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DERMOSCOPIC FEATURES OF CUTANEOUS MELANOMA ARE ASSOCIATED WITH CLINICAL CHARACTERISTICS OF PATIENTS AND TUMORS AND WITH *MC1R* GENOTYPE

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Abstract

Background.—Several algorithms are available for the dermoscopic diagnosis of pigmented skin lesions. The *MC1R* gene is a key determinant of pigmentation characteristics that are established host-related melanoma risk factors.

Objectives.—To investigate the association of dermoscopic features of sporadic cutaneous melanomas with clinical characteristics of patients and corresponding tumors and with genetic changes in the *MC1R* and *BRAF* genes.

Methods.—64 dermoscopic images of 62 patients were scored by ABCD rule and modified pattern analysis. Detailed patients' and melanomas' characteristics were collected. Patients were screened for germline *MC1R* variants and related melanomas for somatic V600 *BRAF* mutations.

Results.—A lower TDS score was observed in melanomas of patients with red hair (p=0.019), due to reduced dermoscopic structures (p<0.0001). Thicker melanomas showed higher TDS values (p=0.021) due to sharper borders (p<0.0001) and higher number of colors (p=0.004). An atypical pigment network was prevalent in superficial spreading melanomas (p=0.010), in individuals with dark skin (p=0.043) and hair color (p=0.001). An atypical vascular pattern was more frequent in nodular (p<0.0001) and thick (p<0.0001) melanomas, in individuals with skin type I-II (p=0.037), blond or red hair color (p=0.032) and blue or green eyes (p=0.014). Melanomas of *MC1R* R carriers showed lower TDS value (p=0.037), reduced dermoscopic structures (p=0.001) and lower prevalence of atypical pigment network (p=0.001). No differences were identified between *BRAF*-mutated or wild-type melanomas.

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Conclusions.—We suggest a phenotypic/*MC1R* profile for melanoma patients and their tumors. Melanomas of *MC1R* R carriers show a significant lower TDS value, with reduced dermoscopic structures, and a lower prevalence of an atypical pigment network. Noncarriers of *MC1R* R variants develop melanomas dermoscopically characterized by an atypical pigment network which is prevalent in superficial spreading melanomas, in patients with dark complexion and less frequent in red-haired individuals.

Keywords

ABCD rule; dermoscopy; *BRAF*; *MC1R*; melanoma; pattern analysis; total dermoscopy score

INTRODUCTION

A marked improvement in the accuracy of melanoma diagnosis has been achieved with the introduction of dermoscopy which allows a better visualization of morphological structures and colors not visible by the naked-eye.[1,2] Various dermoscopic algorithms have been developed to differentiate benign from malignant melanocytic skin lesions, namely pattern analysis,[3,4] ABCD rule,[5] Menzies' scoring method[6] and 7-point checklist.[7] The most sensitive and specific approach is pattern analysis, based on detailed, qualitative assessment of numerous dermoscopic criteria, with each category of pigmented skin lesions being characterized by few global patterns and a rather distinctive combination of specific local features.[3,4,8] The ABCD rule of dermoscopy is a simple and reliable semiquantitative method for diagnosing early melanoma.[5,8]

The *MC1R* gene is the major determinant of human pigmentation, encoding a G-protein coupled receptor with a high affinity for the α-melanocyte-stimulating hormone (αMSH). Upon αMSH activation, MC1R stimulates cAMP production inducing a switch of pigment production from pheomelanin to eumelanin. The *MC1R* is highly polymorphic in white populations with specific variants resulting in increased pheomelanin production and being associated with a UV-radiation sensitive phenotype, characterized by red hair, fair skin, freckling and poor tanning ability (the red hair color or RHC phenotype).[9-11] *MC1R* variants have been classified into R (D84E, R142H, R151C, I155T, R160W, D294H) and r (V60L, V92M, R163Q) alleles, according to the strength of their association with the RHC phenotype.[12,13] Studies in different populations worldwide demonstrated that *MC1R* variants are associated with increased risk of cutaneous melanoma[14,15] and are able to modify melanoma risk in *CDKN2A* mutation-positive families.[16]

The *BRAF* oncogene encodes a serine/threonine kinase that acts in the Ras-RAF-MAPK pathway, involved in the regulation of cell proliferation in response to extracellular mitogenic signals. Somatic *BRAF* mutations have been reported in over 60% of cutaneous melanomas, mostly at codon 600 of exon 15.[17] An association between germline *MC1R* variants and the development of *BRAF*-mutant melanomas has been reported with controversial results.[18-23] More recently, *MC1R* deficiency has been demonstrated to cooperate with $BRAF^{V600E}$ to drive melanomagenesis through elevated PI3K/AKT signaling.[24]

The association between specific dermoscopic features of melanoma and the *MC1R* genotype has been investigated with controversial results in 2 small series of high-risk melanoma patients carrying *CDKN2A* mutations[25,26] while no data are available in the general population.

In the present study, we investigated the association of dermoscopic features of cutaneous sporadic melanomas, as scored by the ABCD rule[5] and modified pattern analysis[3,4,8], with clinical characteristics of patients and melanomas and with genetic changes in the *MC1R* and *BRAF* genes.

MATERIALS AND METHODS

Study population and data collection

We analyzed a series of 64 cutaneous melanomas diagnosed between 2000 and 2002 at the Departments of Dermatology of the Universities of L'Aquila, Modena and Florence in central Italy, which had been included in a previously reported larger genetic case-control study.[19] Digital dermoscopic images of the excised melanomas were available for 64 of the initial 165 melanomas. No substantial difference was observed between selected and unselected melanomas from the initial 165 tumors with regard to gender (p=0.559) and age (p=0.530) of patients, anatomical location (p=0.381) and Breslow thickness (p=0.163).

A standardized questionnaire and skin examination were used to collect patients' demographics and clinical information on pigmentation characteristics (skin type, hair and eye color) as previously described.[27] In addition, patients' age at diagnosis, anatomical site and histopathological data of melanoma (clinico-pathological variant, Breslow thickness) were recorded.

The Medical Ethics Committee approved the study protocol. Written informed consent was signed by all participants and the study was conducted according to the Declaration of Helsinki Principles.

Dermoscopic analysis

Images were acquired with a digital imaging dermoscopic system using a standardized balance of colors and light (Dermogenius, version 1.6-SP2; Linos AG, Goettingen, Germany) or with a special dermoscopy objective coupled with a digital camera (Nevuscreen, Arkè s.a.s., Avezzano, Italy). Images of insufficient quality or showing only part of the lesion were excluded from the analysis. Lentigo maligna melanoma and acral lentiginous melanoma were excluded due to location-specific dermoscopic features that were unsuitable for ABCD score evaluation. The digital dermoscopic images were converted into JPEG format, named with identification codes and randomly ordered for evaluation.

For calculating the ABCD score, the Asymmetry (A), Border (B), Colors (C), and Dermoscopic structures (D) criteria were assessed semiquantitatively. The different dermoscopic structures included pigment network, dots, globules, streaks and structureless or homogeneous areas. Each of the criteria was then multiplied by a given weight factor to yield a total dermoscopic score (TDS). TDS values less than 4.75 indicate a benign

melanocytic lesion, values between 4.8 and 5.45 indicate a suspicious lesion, and values greater than 5.45 are highly suggestive of melanoma.[5]

Global and local dermoscopic features were classified according to modified pattern analysis.[3,4,8,28] Dermoscopic melanoma-specific criteria included structural asymmetry with regards to shape, colors and/or dermoscopic structures, a multicomponent pattern, atypical pigment network, irregular dots and globules, irregular streaks, irregular pigmentation, regression structures, blue-whitish veil, atypical vascular pattern, red globules and reticular depigmentation.

The presence or absence of dermoscopic features according to the ABCD and pattern analysis algorithms was agreed on by 3 dermatologists (MCF, DP, KP), blinded to genetic status.

MC1R and BRAF genetic analysis

The 951 bp *MC1R* coding region was analyzed in two overlapping fragments by PCR followed by direct sequencing of the amplicons in blood genomic DNA from all patients. Molecular analysis of *BRAF* exon 15 was carried out on somatic DNA, extracted by manual microdissection. Specific primers and sequencing chemistries for *MC1R*[29] and for *BRAF* exon 15[18] have been previously described. Each PCR amplification was performed twice, and complete sequencing of the PCR products, obtained in independent reactions, was performed on both strands. Results were analyzed using the Sequencing Analysis Software, version 1.0.1 or 5.1 (Applied Biosystems).

Statistical analysis

Analysis of variance (ANOVA) models were used to evaluate the univariable association between TDS or each ABCD sub-score with patients' and lesions' characteristics, germline *MC1R* variants and somatic *BRAF* mutations. To test differences in the prevalence of local features in melanomas according to patients' and melanomas' characteristics, germline *MC1R* variants and somatic *BRAF* mutations, chi-square or Fisher exact test, when appropriate, were used.

For statistical analysis, the D84E, R142H, R151C, I155T, R160W, D294H *MC1R* alleles which cause significant changes in receptor functioning were grouped as *R* variants. The 86_87insA and the Y152X alleles were added to the *R* group since they both result in a truncated, non-functional receptor. All other non synonymous variants (V60L, S83P, V92M, T95M, A111V, R163Q, R213W, N279K, C315R) were considered as r variants. Synonymous amino acid changes were considered as wild type alleles. To analyze the association of germline variants in the *MC1R* gene with the dermoscopic criteria, three classifications were used: i) patients with no variant were compared with patients with any *MC1R* variant (R or r variants); ii) patients with one or two r variants (but not R) were compared with patients with one or two R variants; iii) patients were categorized in three groups based on the number of *MC1R* R variants in the genotype: no R variants, one R variant and two R variants.

RESULTS

Patients' and melanomas' characteristics

Sixty-four images of histopathologically confirmed cutaneous melanomas of 62 white patients (33 males, 29 females), aged 22 to 80 years (mean age: 51.3 years), were eligible for the analysis. Table 1 summarizes demographic, phenotypic and genetic characteristics of patients and tumors enrolled in the study. One patient had a personal history of multiple primary melanomas (n=3) in the absence of a familial background and germline *CDKN2A* or *CDK4* mutations. Thirty (46.9%) melanomas were located on the trunk, 23 (35.9%) on the lower extremities and 11 (17.2%) on the upper extremities. Fifty-one (79.7%) melanomas were of the superficial spreading type, 8 (12.5%) of the nodular type and in 5 (7.8%) cases data were not available. Eighteen (28.1%) melanomas were *in situ*, 30 (46.9%) had a Breslow thickness ≤ 1.00 mm, 13 (20.3%) > 1.00 mm while data were not available in 3 (4.7%) cases. Breslow thickness ranged from 0.1 to 8.7 mm (mean tumor thickness: 1.13 ± 1.46 mm; median tumor thickness 0.63 mm). Sixty were pigmented melanomas and 4 were hypo- or amelanotic lesions.

MC1R variants and BRAF mutations

Nonsynonymous *MC1R* variants were detected in 51 of 62 (82.2%) patients and are listed in Table S1. In addition, two synonymous *MC1R* variants (Q233Q and T314T) were identified. As previously observed in Mediterranean populations, the most frequent *MC1R* variant was V60L (21%), followed by R160W (9.7%), R151C (8.0%), V92M (6.4%) and R142H (3.2%).

There was a strong association between R variants and red hair: all 9 red-haired individuals included in the study carried at least one R variant, with 5 of them carrying two R variants and 4 being heterozygous R/r. In addition, among the seven patients with two R variants in the genotype, five were red-haired and the remaining two had light brown hair with shades of red.

Given the small size of melanoma lesions and the need to use most of the lesion for diagnosis, sufficient/good quality DNA for *BRAF* mutation analysis could be collected from 51 of the 64 melanomas included in the study. Cases with available data on *BRAF* mutation status (n=51) and those without (n= 13) did not substantially differ for subjects' characteristics, including gender (p=0.222) and age (p=0.238), and for melanomas' characteristics, such as site (p=0.812) and Breslow thickness (p=0.227), while differed for histopathologic variant, with more superficial spreading melanomas analyzed as compared to nodular melanomas (p=0.014).

Somatic *BRAF* mutations at codon 600 were identified in 23/51 (45.0%) melanomas with the V600E change in 20 (87%) melanoma tissues and the V600K in 3 (13%).

Dermoscopic features according to patients' and melanomas' characteristics

Table 2 summarizes patients' and melanomas' characteristics according to ABCD criteria and prevalence of local features.

Interestingly, a significantly lower TDS score was observed in melanomas of patients with red hair (p=0.019), mainly due to a reduced number of dermoscopic structures (p<0.0001). In line with this result, a significant lower D value (p=0.041) was present in melanomas of patients with skin type I-II as compared to patients with skin type III-IV. With regard to melanomas' features, thicker melanomas showed significantly higher TDS values (p=0.021) as compared to thinner ones due to sharper borders (p<0.0001) and higher number of colors (p=0.004). Nodular melanomas showed indeed sharper borders (p<0.0001) as compared to superficial spreading melanomas.

With regard to pattern analysis, an atypical pigment network was more prevalent in melanomas of the superficial spreading type (p=0.010) in individuals with dark complexion (skin type III-IV vs skin type I-II, p=0.043) and less prevalent in individuals with red hair color (p=0.001). An atypical vascular pattern was more frequent in melanomas of the nodular type (p<0.0001) with a Breslow thickness > 1.00 mm (p<0.0001) in individuals with skin type I-II (p=0.037), blond or red hair color (p=0.032) and blue or green eyes (p=0.014).

Dermoscopic features according to MC1R and BRAF genetic changes

We investigated the association of germline variants in the *MC1R* gene and of the V600 somatic mutation in the *BRAF* gene with the TDS score and the different criteria of the ABCD rule as well as with global and local features of pattern analysis (Table 3).

The mean TDS differed according to the number of R variants (p=0.037) in the genotype: more specifically, mean TDS was significantly lower in carriers of two R variants as compared to noncarriers of R variants (5.8 ± 0.78 vs 6.59 ± 0.74, p=0.021). Carriers of two R variants and noncarriers were mainly distinguished by a significant reduction in the number of structures in carriers (p=0.001).

A global multicomponent pattern was present in 61 of 64 melanomas with the remaining three being either homozygous for R variants (n=2) or for r variants (n=1) (data not shown). With regard to local features, a significant lower prevalence of an atypical pigment network was observed in carriers of two R variants as compared to noncarriers or carriers of one R variant (p=0.001) (Fig. 1). Carriers of *r* variants were more likely to develop melanomas with an atypical pigment network (p=0.022). Melanomas in carriers of any *MC1R* variant were strongly associated with the presence of irregular streaks (p=0.013) although this effect was neither confined to *R or r* variants.

With regard to clinico-pathological variants, *MC1R* R variants presented a borderline association with the nodular type of melanoma (p=0.058) with 75% of nodular melanomas developing in carriers of R variants and 61% of superficial spreading melanomas in wild type *MC1R* patients (data not shown).

Finally, melanomas harboring *BRAF* mutations at codon 600 did not show any significant difference in TDS value, specific ABCD criteria and local features as compared to melanomas with wild type *BRAF*.

DISCUSSION

We investigated the association between dermoscopic features of sporadic cutaneous melanomas, as scored by ABCD rule and pattern analysis, and clinical characteristics of melanoma patients, features of the corresponding tumors and genetic changes in the *MC1R* and *BRAF* genes.

Our findings in a series of sporadic cutaneous melanomas showed a significant lower TDS value in carriers of two *MC1R* R variants as compared to noncarriers, which was mainly due to a reduced number of dermoscopic structures. Dermoscopic features of melanoma, as scored by ABCD rule, and *MC1R* genetic changes have been associated with controversial results in 2 studies including a small number of melanomas from high risk melanoma patients.[25,26] Early melanomas from *CDKN2A* mutation-positive Spanish patients showed a significant lower TDS value in carriers of 2 *MC1R* RHC variants than in noncarriers of RHC variants, due to low number of colors and structures.[25] Conversely, no significant difference in the TDS score between carriers of 2 RHC variants and 0 RHC variants was detected in melanomas of carriers of the p16-Leiden founder mutation.[26] The different *CDKN2A* mutations, a variable categorization of *MC1R* variants or the small melanoma sample size might be the reason for these discrepant observations.

In the present study, global and local dermoscopic features of melanoma, as classified by pattern analysis, were associated for the first time with *MC1R* genetic status of melanoma patients. An atypical pigment network was prevalent in melanomas of patients who were noncarriers of *R* variants, presented dark skin and dark hair color, and developed a melanoma of the superficial spreading type. An atypical vascular pattern was observed more frequently in melanomas of patients with fair skin type, light hair and eye color, who developed thick melanomas, mainly of the nodular type. We also observed a tendency for an increased presence of atypical vascular pattern with the increasing number of R variants in the genotype and a borderline association between *MC1R* R variants and nodular melanoma which need to be confirmed in larger studies.

Dermoscopic features of melanocytic nevi have been previously characterized in high-risk patients carrying *CDKN2A* and/or *MC1R* genetic changes and included structureless areas, atypia, vessels and absence of pigmentation.[26,30]

The association of *MC1R* RHC variants and melanomas lacking significant pigmentation has been described in two case-reports.[31,32] A germline homozygous *MC1R* R151C variant was detected in a woman with skin type I, red hair and “white” dysplastic nevi who developed two amelanotic melanomas.[31] We recently reported the occurrence of concomitant primary hypomelanotic melanoma on the same body site in a pair of red-haired monozygotic twins, heterozygous for two *MC1R* R variants.[32] In the present series, four patients presented a hypo/amelanotic melanoma and all carried at least one R variant in the *MC1R* genotype two being homozygous for R variants (R151C/R160W and R142H/R151C), one heterozygous R/r (R151C/V60L) and one R/wt (R160W/wt).

The influence of somatic *BRAF* alterations on the dermoscopic appearance of melanocytic lesions has been previously investigated in nevi[33] but never in melanoma. In our series,

45.0% of melanomas harbored somatic *BRAF* mutations at codon 600, but no difference by ABCD rule or pattern analysis was observed between *BRAF*-mutant and *BRAF*-wild-type melanomas. Although distinct histopathological features have been reported for *BRAF*-mutant melanomas,[34] the interaction of *BRAF* mutations with unknown germline and/or somatic mutations of other genes might differently influence the resulting phenotype and dermoscopic appearance of melanoma.

Our study has strengths and limitations. Major strengths are: i) this is the first study to investigate the association of *MC1R* variants and dermoscopic features in melanoma in the general population since previous small reports only focused on high risk melanoma patients; ii) availability of clinical and molecular data for all eligible dermoscopic images; iii) *BRAF* mutations and dermoscopic features have never been investigated in melanoma, but only in benign melanocytic lesions. Main limitation of our study is the limited number of available images with prevented us to evaluate all *MC1R* genotypes.

In conclusion, we demonstrated the association of specific clinico-dermoscopic features of melanoma with phenotypic characteristics and *MC1R* status of the patient which might help in melanoma diagnosis. Melanomas of noncarriers of R variants are dermoscopically characterized by an atypical pigment network which is prevalent in superficial spreading melanomas, in darkly-pigmented patients and less frequent in individuals with red hair color. *MC1R* R carriers develop melanomas with a significant lower TDS value, reduced dermoscopic structures, and a lower prevalence of atypical pigment network. The association of *MC1R* R variants with nodular melanoma and the presence of an atypical vascular pattern needs to be confirmed in larger series.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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None

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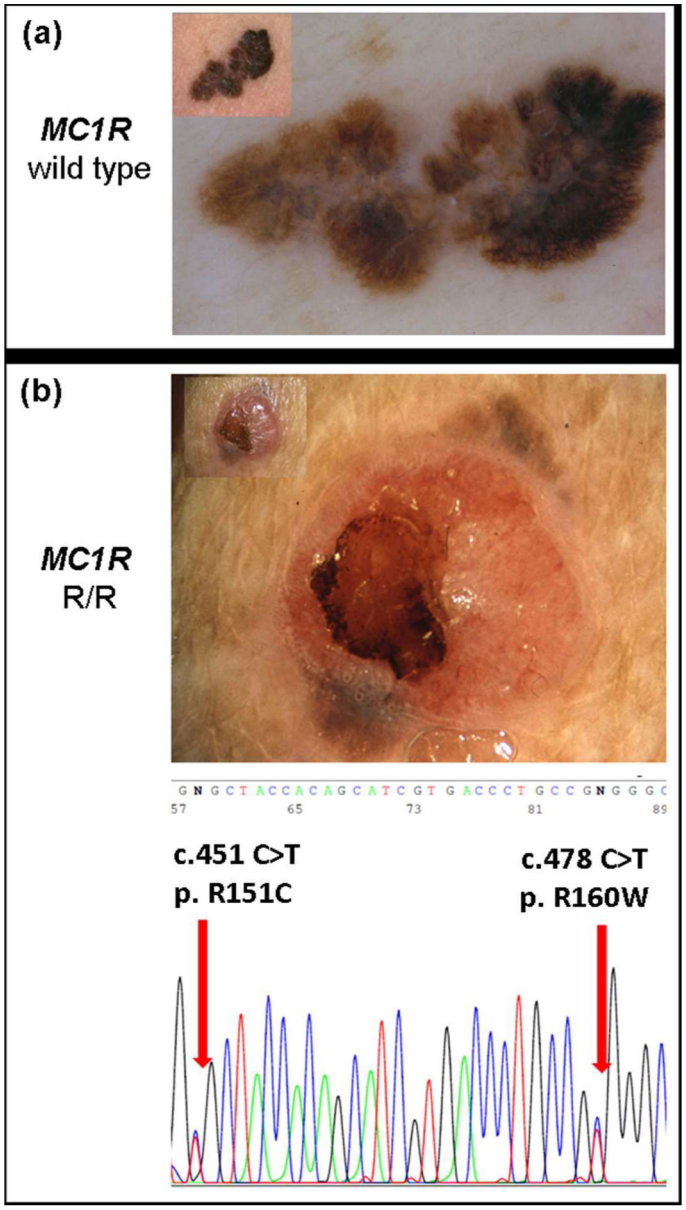

Figure 1.

Clinico-dermoscopic images of 2 melanomas according to *MC1R* genotype. a) Superficial spreading melanoma in a patient with wild-type *MC1R*; b) hypomelanotic nodular melanoma in a carrier of two *MC1R* R variants, p.R151C and p.R160W.

Table 1.

Distribution of melanoma patients and tumors according to demographic, phenotypic and genetic characteristics

Variable		No. of cases (%) n=62
Gender	Male	33 (53.2)
	Female	29 (46.8)
Age	≤ 40	14 (22.6)
	41-55	27 (43.5)
	> 55	21 (33.9)
Skin type	I-II	34 (54.8)
	III-IV	28 (45.2)
Hair color	Black/Dark brown	17 (27.4)
	Light brown	28 (45.2)
	Blond	8 (12.9)
	Red	9 (14.5)
Eye color	Dark Brown	18 (29.0)
	Light brown	20 (32.3)
	Green	14 (22.6)
	Blue	10 (16.1)
***MC1R* status**	Wt	11 (17.7)
	R	23 (37.1)
	r/wt	*15*
	r/r	*8*
	R	28 (45.2)
	1R	*21*
	2R	*7*
Variable		**No. of melanomas (%) n=64**
Clinico-pathological variant	Superficial spreading	51 (79.7)
	Nodular	8 (12.5)
	Not available	5 (7.8)
Breslow thickness	In situ	18 (28.1)
	≤1.00 mm	30 (46.9)
	>1.00 mm	13 (20.3)
	Not available	3 (4.7)
Site of melanoma	Trunk	30 (46.9)
	Upper Extremities	11 (17.2)
	Lower extremities	23 (35.9)
BRAF mutations	No	28 (55.0)
	Yes	23 (45.0)

Variable		No. of cases (%) n=62
	V600E	20
	V600K	3
	Not available	13

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Table 2.

Mean and SD of ABCD TDS and prevalence of local features in melanomas according to patients' and lesions' characteristics

Dermoscopic criteria	*Skin type*			*Hair color*					*Eye color*				*Histopathological type*			*Breslow thickness (mm)*			
	I - II	**III - IV**		**Black or dark brown**	**Light Brown**	**Blond**	**Red**		**Brown**	**Green**	**Blue**		**Superficial spreading**	**Nodular**		**In situ**	**≤1.00 mm**	**>1.00 mm**	
	n=34	**n=30**		**n=17**	**n=30**	**n=8**	**n=9**		**n=38**	**n=16**	**n=10**		**n=51**	**n=8**		**n=18**	**n=30**	**n=13**	
	Mean (SD)	**Mean (SD)**	**p**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**p**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**p**	**Mean (SD)**	**Mean (SD)**	**p**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**p**
TDS	6.4 (0.15)	6.68 (0.14)	0.175	6.97 (0.79)	6.48 (0.74)	6.49 (0.82)	5.94 (0.81)	**0.019**	6.51 (0.84)	6.53 (0.99)	6.63 (0.43)	0.922	6.5 (0.86)	6.89 (0.76)	0.233	6.16 (0.94)	6.64 (0.69)	6.95 (0.72)	**0.021**
A	2.41 (0.47)	2.51 (0.33)	0.311	2.52 (0.32)	2.51 (0.33)	2.27 (0.6)	2.31 (0.57)	0.294	2.43 (0.45)	2.44 (0.44)	2.6 (0)	0.494	2.42 (0.45)	2.6 (0)	0.272	2.31 (0.56)	2.51 (0.33)	2.6 (0)	0.089
B	0.52 (0.15)	0.49 (0.15)	0.411	0.54 (0.09)	0.5 (0.15)	0.54 (0.18)	0.43 (0.2)	0.362	0.48 (0.14)	0.54 (0.17)	0.53 (0.15)	0.379	0.74 (0.07)	0.46 (0.12)	**<0.0001**	0.42 (0.12)	0.49 (0.12)	0.66 (0.13)	**<0.0001**
C	1.81 (0.37)	1.83 (0.3)	0.774	1.91 (0.26)	1.75 (0.37)	2 (0.27)	1.72 (0.36)	0.133	1.78 (0.3)	1.91 (0.46)	1.85 (0.24)	0.422	2.06 (0.32)	1.81 (0.33)	0.052	1.67 (0.24)	1.82 (0.31)	2.04 (0.32)	**0.004**
D	1.65 (0.38)	1.85 (0.4)	**0.041**	2 (0.4)	1.72 (0.31)	1.81 (0.37)	1.28 (0.26)	**<0.0001**	1.78 (0.4)	1.72 (0.41)	1.65 (0.41)	0.654	1.63 (0.52)	1.76 (0.39)	0.373	1.67 (0.38)	1.82 (0.38)	1.73 (0.48)	0.456
	%	**%**	**p**	**%**	**%**	**%**	**%**	**p**	**%**	**%**	**%**	**p**	**%**	**%**	**p**	**%**	**%**	**%**	**p**
Atypical pigment network	64.7	86.7	**0.043**	100.0	70.0	87.5	32.3	**0.001**	81.5	56.3	80.0	0.135	80.4	37.5	**0.010**	83.3	80.0	61.5	0.314
Irregular streaks	23.5	53.3	**0.014**	47.1	40.0	37.5	11.1	0.332	39.5	43.8	20.0	0.441	37.3	37.5	0.989	22.2	43.3	53.9	0.169
Irregular pigmentation	79.4	86.7	0.443	94.2	83.3	87.5	55.6	0.096	84.2	87.5	70.0	0.484	80.4	87.5	0.631	61.1	90.0	92.3	**0.023**
Regression structures	50.0	56.7	0.594	52.9	56.7	62.5	33.3	0.604	47.4	56.3	70.0	0.425	58.8	50.0	0.639	61.1	56.7	38.6	0.424
Blue/whitish veil	23.5	20.0	0.733	35.3	13.3	25.0	22.2	0.375	18.4	31.2	20.0	0.574	19.6	50.0	0.060	11.1	13.3	53.9	**0.005**
Atypical vascular pattern	20.6	3.3	**0.037**	0.0	10.0	37.5	22.2	**0.032**	2.6	25.0	30.0	**0.014**	2.0	87.5	**<0.001**	0.0	0.0	61.5	**<0.001**

n=number of cases; SD, standard deviation; TDS, total dermoscopic score; A, asymmetry; B, borders; C colors; D, different dermoscopic structures

Results in bold represent those with associated $p < 0.05$

Lentigo maligna melanoma and acral lentiginous melanomas were excluded

Table 3.

Mean and SD of ABCD TDS and prevalence of local features in melanomas according to *MC1R* variants and *BRAF* mutations

	MC1R										***BRAF***		
	No variant	***Any variant***		***r***	***R***		***0 R***	***1 R***	***2 R***		***Wild type***	***V600 mutant***	
	n=13	**n=51**		**n=23**	**n=28**		**n=36**	**n=21**	**n=7**		**n=28**	**n=23**	
	Mean (SD)	**Mean (SD)**	**p§**	**Mean (SD)**	**Mean (SD)**	**p‡**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**p***	**Mean (SD)**	**Mean (SD)**	**p**
TDS	6.35 (0.79)	6.58 (0.83)	0.380	6.72 (0.69)	6.47 (0.93)	0.290	6.59 (0.74)	6.69 (0.88)	5.8 (0.78)	**0.037**	6.53 (0.71)	6.63 (0.98)	0.659
A	2.5 (0.36)	2.45 (0.42)	0.680	2.49 (0.37)	2.41 (0.46)	0.547	2.49 (0.36)	2.41 (0.47)	2.41 (0.49)	0.760	2.46 (0.41)	2.49 (0.37)	0.814
B	0.47 (0.18)	0.51 (0.14)	0.363	0.49 (0.10)	0.53 (0.17)	0.357	0.48 (0.13)	0.53 (0.15)	0.53 (0.24)	0.491	0.48 (0.15)	0.52 (0.13)	0.374
C	1.69 (0.38)	1.85 (0.32)	0.127	1.89 (0.34)	1.82 (0.31)	0.445	1.82 (0.36)	1.88 (0.31)	1.64 (0.24)	0.275	1.77 (0.29)	1.87 (0.31)	0.231
D	1.69 (0.25)	1.75 (0.43)	0.617	1.85 (0.38)	1.68 (0.46)	0.163	1.79 (0.35)	1.83 (0.4)	1.21 (0.27)	**0.001**	1.75 (0.35)	1.8 (0.45)	0.621
	%	**%**	**p§**	**%**	**%**	**p‡**	**%**	**%**	**%**	**p***	**%**	**%**	**p**
Atypical pigment network	76.9	74.5	0.858	91.3	60.7	**0.022**	86.1	76.2	14.3	**0.001**	85.7	78.3	0.487
Irregular streaks	7.7	45.1	**0.013**	52.2	39.3	0.357	36.1	42.9	28.6	0.769	32.1	52.2	0.148
Irregular pigmentation	76.9	84.3	0.528	91.3	78.6	0.269	86.1	80.9	71.4	0.618	75.0	82.6	0.511
Regression structures	61.5	51.0	0.496	52.2	50.0	0.877	55.6	52.4	42.9	0.824	64.3	43.5	0.137
Blue/whitish veil	15.4	23.5	0.526	26.1	21.4	0.696	22.2	23.8	14.3	0.867	10.7	30.4	0.078
Atypical vascular pattern	7.7	13.7	0.557	8.7	17.9	0.344	8.3	14.3	28.6	0.275	7.1	8.7	0.837

n, number of melanomas; SD, standard deviation; TDS, total dermoscopic score; A, asymmetry; B, borders; C colors; D, different dermoscopic structures Results in bold represent those with associated $p < 0.05$

MC1R alleles which cause significant changes in receptor functioning were grouped as R variants (D84E, R142H, R151C, I155T, R160W, D294H, 86_87insA and the Y152X). All the other non-R variants (V60L, S83P, V92M, T95M, A111V, R163Q, R213W, N279K, C315R) excluding synonymous changes were considered as r variants. Synonymous variants were considered as wild type alleles

§ patients with no variant were compared with patients with any *MC1R* variant (R or r variants)

‡ patients with one or two r variants (but not R) were compared with patients with one or two R variants

* patients were compared on the base of the number of *MC1R* R variants in the genotype: no R variants, one R variant and two R variants.