Reviewer 1 Comments for the Author...

The new version of the manuscript has shown quite an improvement over the previous version. It's definitely more clear and technically more sound. The authors have done a great job in bringing it to its current version.

There are three minor format-related points that I noticed:

- In the comparative genomic analysis part that has been moved to Discussion, the figure that was referred to is Supplementary Figure 3A. I believe this should be Supplementary Figure 4A instead.

- There's also an inconsistency in how the supplementary figures are referred to throughout the text, for ex. Supplementary Figure 1, Fig S2 etc.

- The Supplementary Figure S11 comes before Supplementary Figure S10 in the text. The order needs to be switched.

Response: We thank the reviewer for pointing out these issues. We changed all the “Supplementary Figure xx” to “Fig. Sxx” to make the format consistent in the whole manuscript, figure and table legends. We checked the order of all Supplementary Figures and Figure S10 and Figure S11 have been exchanged including Supplementary Figure Legends. We are sincerely grateful to the discerning eye of both the reviewers which dramatically improved the manuscript. We are now conducting similar genetic scans in other diseases and hope that this manuscript serves as a solid base for these subsequent studies. As such, the wonderful input from the reviewers has been extremely important for our research program.

Reviewer 2 Comments for the Author...

The answers to the points I raised and the novel experiments are satisfactory and the manuscript improved.

There are still some minor imprecision's

- in Materials and Methods it is stated that the cells were cultured in 1 uM FAC and 50 uM ascorbate, while in the legend of fig 3A is 10 uM FAC and 500 uM ascorbate.

- In the legend of fig 4E,F the concentration of the FAC is not indicated.

- the description of HEPH in the legend of fig 4A is missing.

Response: We thank the reviewer for pointing out these imprecisions. The Materials and Methods section was written incorrectly. The concentration in the Figure legends is correct. In the experiments, solutions of 1mM FAC and 50mM ascorbate were added into the media until the cell culture media was raised to a concentration of FAC and ascorbate of 10uM and 500uM, respectively. We have changed the Materials and Methods section to indicate the appropriate values. Figure 3 and Figure 4 are same for the FAC and ascorbate concentration which are 10uM and 500uM, respectively. We added the correct concentration of FAC in Figure 4E and 4F in the revised version. We added the description of HEPH in the legend of Figure 4A in the revised version. We thank the reviewers for the extraordinarily helpful reviews which have significantly increased the quality of the manuscript.