Point-by-point Reply to Reviewers

Reviewer #1

Please include more studies. There is no need to be so rigorous when selecting studies. "As a result, 112 full-text articles have been identified as potentially eligible for this systematic review, because those included some information on the HLA genotype of the respective CD study population. However, as summarized in Table 1, only 38 studies were finally included in the present systematic review, because they only provided details of the HLA-DQB1 genotype in such a way that could allow to assess the HLA-DQB1*02 carrier frequency among CD patients, along with the evidence of the appropriate diagnostic work-up to achieve a correct and final diagnosis of CD" . I doubt that out of 112 articles in 74 articles the diagnosis of celiac disease was incorrect. If we have more studies we have no limitations of your study.

We thank the reviewer for highlighting this point, which allow us to further clarify this aspect. Indeed, we could include only all those articles reporting enough information about the HLA-DQ genotype for each patients or groups of patients, according to the specific study design. Thus, our strict selection was not driven only by the appropriateness of the CD diagnosis, but rather by the availability of the information about the HLA-DQB1 alleles and, in detail, HLA-DQB1*02 allelic variant, in order to allow us the quantitative evaluation of carriers. Therefore, all the articles fulfilling both criteria (diagnostic evidence and appropriate HLA-DQB1 genotype description) have been already included in Table 1 and, thus, in our analysis, as described in the material and methods.

Reviewer #2

The Authors of this systematic review of articles tackling the frequency of HLA-DQB1*02 allele in patients with celiac disease (CD) reported their results in support of genetic testing in average risk population. The manuscript is well written and informative.

- We thank the reviewer for appreciating our study.

However, I have the following comments/suggestions: 1. The introduction section is too long (word count 574). This should be shortened to approximately 350-400 words, in order to improve the readability of the manuscript.

- We shortened the introduction, according to the reviewer's recommendation.

2. The results of the review should be reported in a separate table.

- The results of this systematic review basically consist of the assessment of the overall carrier frequency in all eligible studies, which is reported in the manuscript. Table 1 provides information about the main aspects of the selected studies, in order to allow the readership to be aware of the type ad potential limitations of those articles.

3. The discussion section should start by stating the main results and their significance.

- We improved the beginning of the discussion, according to the reviewer's advice.

4. The limitations of this study should be clearly stated.

- As suggested, we further highlighted and discussed the limitations of this systematic review.

Reviewer #3

To: Editorial Board World Journal of Gastroenterology Title: "Carrier frequency of HLA-DQB1*02 allele in patients affected with Celiac Disease (CD): a systematic review assessing the potential rationale of a targeted allelic genotyping as a first-line screening" Dear Editor, I read this manuscript and I think that the paper is good and well written.

- We thank the reviewer for appreciating our study.

I would like to provide some preliminary comments on the re-review of the edited manuscript that we have been working on together during the last few weeks.

I am happy to see that the reviewer 00069819 supported our publication now, changing his recommendation from major revision to accept, as well as reviewer 02520738 already did with the first version of the manuscript.

As for reviewer 02627036, if the problem is Figure 1, it is not a problem to add some specifications in the legend. However, some peculiar aspects (exclusion criteria, incomplete genetic data, inappropriate population) are described in the materials and methods, whereas others (like duplicate publications, unclear methods) represent a general background of knowledge when applying the PRISMA guidelines (anyway, if needed, we can include some specifications in the legend, even if this is not the usual practice, according to our and others' previously published systematic reviews). Actually, in our reply to this reviewer, we clarified the strict criteria that we had to apply in order to make sure that we are analyzing a population with a safe diagnosis of CD and without any genetic pre-selection (bias). Of course, the availability of the appropriate information on HLA-DQB1*02 and its carrier frequency in each cohort of patients, was another mandatory criterion to include the studies in our systematic review, as explained in our previous response to this reviewer (see below).

Thus, our strict selection was not driven only by the appropriateness of the CD diagnosis, but rather by the availability of theinformation about the HLA-DQB1 alleles and, in detail, HLA-DQB1*02 allelic variant, in order to allow us the quantitative evaluation of carriers. Therefore, all the articles fulfilling both criteria (diagnostic evidence and appropriate HLA-DQB1 genotype description) have been already included in Table 1 and, thus, in our analysis, as described in the material and methods.

Thank you for your attention and fruitful collaboration. Please, do not hesitate to contact me if you need any further clarifications.

Best regards,

Dimitri