Author’s response to reviews

Title: Spectrum of PAH gene variants among a population of Han Chinese patients with phenylketonuria from Northern China

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Author’s response to reviews:

Dear Editor,

We, along with our co-authors, thank you very much for giving us an opportunity to revise our manuscript. We greatly appreciate the editor’s and reviewers’ positive and constructive comments and suggestions regarding our manuscript. To strengthen our paper, we have revised our manuscript according to these comments. Attached, please find the modified version of our manuscript (all amendments are marked in red font), which we would like to submit for your kind consideration. We deeply appreciate the time and effort you have spent in reviewing our paper.

We look forward to hearing from you regarding our submission, and would be happy to respond to any further questions or comments that you may have.
Thanks again and best regards!

Sincerely,
Ning Liu and Xiangdong Kong

Response to Pro. Nenad Blau (Reviewer 2)

Major:
Comments 1: To understand the background of the study (patients' characteristics) and to give the reader opportunity to investigate presented data in more detail, authors should provide a supplementary table with all patients, corresponding genotype, phenotype and initial (pre-treatment) blood Phe levels. At least the genotype and phenotype would be mandatory.

Response: We appreciate the reviewer’s suggestion. Accordingly, we have provided a supplementary table containing each patient’s corresponding genotype, phenotype, and initial (pre-treatment) blood Phe levels. Unfortunately, however, the data are incomplete as the initial blood Phe levels of some patients were not available for various known or unknown reasons.

Minor:
Comments 2: Page 3, line 48: I would replace the word 'polymorphism' with 'variation'

Response: We agree with the reviewer’s suggestion. We have therefore replaced the term 'polymorphism' with 'variation' on Page 3, line 48. This change is highlighted in red font.

Comments 3: Page 3, line 56: To my knowledge BH4 deficiency is NOT associated with GFRP variants. Otherwise, cite the reference publication.

Response: We appreciate your suggestion. There are five BH4-D-associated genes, including those encoding BH4-biosynthesis enzymes (PTS and GCH1) and the BH4 regeneration enzymes (PCBD1 and QDPR). Lastly, GFRP is known to interact with GCH1 in the liver. We have provided the appropriate references in the revised manuscript:


Page 14, line 251 and page 15, line 285: this reference (Blau et al. 2014) is cited twice.

Response: Thank you for your careful reviewing; we apologize for our negligence. To correct this error, we have deleted the duplicate reference (#16).

Comments 4: Figure 1: Do authors assume that in PAH deficiency the BH4 loading test is negative? This is not the case and this figure is more complex. Also, authors did not mention hyperphenylalaninemia in patients with biallelic DNAJC12 variants. Shouls be included in the figure.

Response: Thank you very much for the helpful comments. Generally, in cases of PAH deficiency, the BH4 loading test is always negative but in BH4-responsive genotypes. In addition, the BH4 loading test is sometimes negative in cases of DHPR deficiency. The DNAJC12 gene has, therefore, been added to the figure. We have also made corrections to the manuscript to address the reviewer’s comments (Page 3, lines 54 and 55).