Association of LPP and TAGAP Polymorphisms with Celiac Disease Risk: A Meta-Analysis

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Figure S1. Funnel plot for LPP rs1464510 (A vs. C) with CD.

Figure S2. Funnel plot for TAGAP rs1738074 (A vs. G) with CD.

Table S1. Risk of bias assessment for genetic association studies of CD of studies included in the meta-analysis.

| Domain and Item                                   | Low Risk of Bias |
|---------------------------------------------------|------------------|
| Information bias                                  |                  |
| Ascertainment of CD                               |                  |
| Clearly described objective criteria of diagnosis of CD | Yes              |
| Not clearly identified                            | No               |
| Did not mention                                   | Unclear          |
| Ascertainment of controls                         |                  |
| Controls were non-CD and without family history   |                  |
| Mentioned the sources of controls                 | No               |
| Not described                                     | Yes              |
| Ascertainment of genotyping examination           | Unclear          |
| Genotyping done under “blind” conditions of case specimens and control specimens | Yes |
| Genotyping of cases and controls was performed together | Yes |
| Genotyping error rate < 5% | Yes |
| Quality control procedure (e.g., reanalysis of random specimens, by using different genotyping methods for analysis, analysis if replicate sample) | Yes |
| Unblind | No |
| Genotyping error rate > 5% | No |
| Did not mention what was done | Unclear |

Confounding bias

Population stratification

- No difference in ethnic origin between cases and controls | Yes |
- Use of controls who were not related to cases with clearly identification | Yes |
- Use of some controls who came from the same family | No |
- No report of what was done | Unclear |

Other confounding bias

- Controls for confounding variables (e.g., age, gender, or BMI) in analysis | Yes |
- Not controlled for confounding variables | No |
- Not mentioned | Unclear |

Selective reporting (for replication studies)

- Reported results of all polymorphisms mentioned in the objectives, no significant or not | Yes |
- Reported results of only significant polymorphisms | No |

HWE

- HWE in the control group | Yes |
- HWD in the control group | No |
- HWE not checked or mentioned | No |
Table S2. MOOSE checklist: The association of LPP and TAGAP genes with CD risks: a meta-analysis.

| Criteria                                      | Brief Description of How the Criteria were Handled in the Review                                                                                                                                                                                                 |
|-----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Reporting of background                       |                                                                                                                                                                                                                                                                |
| √ Problem definition                          | The epidemiology of celiac disease.                                                                                                                                                                                                                           |
| √ Hypothesis statement                        | The conflict results of genetic risk with celiac disease in different population based studies.                                                                                                                                                                 |
| √ Description of study outcomes               | We propose there are associations between gene polymorphisms LPP rs1464510 and TAGAP rs1738074 and celiac disease.                                                                                                                                                      |
| √ Type of exposure                            | Genetic markers                                                                                                                                                                                                                                              |
| √ Type of study designs used                  | The population based genetic epidemiological observational studies of celiac disease.                                                                                                                                                                          |
| √ Study population                            | The populations from the whole world are all considered our analysis.                                                                                                                                                                                             |
| Reporting of search strategy should include   |                                                                                                                                                                                                                                                                |
| √ Qualifications of searchers                 | Two reviewers independently went through all titles and abstracts of the identified studies. Time period: from inception of PubMed, Web of Science and Embase up to October 2016. Search strategy: (((LPP or 3q28 or rs1464510 or “lipoma preferred partner”) or “lim domain containing preferred translocation protein”) and celiac disease) and celiac disease) or ((TAGAP or 6p25 or rs1738074 or “T-cell activation GTPase activating protein”) AND celiac disease). |
| √ Search strategy, including time period      | Databases and registries searched: PubMed, Web of Science and Embase. Search software used, name and version, including special features: PubMed, was accessed from the National Library of Medicine (free), Web of Science is available on the website of Jinan University Library, Embase is purchased in internet. |
| included in the synthesis and keywords        | We searched bibliographies of retrieved papers and those of previous reviewers on the subject were examined for further relevant studies.                                                                                                                                 |
| √ Databases and registries searched           | Details of the literature search process are outlined in the flow chart. The citation list for excluded studies is available upon request.                                                                                                                                 |
| √ Search software used, name and version,     | We had a restriction on language; our searching was limited to English.                                                                                                                                                                                            |
| including special features                    | Method of addressing articles published in languages other than English. We included proceedings papers and assessed them for eligibility according to our inclusion and exclusion criteria. Unpublished studies were excluded in our analysis. |
| √ Use of hand searching                       | Description of any contact with authors: It is applicable; we contact the authors when we needed.                                                                                                                                                                 |
| √ List of citations located and those excluded, including justifications |                                                                                                                                                                                                                                                                |
| Reporting of methods should include           | Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested: Detailed inclusion and exclusion criteria are described in the Methods section.                                                                                  |
Data extracted from each of the studies were relevant to the population characteristics name of first author, year of publication, region of study population, source of controls, genotype method, diagnostic criteria, the number of cases and controls, the risk allele frequency in cases and controls, and the Hard-Weinberg Equilibrium (HWE). Detailed inclusion is described in the Methods section.

Sensitivity analyses by several quality indicators such as study size, study objects’ ethnic, and another influential factors, in the Methods section.

Heterogeneity of the studies was explored with $I^2$ statistic that provides the relative amount of variance of the summary effect due to the between-study heterogeneity, detailed inclusion is described in the Methods section.

Description of methods of meta-analyses, sensitivity analyses, meta-regression and assessment of publication bias are detailed in the methods. We performed fixed effects and random effects meta-analysis with Stata (Ver. 12) and the Comprehensive Meta-Analysis software (Ver. 12).

95% confidence intervals were presented with all summary estimates, $I^2$ values and results of sensitivity analyses.

The forest plot and Egg’s regression.

All studies were excluded based on the pre-defined inclusion criteria in methods section.

Brief discussion included in Methods section.

Discussed in the context of the results.

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We recommend analyses that would correct for regression dilution bias.

No separate funding was necessary for the undertaking of this systematic review.
Table S3. The sensitivity analysis of LPP rs1464510 and CD risk (A vs. C).

| Excluded Study        | Country      | Pooled OR | 95% CI     | p       | I² (%) | p-Value for I² |
|-----------------------|--------------|-----------|------------|---------|--------|---------------|
| Plaza-Izurieta et al. [7] | Spain        | 1.26      | 1.23–1.30  | <0.001 | 29.86  | 0.126         |
| Sperandeo et al. [31] | Italy        | 1.25      | 1.21–1.29  | <0.001 | 26.38  | 0.141         |
|                       | UK 1         | 1.25      | 1.21–1.29  | <0.001 | 30.34  | 0.103         |
|                       | UK 2         | 1.24      | 1.20–1.28  | <0.001 | 19.77  | 0.213         |
|                       | Finland 1    | 1.26      | 1.22–1.30  | <0.001 | 33.20  | 0.080         |
|                       | The Netherlands | 1.26  | 1.23–1.30  | <0.001 | 29.51  | 0.111         |
|                       | Italy 1      | 1.26      | 1.22–1.30  | <0.001 | 32.38  | 0.086         |
|                       | USA          | 1.26      | 1.22–1.30  | <0.001 | 32.98  | 0.082         |
| Dubois et al. [8]     | Hungary      | 1.26      | 1.22–1.30  | <0.001 | 33.23  | 0.080         |
|                       | Ireland      | 1.26      | 1.22–1.30  | <0.001 | 33.30  | 0.080         |
|                       | Poland       | 1.26      | 1.22–1.30  | <0.001 | 31.88  | 0.090         |
|                       | Spain        | 1.26      | 1.22–1.30  | <0.001 | 33.20  | 0.080         |
|                       | Italy 2      | 1.25      | 1.21–1.29  | <0.001 | 23.60  | 0.170         |
|                       | Finland 2    | 1.26      | 1.22–1.30  | <0.001 | 32.32  | 0.087         |
| Coenen et al. [30]    | The Netherlands | 1.27  | 1.23–1.31  | <0.001 | 11.63  | 0.312         |
| Romanos et al. [33]   | Italy        | 1.26      | 1.22–1.30  | <0.001 | 32.44  | 0.086         |
|                       | UK           | 1.25      | 1.22–1.29  | <0.001 | 31.34  | 0.095         |
| Hunt et al. [9]       | Ireland      | 1.26      | 1.22–1.30  | <0.001 | 30.31  | 0.104         |
|                       | The Netherlands | 1.27  | 1.23–1.30  | <0.001 | 22.92  | 0.177         |
| Van Heel et al. [10]  | UK           | 1.26      | 1.22–1.30  | <0.001 | 32.98  | 0.082         |

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