Author's response to reviews

Title: MC1R variants predisposing to concomitant primary cutaneous melanoma in a monozygotic twin pair

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Author's response to reviews: see over
Dear Editor,

We thank the Referees for their helpful comments. We are submitting the revised version of the article entitled “MC1R variants predisposing to concomitant primary cutaneous melanoma in a monozygotic twin pair” by Cristina Pellegrini, Maria Concetta Fargnoli, Mariano Suppa and Ketty Peris (MS: 1049176449747216), for consideration for publication in the section “Case reports” of BMC Medical Genetics.

We answered referees’ comments here below, and indicated changes in red in the attached revised version of the manuscript. The revised manuscript conforms to the journal style.

We appreciate your consideration of our manuscript, and we thank you in advance for your attention in this matter.

Sincerely Yours,

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REFEREES' COMMENTS:

Reviewer 1:

“This is an interesting and well written case report of two twins genetically identical that both were diagnosed of melanoma at the same time in a similar location. They were also studied for the main susceptibility gene for melanoma being carriers of two polymorphisms in the MC1R. This is the first time that genetic studies were reported in this situation highlighting the importance of genetic susceptibility in melanoma.”

We thank very much the reviewer for appreciation of our manuscript.

Reviewer 2:

“This is an interesting report and shows the role of genetic factors in the aetiology of melanoma. However the role of MC1R variants in the causation of the 2 melanomas in this twin pair cannot be confirmed and the authors should acknowledge that many individuals have several variants of the MC1R and will never develop a melanoma. To put things into context may be the authors should give the prevalence of one or two variants in individuals with fair skin.”

We agree with the reviewer that many individuals carrying variants of the MC1R gene never develop melanoma, although we believe that the type of variant is important since they differently impact melanoma risk. A sentence reporting the risk of developing melanoma associated with carrying MC1R variants has been included in the conclusions (page 7, lines 13-14).

“In the introduction, the authors mention the role of rare and high penetrance genes in melanoma and only one common low penetrance gene such as MC1R. However, there are many other low penetrance genes recently discovered which confer an increased risk of melanoma and many of those are pigmentation genes which the authors should mention and discuss the fact that these were not genotyped but may have been involved. Nevus genes have also been identified and this is relevant as the twins have an excess number of nevi.”

A paragraph mentioning the other low-penetrance melanoma susceptibility genes has been added as well as their possible involvement in our patients due to the lack of genotyping (page 8, lines 5-10). An additional reference (no. 12) reviewing low-penetrance melanoma susceptibility genes has been listed (page 15, lines 1-3).
“The authors should also mention the possible screening bias as the second twin is more likely to come forward for screening or be called back for screening because the co-twin has just been diagnosed with melanoma. The second twin indeed has a very thin melanoma and these lesions can be very borderline pathologically especially with a Breslow thickness of 0.33 mm. In patients with the atypical mole syndrome, it is not uncommon to remove lesions which did not look that suspicious clinically and find melanomas which are borderline with very low Breslow thickness. This should also be discussed.”

Both our patients were included in a surveillance program at our Pigmented Lesion Clinic but had been lost of follow-up over the last two years due to the 2009 earthquake in L’Aquila, as indicated in the “case presentation”. They were both observed for their routine follow-up visit at a very close interval and referred a pre-existing pigmented lesion which changed in color and size over a 1-year period and a 4 months-period, respectively. Therefore, we do not believe there was a screening bias.

Lesion of twin-2 was removed because of the atypical dermoscopic features (i.e. polymorphous vascular pattern) and the history of a recent change reported by the patient. Histopathological diagnosis of melanoma was confirmed by two independent pathologists.

Reviewer 3:

“This referee thus agrees that “the concordance for cutaneous melanoma as well as the congruence for its location and identity of the age of onset in monozygotic twins support the role of genetic rather than environmental factors” in the development of melanoma. However, a number of low-penetrance melanoma genes have been identified to date.”

A sentence reporting the description of other low-penetrance melanoma risk alleles has been added to the conclusions (page 8, lines 5-10).

“Furthermore, previous findings on the rare Y152X variant suggest that despite its truncating effect this variant may not only require additional MC1R variants but also other genetic/environmental risk factors to actually increase risk (i.e., Galore et al. Melanoma Research 2007, a reference that could be added). The authors should therefore reduce the emphasis they place on the contribution of MC1R variants to melanoma susceptibility in these patients, and add a concluding sentence that leaves
the door open to the possibility that other known or as yet unknown genetic risk factors may be involved."

The reference by Galore et al. has been listed as reference no. 15 (page 15, lines 9-11). We agree with the reviewer comment and therefore the concluding sentence was modified leaving the possibility that other known or yet unknown genetic factors might be involved (page 8, lines 16-17).

“This referee suggests to substitute “the importance of low penetrance genes” in the final line with “the contribution of” or “the role of”.”

We changed the word “importance” with “contribution” as suggested by the reviewer in the final line of the abstract (page 2, line 22) and text (page 8, line 15).

Reviewer 4:

“Whereas at present it is possible to identify the gene mutation responsible for melanoma susceptibility in only 40% of the genealogies, it cannot be excluded that genetic predisposition in their patients is due to a mutation in an unknown gene. This hypothesis should be considered in the discussion.”

The possible involvement of other unknown genes has been added to the conclusions (page 8, lines 16-17).

“To reinforce their conclusions the authors should extend molecular analysis of MC1R in more subjects of the same family to evaluate/exclude the presence of further healthy individuals with the same genetic condition.”

We appreciate the suggestion of the reviewer and we also planned to screen other family members, but our twins have no children; they have the mother and one sister who unfortunately were not available for screening as well as molecular analysis.