among men. Due to a paucity of literature data additional prospective studies focused on possible association of MC1R mutations and melanoma prognosis are needed.

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