RESPONSE TO EDITOR AND REVIEWERS

Dear Editor-in-Chief,

Thank you, and the reviewers, for the valuable comments as well as the constructive criticisms. Particularly, we have contacted an expert statistician to solve and check the statistical analyses adequately.

The following pages contain our itemized responses. Where necessary, we have made appropriate changes in the text and highlighted them in red for ease of review/access. Hopefully, the changes we have made have improved the quality of the manuscript sufficiently to be acceptable to the Journal.

We look forward to your opinion on the revised m/s,

Yours sincerely,

Javier Ampuero, MD, Ph.D.,

Unit of Digestive Diseases and CIBERehd,

Virgen del Rocio University Hospitals,

Avenida Manuel Siurot s/n,

41013 Sevilla, Spain

E-mail: jampuero-ibis@us.es

Phone: (+34) 955-015761 Fax: (+34) 955-015899

REVIEWERS' COMMENTS TO AUTHOR

Reviewer: 1

Point 1: Title is very uninformative and the reader cannot be sure what is the purpose of the article.

Response: We understand the opinion of the reviewer. However, the title was accepted by the Editorial Board previously to write the review.

Point 2: Abstract should contain the description of the article type - in this case it is a narrative review.

Response: Thanks for the suggestion. Now, we have included that this article is a narrative review (Page 2, Line 18).

Point 3: Genetics - authors should mention the current discussion about the penetrance, which may be lower than typically believed 100%, thus increasing the prevalence of asymptomatic forms (see Eur J Clin Invest. 2019 Aug; 49(8): e13147. Published online 2019 Jun 20. doi: 10.1111/eci.13147).

Response: We agree. Thus, we have included this information in the manuscript (Page 3, Lines 24-26).

Point 4: Authors should briefly also mention epigenetic alterations which may influence phenotype of the disease.

Response: As the reviewer can see, we have included some information about epigenetics influencing the phenotype of the disease (Page 3, Lines 30-31).

Point 5: Diagnosis - "Free copper" - at first appearance of this term, it should be explained that it is non-ceruloplasmin (albumin bound) copper, since truly free molecular copper is not present in the plasma.

Response: Ok, done (Page 7, Lines 17-18).

Point 6: Consider changing very categorical statement about immunological determination of ceruloplasmin, when discussing the calculation of free copper. (E.g. It is preferable to use enzymatically determined ceruloplasmin levels

when calculating free copper). Also maybe a wider discussion about poor correlation between ceruloplasmin levels and ceruloplasmin activity can be included - e.g. PMID: 15614251 DOI: 10.1016/j.lab.2004.08.005.

Response: Thanks for this interesting suggestion. This information is now included in the review (Page 6, Lines 30-31).

Point 7: Some efficacy data for DPA and trientine may be included - e.g. DOI: 10.1016/j.cgh.2013.03.012.

Response: We have included this information (Page 11, Lines 12-13) (Page 11, Line 27).

Reviewer: 2

Point 1: Lot of English language mistakes and needs to be revised by a native English speaker.

Response: We have made an extensive edition of the manuscript by a native English speaker.

Point 2: KF not KR ring.

Response: We have edited it (Page 6, Line 9).

Point 3: Values greater than 250 g/g (4 μmol/g) are diagnostics….Values greater than 250 μg/g (4 μmol/g) are diagnostics.

Response: Thanks for the suggestion. We have changed it (Page 9, Line 11).

Point 4: while values less than 50 g/g (0.8 μmol/g) ……while values less than 50 μg/g (0.8 μmol/g).

Response: Thanks for the suggestion. We have changed it (Page 9, Line 12).

Point 5: Finally, metanobactins are a novel approach……What are your References???

Response: We have included a reference supporting this statement (no. 65).