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Clinical, dermoscopic and confocal microscopy features of multiple primary melanomas according to pathogenic germline variant status: a retrospective, hospital-based study

Marco Spadafora[1,2] **Beatrice Melli**[3] **Jonida Bardhushi**[1] **Stefania Borsari**[1] **Simonetta Rosato**[4] **Stefano Giuseppe Caraffi**[4] **Chiara Cattani**[4] **Vincenza Ylenia Cusenza**[3] **Davide Nicoli**[3] **Shaniko Kaleci**[2] **Iris Zalaudek**[5] **and Caterina Longo**[2]

[1]Azienda Unità Sanitaria Locale – IRCCS di Reggio Emilia, Skin Cancer Center, Reggio Emilia, Italy
[2]Department of Surgery, Medicine, Dental Medicine and Morphological Sciences, University of Modena and Reggio Emilia, Modena, Italy
[3]Molecular Pathology, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy
[4]Medical Genetics Unit, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy
[5]Department of Dermatology and Venereology, University of Trieste, Trieste, Italy
Correspondence: Caterina Longo. Email: caterina.longo@unimore.it

Abstract

Background Familial melanoma comprises approximately 10% of cutaneous melanomas. Individuals with pathogenic germline variants have a higher risk of developing multiple primary melanomas (MPMs) than individuals who lack these variants. However, differences in clinical, dermoscopic and reflectance confocal microscopy (RCM) features between variant carriers and noncarriers are not well established.

Objectives To compare the clinical, dermoscopic and RCM characteristics of patients with MPMs with or without the pathogenic germline variants associated with familial melanoma.

Methods This retrospective study included 45 patients with MPMs who underwent Sanger sequencing and/or custom next-generation sequencing (NGS) panels between 2020 and 2023. Clinical, dermoscopic and RCM images were reviewed and compared between pathogenic germline variant-positive and pathogenic germline variant-negative groups.

Results Pathogenic germline variants in moderate-risk to high-risk melanoma genes were found in 15 patients. Carriers were diagnosed at a younger age than noncarriers [mean (SD) 41.8 years (10.1) vs. 53.5 (10.4); $P<0.001$], more frequently had a family history of melanoma ($P=0.02$), had more melanomas arising from pre-existing naevi ($P<0.001$) and less actinic damage ($P=0.05$). *CDKN2A* carriers were younger [38.9 years (11.4) vs. 45.3 (7.8)] and had fewer melanomas [2.7 (1.3) vs. 4.1 (1.2); $P=0.05$] than *MITF* or *POT1* carriers. *CDKN2A* carriers had low ($n=5$), medium ($n=1$) or high ($n=2$) naevus counts, while *MITF* carriers had medium ($n=1$) to high ($n=4$) counts. Dermoscopically, pathogenic germline variant carriers showed fewer regression structures (8.3% vs. 39.8%; $P=0.01$). RCM findings indicated a nonsignificant trend toward more dendritic cell-type melanomas in noncarriers (33.9% vs. 19.4%).

Conclusions Patients with MPMs who carry pathogenic germline variants demonstrate distinct clinical and imaging profiles compared with patients who do not carry these variants. These findings support personalized surveillance of individuals at high risk of developing MPMs and the integration of genetic testing into melanoma management. Further studies with larger cohorts are needed to refine genotype–phenotype associations.

What is already known about this topic?

- Familial melanoma accounts for approximately 10% of cutaneous melanomas.
- It is linked to pathogenic germline variants in genes such as *CDKN2A*, *MITF* and *POT1*.
- However, distinctions in clinical, dermoscopic and confocal microscopy features between patients with and without these variants remain unclear.

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What does this study add?

- This study reveals that patients with multiple primary melanomas who have pathogenic germline variants, compared with patients who lack such variants, exhibit a younger age of onset, more naevus-associated melanomas, and distinct dermoscopic and confocal features, supporting personalized screening and surveillance strategies.

Patients diagnosed with melanoma are at increased risk of developing subsequent primary melanomas compared with the general population.[1] Several individual and environmental risk factors have been associated with multiple primary melanomas (MPMs), including the presence of numerous naevi, a family history of melanoma, being male, early onset of the first melanoma, lighter skin phototype, and exposure to ultraviolet (UV) radiation from natural or artificial sources.[2–5] It has been reported that up to 8% of individuals with a prior diagnosis of melanoma may develop MPMs, and this risk increases to approximately 19% in individuals with a family history of melanoma.[6]

Familial melanomas account for approximately 10% of all cutaneous malignant melanomas and typically follow an inheritance pattern suggestive of autosomal dominant pathogenic germline variants with incomplete penetrance.[7] Mutations in cyclin-dependent kinase inhibitor 2A (*CDKN2A*) are those most consistently associated with susceptibility to hereditary melanoma.[8] Other genes linked with susceptibility to hereditary melanoma include cyclin-dependent kinase 4 (*CDK4*), breast cancer-associated protein-1 (*BAP1*), protection of telomeres 1 (*POT1*), adrenocortical dysplasia protein homologue (*ACD*), telomeric repeat-binding factor 2-interacting protein 1 (*TERF2IP)* and telomerase reverse transcriptase (*TERT*).[9] Specific variants of microphthalmia-associated transcription factor (*MITF*) have been identified as moderate-risk alleles,[10] while polymorphisms in melanocortin 1 receptor (*MC1R*) are generally considered low-risk variants and are not included in diagnostic pipelines. Pathogenic germline variants linked to an increased risk of developing MPMs can also be associated with a predisposition to other malignancies, usually on a gene-specific basis, most notably pancreatic cancer for *CDKN2A* variants.[7,9]

Predicting the presence of melanoma-associated germline variants remains challenging due to the confounding influence of environmental factors as well as complex polygenic inheritance patterns that have yet to be fully characterized. Certain clinical features have been reported among carriers of familial melanoma-associated variants, such as a large number of naevi and specific dermoscopic patterns.[11,12] Early genetic testing and the identification of high-risk variants are essential for appropriate family surveillance and management.[13] In this retrospective study, we aimed to analyse and compare clinical phenotypes as well as dermoscopic and reflectance confocal microscopy (RCM) features in patients diagnosed with MPMs, with and without confirmed pathogenic germline mutations associated with familial melanoma.

Materials and methods

We conducted a retrospective, hospital-based study involving patients diagnosed with MPMs at the Skin Cancer Center of Reggio Emilia, Italy, between January 2020 and September 2023. Patients with risk factors for hereditary melanoma were referred to the Medical Genetics Unit of the AUSL-IRCCS of Reggio Emilia for genetic counselling if (i) they had a personal history of cutaneous melanoma and a family history (in at least one first-degree relative) of melanoma or a melanoma-associated tumour (e.g. pancreatic cancer), or (ii) they had a personal history of MPMs (at least two melanomas, with one being invasive), irrespective of their family history.[7,14]

Each participant enrolled in the study underwent genetic testing using the standard method as recommended by the Italian National Health Service (Sanger sequencing for *CDKN2A* and *CDK4*) and/or a custom next-generation sequencing (NGS) panel aimed at detecting pathogenic variants in familial melanoma-associated genes, including *CDKN2A*, *CDK4*, *BAP1*, *MITF*, *POT1*, *ACD*, *TERF2IP* and *TERT*. Patients' DNA was extracted from blood specimens. Sanger sequencing was performed using a Maxwell®16 LEV Blood DNA Kit (Promega, Madison, WI, USA), while the NGS custom panel was performed using an xGen™ Lotus™ DNA Library Prep Kit (Integrated DNA Technologies, Coralville, IA, USA) and sequenced on a MiSeq instrument (Illumina, San Diego, CA, USA).

Further relevant demographic and clinical data were retrospectively collected from clinical reports and from archived clinical images in the institutional database (Table 1). Enrolled patients with MPMs were stratified according to the presence or absence of pathogenic germline variants associated with hereditary melanoma.

Clinical images of patients were acquired using total body photography. For each patient, dermoscopy was used to randomly record 1–10 naevi per body region (trunk and limbs). Clinical and dermoscopic images were acquired using a polarized dermatoscope camera (DermLite FOTO dermoscopy system; 3Gen, Inc., San Juan Capistrano, CA, USA). RCM imaging was performed using a reflectance confocal microscope (VivaScope1500; VivaScope GmBH, Munich, Germany).[15]

We performed a melanoma sub-analysis that only included patients who had at least one high-quality dermoscopic and/or RCM image of the excised melanoma. The included images were then evaluated according to selected clinical, dermoscopic and RCM criteria by three experienced dermatologists (S.B., C.L. and J.B.) (Table 2).[16,17] In addition, we conducted a sub-analysis of carriers of pathogenic germline variants, focusing on demographic, clinical and dermoscopic data.

Statistical analysis

We used the χ^2 or Fisher's exact tests for categorical variables, while independent *t*-tests or ANOVA were applied for continuous variables. Significant differences between

Table 1 Clinical features of patients with multiple primary melanomas with and without pathogenic germline gene variants

	Pathogenic germline variant status			
Clinical characteristics	**Total, *n* = 45 (100%)**	**Noncarrier, *n* = 30 (67%)**	**Carrier, *n* = 15 (33%)**	***P*-value**
Sex, male	26 (58)	17 (57)	9 (60)	0.83
Age at first melanoma diagnosis (years), mean (SD) (range)	59.6 (11.6) (22–73)	53.5 (10.4) (34–73)	41.8 (10.1) (23–55)	**< 0.001**
Family history				
Melanoma	16 (36)	7 (23)	9 (60)	**0.02**
Pancreatic cancer	1 (2)	0 (0)	1 (7)	0.15
Melanocytic lesion counts				
Melanoma, mean (SD) (range)	3.9 (1.7) (2–9)	3.9 (1.9) (2–9)	3.6 (1.2) (2–5)	0.58
Naevi				
< 50	7 (16)	1 (3)	6 (40)	**0.005**
50–100	12 (27)	10 (33)	2 (13)	
> 100	26 (58)	19 (63)	7 (47)	
Skin phototype				
Light (I and II)	23 (51)	15 (50)	8 (53)	0.83
Medium (III)	22 (49)	15 (50)	7 (47)	
Actinic damage				
Mild	3 (7)	0 (0)	3 (17)	**0.05**
Moderate	20 (44)	11 (41)	9 (50)	
Severe	22 (49)	16 (59)	6 (33)	
Main naevi distribution (> 70%)				
Trunk	25 (56)	14 (52)	11 (61)	0.56
Limbs	1 (2)	1 (4)	0 (0)	
Diffuse	18 (40)	12 (44)	6 (33)	
Main naevi pigmentation type				
Amelanotic/hypopigmented	4 (9)	2 (7)	2 (11)	0.74
Pigmented	23 (51)	13 (48)	10 (56)	
Mixed	18 (40)	12 (44)	6 (33)	
Mean naevi size				
Small, ≤ 1 cm	33 (73)	22 (73)	11 (73)	0.71
Large, > 1 cm	11 (24)	8 (27)	3 (20)	
Missing	1 (2)	0 (0)	1 (7)	
Main naevus dermoscopic pattern				
Reticular	18 (40)	13 (43)	5 (33)	0.45
Globular	0 (0)	0 (0)	0 (0)	
Homogeneous	0 (0)	0 (0)	0 (0)	
Complex[a]	23 (51)	14 (47)	9 (60)	
Multicomponent[b]	2 (4)	2 (7)	0 (0)	
Aspecific	0 (0)	0 (0)	0 (0)	
Missing	2 (4)	1 (3)	1 (7)	

All data are presented as *n* (%) unless otherwise stated. [a]Refers to two patterns within a single lesion; [b]refers to three or more patterns within a single lesion. Bold font indicates a statistically significant result.

groups were further explored using Bonferroni-corrected post hoc tests. Missing data were handled using pairwise deletion. *P*-value < 0.05 was considered statistically significant. All analyses were performed using Stata version 17 (StataCorp, College Station, TX, USA).

Results

In our study, 78 patients with risk factors for hereditary melanoma underwent Sanger sequencing and NGS testing. Of these, 73 were naïve participants, i.e. were not from families with a known history of hereditary melanoma, and 5 were first-degree relatives from four distinct pathogenic germline variant-carrier families.

MPMs were confirmed in 45 patients (58%). Pathogenic germline variants were detected in 15 patients; the remaining 30 patients with MPMs tested negative according to the genetic assessment. When restricting the analysis solely to the first diagnosed family member in each carrier family, the detection incidence was 27%. Pathogenic germline variants identified included *CDKN2A* (*n* = 8), *MITF* (*n* = 5; p.Glu425Lys variant) and *POT1* (*n* = 2) (Figure 1; Table S1, see Supporting Information).

As shown in Table 1, significant differences were found between patients carrying pathogenic mutations and noncarriers of pathogenic mutations. These included a younger mean (SD) age [41.8 years (10.1) vs. 53.5 (10.4); *P* < 0.001], a higher frequency of family history of melanoma (60% vs. 23%; *P* = 0.02), milder actinic damage (*P* = 0.05) and a more heterogeneous naevi count in carriers compared with a medium-to-high number of naevi in noncarriers (*P* = 0.01) (Figure 2).

The anatomical distribution of naevi, predominant pigmentation type and mean size were similar between the two subgroups. The main dermoscopic patterns observed for naevi were reticular and complex, with no substantial differences between subgroups.

In our melanoma sub-analysis (Table 2), we evaluated 154 melanomas from 39 patients (36 and 118 in carriers and noncarriers of mutations, respectively). A mean (SD) Breslow

Table 2 Clinical, dermoscopic and reflectance confocal microscopy (RCM) features of melanomas diagnosed in patients with multiple primary melanomas (MPMs)

	Pathogenic germline variant status			
Clinical characteristics	**Total *n* = 154**	**Noncarrier, *n* = 118 (76.6)**	**Carrier, *n* = 36 (23.4)**	***P*-value**
Breslow thickness (mm), mean (SD) (range)	0.38 (0.5) (0–4.2)	0.38 (0.5) (0–4.2)	0.38 (0.6) (0–3.4)	0.98
Naevus-associated melanoma				
No	101 (65.6)	90 (76.3)	11 (40)	**0.001**
Yes	22 (12.3)	13 (11.0)	9 (25)	
Missing	31 (20.1)	15 (13.7)	16 (44)	
Anatomical location				
Head and neck	6 (3.9)	4 (3.4)	2 (6)	0.16
Trunk	92 (59.7)	76 (64.4)	16 (44)	
Limbs	44 (28.6)	29 (24.6)	15 (42)	
Acral	3 (1.99)	2 (1.7)	1 (3)	
Missing	9 (5.8)	7 (5.9)	2 (6)	
Pigmentation				
Amelanotic or hypopigmented	54 (35.1)	44 (37.3)	10 (28)	0.61
Pigmented	73 (47.4)	62 (52.5)	11 (31)	
Missing	27 (17.5)	12 (10.2)	15 (42)	
Size				
< 0.5 cm	30 (19.5)	24 (20.3)	6 (17)	0.81
0.5–1 cm	68 (44.2)	57 (48.3)	11 (31)	
> 1 cm	29 (18.9)	25 (21.2)	4 (11)	
Missing	27 (17.5)	12 (10.2)	15 (42)	
Seven-point checklist				
Atypical network	70 (45.4)	56 (47.5)	14 (39)	0.21
Blue–white veil	13 (8.4)	12 (10.2)	1 (3)	0.37
Atypical vessels	46 (29.9)	41 (34.7)	5 (14)	0.20
Irregular blotches	48 (31.2)	43 (36.4)	5 (14)	0.15
Irregular dots/globules	49 (31.8)	41 (34.7)	8 (22)	0.99
Irregular streaks	8 (5.2)	5 (4.2)	3 (8)	0.10
Regression structures	50 (32.5)	47 (39.8)	3 (8)	**0.01**
Seven-point checklist score				
< 4	76 (49.3)	62 (52.5)	14 (39)	**0.001**
4–6	41 (26.6)	35 (29.6)	6 (17)	
> 6	5 (3.2)	5 (4.24)	0 (0)	
Missing	32 (20.8)	16 (13.6)	16 (44)	
RCM melanoma type				
Nonclassifiable	19 (12.3)	17 (14.4)	24 (59)	0.15
Dendritic cell	47 (30.5)	40 (33.9)	7 (19)	
Round cell melanoma	18 (11.7)	13 (11.0)	5 (14)	
Dermal nest melanoma	1 (0.6)	1 (0.9)	0 (0)	
Combined-type melanoma (combination of the three patterns)	2 (1.3)	2 (1.7)	0 (0)	
Missing	67 (43.5)	45 (38.1)	22 (61)	

All data are presented as *n* (%) unless otherwise stated. Bold font indicates a statistically significant value.

thickness of 0.38 (0.5) mm was reported, with no significant difference between subgroups.

A significantly higher incidence of melanoma arising on a pre-existing naevus was observed in carriers of mutations ($P < 0.001$). No substantial differences in the anatomical location, pigmentation or size of melanomas were observed between the two subgroups.

Among melanomas evaluated using the seven-point checklist, patients carrying pathogenic germline variants had lower scores (no patients with a score higher than 6) than noncarriers. Moreover, regression structures were less frequently observed in melanomas from patients with mutations (8.3% vs. 39.8%; $P = 0.01$) (Figure 3).

RCM was recorded in 87 melanomas (14 melanomas in mutation carriers and 73 melanomas in noncarriers). Although not significant, a trend was observed in the RCM assessment, with dendritic cell-type melanomas more frequently observed in noncarriers than in mutation carriers (33.9% vs. 19.4%) (Figure 4).

Among carriers of pathogenic germline variants, individuals with *CDKN2A* variants were younger [mean (SD) 38.9 years (11.4) vs. 45.3 (7.8); $P = 0.8$] and had fewer melanomas [2.7 (1.3) vs. 4.1 (1.2); $P = 0.05$] than individuals with *MITF* or *POT1* variants. A sub-analysis of naevus counts showed that carriers of *CDKN2A* variants exhibited a low ($n = 5$), medium ($n = 1$) or high ($n = 2$) naevus count, *MITF* variant carriers had a medium ($n = 1$) or high naevus count ($n = 4$), while carriers of *POT1* variants exhibited both low ($n = 1$) and high ($n = 1$) naevus counts, although these differences were not statistically significant.

Discussion

In this study, we aimed to investigate the clinical, dermoscopic and RCM differences in patients with MPMs with or without germline mutations associated with familial melanoma. In our cohort, patients with pathogenic or probably

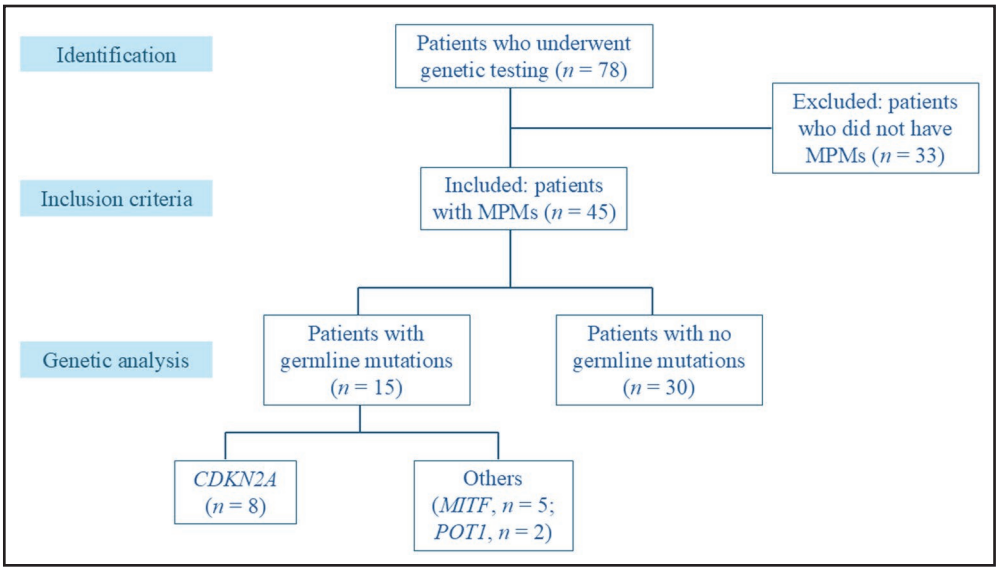

Figure 1 Flowchart showing the pathway of patients included in the present study. MPMs, multiple primary melanomas.

pathogenic germline variants were diagnosed at a significantly younger age and were more likely to have had a family history of melanoma than patients who did not carry these variants. This observation is consistent with those of previous studies highlighting the earlier onset of melanoma in familial cases and the critical role that early genetic counselling and targeted surveillance strategies in high-risk populations can play.[7,18,19] However, it should be noted that the earlier and more intensive screening typically performed in individuals with a family history of melanoma may lead to earlier detection and overrepresentation of certain clinical features, representing an important confounder in our comparisons.[20,21]

A notable clinical observation was the higher prevalence of melanomas arising from pre-existing naevi in carriers of pathogenic germline variants than in noncarriers. To the best of our knowledge, this is the first study to report a higher prevalence of naevus-associated melanomas in pathogenic germline variant carriers. Previous studies of MPMs have indicated an incidence of approximately 20% for melanomas arising from pre-existing naevi,[10,22] consistent with data regarding naevus-associated melanoma in the general population.[23]

Zocchi *et al.* emphasized the relevance of naevus phenotype in patients with familial melanoma, pointing out that carriers of the *CDKN2A* variant have a greater number of naevi than naïve patients.[11] Interestingly, our data showed that carriers of pathogenic germline variants had a more heterogeneous naevus count distribution than noncarriers, who more frequently manifested with a medium-to-high naevus count ($P=0.005$). Additionally, we observed that carriers of *CDKN2A* variants can exhibit a low-to-high naevus count,

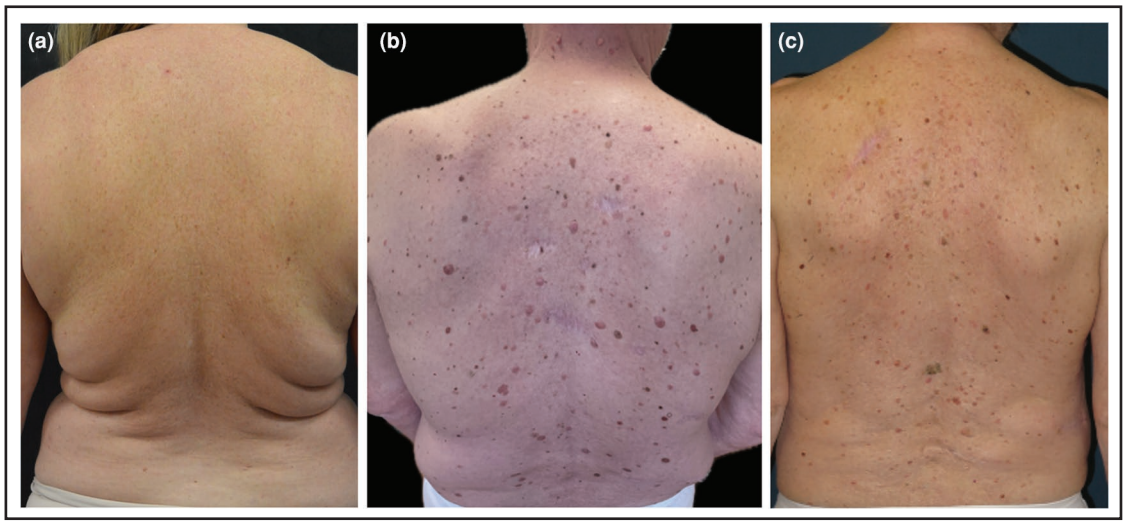

Figure 2 Clinical photographs of the backs of selected patients with MPMs. (a) A carrier of the *CDKN2A* pathogenic germline variant with a low naevus count; (b) a carrier of the *MITF* Glu425Lys variant with a high naevus count; and (c) a noncarrier of a pathogenic germline variant with a high naevus count and actinic damage.

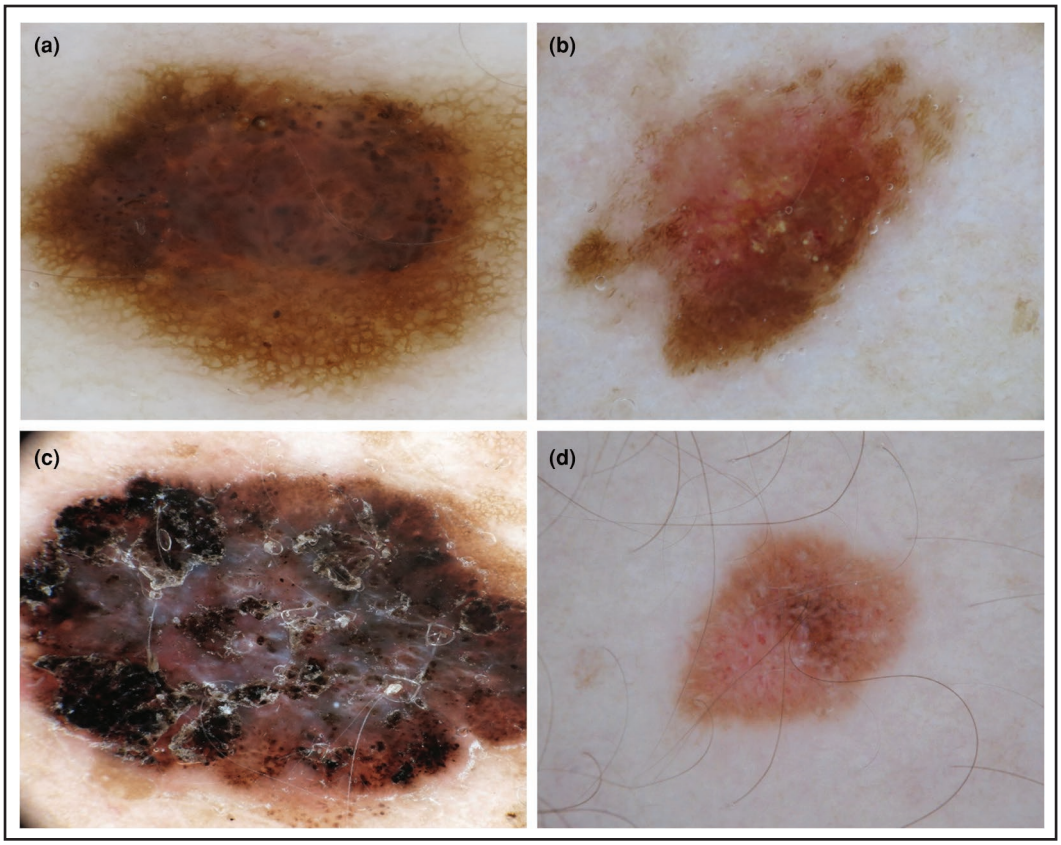

Figure 3 Dermoscopic images of melanomas from patients with MPMs. (a) A melanoma of Breslow thickness 0.9 mm in a patient who was a carrier of a *CDKN2A* pathogenic germline variant, with a score of < 4 on the seven-point checklist. (b) A naevus-associated melanoma of Breslow thickness 0.4 mm in a patient who was a carrier of a *CDKN2A* variant, with a score of < 4 on the seven-point checklist. (c) A melanoma of Breslow thickness 0.7 mm in a noncarrier patient, with a score of ≥ 4 on the seven-point checklist. (d) A melanoma of Breslow thickness 0.6 mm in a noncarrier with a score of ≥ 4 on the seven-point checklist.

with more than half of these individuals having a low naevus count, while carriers of *MITF* variants more frequently exhibited a medium-to-high naevus count. Although our observation was not statistically significant, probably due to the small cohort, it is consistent with the findings of previous studies that showed an overall low naevus count in carriers of *CDKN2A* variants, underscoring the conflicting nature of the evidence in the literature.[24,25] The variability in naevus count observed among carriers of *CDKN2A* variants in our study, as well as in previously published reports, may

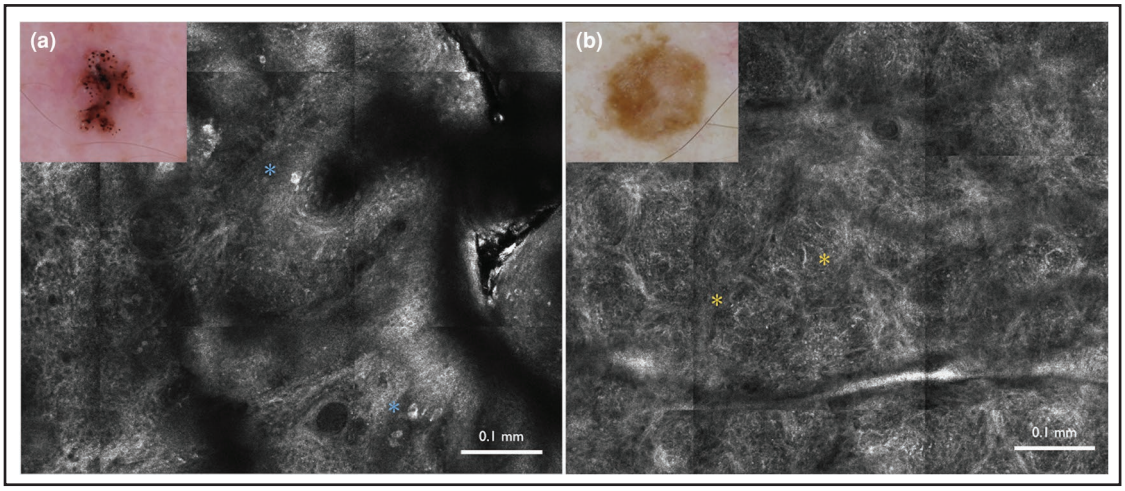

Figure 4 Reflectance confocal microscopy imaging from patients with MPMs. (a) A naevus-associated melanoma of Breslow thickness 0.2 mm in a patient who was a carrier of a pathogenic germline variant (*CDKN2A*), showing rounded pagetoid cells (asterisks). (b) A melanoma of Breslow thickness 0.3 mm in a noncarrier patient, showing dendritic pagetoid cells (asterisks).

represent a potential confounder in the assessment of naevus phenotype within this patient cohort. This issue could be addressed by conducting larger, multicentric studies.

An additional finding in our cohort was the relatively high prevalence of the *MITF* variant p.Glu425Lys (also known as p.Glu318Lys or 'E318K' depending on the transcript),[26] at 6.4%, higher than the 2–3% prevalence typically reported.[14] This finding emphasizes the importance of using NGS custom panels instead of more targeted testing strategies such as Sanger sequencing, which may miss relevant mutations in non-*CDKN2A* susceptibility genes.

A novel finding of our study was the significantly higher prevalence of moderate-to-severe actinic damage in noncarriers of pathogenic germline variants compared with carriers. This suggests that the development of MPMs in noncarriers may be highly influenced by UV radiation. Conversely, it remains unclear whether cumulative exposure to UV radiation plays a less important role in the development of melanoma for carriers of pathogenic germline variants or whether even low levels of exposure to UV radiation, insufficient to manifest as actinic damage in a patient, are sufficient to trigger melanoma in this group. This result warrants investigation in larger cohorts to confirm its relevance and explore the underlying biological impact of exposure to UV radiation in patients with MPMs.

Our dermoscopic analysis revealed that melanomas in carriers of pathogenic germline variants usually showed fewer typically malignant features. In particular, regression structures were less frequently observed, along with lower scores for the seven-point checklist. These findings align with previous evidence suggesting that familial melanoma may lack clear-cut melanoma criteria and can only be identified by highly experienced dermatologists.[12,27] Longo *et al*. demonstrated that a comparative approach, i.e. comparing equivocal lesions with a patient's other naevi and previous melanomas, can aid in the detection of melanoma among carriers of mutations, where diagnosis is often challenging.[28]

In terms of RCM features, a trend was found indicating a higher frequency of dendritic cell-type melanomas among noncarriers than carriers (33.9% vs. 19.4%), although this was not significant. Dendritic cell-type melanoma has previously been described as a melanoma that, under RCM, shows a population of predominantly dendritic melanocytes within the epidermis, compared with round cell melanoma, which is defined by a different type of pagetoid spread in the suprabasal layers.[17] While previous work by Bassoli *et al*. focused on benign lesions in patients with MPMs and described RCM differences linked to *CDKN2A* and *MC1R* status,[29] our study extended this comparison to malignant lesions. Similarly, Grazziotin *et al*. reported that dendritic cell-type melanomas were more common in older patients with a history of intense sun exposure and prominent solar lentigines; they also found that carriers of *CDKN2A* variants may develop both dendritic and round cell-type melanoma.[27]

The co-occurrence of greater actinic damage and a slightly increased prevalence of dendritic cell morphology in noncarriers may support the hypothesis of divergent pathogenetic pathways in patients with MPMs who are noncarriers compared with carriers of pathogenic germline variants. This observation warrants further investigation in larger cohorts, which may provide stronger evidence. A patient's genetic background may not only influence the appearance of benign lesions (as previously demonstrated) but also the morphological characteristics of melanomas themselves.[29]

Our study was limited by its small sample size, which reflects both the monocentric design of the study and the relatively low incidence of MPMs in the screened population. The small cohort may affect the robustness of our findings. Missing data in this study were primarily due to the retrospective nature of the dataset, which relied on pre-existing clinical records and genetic analyses. There was incomplete information for certain variables, such as details of familial histories, imaging, and specific pathological features, probably due to the variability in clinical records and the fact that the genetic sequencing techniques may not have been consistently employed for earlier patients. Missing RCM data, mainly due to clinical workflow constraints, represent an additional limitation and may affect the generalizability of our results. To mitigate the impact of missing data, pairwise deletion was applied during the statistical analyses to ensure that the information available for each variable was maximally utilized without compromising the validity of the results. While this approach maintains the integrity of the analyses, we acknowledge that missing data may introduce some level of bias. Furthermore, the clinic-based, high-risk cohort introduced a potential selection bias, while the lack of a blinded histopathological review of our dataset may contribute to diagnostic review bias; both limit the broader applicability of the results. Prospective studies with standardized data collection protocols are desirable to address these limitations.

The findings of our study underscore key clinical and imaging features in patients with MPMs, such as earlier onset and distinct naevus-related features in germline variant carriers and a hypothesized UV radiation-related pathogenesis in noncarriers, suggesting different pathogenic pathways and supporting the notion that melanoma development is complex. Moreover, our observations underscore the value of recommending genetic testing in younger patients with MPMs or individuals with a familial history of this disease. They also highlight the potential role of dermoscopic monitoring strategies tailored according to the presence of underlying pathogenic germline variants. Future research involving larger cohorts will be essential to deepen our understanding of hereditary melanoma syndromes and to develop effective diagnostic and preventive strategies for high-risk populations.

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

Ethics statement

This study was approved by the Institutional Review Board of AUSL-IRCCS Arcispedale Santa Maria Nuova di Reggio Emilia, study number: 212/2020/SPER/AUSLRE; protocol code PFM2020; SIRER: N/A.

Patient consent

The participants provided written informed consent for publication of their case details.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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