Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 2024-review.doc).

Title: Children with celiac disease and high tTGA are genetically and phenotypically different

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The manuscript has been improved according to the reviewers' suggestions.

1. The format has been updated:

- The authors' names have been listed differently upon request
- Author contributions are now provided
- The professional title of the corresponding author has been provided
- The methods section in the abstract has been extended
- The layout of the phonenumbers has been changed
- A core tip has been added
- The layout of the references has been changed
- A comment section has been added
- Additional references have been added

2. The following revisions have been made according to the reviewers' suggestions:

- Reviewer No 00180535, No 00343118 and No 00742123 had no comments.
- Reviewer No 00503513 requested the following changes:
    - On the original Page 9, an explanation of the abbreviation "SDS" is now provided.

- On the original Page 9, Morbus Graves has been changed to Graves disease.
- The abbreviation list is completed in the legends of Tables 1 and 2.
- In Table 4, an explanation of the n=33 and n= 73 patients who underwent both duodenal bulb and distal duodenal biopsies is now given in the legend.
- The most recent Oslo definitions of celiac disease are now included and cited.

- Reviewer No 00068093 asked whether there were any patients with normal tTGA in the low tTGA group.
  - This question is answered in the first paragraph of the results section:
    - "Within the low tTGA group, 2 patients, a 10-month-old girl and a 2-year-old boy, had a tTGA level <10 U/ml and negative EMA,"
- Reviewer No 00009530had the following comments:
  - The reviewer stated that the 2 subjects with tTGA < 1:10 and negative EMA probably do not have CD. We completely agree that many patients with negative serology who are diagnosed with CD turn out to have been misdiagnosed. However, in some cases (for example, in very young children)serology may be false negative. This has been shown in a number of studies and is also addressed in the new ESPGHAN guidelines. Indeed, both of the children with negative serology in our study were ≤2 years. They were clear-cut cases of Marsh III lesions in whom the pathologist did not doubt the diagnosis at all, and they also responded well to the diet. Taking all this together, we had no reasons to exclude these 2 patients from the analysis. A short statement has been added in the results section to clarify this:
    - "Within the low tTGA group, 2 patients, a 10-month-old girl and a 2-year-old boy, had a tTGA level <10 U/ml and negative EMA, which is not an uncommon finding in very young children [11, 14-18]. All of the remaining patients had positive EMA levels.
  - The reviewer correctly states that on Page 9, it is unclear whether the 4 patients with DM also had Down syndrome. In fact, the 4 patients with DM did not have Down syndrome. To make this clear, the sentence was separated into 2 sentences, and the word "another" was added:
    - "Regarding comorbidity, 5 (4.3%) patients had Down syndrome, and 1 (0.86%) of those also had hypothyroidism. Another 4 (3.4%) patients had diabetes mellitus Type I, 1 (0.86%) patient had juvenile rheumatoid arthritis and 1 (0.86%) patient had Graves disease."
  - The reviewer requested an explanation of why a CD family history is more frequent (although not significantly so) in patients with low t-

TGA. This has been added as an additional paragraph in the discussion section.

- "Finally, we showed that patients in the low tTGA group more often have a positive family history for CD (26.5% *vs*. 17.1%), although this difference was not statistically significant. This difference could have resulted because patients with a positive family history are detected earlier than those without a positive history, before a very high tTGA level is reached. Conversely, patients with comorbidity were found more frequently (although statistically not significant) in the high tTGA group (12.2% *vs*. 2.9%), which might be due to a more advanced disease progression in this group."

  - The recent review article by Fasano & Catassi (NEJM 2012) has been added to the reference list.

- Reviewer No 00742022made the following requests:
  - The reviewer requested that the discussion section emphasize that this is a pediatric study and that the results might not be the same in adults. We have added a statement to this effect to the last paragraph of the discussion:
    - "Our combined data confirm, in a pediatric population, the hypothesis that patients with tTGA ⩾100 U/ml have more advanced disease, given the more severe histological involvement and the increased incidence of extraintestinal manifestations and lower body weight. Pathophysiologically, these patients also express more CD-associated HLA-heterodimers on their cells. These findings should also be investigated in adults."

3. References and typesetting were corrected.

Thank you again for considering our manuscript for the *World Journal of Gastroenterology*.

Sincerely yours,

Dr. Amani Mubarak