Analysis of HLA and non-HLA alleles can identify individuals at high risk for celiac disease

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Abstract

**BACKGROUND AND AIMS**

Celiac disease (CD) is a common chronic disorder of the small intestine, resulting from aberrant cellular responses to gluten peptides, often remains undiagnosed. It is a complex genetic disorder although 95% of the patients carry the risk heterodimer HLA-DQ2. Genome-wide association studies on CD have identified nine non-HLA loci that also contribute to CD risk, most of which are shared with other immune-related diseases. Our aim is to predict the genetic risk for CD using HLA and non-HLA risk alleles.

**METHODS**

We selected ten independent polymorphisms in 2308 cases and 4585 controls from Dutch, UK, and Irish populations and categorized the individuals into three risk groups, based on their HLA-DQ2 genotype. We used the summed number of non-HLA risk alleles per individual to analyze their cumulative effect on CD risk, adjusting for sex and population group in logistic regression analysis. We validated our findings in 436 Italian cases and 532 controls.

**RESULTS**

CD cases carried more non-HLA risk alleles than controls: individuals carrying 13 or more risk alleles had a higher CD risk (OR = 6.2; 95% CI 4.1-9.3) compared to those carrying zero to five risk alleles. Combining HLA and non-HLA risk genotypes in one model increases sensitivity by 6.2% compared to using only HLA for identification of high-risk individuals with slight decrease in specificity.

**CONCLUSIONS**

We can use non-HLA risk factors for CD to improve identification of high-risk individuals. Our risk model is a first step towards better diagnosis and prognosis in high-risk families and population-based screening.

**Keywords:** celiac disease, risk prediction, SNP

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