Author's response to reviews

Title: Role of the EGF +61A>G polymorphism in melanoma pathogenesis: an experience on a large series of Italian cases and controls.

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Author's response to reviews:

Dear Editor,

Please find enclosed the manuscript by Casula et al., entitled “Role of the EGF +61A>G polymorphism in melanoma pathogenesis: an experience on a large series of Italian cases and controls” (MS# 1673532550266316).

Revision of the manuscript was based on the Reviewers' remarks. Changes have been highlighted (in yellow) into the paper and here listed point-by-point:

Reviewer 1 (Balraj Mittal)

Major Revisions

1. In INTRODUCTION (page 3, paragraph 2), frequencies of both the A and G alleles into the European Caucasian population have been provided. To better clarify the frequencies of the A and G alleles between cases and controls in our series, we added such information into the Table 1C.

2. In METHODS (page 4, paragraph 1), indications about the screening approach and the type of nevi have been added (providing also more details about screening of subjects: "About 1,500 individuals underwent a whole-body skin examination using the epiluminescence microscopy. Melanocytic nevi were found in the range between 1-9 and 10-100 in about 23% and 68% of the participants, respectively; about 9% of them had more than 100 benign melanocytic nevi").

3. In RESULTS AND DISCUSSION (page 6, end of paragraph 2), data about the Clark levels of invasion have been added (it has been specified that "the G/G genotype was found in about 17% of Clark I-II cases, 16% of Clark III cases, and 16% of Clark IV-V cases").
4. As already indicated in RESULTS AND DISCUSSION (page 7, paragraph 1),
the variability in melanoma risk between North and South Italy has been
previously reported by our group [Casula et al., Eur J Cancer 2007 (ref. 9 of this
new version of the manuscript)].

Minor Revisions
1. In ABSTRACT, the conclusion has been changed as rightly noticed by
Reviewer (it has been specified that “our findings further suggest that EGF
+61A>G polymorphism may have a limited impact on predisposition and/or
pathogenesis of melanoma and its prevalence may vary in different
populations”).

2. Throughout the manuscript (including the Title), the nomenclature of the EGF
sequence variant has been changed and reported according to the recent
nomenclature system (EGF +61A>G).

3. In INTRODUCTION (page 3, beginning of paragraph 2), the "rs number" of the
EGF +61A>G variant has been provided.

4. We have carefully revised the manuscript for the English language.

5. In ABSTRACT (Background section), the genetic change has been corrected
in A>G.

6. In INTRODUCTION (page 3, middle-end of paragraph 2), the 95%CI values
have been provided.

Reviewer 2 (Julia Newton Bishop)
- In METHODS (page 4, paragraph 1), more information about recruitment and
clinical ascertainment of cases and controls have been provided (see also
answer to Point 2 of Reviewer 1).
- As specified in RESULTS AND DISCUSSION (page 6, beginning of paragraph
2), the individuals with different number of benign nevi were considered as a
healthy control group in comparison to the subset of melanoma patients (into the
text, they were indeed reported as "non-melanoma" controls). Moreover, this did
not affect the evaluation of the EGF +61A>G polymorphism from the statistical
point of view since "both the G/G genotype and the G allele frequencies did not
significantly differ according to the total number of bening nevi".
- In RESULTS AND DISCUSSION (end of page 6 and beginning of page 7), it
has been clearly indicated that "absence of impact of the EGF +61A>G
polymorphism on either development of nevi or melanoma susceptibility in Italy is
consistent with data reported in other populations"; however, our negative results
seem to be peculiar since, as underlined at this level into the text, "an evident
discrepancy in prevalence distribution of such a gene sequence variant was
observed among cases originating from northern and southern Italian regions".

A reference (No. 8 of this new version) has been added.

An author, Grazia Palomba (we wrongly missed into the previous version), has
been added.
Hoping to have addressed all issues and looking forward to receiving good news from You.

Sincerely Yours,

Giuseppe Palmieri