



HLA is better than serological screening for celiac diseases in rheumatological arthritis

Dear Editor,

We welcomed with great pleasure the recent article published in the Turkish Journal of Gastroenterology by Dr. Moghtaderi et al. (1) about gluten intolerance screening in patients with rheumatological diseases. We would like to highlight the added value of human leukocyte antigen (HLA) typing in such screening studies.

The major histocompatibility complex (MHC) is located on chromosome 6 and includes more than 200 genes, most of which such as those encoding HLA are a mandatory requisite for the immune system. In particular, the HLA class II genomic region encodes proteins (namely HLA DR, DQ, and DP) involved in the presentation of extracellular peptides to HLA class II T helper cells (Thelper) that mediates the adaptive immunity; thus, this region is frequently associated with autoimmune disorders (2).

Rheumatoid arthritis (RA) and coeliac disease (CD) are both autoimmune, inflammatory conditions that share a strong association with HLA class II genes: individuals carrying HLADQ2.5 and/or HLADQ8 alleles present an increased risk of developing CD, whereas those carrying HLADRB1 alleles present an increased risk of developing RA (3).

Also, the authors' choice of juvenile idiopathic arthritis (JIA) as an autoimmune disease in pediatric patients without any stratification is very questionable: some children diagnosed with JIA exhibit a nonautoimmune systemic type, the Still's disease or systemic-onset JIA, that is regarded more as an autoinflammatory syndrome unlike the other types of JIA that seem to be of an autoimmune origin (4).

In contrast, polyarticular rheumatoid factor-positive juvenile arthritis (considered as the childhood form of adult seropositive RA) represents one tenth of all JIA cases and recent works confirm the cornerstone role of the HLA DRB1 gene variants in the development of pediatric RF positive disease, just similar to the adult RA (3).

Screening for CD by HLA typing confers a high (more than 99%) negative predictive value, and patients with negative HLA (i.e., neither DQ2 nor DQ8) will quasi never present CD; thus, a logical strategy would first include an HLA screening test to avoid unnecessary CD repeated serology in genetically non-susceptible patients (5).

In conclusion, HLA genes are strongly associated with a myriad of autoimmune conditions, including CD and RA, and performing HLA first prior to serological analysis for CD could be a reasonable and probably a cost-effective and time-saving approach.

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Hakim Rahmoune, Nada Boutrid, Mounira Amrane, Belkacem Bioud

University Hospital of Setif, Setif 1 University, Pediatrics Setif, Setif, DZ, Algeria

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Address for Correspondence: Hakim Rahmoune

E-mail: rahmounehakim@gmail.com

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Author's Reply

Dear Editor,

Thank you for giving us this opportunity to answer to the Letter to the Editors by Rahmoune et al. (1), regarding our recent publication entitled "Screening of patients with juvenile idiopathic arthritis and those with rheumatoid arthritis for celiac disease in southwestern Iran Population" (2).

In reply to their comments, the etiology of JIA is unknown and in addition to different genetic factors e.g. various human leukocyte antigen (HLA) alleles, triggering environmental factors also play roles (3). On the other hand, the diagnosis of juvenile idiopathic arthritis (JIA) is based on clinical criteria and exclusion of other forms of arthritis (4).

Regarding to the guidelines produced by ESPGHAN, modified by BSPGHAN, HLA typing could be done in 'high risk' populations to rule out celiac disease (CD) (5,6). We believe submitted comment requires that patients with rheumatologic diseases consider as high risk population for CD.

HLA-DQ2 or HLA-DQ8 is necessary for disease development but is not sufficient for disease development; its estimated risk effect is only 36-53% (7). HLA-DQ2 and -DQ8 alleles have a strong negative predictive value but a very weak positive predictive value for diagnosing of CD patients. About 0-12% of European population with CD showed lack of both these alleles (8). Approximately 25-40% of white normal Caucasians have HLA-DQ2/DQ8 haplotype while only 1-2% of the whole population would have CD (9,10). The frequency of different alleles is variable in different populations. Accordingly, Khosravi et al. (11) reported that the frequency of DQ8 among Iranian normal population is even higher than those reported by European countries.

Moreover, patients with different types of JIA may have similar HLA-DQ2/DQ8 alleles but not involved with CD at the same time. However, further investigations are needed to find out the association between JIA categories and certain HLA alleles. The cost-effective of HLA typing for screening in all patients

with rheumatologic disease depends on the cost of genotyping and the frequency of CD in these patients.

We conclude that HLA genotyping is not a powerful indicator for the screening of CD in patients with rheumatologic diseases and needs to further investigations.

Mozhgan Moghtaderi¹, Shirin Farjadian^{1,2}, Elham Aflaki³, Naser Honar⁴, Soheila Alyasin¹, Maryam Babaei¹

¹Allergy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

²Department of Immunology, Shiraz University of Medical Sciences, Shiraz, Iran

³Department of Rheumatology, Shiraz University of Medical Sciences, Shiraz, Iran

⁴Department of gastroenterology, Shiraz University of Medical Sciences, Shiraz, Iran

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Address for Correspondence: Shirin Farjadian

E-mail: farjadsh@sums.ac.ir