Austin Journal of Nutrition and Food sciences

Open Access

Austin Publishing Group

Review Article

Nomenclature of Genes, Risk Factors, Alleles and Haplotypes Related to Genotyping of HLA-DQ2 and HLA-DQ8 Risk Alleles

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Received: May 17, 2024

Accepted: June 10, 2024

Published: June 17, 2024

Abstract

The HLA-DQ genotyping test is a simple, non-invasive and reliable method. The identification of risk haplotypes by genotyping contributes to a faster and earlier diagnosis, improving the prognosis of patients and avoiding complications. However, it is a challenge for healthcare professionals, when reading articles about the HLA-DQ test to notice differences in terms of names of alleles, HLA classes, loci, risk factors, genes, haplotypes, arrangement in homologous chromosomes, proteins and heterodimers, which makes it difficult to understand the studies and to interpret genetic tests. This is also difficult for researchers starting in celiac disease studies inhibiting them to join this area. Therefore, the aim of this study is to review the updated nomenclature used in HLA analysis. Therefore, recent bibliographies and nomenclature databases were analyzed to present the updated nomenclature of HLA-related risk factors from molecular to pathophysiological terms. The result is a brief review and simple table showing all levels of HLA risk-related factors and their relationships.

Keywords: Genetic markers; Gastroenteritis; Nutrition; Malnutrition

Introduction

For a better understanding how, genetic factors influence the predisposition to develop typical CD intestinal lesions, it is necessary to understand the molecules involved in the pathogenesis of CD and how the genes encoding them are structured in the human genome. Therefore, we can recognize how allelic variations segregate and how those variations predispose to the risk for disease development.

The immune system is directly involved in the pathogeny of CD. Dendritic cells located in the lamina propria acquire a pro-inflammatory phenotype, migrating to the mesenteric lymph nodes. They present there gluten peptides via MHC class II complex, mainly by HLA heterodimers (combining alpha-1 and beta-1subunits of HLA-DQ proteins) to naive CD4 T cells and promoting T cell activation [1]. The presentation of gluten peptides depends on genetic predisposition conferred by some risk alleles of alpha-1 and beta-1 HLA-DQ genes. Those alleles generate the major heterodimer risk for CD predisposition (HLA-DQ2 and HLA-DQ8). The loci of those alleles are very close to each other and they are also very near to the HLA-DR locus [1]. The proximity of those genes reduces the probability for a crossing over recombination, resulting in almost fixed segregation. Therefore, the concept of HLA-haplotype is important for the genetic hereditability of those alleles, as they have a very strong genetic linkage and are inherited together during the meiosis phase of the sexual reproduction. In Table 1 it is organized the current nomenclature of the main HLA risk alleles for CD including: loci, genes, risk alleles, haplotypes, heterodimers and risk grade for the disease development.

The main important risky alleles for CD can be located on the same chromosome in cis configuration (DR3-DQ2 haplotype) or separately on homologous chromosomes in trans configuration (DR5-DQ7 plus DR5-DQ2 haplotypes) [2]. The risky haplotypes for CD are those containing the following alleles: A) the DQA1*05:01 and DQB1*02:01 alleles (DR3-DQ2 haplotype

Citation: Flores da Silva CS, Schneider A, Schadock I, Botelho FT, Barros CC. Nomenclature of Genes, Risk Factors, Alleles and Haplotypes Related to Genotyping of HLA-DQ2 and HLA-DQ8 Risk Alleles. Austin J Nutri Food Sci. 2024; 12(1): 1178.

that generate DQ2.5 heterodimer associated to a very high risk for CD), B) the combination of the haplotypes containing the DQA1*05:05 and DQB1*02:02 alleles (DR5-DQ7 and DR7-DQ2 haplotypes respectively, that combined also generate the DQ2.5 heterodimer), C) the haplotype containing DQA1*02:01 and DQB1*02:02 alleles (DR7-DQ2 haplotype that generate DQ2.2 heterodimer associated to a low risk for CD), and D) the haplotype containing the DRB1*04 allele (DR4-DQ8 haplotype that generates DQ8 heterodimer associated to a high risk for CD). All those allele combinations encode the DQ2 and DQ8 heterodimers, which are part of the antigen recognition site of the HLA molecule present at the surface of the antigen-presenting cells [3] are associated with CD development (Table 1).

The HLA-DQ2 and HLA-DQ8 heterodimers play an important role in the development of CD, as they present the gliadin peptides and the deaminated gliadin peptides, that reach the lamina propria, to the CD4+ T lymphocytes. This association of CD to the HLA-DQ heterodimers was demonstrated by isolating gliadin-reactive T cells from the intestinal mucosa. An important part of these activated T cells recognizes gluten when in contact with the HLA-DQ heterodimer, demonstrating the association of cells T to the HLA-DQ heterodimer and the CD [4].

Most celiac patients carry HLA-DQ2 heterodimers (90%) encoded by DQA1*05:01/DQB1*02:01 alleles and a minority (5%) carry HLA-DQ8 encoded by DQA1*03/DQB1*03:02 alleles [5]. Since most CD patients have HLA-DQ2 and HLA-DQ8 heterodimers, those genetic markers together have a high negative predictive value [6]. This way, the genotyping test can be used to exclude celiac disease in symptomatic patients who have started a gluten-free diet and can also be useful in clarifying a diagnosis, as well as in patients who had equivocal serology or biopsy findings and/or incomplete gluten elimination [7].

Table 1: Relations between HLA genetic loci and proteins complexes.

Chromosome band	HLA class	Loci	Risk factor group	Haplotype names[1]	Alleles[1,2,3]	Chromosome disposition[1]	HLA-DQ Heterodimer[1]	Celiac disease predisposition[1]
6p21.3	HLA class II	HLA-DQA1 and HLA-DQB1	HLA-DQ2	DR3-DQ2	**DQB1*02:01, DQA1*05:01** and DRB1*03:01	*cis*	DQ2.5	Very high
				DR5-DQ7	DQB1*03:01, **DQA1*05:05** and DRB1*11/12	*trans*	DQ2.5	Very high
				plus				
				DR7-DQ2	**DQB1*02:02**, DQA1*02:01 and DRB1*07			
				DR7-DQ2	**DQB1*02:02, DQA1*02:01** and DRB1*07	*cis*	DQ2.2	Low
			HLA-DQ8 ->	DR4-DQ8	**DQB1*03:02, DQA1*03** and DRB1*04	*cis*	DQ8	High

1- Data extract from (1)
2- Nomenclature formatted as described on http://hla.alleles.org/nomenclature/naming.html/ at January 2020.
3- The risky alleles for celiac disease are marked in bold.

Discussion

This work seeks to clarify and understand the nomenclature of genes, factors, risk alleles and haplotypes related to the genotyping of HLA-DQ2 and HLA-DQ8 and the role of those haplotypes in CD. As a result, an easy-to-read mini-review and a very useful table are presented to visualize all the updated terms used to describe the factors involved in CD. As a result, non-CD healthcare professionals now have now a simple CD factor nomenclature guide to help them understand the terms and interpret the results of several tests measuring the risk for CD development.

The genotyping test is a non-invasive, fast, simple and reliable method that can be performed using blood samples or cells from the oral mucosa. Therefore, this test can be used as a tool in the Nutrition area, for example, where HLA-DQ genotyping can help in the CD diagnosis, because in the presence of risk haplotypes and gastrointestinal symptoms, the nutritionist can guide the patient to seek medical help and thus investigate the possible CD diagnosis, reducing the risk of future complications such as nutritional deficiencies and generalized malnutrition. In the medical field, the genotyping test serves as a contributor to the medical CD diagnosis, as the HLA test can help to exclude the presence of CD in symptomatic patients who started a gluten-free diet and in patients who presented serology or uncertain findings on the biopsy.

With the discovery of the human genome, genotyping tests became more accessible, thus beginning to be inserted into clinical practice. However, it was observed that the major challenge of ordering genetic tests is the interpretation and connection of these results to the personalized diagnosis and treatment. The difficulty to understand the nomenclature related to the risk factors for CD, such as the names of the haplotypes, alleles, genes, cluster factors, proteins, heterodimers, loci and chromosomal arrangement inhibit health professionals and graduate students, also making it difficult the reading and interpretation of genetic tests, increasing the risk of misinterpretation and delayed diagnosis.

In this sense, this mini review aimed to describe and explain the nomenclature of the risk factors for CD, providing a major understanding and knowledge to non-specialized health professionals.

Material and Methods

This mini-review aimed to summarize the concepts and nomenclatures involved in the studies of the risk factors for CD. Articles relating CD and the genetic diagnosis of the main risk haplotypes for CD related to HLA-DQ groups were selected, as well as revision articles on pathological mechanisms and description of HLA-DQ groups in the last five years.

The articles were compared to the nomenclature stored on the international organization “HLA Nomenclature” available at http://hla.alleles.org/ nomenclature/naming.html/ at January 2020. Therefore, the articles that presented the nomenclature in the old format were discarded. Therefore, the data found were summarized as text in the form of a short review, and the

updated nomenclature summarized in a simple table connecting all levels from chromosome position to the risk level.

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