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Carrier frequency of HLA-DQB1*02 allele in patients affected with celiac disease: A systematic review assessing the potential rationale of a targeted allelic genotyping as a first-line screening

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Abstract

BACKGROUND

Celiac Disease (CD) is an immune-mediated disorder, in which the HLA immunogenetic background (DQ2 and DQ8 heterodimers) and environmental trigger (gluten) are well established. Indeed, both factors are necessary – but not sufficient – to develop CD. However, it is very likely that CD is underdiagnosed in both developing and developed countries, due to several aspects, including the fact that a lot of patients present mild and/or atypical symptoms, without the presence of any recognized risk factors. Therefore, the possibility and feasibility of widened screening strategies to identify CD patients are debated.

AIM

To provide further evidence of the main epidemiological importance of HLA-DQB1*02 allele in the population of CD patients.

METHODS

We performed a systematic search in PubMed, EMBASE, Cochrane, Web of Science and Scopus databases, in order to produce a systematic review assessing the carrier frequency of HLA-DQB1*02 allele in the celiac population. Following the PRISMA guidelines, we retrieved all the original articles describing CD patients' HLA-DQB1 genotype in such a way that could allow to assess the HLA-DQB1*02 carrier frequency among CD patients, along with the evidence of the appropriate diagnostic work-up to achieve a correct and final diagnosis of CD.

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RESULTS

The final output of this systematic search in the medical literature consisted of 38 studies providing the appropriate HLA-DQB1 genotype information of the respective CD population. According to this systematic review, including a pool of 4945 HLA-DQ genotyped CD patients, the HLA-DQB1*02 carrier frequency was 94.94%, meaning that only 5.06% of CD patients were completely lacking this allelic variant. Interestingly, if we consider only the studies whereby the prevalence of CD patients affected with type 1 diabetes mellitus was supposed or clearly established to be very low, the frequency of non-HLA-DQB1*02 carriers among CD patients dropped to 3.65%.

CONCLUSION

Such a high carrier frequency of the HLA-DQB1*02 allelic variant (which is > 95%-96% in CD patients without risk factors, like type 1 diabetes mellitus comorbidity) might be exploited to consider a cost-effective and widened screening approach. If a sustainable strategy could be implemented through a low-cost targeted genetic test to detect the individual presence of HLA-DQB1*02 allele, an appropriate algorithm for serological screening in individuals resulting to be genetically predisposed to CD, might be considered.

Key words: Celiac Disease; Children; HLA-DQB1*02; DQ2 heterodimer; Screening; Systematic review

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Core tip: It is well known that HLA-DQ genotyping is useful to assess the individual susceptibility to Celiac Disease (CD) with very high - if not absolute - discriminatory power. Indeed, it is very unlikely that individuals who do not carry specific HLA-DQ alleles coding MHC-DQ2 and MHC-DQ8 heterodimers, may develop CD. Here, we aim at providing further evidence of the specific epidemiological importance of HLA-DQB1*02 allele in the population of CD patients. Briefly, based on 38 original articles that we included in this systematic review (which provided a pool of 4945 HLA-DQ genotyped CD patients, overall), we could find a very high carrier frequency of the HLA-DQB1*02 allelic variant. Indeed, > 95%-96% of CD patients resulted to carry at least one copy of the HLA-DQB1*02 allele. This knowledge might be exploited to consider a cost-effective and widened screening approach: If a sustainable strategy could be implemented through a low-cost targeted genetic test for CD, an appropriate algorithm for serological screening in individuals resulting to be genetically predisposed to CD, might be considered.

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INTRODUCTION

Celiac Disease (CD) is a systemic autoimmune disease triggered by the dietary intake of gluten in a minority of HLA genetically predisposed individuals^[1]. The world prevalence of CD in the general population is estimated to be around 1%, despite some geographical and ethnic variations. Recent epidemiological analyses suggested that the CD prevalence in children may be even greater than 1%^[2-4].

In the landscape of non-communicable autoimmune diseases, CD presents some peculiar etiological aspects. As mentioned, the necessary environmental trigger for CD is well-known, namely the dietary exposure to gluten, which can lead to CD in a minority of all individuals expressing DQ2 and/or DQ8 heterodimers. Respectively, these antigen-presenting molecules are encoded by the specific alleles DQA1*0501-DQB1*02 and DQA1*0301-DQB1*0302. In North America and Europe, the individuals

with such an immunogenetic predisposition to CD are 30%-40% of the general population, but only a minority of them (around 3%) will actually develop CD during life, despite a comparable exposure to gluten foods^[1,2].

However, CD is under-diagnosed, even in developed countries. Indeed, according to the so-called “celiac iceberg” epidemiological model, only a minority of cases (the emerged tip of the iceberg) are clinically well-evident, whereas most part (the iceberg mass under the water surface) have atypical and/or pauci-symptomatic clinical presentations, making CD diagnosis be under-considered and/or significantly delayed^[2,5]. Case-finding screening strategies helped to diagnose patients with some clinical and family risk factors, but the numerical impact of this approach in terms of number of new CD diagnoses, is quite limited. Indeed, most CD patients do not have any of these specific risk factors^[6,7]. Moreover, the onset age of CD is extremely variable, which means that the serological screening should be periodically repeated in at-risk individuals^[8].

Therefore, the debate about the opportunity to implement universal and/or widened screening strategies for CD is still open, especially in children, who may experience worse consequences than adults in case of missed or delayed CD diagnosis, due to their longer life expectancy and disease onset during the growth process^[6,8-11].

Of course, it is not sustainable to propose a universal CD serological screening; however, the identification of HLA genetically predisposed individuals through a cheap analytic method could exclude that larger part of individuals, who will never develop CD. Through this systematic review, we assessed the percentage of CD patients who are carriers of at least one copy of the HLA-DQB1*02 allele, specifically.

MATERIALS AND METHODS

Protocol

This systematic review was performed according to the PRISMA guidelines, as described in [Figure 1](#), which shows the complete PRISMA flow diagram. Through this systematic review, we aimed at evaluating the carrier frequency of the specific allelic variant HLA-DQB1*02 (coding the β chain of DQ2 heterodimer) in the population of patients diagnosed with CD.

Search strategy

We performed a systematic search in PubMed, EMBASE, Web of Science, Scopus and Cochrane databases, by retrieving all original articles (case series, case-control, cross-sectional, and retrospective cohort studies) describing CD patients' HLA-DQB1 genotype in detail. We searched all English, French, Spanish, Italian, German, Portuguese articles published up to September 2019.

In detail, an expert librarian performed the following searches in the following medical databases: (1) PubMed: ("celiac disease"[Mesh] OR "celiac disease" OR "coeliac disease" OR CD) AND ("HLA-DQ Antigens" [MeSH] OR "HLA-DQB1" OR "HLA-DQ2" OR "HLA-DQB1*02") AND ("alleles"[MeSH] OR allele* OR "Genes"[MeSH] OR gene OR genes OR variant* OR type* OR genotype[Mesh] OR genotyp*); (2) EMBASE: ('celiac disease'/exp OR 'celiac disease':ti,ab OR 'coeliac disease':ti,ab OR CD:ti,ab) AND ('HLA DQ antigen'/exp OR 'HLA-DQB1':ti,ab OR 'HLA-DQ2':ti,ab OR 'HLA-DQB1*02':ti,ab) AND ('allele'/exp OR allele*:ti,ab OR 'Gene'/exp OR gene:ti,ab OR genes:ti,ab OR variant*:ti,ab OR type*:ti,ab OR 'genotype'/exp OR genotyp*:ti,ab) AND [embase]/lim; (3) Web of Science: TS= ("celiac disease" OR "coeliac disease" OR CD) AND ("HLA-DQ Antigen*" OR "HLA-DQB1" OR "HLA-DQ2" OR "HLA-DQB1*02") AND (allele* OR gene OR genes OR variant* OR type* OR genotyp*); (4) Scopus: ("celiac disease" OR "coeliac disease" OR CD) AND ("HLA-DQ Antigen*" OR "HLA-DQB1" OR "HLA-DQ2" OR "HLA-DQB1*02") AND (allele* OR gene OR genes OR variant* OR type* OR genotyp*): ti,ab; and (5) Cochrane: ("celiac disease"[Mesh] OR "celiac disease":ti,ab,kw OR "coeliac disease":ti,ab,kw OR CD:ti,ab,kw) AND ("HLA-DQ Antigens" [MeSH] OR "HLA-DQB1":ti,ab,kw OR "HLA-DQ2":ti,ab,kw OR "HLA-DQB1*02":ti,ab,kw) AND ("alleles"[MeSH] OR allele*:ti,ab,kw OR "Genes"[MeSH] OR gene:ti,ab,kw OR genes:ti,ab,kw OR variant*:ti,ab,kw OR type*:ti,ab,kw OR genotype[Mesh] OR genotyp*:ti,ab,kw).

Data extraction

After a critical reading of the articles, two investigators independently performed data extraction according to the following inclusion criteria: Any original articles in which CD patients' HLA-DQB1 genotype was described in such a way and detail that the

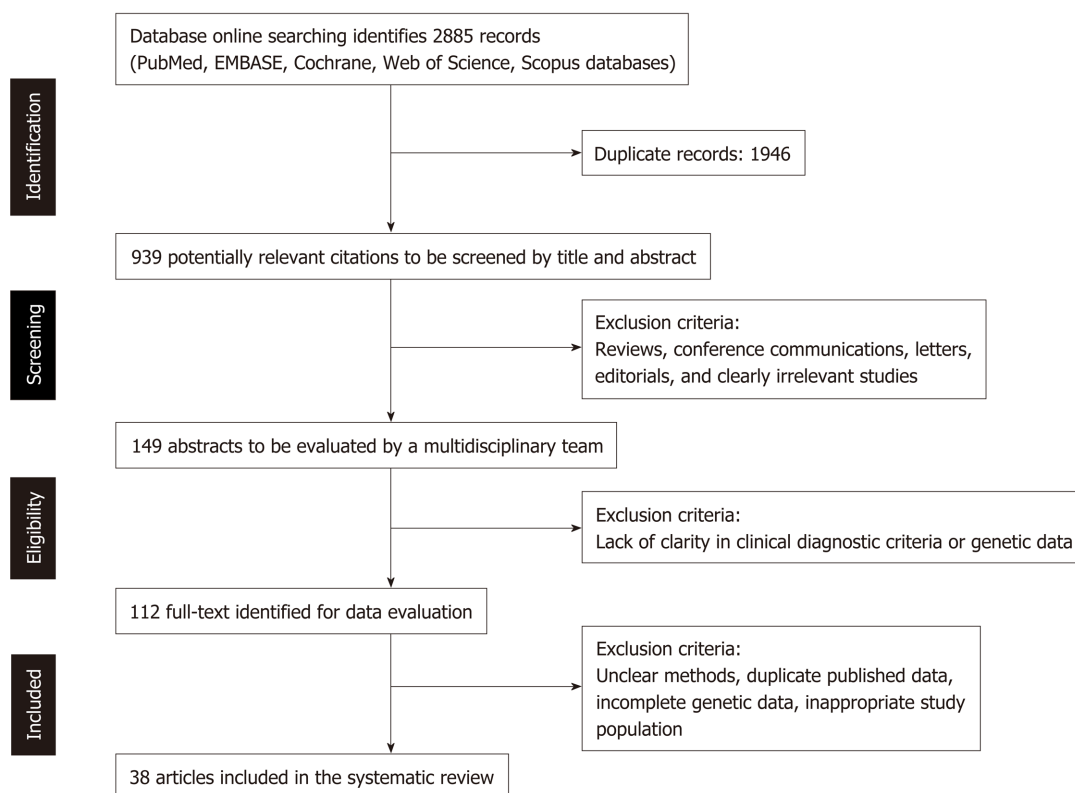


Figure 1 PRISMA flow-chart of the systematic review.

number of HLA-DQB1*02 carriers could be clearly defined within the total of the respective CD population. Only articles defining CD cases based on the typical histopathological findings, in addition to the specific serology, were considered. Most of them referred to specific diagnostic criteria, such as those set by Meeuwisse^[12], Walker-Smith *et al*^[13] and Husby *et al*^[14], according to the study period. In detail, the following items were extracted from each study: First author's last name, publication date, country of origin, numbers of male/female patients, patient's age range and HLA-DQB1 genotype (in terms of HLA-DQB1*02 carriers or not).

RESULTS

Study selection

The process of literature screening and selection according to the PRISMA guidelines, is summarized in Figure 1. As a result, 112 full-text articles have been identified as potentially eligible for this systematic review, because those included some information on the HLA genotype of the respective CD study population. However, as summarized in Table 1, only 38 studies were finally included in the present systematic review, because they only provided enough details of the HLA-DQB1 genotype to appropriately assess the HLA-DQB1*02 carrier frequency among CD patients, along with the evidence of the appropriate diagnostic work-up to achieve a correct and final diagnosis of CD^[15-56].

Indeed, as already mentioned, the aim of this systematic review is to assess the frequency of the HLA-DQB1*02 carriers (at least one copy) in the population of CD patients, including both children and adults. This final research output resulted from the analysis of all retrieved full-length original articles, describing the HLA-DQ genotype in CD patients with appropriate resolution and details. Indeed, in order to be considered, the papers had to provide information about the complete HLA-DQB1 genotype for each patient or group of patients affected with CD; or enough information to certainly establish how many CD patients were carriers of at least one copy of the HLA-DQB1*02 allele. Therefore, the original articles reporting only the HLA-DQ allelic frequencies in the study populations were necessarily excluded, since the endpoint is not to assess how frequent is HLA-DQB1*02 in the CD population, but how many of them are carrier of at least one copy of this specific allelic variant.

After this qualitative selection of papers (according to the required information

Table 1 Original articles selected and included in this systematic review

Ref.	Country	Total number of CD patients	¹ Age (yr)	Sex ratio (M/F)	HLA-DQB1*02 carriers	Non-HLA-DQB1*02 carriers	² Notes	Clinical Background	³ DM1 patients (< 3%)
Congia <i>et al</i> ^[15] , 1994	Italy	62	Group I (3.08 ± 2.05) Group II (5.7 ± 3.1)	24/38	61	1	HLA-DQ genotyping of patients previously diagnosed with CD (ESPGHAN criteria) ^[12]	Symptomatic patients classified as classic (group I) or atypical (group II) CD	+
Herrera <i>et al</i> ^[16] , 1994	Argentina	62	Children	12/50	51	2	HLA-DQ genotyping of 53 patients previously diagnosed with CD (ESPGHAN criteria) ^[12]	NA. Patients were diagnosed at the gastroenterology unit	?
Fernández-Arquero <i>et al</i> ^[17] , 1995	Spain	70	1.7 (NA)	NA	67	3	HLA-DQ genotyping of patients previously diagnosed with CD (ESPGHAN criteria) ^[12]	NA	?
Polvi <i>et al</i> ^[18] , 1996	Finland	49	Index cases: 8 (1-34) FDR: (NA)	25/24	49	0	HLA-DQ genotyping of patients previously diagnosed with CD (ESPGHAN criteria) ^[13]	35 patients diagnosed on a clinical basis (not specified) and 14 FDR diagnosed by case-finding screening	+
Catassi <i>et al</i> ^[19] , 2001	Algeria	79	8 (2-37)	33/44	68	1	HLA-DQ genotyping of 69 patients previously diagnosed with CD (confirmed with intestinal biopsy)	NA	?
Kaur <i>et al</i> ^[20] , 2002	India	35	8.42 (1.5-15.6)	18/17	35	0	HLA-DQ genotyping of patients previously diagnosed with CD (ESPGHAN criteria) ^[13]	Symptomatic patients with consistent GI or extra-GI symptoms	+
Zubillaga <i>et al</i> ^[21] , 2002	Spain	133	3.1 (0.5-18)	59/74	132	1	HLA-DQ genotyping of patients previously diagnosed with CD (ESPGHAN criteria) ^[13]	Patients with classic (71.4%) or non-classic (21.8%) CD. Nine asymptomatic patients diagnosed by case-finding screening (5 FRD, 3 DS, 1 DM1)	+

Mustalahti <i>et al</i> ^[22] , 2002	Finland	56	NA	18/38	49	0	HLA-DQ genotyping of symptomatic patients previously diagnosed with CD. Seven patients did not undergo the intestinal biopsy (and, thus, have been excluded)	Twenty-eight symptomatic patients with consistent GI or extra-GI symptoms; and 28 asymptomatic siblings by case-finding screening	+
Karinen <i>et al</i> ^[23] , 2006	Finland	54	43.7 ± 14.7 (1-79)	NA	53	1	HLA-DQ genotyping of patients previously diagnosed with CD (confirmed with intestinal biopsy)	NA (based on clinical symptoms)	+
Catassi <i>et al</i> ^[24] , 2007	United States	22	(19-83)	18/4	21	0	HLA-DQ genotyping in the context of a multicenter and prospective study (ESPGHAN criteria). HLA-DQ genotyping not done in only one of the 22 new CD diagnoses	Patients enrollment based on specific GI/extra-GI symptoms; or criteria for case-finding screening. Only 1 CD patients with DM1	?
Murray <i>et al</i> ^[25] , 2007	United States	84	(26-68)	35/49	80	4	HLA-DQ genotyping of patients previously diagnosed with CD (confirmed with intestinal biopsy)	Patients with consistent GI and/or extra-GI symptoms	+
Dezsofi <i>et al</i> ^[26] , 2008	Hungary	100	16 (3-40)	47/53	96	4	HLA-DQ genotyping of patients previously diagnosed with CD (ESPGHAN criteria) ^[13]	NA. Anyway, this group was declared as not affected with DM1	+
Megiorni <i>et al</i> ^[27] , 2009	Italy	437	5.7 (NA; only children)	NA	392	45	HLA-DQ genotyping of patients previously diagnosed with CD (ESPGHAN criteria) ^[13]	"Patients were divided on the basis of the clinical manifestations and gastrointestinal symptoms in typical, atypical, and silent forms". No further numerical information is provided and, thus, it cannot be estimated number of DM1 patients	?

Thomas <i>et al</i> ^[28] , 2009	United Kingdom	384	44 (16-84)	102/282	346	14	HLA-DQ genotyping available for 360 patients previously diagnosed with CD (confirmed with intestinal biopsy)	Patients with consistent GI and/or extra-GI symptoms. Only 7 patients were affected with DM1 as well	+
Martins <i>et al</i> ^[29] , 2010	Brazil	90	15.5 (1-55)	35/55	84	6	HLA-DQ genotyping of patients previously diagnosed with CD (ESPGHAN criteria) ^[13]	NA. Patients were diagnosed at the gastroenterology unit	?
Srivastava <i>et al</i> ^[30] , 2010	India	30	9.5 (3-17)	15/16	29	1	HLA-DQ genotyping of patients previously diagnosed with CD (ESPGHAN criteria) ^[13]	NA. Patients were diagnosed at the gastroenterology unit	?
El-Akawi <i>et al</i> ^[31] , 2010	Jordan	44	13.5 (1-39)	12/32	44	0	HLA-DQ genotyping available for 360 patients previously diagnosed with CD (confirmed with intestinal biopsy)	NA	?
Alarida <i>et al</i> ^[32] , 2010	Libya	31	9.2 (5-18)	9/22	29	2	HLA-DQ genotyping of patients diagnosed with CD (confirmed with intestinal biopsy)	School children undergone mass screening through anti-TG IgA	?
Castro-Antunes <i>et al</i> ^[33] , 2011	Brazil	73	NA (Children and adults)	37/36	60	13	HLA-DQ genotyping of patients previously diagnosed with CD (ESPGHAN criteria) ^[13] ; One patient did not undergo HLA analysis	Patients enrollment based on specific GI/extra-GI symptoms; or criteria for case-finding screening (15: FDR or DM1, whose proportion is not specified)	-
Mubarak <i>et al</i> ^[34] , 2012	the Netherlands	70	5.7 (NA; only children)	20/50	70	0	HLA-DQ genotyping of patients diagnosed with CD (confirmed with intestinal biopsy)	NA	?

Mubarak <i>et al</i> ^[34] , 2012	the Netherlands	85	6.2 (NA; only children)	25/60	81	4	HLA-DQ genotyping performed in all consecutive CD patients (confirmed with intestinal biopsy) at the time of the diagnosis	NA	?
Piccini <i>et al</i> ^[35] , 2012	Italy	89	NA (< 18)	27/62	81	8	HLA-DQ genotyping of patients previously diagnosed with CD (ESPGHAN criteria) ^[13]	NA	?
Krini <i>et al</i> ^[36] , 2012	Greece	118	NA (< 18)	NA	105	13	HLA-DQ genotyping of patients previously diagnosed with CD (ESPGHAN criteria) ^[13]	NA	?
Fernández-Cavada-Pollo <i>et al</i> ^[37] , 2013	Spain	355	NA (0.5-76; children: $n = 214$, adults: $n = 141$)	NA	335	20	HLA-DQ genotyping of patients previously diagnosed with CD (ESPGHAN criteria) ^[13]	Patients with consistent GI and/or extra-GI symptoms	+
Delgado <i>et al</i> ^[38] , 2014	Spain	91	6.9 (NA; only children)	23/68	88	3	HLA-DQ genotyping of patients previously diagnosed with CD (ESPGHAN criteria) ^[14]	Patients with consistent GI and/or extra-GI symptoms; or with an affected FDR	+
Cilleruelo <i>et al</i> ^[39] , 2014	Spain	513	NA (0.5-15)	NA	496	17	HLA-DQ genotyping in the context of a multicenter and prospective study (ESPGHAN criteria) ^[13]	Patients enrollment based on classic or atypical symptoms consistent with CD; or criteria for case-finding screening. DM1 is reported in 2.2% ($n = 11$) of CD patients	+
Stanković <i>et al</i> ^[40] , 2014	Serbia	73	12 (1-22)	19/54	71	2	HLA-DQ genotyping in the context of a multicenter and prospective study (ESPGHAN criteria) ^[13]	NA	?

Uenishi <i>et al</i> ^[41] , 2014	Brazil	5	NA (7-75)	1/4	5	0	HLA-DQ genotyping of patients diagnosed with CD (confirmed with intestinal biopsy)	FDR case-finding screening	+
Oliveira <i>et al</i> ^[42] , 2014	Portugal	39	1.8 (0.5-17)	18/21	37	1	HLA-DQ genotyping of patients previously diagnosed with CD (ESPGHAN criteria) ^[14] . One patient did not undergo HLA typing	Patients with consistent GI and/or extra-GI symptoms	+
Almeida <i>et al</i> ^[43] , 2016	Brazil	237	22 (1-75)	73/164	222	15	HLA-DQ genotyping of patients previously diagnosed with CD (ESPGHAN criteria) ^[13]	NA	?
Viken <i>et al</i> ^[44] , 2017	Norway	327	NA (Both children and adults)	NA	310	17	HLA-DQ genotyping of patients previously diagnosed with CD (ESPGHAN criteria) ^[13]	NA. Patients with DM1 have been excluded	+
Murad <i>et al</i> ^[45] , 2018	Syria	49	9.5 (1-18)	14/35	45	4	HLA-DQ genotyping of patients diagnosed with CD (confirmed with intestinal biopsy)	NA	?
Martínez-Ojinaga <i>et al</i> ^[46] , 2019	Spain	463	2.6 (0.6-14)	NA	454	9	HLA-DQ genotyping of patients previously diagnosed with CD (ESPGHAN criteria) ^[13,14]	Patients with consistent GI/extra-GI symptoms; or criteria for case-finding screening (not specified)	+
Poddighe <i>et al</i> ^[47] , 2019	Italy	184	NA (1-16)	70/114	179	5	HLA-DQ genotyping of 184 patients previously diagnosed with CD (ESPGHAN criteria) ^[13,14]	Patients with consistent GI (<i>n</i> = 75) or extra-GI (<i>n</i> = 69) symptoms; or criteria for case-finding screening (<i>n</i> = 40)	+

Kauma <i>et al</i> ^[48] , 2019	Finland	100	CD index cases (3.08 ± 2.05)	19/81	64	2	HLA-DQ genotyping was available for 132 patients diagnosed with CD (confirmed with intestinal biopsy) in the context of a research study considering pairs of siblings both affected with CD	Patients with consistent GI/extra-GI symptoms. There is only one patient with IDDM among CD index cases	+
Kauma <i>et al</i> ^[48] , 2019	Finland	100	CD siblings (5.7 ± 3.1)	37/63	59	7	See previous notes (same study/article)	Patients with consistent GI/extra-GI symptoms. There are 4 patients with DM1 among sibling CD cases	-
⁴ Lopes <i>et al</i> ^[49-51] , 2019	Brazil	7	7.5 (6-12)	NA	7	0	HLA-DQ genotyping of patients previously diagnosed with CD (ESPGHAN criteria) ^[13]	FDR case-finding screening. 7 CD cases out of 114 screened FDR	+
⁴ Bajor <i>et al</i> ^[52-54] , 2019	Hungary	105	31.2 (0.5-78)	32/73	97	8	HLA-DQ genotyping of patients diagnosed with CD (confirmed with intestinal biopsy)	Patients with consistent GI or extra-GI symptoms; or criteria for case-finding screening. No CD patients with DM1	+
Al-Hussaini <i>et al</i> ^[55] , 2019	Saudi Arabia	100	Group 1 (7 ± 3.2)	19/27	43	3	HLA-DQ genotyping of patients previously diagnosed with CD (ESPGHAN criteria) ^[13,14]	Patients with consistent GI or extra-GI symptoms (Group 1, <i>n</i> = 46). No data about comorbidity (<i>e.g.</i> , DM1)	+
Al-Hussaini <i>et al</i> ^[55] , 2019	Saudi Arabia	100	Group 2 (11.3 ± 2.5)	11/43	45	9	Refer to the previous notes (same study/article)	Patients diagnosed through a mass screening among school children (Group 2, <i>n</i> = 54). No data about comorbidity (<i>e.g.</i> , DM1)	-
Ramosaj-Morina <i>et al</i> ^[56] , 2019	Kosovo	60	5.5 (1.5-18)	20/40	55	5	HLA-DQ genotyping of patients previously diagnosed with CD (ESPGHAN criteria) ^[13,14]	NA	?

¹This column describe the age of the patients, in terms of mean ± SD or median (age range).

²This column describes the version of ESPGHAN guidelines that each article refers to, if provided: If a superscript number is present, it refers to the specific reference. Anyway, all articles included in this systematic review based the final celiac disease (CD) diagnosis on the duodenal biopsy, even if no specific guidelines are reported in the original article (in this case, no superscript number is present).

³This column assesses the presence of patients affected with type 1 diabetes mellitus (DM1) in the population of CD patients included in the respective article (+: it indicates that the study includes or is estimated to include < 3% of CD patients with DM1; ?: it indicates that the article provided no data to estimate the actual percentage of CD patients affected with DM1; -: it indicates that the study clearly indicates the number of CD patients with DM1 and those are at least 3% of the study cohort).

⁴These articles have been completed with additional references, in order to provide all necessary information about the HLA-DQB1*02 carrier status in the CD patients included in the respective studies. List of abbreviations. CD: Celiac disease; DM1: Type 1 diabetes mellitus; FDR: First degree relative; TG: Transglutaminase; DS: Down syndrome; GI: Gastrointestinal; NA: Not available.

about the HLA-DQ genotype), we excluded all researches including a genetically biased CD population, namely those with a CD population resulting from a preliminary HLA genetic screening. Moreover, according to our main focus on those individuals that are not considered to be at risk in the current clinical recommendations of CD case-finding screening strategies, we have included as far as possible only those articles in which the CD study population was not pre-selected through a specific (autoimmune) comorbidity and, in particular, type 1 diabetes mellitus (DM1). Indeed, it is clearly established that patients with DM1 must be followed-up for the potential CD onset, due to the common background of HLA-DQ genetic predisposition, whereas our analysis aims to provide a preliminary information that could be useful to design a potential strategy of mass screening for that majority of CD patients without any comorbidity, who are actually more likely to have a delayed diagnosis or remain undiagnosed.

Study quality

The quality of selected studies in terms of laboratory methods, methods description, statistical methodology and clinical features was assessed according to PRISMA standards and resulted to be appropriate.

Carriers frequency of the HLA-DQB1*02 carriers in the CD population

Based on the 38 selected articles (Table 1), a total of 5065 patients affected with CD were included in this systematic review, but the HLA-DQ genotyping was not available for 120 of them. Among 4945 HLA-DQ genotyped CD patients, 4695 resulted to be carriers of at least one copy of the HLA-DQB1*02 allele, whereas 250 carried different allelic variants at both HLA-DQB1 loci (HLA-DQB1*0302 or others). Therefore, the HLA-DQB1*02 carrier frequency resulted to be 94.94%, meaning that only 5.06% of CD population was completely lacking this allelic variant.

If only the CD pediatric population ($n = 2710$) is considered, similar figures are obtained: 94.69% of CD children carry the HLA-DQB1*02 allele, whereas only 5.31% is lacking a copy of this allelic variant.

Finally, if we consider only the studies whereby the prevalence of CD patients also affected with DM1 was supposed or clearly established to be very low (< 3%), the frequency of non-HLA-DQB1*02 carriers among CD patients dropped to 3.65%.

DISCUSSION

Through this systematic review, we demonstrate that around 95% of all patients affected with CD carry the HLA-DQB1*02 allele, at least in one copy. Importantly, this figure raises up to > 96%, if only CD patients without DM1 are considered. This finding may contribute to the implementation of a cost-effective and preliminary genetic test to assess the existence of CD predisposition, through the targeted qualitative analysis of HLA-DQB1*02 allelic presence. This knowledge might help to optimize the use of the serological analyses for CD and, at the same time, extend the screening possibility, at least in the pediatric population.

As described in the introduction, the HLA-DQ genetic background is fundamental to determine the predisposition to develop CD. The coupled alleles DQA1*0501-DQB1*02 and DQA1*0301-DQB1*0302 respectively code the class II MHC heterodimers DQ2 and DQ8, which have been demonstrated to be expressed in almost all patients affected with CD. Indeed, several studies confirmed the very high negative predictive value associated with the absence of any genotypes coding MHC-DQ2 and/or -DQ8^[1,2]. Practically, this specific knowledge can be applied to those patients with a suspect of CD, whenever the histopathological findings are not straightforward or the presence of concomitant diseases impairs the reliability of the serological tests for CD (*e.g.*, IgA deficiency, Common Variable Immunodeficiency, *et al*). Therefore, the high-resolution analysis of HLA-DQ loci resulted to be particularly

useful to refine and/or complete the diagnostic work-up for CD in some complex clinical cases, where the absence or presence of DQ2/DQ8 heterodimers can respectively rule out or support the final diagnosis of CD. Of course, the routine use of this expensive HLA analysis is completely inappropriate, because it can only assess the predisposition to develop CD (and not the actual presence of the disease). Indeed, large part of the general population (around 30%-40%, according to some geographical variability) possesses the appropriate HLA background to potentially develop CD^[14].

Several studies investigated the relationship between HLA-DQ genotype of CD patients and some clinical characteristics, histopathological features, age of disease onset and even the risk to develop CD^[21,25,46,52]. In this specific regard, several original articles reported a risk gradient for CD according to the particular HLA-DQ genotype: People with DQ2 homozygosity and DQ2/DQ8 double heterozygosity resulted to be have the highest risk and, importantly, a comparable risk of CD development was present in individuals carrying a double dose of HLA-DQB1*02 alleles, no matter the paired HLA-DQA1 alleles^[27,43,57]. Recently, two meta-analysis by our group supported this finding (OR > 5, compared to the general population) and further emphasized that also a single “dose” of HLA-DQB1*02 is associated with a relatively high risk (OR ≈ 4), as regards pediatric CD^[58-59]. In detail, we described that the HLA-DQB1*02 allele was present in 90%-95% of pediatric CD patients^[58] and, in our monocentric clinical experience, we found > 95% of CD children who were carriers of at least one copy of HLA-DQB1*02 allele^[50]. Therefore, we speculated that such a knowledge might be potentially used to consider the implementation of a widened screening strategy for CD in children, through a qualitative analysis targeting the HLA-DQB1*02 allele exclusively, as a first step, followed by the serological screening, to be applied to positive individuals only^[11,50].

In order to further consider this potential idea, we decided to quantitatively assess the actual presence of at least one copy of this allele among the CD population and, thus, understand how many patients would be lost if only the HLA-DQB1*02 positive individuals should undergo the serological screening for CD. If the loss of potential CD patients (those negative for HLA-DQB1*02 and, basically, carrying the DQ8 heterodimer only) could result acceptably low, then this approach might prevent the request (and the periodical re-testing) of any serological screening to most children. Anyway, the serological screening could be performed anytime in all those HLA-DQB1*02 negative patients developing symptoms consistent with CD, of course.

The present systematic review estimated that only 5% of the general CD population (including both adults and children) is devoid of HLA-DQB1*02 allele at all. If we could consider a mass screening looking for the carrier status of HLA-DQB1*02 only, we may identify 95% of CD predisposed patients and, concomitantly, rule out (with no more than a 5% error) the lifetime risk of disease in 60%-70% of the general population: These non-predisposed individuals should never receive the serological screening, unless any consistent clinical symptoms appear at some point of the existence without any other explanation.

Actually, according to this last consideration, that error may be even over-estimated. Indeed, if we consider only the articles describing cohorts of CD patients with a low prevalence of concomitant DM1 (Table 1), the percentage of non-HLA-DQB1*02 carriers decrease to 3.65%. Although the genetic predisposition to DM1 relies on both DQ2 and DQ8 heterodimers as well, this disease-genotype association for DM1 is less strong than in CD and, importantly, the DQ8 role and frequency resulted to be more relevant in patients with DM1, as evidenced by several studies. In a pediatric study from northwestern Mexico, including both CD and DM1 patients, Mejía-León *et al*^[60] showed that the HLA-DQ8 combinations with DQ2 or one of its alleles conferred the highest risk for the combination of both diseases. Smigoc Schweiger *et al*^[61] reported that DQ2 and DQ8 were present in 52% and 76% of DM1 patients in their Slovenian cohort, respectively. Mitchell *et al*^[62] described the DQ2/DQ8 analysis of 176 Scottish children with DM1: At least 50%-55% were DQ8 carriers and, importantly, it was not associated with DQ2 in around 20% of patients. In summary, the frequency of the homozygous HLA-DQ8 genotype and, in general, heterozygous HLA-DQ8 without any copy of HLA-DQB1*02 is expected to be higher in DM1 patients than in patients with CD.

Moreover, some studies included in this systematic review paired patients with CD only and cohorts of patients affected with DM1 and DM1+CD. In the study by Dezsöfi *et al*^[26], DQ2 negative patients affected with CD only were as few as 4%, whereas DQ2 negative patients were 10.6% in CD patients affected with DM1, and 35% in patients with DM1 only. Viken *et al*^[44] adopted a similar - but larger - study design to investigate the HLA class II alleles in Norwegian patients with coexisting DM1 and CD. Whereas DQ2 negative (all DQ8 homo- or heterozygous) patients do not exceed 5% in the CD-only cohort, they reach 30% in CD+DM1 patients and exceed this

percentage in patients with DM1 only. In the study by Kauma *et al*^[48], two groups of CD patients were considered (namely, CD index cases and siblings affected with CD) and the number of patients with concomitant DM1 was quite different (1/66 and 4/66, respectively): Interestingly, the frequency of non-HLA-DQB1*02 carriers was much more prevalent in the latter group (10.6% *vs* 3%), due to the higher HLA-DQB1*0302 (DQ8) allelic frequency in the DM1 subgroups of CD patients.

This systematic review is limited by the fact that only studies providing enough and appropriate information about the HLA-DQB1 genotype for each patient or groups of patients, could be included in our analyses. However, genetic pre-selection biases were carefully considered and, thus, avoided, in order to provide reliable findings for our analysis purposes.

A potential HLA-DQB1*02-targeted screening approach would be addressed to all those people that does not fall into the ESPGHAN groups at risk for CD (and, thus, receiving a periodical serology screening anyway), because this case-finding strategy leaves the majority of asymptomatic or pauci-symptomatic CD patients undiagnosed^[63,64]. Of course, it is not currently sustainable to propose a periodical serology screening for CD to the general population, even if limited to children, who may be more vulnerable to the negative long-term consequences of undiagnosed or belatedly diagnosed CD^[6]. If the HLA-DQB1*02 qualitative (present/not present) screening could be feasible after a rigorous economical and ethical assessment, it would allow to identify almost all CD-predisposed children, who should be around 30-40% of the general pediatric population. Therefore, 60-70% should not be eligible to receive the serology screening anymore, and a (periodic) serological test could be proposed to the HLA-DQB1*02 predisposed children only. At the end, this approach might also lead to some savings on the costs currently allocated to the CD serological screening, if we consider that these tests are often over-requested by patients and practitioners^[64-66].

The cost of CD diagnostic testing variably affects both patients and the healthcare system. The gold standard for diagnosis uses a combination of methods, which usually begins with a serological testing that includes immunoglobulin A (IgA) and tissue transglutaminase (TTG) IgA^[67]. A study (including 250 healthy children) from Europe reported that screening with serum TTG cost €5000 annually, rising to €11250 if anti-endomysium (EMA) testing was additionally performed on every child. Therefore, in Europe, each ELISA-based TTG test costs approximately €20, without considering the total IgA measurement^[68]. Identifying that majority of children who do not need the serological screening because they are not genetically predisposed to CD, might result in a significant reduction of costs sustained for CD serology. According to the findings of this systematic review, < 5% of CD-predisposed children may be lost through this screening approach and, if a patient should develop symptoms consistent with CD at any time during own life, the serology test could be performed anyway on a clinical basis.

Low-cost molecular methods for targeted and qualitative HLA-typing can be at the horizon. For instance, Verma *et al*^[69] recently proposed a rapid HLA-DQ typing method to identify subjects genetically susceptible to CD by performing a PCR through a kit containing all four HLA-DQ target alleles only. The cost of such an HLA-DQ genotyping was about €15 and, probably, may be further reduced by using reagents to detect the HLA-DQB1*02 allele only. Children would receive this test only one time and 30%-40% of them (those with positive results) could be identified as CD-predisposed and, then, eligible to serology screening at specific time points to be established.

In conclusion, a cost-effective and widened screening approach may be very helpful in both developed and developing countries, if a sustainable strategy could be implemented through a low-cost targeted genetic test for the HLA-DQB1*02 allelic presence, along with appropriate algorithms for serological screening in the individuals with this specific HLA-DQ predisposition to CD. Of course, specific pharmaco-economic studies and ethical considerations would be needed, before a specific strategy can be proposed.

ARTICLE HIGHLIGHTS

Research background

Celiac Disease (CD) is an immune-mediated disorder in which the HLA immunogenetic background (DQ2 and DQ8 heterodimers) is well known. This genetic factor is necessary – but not sufficient – to develop CD. Basically, almost 100% of CD patients are carriers of the aforementioned HLA-DQ background and several studies emphasized the main role of the HLA-DQB1*02 allele in such a genetic predisposition.

Research motivation

CD is underdiagnosed in both developing and developed countries, due to several aspects: Indeed, many patients present mild and/or atypical symptoms, without the presence of any recognized risk factors. Therefore, the possibility and feasibility of widened screening strategies to identify CD patients is still debated and this study might provide some additional insights, in order to find novel screening strategies.

Research objectives

Our aim was to define and assess the carrier frequency of the specific allelic variant HLA-DQB1*02 (coding the β chain of DQ2 heterodimer) in the population of patients diagnosed with CD.

Research methods

In order to achieve our aim, we performed a systematic review, according to the PRISMA guidelines, by retrieving all original articles (case series, case-control, cross-sectional, and retrospective cohort studies) describing CD patients' HLA-DQB1 genotype in detail. Any original articles, in which CD patients' HLA-DQB1 genotype was described in such a way and detail that the number of HLA-DQB1*02 carriers could be clearly defined (within the total of the respective CD population), were considered.

Research results

As a result of our literature search, 38 studies were finally included in the present systematic review, since those provided details of the HLA-DQB1 genotype in such a way that could allow to assess the HLA-DQB1*02 carrier frequency among CD patients. Among 4945 HLA-DQ genotyped CD patients, the HLA-DQB1*02 carrier frequency resulted to be 94.94%, meaning that only 5.06% of CD population was completely lacking this allelic variant. If only the CD pediatric population is considered, similar figures are obtained: Only 5.31% is lacking a copy of this allelic variant. Finally, if we consider only the studies whereby the prevalence of CD patients also affected with type 1 diabetes mellitus (DM1) was supposed or clearly established to be very low, the frequency of non-HLA-DQB1*02 carriers among CD patients dropped up to 3.65%.

Research conclusions

According to the findings of this systematic review, < 4%-5% of CD-predisposed children may be lost through a preliminary evaluation of the presence/absence of HLA-DQB1*02 allele, regardless of the presence of other HLA-DQB1 and HLA-DQA1 CD-predisposing alleles.

Research perspectives

A cost-effective and widened screening approach may be very helpful in both developed and developing countries, if a sustainable strategy could be implemented through a low-cost targeted genetic test for the HLA-DQB1*02 allelic presence, along with appropriate algorithms for serological screening in individuals resulting to be genetically predisposed to CD.

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