

Peer Review File

Article information: <https://dx.doi.org/10.21037/fomm-21-70>

Reviewer A

comment 1: Line 176 - the period in front of the parenthesis should be removed

reply 1: Thank you so much for your improvements. The period in front of the parenthesis has been removed.

comment 2: Line 207 – “xeroderma pigmentosum” does not to be written with capital letter

reply 2: Thank you so much for your improvements. “xeroderma pigmentosum” has be written with a lowercase letter.

comment 3: Line 226 – shouldn’t be XP instead of “skin cancer”?

reply 3: Thank you so much for your comment, but no. According to the reference 88 “Cancer and neurologic degeneration in xeroderma pigmentosum: long term follow-up characterizes the role of DNA repair” (doi:10.1136/jmg.2010.083022), “In the 65 percent (n=69) of patients with skin cancer, non-melanoma skin cancer (NMSC) was increased 10,000–fold and melanoma was increased 2,000-fold in patients under age 20”, skin cancer cannot instead by XP.

comment 4: Line 227 – I suggest change “the first- diagnosis age” to “age of first diagnosis”

reply 4: Thank you so much for your improvement. The sentence has been changed into” Moreover, the median age at first diagnosis of NMSC was significantly younger than melanoma.”

comment 5: Line 232 – change “combined” to “associated”

reply 5: Thank you so much for your improvements. It has been changed to” accompanied by”

comment 6: Line 234 – change “to” to “on”

reply 6: Thank you so much for your improvements, has changed ”to” to” on”.

comment 7: Line 243 – change “milia-like papula” to “milia-like papules”

reply 7: Thank you so much for your improvements, has changed.

comment 8: Line 248 – provide abbreviation for Oculocutaneous albinism in a bracket

reply 8: Thank you so much for your improvements, abbreviation has provided.

comment 9: Line 250 – should be hypopigmentation, not hyperpigmentation

reply 9: Thank you so much for your correction, spelling mistake has been modified.

comment 10 (additional comment): Co-occurrence of malignant melanoma (MM) is

considered rare in patients with OCA, compared with that of non-melanoma skin cancer – it would be worth to add this information. Additional findings from the following two articles should be added:

doi:10.1007/s00403-019-01952-7

<https://doi.org/10.5114/ada.2020.93368>

reply 10: Thank you so much for your improvement. The OCA point and additional findings have been added.

Reviewer B

comment 1: Line 99- this sentence has a conceptual mistake. Activation of the Hh pathway does not regulate nor increase expression of Sonic Hedgehog. This must be corrected.

reply 1: Thank you so much for your correction, the sentence has been corrected.

comment 2: The evidence supporting PTCH2 mutations as a cause of NBCCS is very limited, and the same mutations have been found in the healthy population, arguing against an involvement. The authors should discuss this controversy and explain that the evidence is unclear.

comment 3: The initial paragraph of PTCH, describing the two isoforms, needs some work. The same conceptual mistake appears there ("Sonic Hedgehog expressed by PTCH1"....) and the comparison between the 2 PTCH proteins is disorganised and lacks enough detail.

reply 2-3: Thank you so much for your improvements. This part has been rewritten. The conceptual mistake has been corrected and some related details of ptch have been added.

comment 4: Line 147-PTCH1 mRNA

reply 4: Thank you so much for your correction, has been modified.

comment 5: Line155-this sentence is incorrect. TP53 mutations are very common in BCC and co-exist with PTCH1 mutations.

reply 5: Thank you so much for your comment. Yes, the TP53 mutations co-exist with PTCH1 mutations are very common in BCC. But base on the reference 11” Understanding the Molecular Genetics of Basal Cell Carcinoma” table 1” Frequency of mutations and loss of heterozygosity (LOH) in cancer-related genes across published studies in basal cell carcinoma (BCC)”, the **loss of heterozygosity (LOH)** of P53 appears mutually exclusive with PTCH1.

comment 6: Line 188-this paragraph is poorly written.

reply 6: Thank you so much for your improvements. This paragraph has been rewritten.

comment 7: The function of Tyrosinase should be explained the first time in mentioned in sporadic BCC, before the paragraph of OCA

reply 7: Thank you so much for your improvements, and the function of Tyrosinase has been added before OCA.

additional comment: I recommend some changes to improve the quality and reach of the article: inclusion of figures, depicting the Hh signalling pathway and the UV-induced DNA damage and repair enzymes, addition of a table with the reported frequencies of mutated genes, and thorough English language review since there are several sentences with missing words.

reply: Thank you so much for your comments. The comments above have been revised in the original text and supplemented with the table.