Author's response to reviews

Title: The correlation of WWOX, RUNX2, and VEGFA protein expression in human osteosarcoma

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Author's response to reviews: see over
Dear Prof. Tim Sands,

I would like to thank you and the reviewers for the positive review of our revised manuscript entitled “The correlation of WWOX, RUNX2, and VEGFA protein expression in human osteosarcoma”. The new and revised information is marked as blue text in the revised manuscript. Our detailed response to the critiques is listed below.

**Response:**

We have carefully addressed all the issues and provided a response letter giving the point-by-point response.

**Reviewer:** Rami I. Aqeilan

**Reviewer's report:**

The revised version was improved but there are still language issues as well as confused statements that need to be fixed prior to publication.

**Response:**

We thank the reviewer very much for his good comment and suggestion. At his recommendation, we have had the entire revised manuscript edited by Edanz again.
In the abstract, authors stated they found 30% amplification in WWOX locus while it is deletion according to the data!

Response:
We have corrected the mistake in the abstract.

In the Introduction, authors stated: “The overall recurrent gene copy alteration pattern of these two independent populations in two different countries (China and Canada) were very similar, suggesting distinct genetic alterations underlying the pathogenesis of OS [23]”. It is not clear how it is distinct (different) if the CNVs are very similar? Authors need to better describe what they mean.

Response:
We revised the confused sentence.

In the discussion, when referring to correlation between IHC and aCGH on WWOX, for example, it is fair to say that this result (absence of statistical association) could also stem from the low sample numbers. Authors can cite the following review article that further discuss this issue: Am J Cancer Res 2011;1(5):585-594.

Response:
We thank the reviewer very much for his good comment. At his recommendation, we have revised this part and cited recommended reference.

In the discussion, it is more correct to write that: “Further evidence for this was found by Aqeilan and colleagues [14].”

Response:
We revised the sentence according to the suggestion.

In the discussion, it was confused: “We therefore hypothesize that negative expression of RUNX2 protein might be due to pre-treatment, including chemotherapy” instead, it should post-treatment.

Response: We revised the sentence according to the suggestion.

Frequently, IHC is confused with ICH.

Response:
We have corrected all these mistake.

In the discussion, it should say that VEGFA is known as a target of RUNX2. Also
provide reference.

Response:
We revised the sentence according to the suggestion and added the reference.

In the conclusion, authors stated: “we report for the first time, correlation between WWOX, RUNX2 and VEGFA in human OS, in situ.” and in the sentence they stated: “No significant correlation was observed between these three genes with respect to gene copy number aberration”. This is confusing and should be rephrased.

Response:
We revised the sentence according to the suggestion to make it more precise.

Quality of written English: Needs some language corrections before being published
Response:
we have had the entire revised manuscript edited by Edanz again.

Reviewer: Andrew E Horvai
Reviewer's report:
My questions and suggestions have been adequately addressed with a few minor revisions that I think can easily be made.

Response:
We thank the reviewer for the positive support and revised the manuscript.

1) Although the grammar and style are much improved, I continue to find a few errors. Perhaps this can be sorted out by the journal editorial staff.
Response:
we revised the entire manuscript and have had it edited by Edanz again.

2) The FISH showing amplification of VEGFA (Figure 2B and 2C) still bother me. Panel 2B shows a 3:2 ratio of VEGFA to the centromere signal, which I suppose is greater than 1:1 so technically amplified. But, panel 2C shows increased copies of both the centromere and VEGFA so while that represents increased copy number of VEGFA (for example by polysomy) it doesn't qualify as amplification. Consider, for example, the FISH result of HER2 amplified breast cancer or 12q13-15 amplified liposarcoma in which one sees 2 copies of the respective centromeres and a "cloud" of signal for the amplified gene. I think a slight modification to the text and figure legend, perhaps denoting "increased
copy number" instead of amplification is sufficient to address my concerns.

Response:
We have replaced "VEGFA amplification" with "increased VEGFA gene copy number" in the text and figure legend according to the suggestion.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published

Response:
we revised the entire manuscript and have had it edited by Edanz again.

After completion of these modifications, I hope you will find the revised version suitable for publication in BMC Medical Genomics.

Please do not hesitate to contact me if you need additional information.

Sincerely yours,

Jilong Yang, M.D., Ph.D.