Answer to the Reviewers – Manuscript 67204

We would like to thank all the reviewers for their comments, that helped us improving our review. We report here below all the observations made, with our answers and indications about what has been changed or corrected in the submitted paper.

Reviewer #1:
Scientific Quality: Grade A (Excellent)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: I've carefully read the manuscript entitled "Celiac disease: from genetics to epigenetics". The topic is of great interest for the celiac community – both researchers and healthcare professionals. The authors accurately describe the role of HLA in the genetic predisposition for CD and research targeting other genes that contribute to this genetic susceptibility. Further, the authors present currently available data on epigenetic modifications in CD. Figures are well illustrated, referring to correlation with clinical practice and profiling of patients according to epigenetic changes.

We do thank Reviewer #1 for the positive feedback.

Reviewer #2:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: I pleasantly reviewed this paper about celiac disease. I have no comments on the work except for a suggestion in the description of literature and conclusions. What I think is that the treatment of new data for the development of modeling should be done also using machine learning. Recently, also for CD, these techniques have given indications useful for physician. In my opinion, authors should review and include in the paper: Hegenbart S, Uhl A, Vécsei A Review Survey on computer aided decision support for diagnosis of celiac disease. Comput Biol Med. 2015 Oct 1; 65:348-58. Piccialli, Francesco, Francesco Calabrò, Danilo Crisci, Salvatore Cuomo, Edoardo Prezioso, Roberta Mandile, Riccardo Troncone, Luigi Greco, and Renata Auricchio. "Precision medicine and machine learning towards the prediction of the outcome of potential celiac disease." Scientific Reports 11, no. 1 (2021): 1-10.

We do thank Reviewer #2 for the helpful comments that helped us to improve the overall quality of the manuscript. A paragraph about the application of machine learning in celiac disease has been added before the conclusion and includes also the articles suggested by Reviewer #2 (references number 67 and 74). The machine learning approach has also been addressed in the conclusion and in the "article highlights" section as required by the editors.

Reviewer #3:
Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision
Specific Comments to Authors: The title reflected the main subject/hypothesis of the manuscript. In the abstract some sentences regarding the epigenetics should be added. The key words reflected the focus of the manuscript. The manuscript adequately describe the background, present status and significance of the study. Please add the Methods searching and add the type of selected studies e.g. experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail. The study has made for research progress in this field The manuscript interpreted the findings adequately and appropriately, highlighting the key points concisely, clearly and logically please site the following article as well: Rostami-Nejad M, Romanos J, Rostami K, Ganji A, Ehsani-Ardakani MJ, Bakhshipour AR, Zojaji H, Mohebbi SR, Zali MR, Wijmenga C. Allele and haplotype frequencies for HLA-DQ in Iranian celiac disease patients. World J Gastroenterol. 2014 May 28;20(20):6302-8. doi: 10.3748/wjg.v20.i20.6302. PMID: 24876751; PMCID: PMC4033468.

We do thank Reviewer #3 for the helpful comments that helped us to improve the overall quality of the manuscript. In the abstract, the part regarding epigenetics has been expanded. About the research methods, a dedicated paragraph was added after the introduction, as well as in the section "article highlights" required by the editors. The suggested article has been cited in the introduction, reference number 2 of the bibliography.

Answer to the Science Editor – Manuscript 67204

: 1 Scientific quality: The review manuscript describes Celiac Disease: From genomics to epigenomics. The topic is within the scope of the WJG. (1) Classification: Grade B, Grade B, and Grade C; (2) Summary of the Peer-Review Report: (05932402): I have no comments on the work except for a suggestion in the description of literature and conclusions. What I think is that the treatment of new data for the development of modeling should be done also using machine learning. (04092118): The authors accurately describe the role of HLA in the genetic predisposition for CD and research targeting other genes that contribute to this genetic susceptibility. (01555264): The study has made for research progress in this field The manuscript interpreted the findings adequately and appropriately, highlighting the key points concisely, clearly and logically please site the following article as well: Rostami-Nejad M, Romanos J, Rostami K, Ganji A, Ehsani-Ardakani MJ, Bakhshipour AR, Zojaji H, Mohebbi SR, Zali MR, Wijmenga C. Allele and haplotype frequencies for HLA-DQ in Iranian celiac disease patients. World J Gastroenterol. 2014 May 28;20(20):6302-8. doi: 10.3748/wjg.v20.i20.6302. PMID: 24876751; PMCID: PMC4033468; (3) Format: There are 2 tables and 3 figures; (4) References: A total of 62 references are cited, including 25 references published in the last 3 years; (5) Self-cited references: There are 5 self-cited references;(6) References recommendations: The authors have cited proper references. 2.Language evaluation: Classification: Grade B, Grade A, and Grade A. 3 Academic norms and rules: The authors provided the Non-Native Speakers of English Editing Certificate. 4 Supplementary comments: This is an invited manuscript. The authors declare no conflict of interest. The topic has not previously been published in the WJG. 5 Issues raised: (1)The "Author Contributions" section is not detailed. Please provide the author contributions; (2) The "Article Highlights" section is missing. Please

add the "Article Highlights" section at the end of the main text. 6.Re-Review: Required 7 Recommendation: Conditional acceptance

As suggested by the Science Editor we have written the Article Highlights section, with is reported below.

ARTICLE HIGHLIGHTS

Research background

Celiac Disease (CeD) is a multifactorial autoimmune enteropathy, in which the interaction between the genetic predisposition and the exposure to environmental factors is responsible for the disease development. Epigenetics are inheritable traits that can regulate gene expression and can be influenced by external factors, making them the focus of many recent studies in this field.

Research motivation

Even if the most diffused haplotypes responsible for CeD development are known, many additional predisposing polymorphisms have been discovered in recent years, along with new epigenetic modifications. Since CeD pathogenesis is multifactorial by definition, different elements that can affect the disease predisposition, severity or progress toward complications need to be taken into consideration.

Research objectives

This review wants to give an update on the most recent studies about genetics and epigenetic modifications in CeD, useful to both researchers and clinicians who look into this key part of the molecular research in CeD.

Research methods

The literature revision was carried out on PubMed, searching the key words related to epigenetics and celiac disease. The articles that were considered relevant to the purpose of the review were included, whereas the ones that did not add novelty or did not give clear results were excluded during the critical revision of the literature.

Research results

75 articles have been cited in this review. In particular, the epigenetic modifications addressed in the reviewed studies seem to be linked with different aspects of CeD. Different DNA methylation patterns or histone methylation signatures seem to carry additional predisposition to develop CeD or its complications, whereas lncRNAs and miRNAs act on different targets involved in pathogenic mechanisms; all this elements

reflect on a different gene expression, that seems to be distinct between the healthy population and CeD, but also among the subsets of CeD patients.

Research conclusions

The articles here reviewed highlight the role of epigenetics in CeD development, ranging from DNA methylation to non-coding RNAs. All these elements are needed to fully understand CeD pathogenesis, with some of them potentially useful in stratifying CeD patients or for CeD screening.

Research perspectives

The encouraging results of the considered studies show new elements, useful for researchers dedicated to the study of the molecular development of CeD, but also to clinicians who want to broaden their tools for an early diagnosis and the screening of asymptomatic, predisposed subjects. These new data, coupled with new developing tools like machine learning, could be valid assets in the near future.