Editorial

The puzzling relationship between human leukocyte antigen genes and celiac disease

The human leukocyte antigen (HLA) system, i.e., the major histocompatibility complex (MHC) in humans, plays a pivotal role in the antigen presentation of intracellular and extracellular peptides and the regulation of innate and adaptive immune responses.[1] The HLA polymorphism was identified as a risk locus for celiac disease (CD) nearly 50 years ago. The primary association is with the HLA class II alleles encoding HLA-DQ2.5 (HLA-DQA1*05/HLA-DQB1*02), HLA-DQ8 (HLA-DQA1*03/HLA-DQB1*03:02), and HLA-DQ2.2 (HLA-DQA1*02:01/HLA-DQB1*02) (11–14). HLA-DQ2.5 can be encoded either in *cis* in DR3-DQ2 or in *trans* in DR5-DQ7/DR7-DQ2 individuals. Subjects with a double copy of the DQB1*02 show an increased CD risk (so called gene dosage effect).[2] In the year 1993, Lundin and colleagues showed that HLA-DQ2.5 heterodimers (as well as other celiac disease-associated HLA-DQ molecules) located on antigen-presenting cells, act by their ability to preferentially present gluten antigens to CD4+ T cells.[3] These landmark discoveries definitely established the link between the HLA predisposing genes and the adaptive immune response to gluten triggering CD. The role of HLA-DQ2 and -DQ8 genes has become important not only for the understanding of CD pathophysiology, but also for clinical and diagnostic purposes. Given the very high negative predictive value of HLA determination (close to 100%), lack of HLA-DQ2 and -DQ8 excludes the possibility of CD, in either symptomatic subjects or CD at-risk individuals (e.g., first-degree relatives of CD patients). On the other hand, the presence of HLA-DQ2 and/or -DQ8 add weight to the diagnosis of CD in doubtful cases.[4]

In a group of 192 school-aged Saudi children, as reported in this issue of the Saudi Journal of Gastroenterology,[5] Al-Hussaini and coworkers found that 52.7% carried the CD-associated HLA-DQ molecules: homozygous DQ2.5 (2.6%), DQ2.5/DQ2.2 (4.7%), heterozygous DQ2.5 (28.15%), homozygous DQ8 (4.2%), DQ8/DQ2.2 (3.6%), and double dose DQ2.2 (9.4%). Low-risk CD-associated HLA-DQ molecules (single dose DQ2.2 and heterozygous DQ8) constituted 3.6% and 9.4%, respectively. Authors correctly observe that the overall frequency of CD-predisposing, HLA-DQ genotypes they found among this group of healthy Saudi children is one of the highest worldwide, on average being around 30–40%.[6] This observation might, at least in part, explain the high prevalence of CD that the same authors previously found in the Saudi pediatric population (1.5%).[7]

Al-Hussaini and coworkers should be congratulated for adding a piece to the puzzle of the epidemiology of CD and related determinants. As pointed out by the authors, there is a clear-cut gradient in the prevalence of HLA-related, CD-predisposing genes on a worldwide scale and CD is more common in countries showing higher frequency of these genes.[8] What is less clear is why HLA-DQ2 and -DQ8 genes show an overlapping geographical distribution with the consumption of wheat, the most important gluten-containing cereal. Since current gluten consumption reflects traditional wheat consumption over the last 10,000 years, it would be logical to expect lower frequency of HLA-DQ2 and -DQ8 genes in areas where wheat is traditionally the staple food, due to the reduced survival fitness of CD-affected individuals (negative selective pressure). For 10,000 years, before discovering that CD is cured by the gluten-free diet, CD was indeed a lethal disease, characterized by high and early mortality, and high risk of infertility. By contrast, CD and HLA-DQ2/DQ8 prevalence go "hand in hand" all over the world, the so-called "celiac paradox". To explain these counterintuitive findings, we suggested that the positive selection of HLA CD-predisposing genotypes in areas consuming high quantities of gluten-containing products had nothing to do with CD, but was most likely pushed by the protective effect of these genes against deleterious conditions, e.g., specific infectious diseases such as tuberculosis, leprosy, and dental caries, appearing after the agricultural revolution took place approximately 10,000-12,000 years ago.[8]

Another important aspect of the Al-Hussaini paper is the concept of the "2-step CD-screening approach", i.e., the determination of HLA-DQ genotype as a first step in selecting individuals who must undergo serological testing for celiac autoantibodies, e.g., IgA class anti-transglutaminase, a 2-step procedure that we introduced some years ago.[9] A negative HLA result excludes CD for life, which is not the case for antibodies-based CD screening, given that

CD seroconversion may occur at any age.[10] On the other hand, the proportion of HLA-DQ2 and/or DQ8 positivity in the general population is very high, then the positive predictive value of this genetic testing is very low. For this reason we do not think that individuals bearing the CD-predisposing HLA genotypes should be defined "at high risk" of CD. In the Al-Hussaini study, almost 50% of unselected children were genetically predisposed to CD. It follows that the finding of CD-predisposing HLA genotype in these non-at-risk children carried only a minimal increase of CD risk, approximately from 1.5 to 3%.

Finally, it should be noted that a rapid and cheap HLA testing is nowadays available to detect DQ2 and DQ8 positivity in a yes/no fashion, i.e., without differentiating the various CD-associated genotypes.[11] This simple procedure is particularly valuable for CD screening studies aimed to improve both the knowledge of the epidemiology and the doctors' awareness of CD, i.e., one of the most common human disorders worldwide.

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