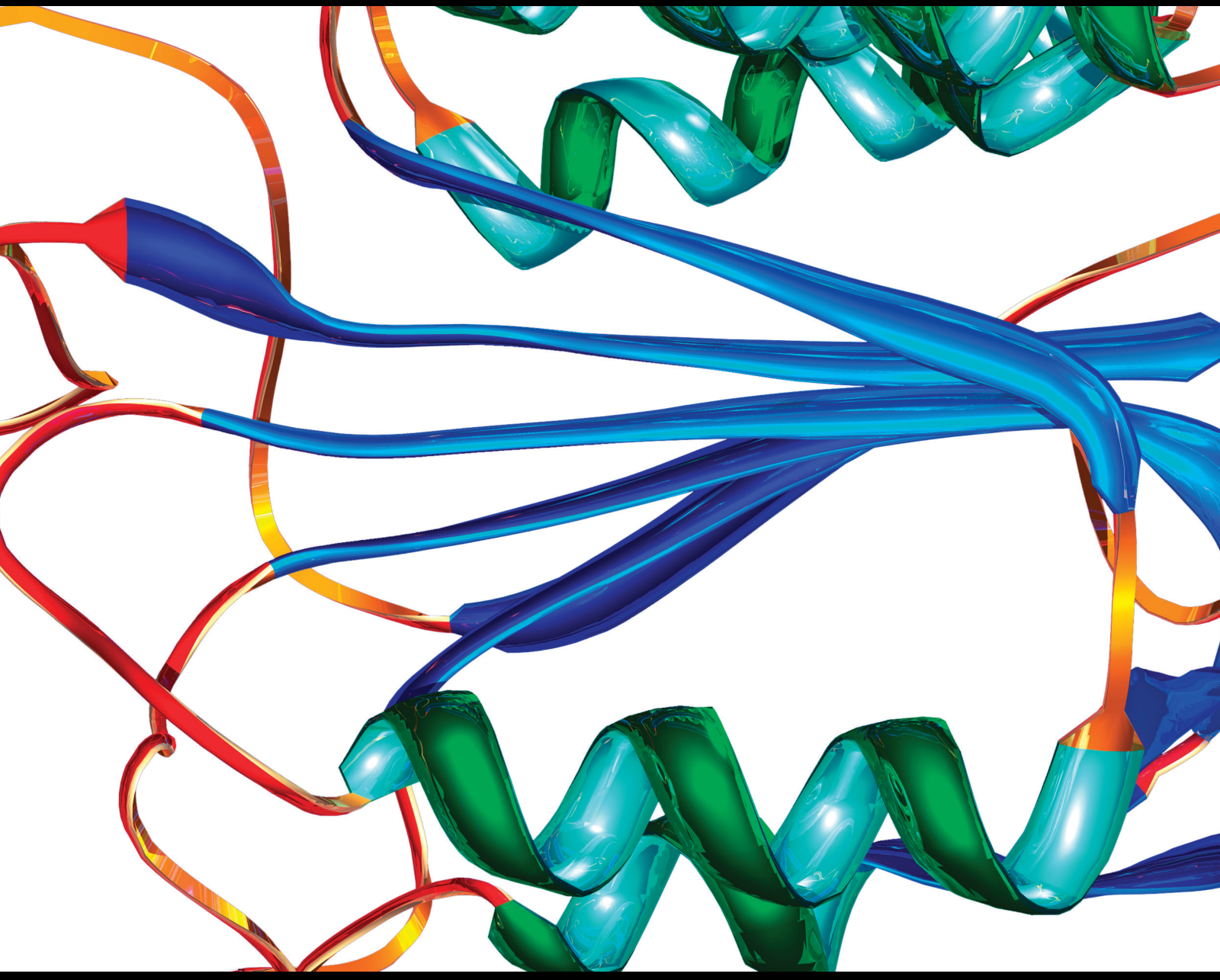
Disease Markers

Human Leukocyte Antigen (HLA) Markers in Immune-Mediated Diseases

Lead Guest Editor: Capittini Cristina
Guest Editors: Annalisa De Silvestri, Chiara Rebuffi, and Dimitri Poddighe



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Review Article

Global Meta-Analysis on the Association between Behcet Syndrome and Polymorphisms from the HLA Class I (A, B, and C) and Class II (DRB1, DQB1, and DPB1) Genes

Cristina Capittini,[1] **Chiara Rebuffi**,[2] **Marco Vincenzo Lenti**,[3] **Antonio Di Sabatino**,[3] **Carmine Tinelli**,[1] **Miryam Martinetti**,[4] **and Annalisa De Silvestri**[1]

[1]*Scientific Direction, IRCCS Policlinico San Matteo Foundation, Pavia, Italy*
[2]*IRCCS Istituto Giannina Gaslini, Scientific Direction, Italy*
[3]*First Department of Internal Medicine, San Matteo Hospital Foundation, University of Pavia, Pavia, Italy*
[4]*University of Pavia, Italy*

Correspondence should be addressed to Cristina Capittini; cristina.capittini@libero.it

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Behcet syndrome (BS) is a multisystemic perivasculitis whose genetic susceptibility is linked to HLA region. We first meta-analysed all HLA class I and II genes involved in BS susceptibility in all ethnic groups worldwide. We identified 1141 articles and finally included 31 case-control studies after multiple rounds of selection. We analysed frequencies for 24 HLA-A alleles (3 alleles for HLA-A∗26 at four digits), 50 HLA-B alleles (11 alleles for HLA-B∗51 at four digits), 15 HLA-C alleles, 16 HLA-DRB1 alleles, 6 HLA-DQB1 alleles, and 15 HLA-DPB1 alleles. We meta-analysed only HLA allelic frequencies from at least three studies; therefore, we investigated 21 alleles out of 140. Going from 7.00 to 1.6 OR, we found 11 class I alleles conferring risk for BS: B ∗ 51 : 08, B ∗ 51, B ∗ 51 : 01, B ∗ 51 : 02, DQB1 ∗ 03, A ∗ 26 : 01, Cw ∗ 14, Cw ∗ 15, Cw ∗ 16, B ∗ 15, and A ∗ 26. Overall, the studies included populations from Europe (Greece, Spain, Italy, Germany, and Ireland), Asia (Korea, China, China Han, and Thailand), Middle East (Israel, Saudi Arabia, and Iran), and Morocco (as no other North-African population was included). We collected a number of ethnical groups sufficient to conduct an ethnic-specific meta-analysis where Europeans showed 11.25 OR for B∗51:08 and Japan 3.50 OR for A ∗ 26 : 01. A remarkable result was that the most frequent HLA – B ∗ 51 two-digit alleles associated with BS were different among populations: HLA – B ∗ 51 : 08 in Europe, HLA – B ∗ 51 : 01 in Turkey, and HLA – B ∗ 51 : 02 in Japan. Overall, we discussed our real-world results with other imputation studies.

1. Introduction

Behcet syndrome (BS) is an autoinflammatory multisystemic neutrophilic perivasculitis characterized by recurrent inflammatory flares causing protean clinical manifestations [1].

Although the diagnosis is based only on clinical signs set by the International Criteria for Behçet's Disease (ICBD), from a genetic point of view, the disease has been historically linked first to human leukocyte antigen- (HLA-) B5 serotype, then to the HLA-B51 molecule/allele [2].

The geographic distribution of BS over the centuries shows a connection with specific populations, in particular those ones settled along the Silk Road, which is a network of trade routes connecting East Asia with Southern Europe passing through Middle East lands and East Africa [3].

The HLA region shows an extensive variation in the number of both genes and alleles. HLA genes are the most polymorphic ones in the human genome, and more than 8450 alleles have been discovered at the HLA-B locus. It is worldwide accepted that the extensive polymorphism of the HLA region is the result of selective pressures driven by the functional role of HLA molecules in the immune response. In fact, the highest degree of polymorphism is toward the peptide-binding region [4].

From 2009 onwards, seven genome-wide association studies (GWAS) in BS have been published. Overall, the following subjects were analysed in worldwide GWAS: 2576 Turkish BS with 2728 healthy controls; 975 Japanese BS with 1013 healthy controls; 336 Western Europeans, Middle Eastern, and Turkish BS with 5843 healthy ethnically matched controls; 379 Korean BS with 800 healthy controls; and 703 Chinese BS with 2110 healthy controls [5–11].

Fei and colleagues performed the first genome-wide association study in a cohort of 152 Turkish BS patients and 172 healthy ethnically matched controls [5]. They identified genetic associations between BS and the following single-nucleotide polymorphisms (SNPs): rs317711 (7p15-p14) in CPVL (carboxypeptidase vitellogenic-like, expressed on human macrophages and trimming peptides for antigen presentation); rs4936742 (11q24) in UBASH3B (ubiquitin-associated and SH3 domain containing B, promotes accumulation of T-cell receptors and EGFR on the cell surface); rs9513584 (13q32) in UBAC2 (ubiquitin-associated domain (UBA) containing 2, negatively regulates the canonical Wnt signaling pathway in the lymphocytes); and rs2061634 (9q22) in KIAA1529 and rs11206377 (1p34) in LOC100129342 that both do not have known function up to now [5]. Overall, although identifying novel candidate SNPs, they did not find the disease-causing polymorphisms.

Remmers and colleagues performed a GWAS with 311,459 SNPs in 1215 Turkish BS and 1278 controls. They confirmed the known association of BS with the HLA-B∗51 alleles and identified an association at rs1518111 (Intron Variant chr1:206771300) IL10 (interleukin-10, controls cytokine activity and the inflammatory response of macrophages). The rs1518111 A allele was associated with diminished mRNA expression and low protein production [6].

Mizuki and colleagues conducted a GWAS in a Japanese cohort of 612 BS patients and 740 controls. They identified two associations: rs12119179 (1p31.3) in IL23R-IL12RB2 and rs1554286 (1q32.1) in IL10 [7].

Hou and colleagues enrolled 149 Chinese BS patients and 951 controls in the initial GWAS and 554 patients and 1159 controls in the replication study. They identified that the susceptibility SNPs rs7574070, rs7572482, and rs897200 around 2q32.2-q32.3 were maps STAT4 (signal transducer and activator of transcription 4, involved in IL12 signaling). Carriers of rs897200 risk genotype AA showed increased expression of STAT4 and increased levels of IL17 messenger RNA and protein. Mainly, the clinical disease severity score was higher in carriers of the rs897200 risk genotype AA [8].

Lee and colleagues performed a GWAS in 379 Korean BD and 800 controls. A replication study was performed in 363 BD Japanese and 272 controls. They found a novel association of BD with SNIPs located in the GIMAP (GTPase IMAP family) cluster (7q36.1): the rs1608157 in a minor allele dominant model and the rs11769828 allele based. Furthermore, using a fine mapping study, they also identified an association with rs1522596 in GIMAP4 (GTPase IMAP family member 4), rs10266069 and rs10256482 in GIMAP2 (GTPase IMAP family member 2), and rs2286900 in GIMAP1 (GTPase IMAP family member 1). Overall, their results suggest that the GIMAP cluster may be involved in BS, even though without any verified connection [9].

Kirino and colleagues performed a GWAS of 779,465 SNPs with imputed genotypes in 1209 Turkish BS individuals and 1278 controls. They identified associations at CCR1 (C-C chemokine receptor type 1) (3p21.31), STAT4, and KLRC4 (NKG2-F type II integral membrane protein, a receptor for the recognition of MHC class I HLA-E molecules by NK cells) (12p13.2). They also found two SNPs in ERAP1 (endoplasmic reticulum aminopeptidase 1 that trims peptide for the generation of most HLA class I-binding peptides) (5q15). They also found evidence for interaction between HLA-B∗51 and ERAP1 [10].

Kappen and colleagues performed a GWAS on 336 Turkish, Western Europeans, and Middle Eastern BD cases and 5843 multiethnic birth cohort (from the Netherlands), using linear regression models corrected for population stratification. They identified SNPs mapping to the HLA region (6p21.33) [11].

Overall, all these GWAS showed a limited number of novel locus associations. In fact, also using the most advanced molecular techniques, the HLA region still remains the most involved in BS susceptibility, mostly in Turkish patients.

Another issue concerns the unequal distribution of BS among different ethnic groups, and the use of GWAS and bioinformatics tools in cohorts of mixed ethnicity does not seem to be an effective solution.

This is the first meta-analysis that considers all HLA class I and II genes involved in BS susceptibility in all ethnic groups worldwide.

2. Materials and Methods

This study followed the PRISMA guidelines [12].

2.1. Protocol. We drafted a protocol including: review question, eligibility criteria, primary and secondary endpoints, search strategy, methods for data extraction, study quality assessment, risk of bias assessment, strategy for data synthesis, and statistical methodology.

On April 29th 2019, the protocol entitled "Association between HLA class I (A, B, and C) and class II (DRB1, DQB1, and DPB1) polymorphisms and Behcet Syndrome: a meta-analysis" was published in the PROSPERO International prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPEROCRD42019130390).

2.2. Search Strategy. We performed a systematic search in PubMed, Embase, Web of Science, and Scopus databases, retrieving all publications (case-control, cross-sectional, and retrospective cohort studies or mixed design like nested case-control and cohort studies) on the association between HLA class I and II alleles and Behcet Syndrome (BS) in adult patients (>18 years).

We searched all English, Italian, Spanish, French, and Turkish-written articles published in up to December 2020. An expert librarian performed the search using the following MeSh terms: ("Behcet Syndrome") AND ("HLA" OR

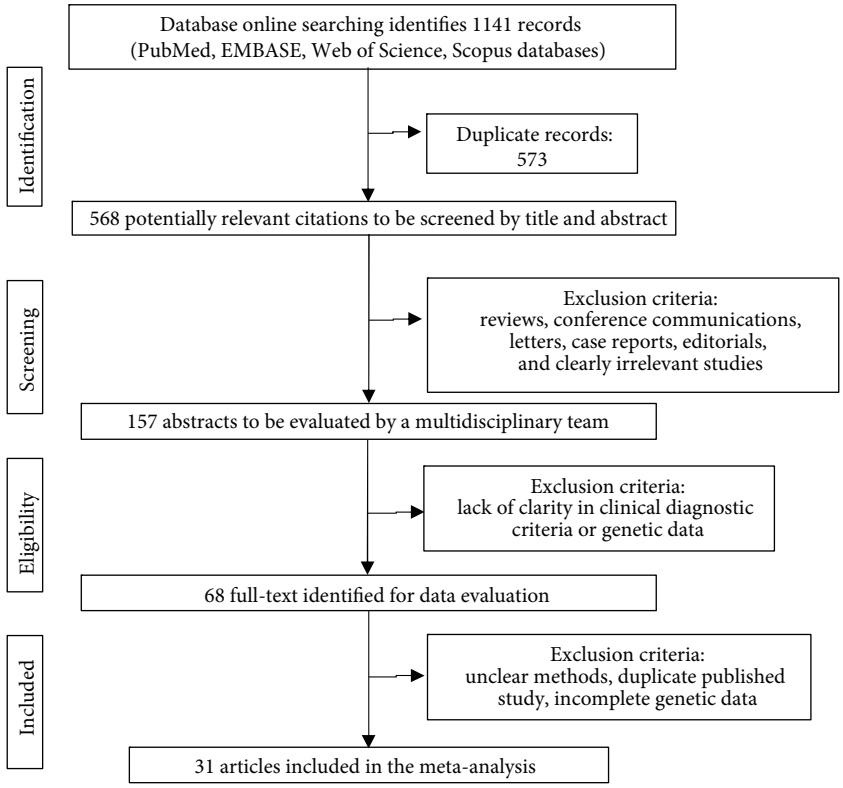

Figure 1: Flow diagram of the study following the PRISMA guidelines.

"human leukocyte antigen") AND ("polymorphism" OR "variant" OR "genotype" OR "allele").

Selection criteria were as follows:

(1) HLA class I and II genes and any A, B, C, DRB1, DQB1, DQA1, and DRB1 alleles or molecules

(2) BS diagnosed following the clinical criteria set by the following:

(i) International study group for Behcet's disease, Criteria for diagnosis of Behcet's disease, Lancet, 1990; 335: 1078-1080 [1]

(ii) International Team for the Revision of the International Criteria for Behcet's Disease. Evaluation of the International Criteria for Behcet's disease (ICBD) Clinical and Experimental Rheumatology. 2006; 24(supplement 42): p. S13 [13]

(iii) International Team for the Revision of the International Criteria for Behcet's Disease. Revision of the International Criteria for Behcet's Disease (ICBD) Clinical and Experimental Rheumatology. 2006; 24(supplement 42):S14–S15 [14]

(iv) International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD). The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. J Eur Acad Dermatol Venereol. 2014; 28(3):338-347 [15]

(v) Behcet's Disease Research Committee of Japan. Behcet's disease guide to the diagnosis of Behcet's disease (1972) Japanese Journal of Ophthalmology. 1974; 18 : 291–294 [16]

(vi) Mizushima Y. Recent research into Behcet's disease in Japan. International Journal of Tissue Reactions. 1988; 10(2):59–65 [17]

2.3. Risk of Bias Assessment. Following a quality assessment tool for genetic data (Quality Assessment of Genetic Studies in Systematic Reviews, QUAGENS) [18], proposed by our multidisciplinary panel (statisticians, clinical epidemiologists, immunogeneticists, clinicians, and meta-analysts), three pairs of reviewers (one for the clinical criteria, one for laboratory issues, and one for methodology tools) working independently and with adequate reliability verified the following aspects:

(1) Clinical data: the presence of spectrum disease biases, the possible enrollment of incident or prevalent cases, the inclusion of controls not selected from the same source population as the case-subjects, and the occurrence of differential participation in cases and controls

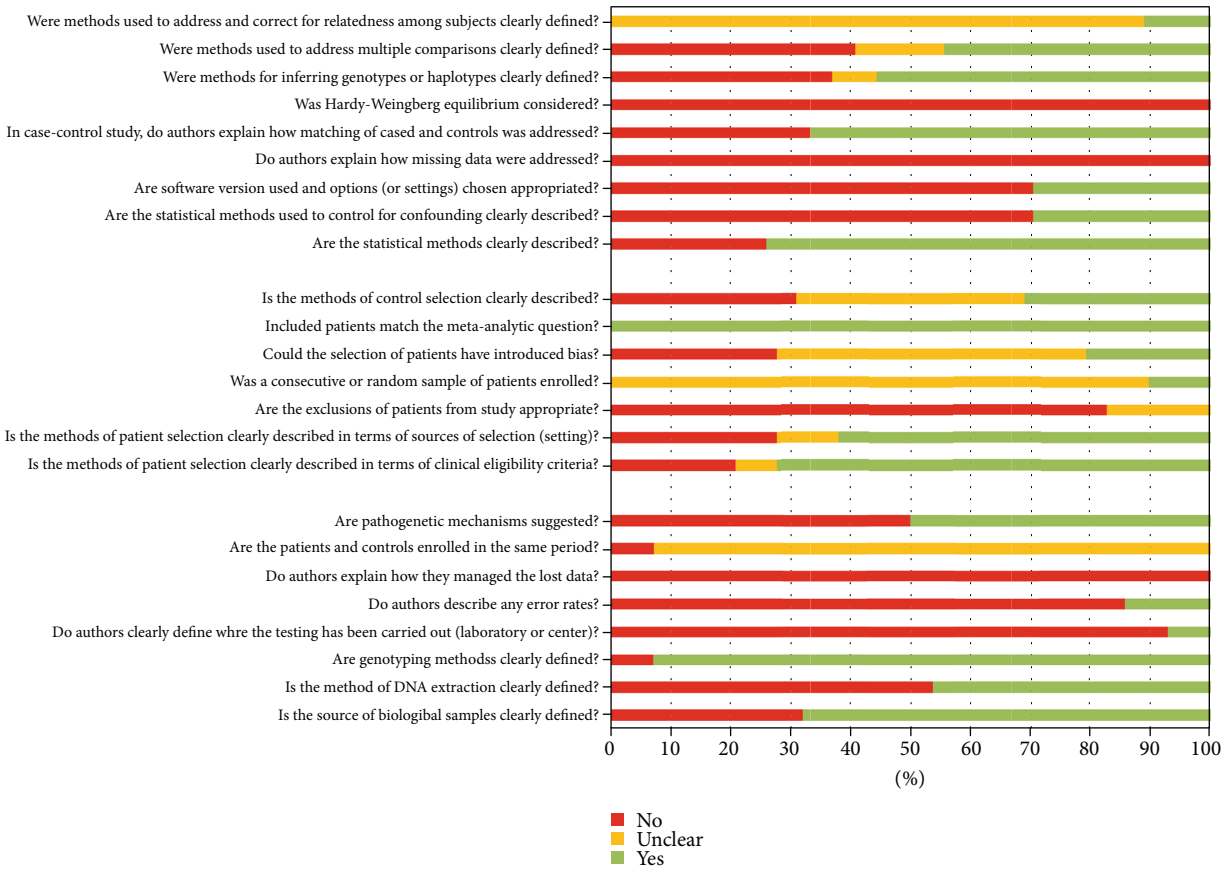

Figure 2: Quality assessment of studies. A series of questions were answered about laboratory methods, methodology, and clinical features. For each question, the answer is yes, no, or unclear.

(2) Laboratory issues: the misclassification of genotypes or serotypes (including the types and quality of samples, timing of collection, and the method used for HLA typing), the actual laboratory staff blinded to outcome, and the mention of quality controls

(3) Methodological features: the possible population stratification, the presence of multiple testing and prestudy odds of true finding (it would be useful interpreting the results in the context of how many polymorphisms have been studied), and the assessment of HW equilibrium in controls

Each question was answered as "yes," "no," or "unclear."

2.4. Data Extraction. After a critical reading of full-text articles, two investigators independently performed data extraction according to the selection criteria. The third participant was consulted for discussion to reach agreement concerning discrepancies. The following items were extracted from each study: first author's last name, publication date, country of origin, numbers of cases and controls, and typing method.

2.5. Data Synthesis and Meta-Analysis. STATA and MetaDiSc was used for statistical analysis to perform the meta-analysis. Heterogeneity was checked by the chi-squared test and the I-squared statistics [19]. Statistical heterogeneity was defined by a P value < 0.10 for the chi-squared test and an I – squared statistics $> 50\%$.

When there was no statistical evidence for heterogeneity in effect sizes, the fixed-effect model was used [20] to meta-analyze ORs or RRs in probands; when significant heterogeneity was identified, the random-effects model was used [21] to explore sources of significant heterogeneity. Also, a subgroup analysis stratified by ethnicity was performed.

3. Results

3.1. Study Characteristics and Quality Assessment. Following the search strategy, we identified 1141 articles, and after multiple rounds of selection, 68 articles were chosen for a full-text evaluation, of which 31 were included in the meta-analysis; 26 of them reported only the frequencies for the HLA – B $*$ 51 allele [22–47].

Figure 1 shows the flow diagram according to the PRISMA statement [12].

The quality of studies in terms of laboratory method description, statistical methodology, and clinical features is depicted in Figure 2.

3.2. Meta-Analysis on the Association between Behcet Syndrome Susceptibility and HLA Alleles from Class I (HLA-A, B, and C) and II (HLA-DRB1, DQB1, and DPB1) Genes. We collected HLA genetic data from 31 case-control studies

Table 1: HLA alleles involved in susceptibility/protection in Behcet syndrome (BS). Number of studies, number of BS patients and the ethnically matched controls, OR, and P values for each HLA allele included in the meta-analysis.

HLA	OR	P	N of BD	N of CTR	N of studies
B ∗ 51 : 08	7.00	<0.0001	503	962	8
B ∗ 51	5.81	<0.0001	1895	7799	26
B ∗ 51 : 01	5.54	<0.0001	988	1571	13
B ∗ 51 : 02	3.14	0.008	544	625	8
DQB1 ∗ 03	2.60	<0.0001	153	399	4
A ∗ 26 : 01	2.48	<0.0001	432	1705	4
Cw ∗ 14	2.35	0.001	279	260	4
Cw ∗ 15	2.34	0.001	279	260	4
Cw ∗ 16	2.23	0.014	279	260	4
B ∗ 15	1.79	0.004	433	5479	5
A ∗ 26	1.70	<0.0001	523	1781	7
B ∗ 35	0.69	0.008	691	5763	10
Cw ∗ 07	0.69	0.035	370	400	5
B ∗ 52	0.58	0.007	715	855	10
B ∗ 07	0.55	0.007	658	5698	9
Cw ∗ 03	0.55	0.002	237	302	3
A ∗ 33	0.53	<0.0001	661	1852	6
B ∗ 18	0.53	0.017	580	623	8
DRB1 ∗ 13	0.51	0.015	267	554	6
B ∗ 54	0.36	<0.0001	445	501	3
DQB1 ∗ 05	0.36	0.002	121	89	3

and retrieved frequencies for 24 HLA-A alleles and 3 alleles for HLA – A ∗ 26 at four digits, 50 HLA-B alleles and 11 alleles for HLA – B ∗ 51 at four digits, 15 HLA-C alleles, 16 HLA-DRB1 alleles, 6 HLA-DQB1 alleles, and 15 HLA-DPB1 alleles.

We evaluated the strength of the association between specific HLA alleles and the susceptibility to BS considering both predisposing and protective alleles. We meta-analysed only HLA allelic frequencies from at least three studies; therefore, we investigated only 21 alleles out of 140. Egger's regression test showed no evidence of publication bias (Egger's regression test P values > 0.1).

Table 1 lists the number of Behcet syndrome (BS) patients and the ethnically matched controls and the results of the meta-analyses carried out for each HLA allele to verify the correlation with susceptibility or protection to BS.

Going from 7.00 to 1.6 OR, we found 11 class I alleles conferring risk for BS: B ∗ 51 : 08, B ∗ 51, B ∗ 51 : 01, B ∗ 51 : 02, DQB1 ∗ 03, A ∗ 26 : 01, Cw ∗ 14, Cw ∗ 15, Cw ∗ 16, B ∗ 15, and A ∗ 26. On the contrary, going from 0.36 to 0.69, we found 11 class I alleles conferring a protective role to BS: B ∗ 54, DQB1 ∗ 05, DRB1 ∗ 13, A ∗ 33, B ∗ 18, Cw ∗ 03, B ∗ 07, B ∗ 52, B ∗ 35, and Cw ∗ 07 (Table 1).

Figure 3 depicts the forest plot for the HLA – B ∗ 51 allele, as it has been considered the most relevant genetic marker of the disease. All nationalities are listed on the left side for each included study.

3.3. Ethnicity-Specific Meta-Analysis. Overall, the studies included populations from Europe (Greece, Spain, Italy, Germany, and Ireland), Asia (Korea, China, China Han, and Thailand), Middle East (Israel, Saudi Arabia, and Iran), and Morocco (as no other North-African population was included).

Due to the higher frequency of BS among Japanese and Turkish people, we considered studies from Japanese and Turkish samples separately.

We collected a number of ethnical groups sufficient to conduct an ethnic-specific meta-analysis. Table 2 lists the OR from the HLA alleles for each ethnic-subgroup.

4. Discussion

Since 1978, the autoinflammatory Behcet syndrome (BS) has been linked to the HLA (human leukocyte antigen) genetic system. Using serotype tests, BS was first linked to the HLA-B5 molecule; later, using molecular testing, BS was linked to the HLA-B51 allele, which is still the strongest genetic BS marker [43].

Going from the HLA-B gene to the telomere region of chromosome 6, we have HLA-C and HLA-A genes, while going from the HLA-B gene to the centromere region, we have HLA class III genes (not included in this study) and HLA class II genes, such as HLA-DRB1, HLA-DQB1, and HLA-DPB1.

Here, for the first time, we meta-analysed the HLA class I and II genes involved in BS susceptibility in all ethnic worldwide groups, collecting HLA genetic data from 31 case-control studies and retrieved allelic frequencies for the HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1, and HLA-DPB1 genes.

Our data confirmed the HLA-B51 allele as the genetic HLA marker mostly associated with BS development all over the world among all different ethnic samples (OR 5.81, $P < 0.0001$) (Figure 3).

Notably, considering high-resolution two-digit analysis of the HLA-B51 allele, we observed that the HLA – B ∗ 51 : 08 variant showed the highest OR associated with BS (OR = 7.00, $P < 0.001$) (Table 1), followed by the two-digit HLA – B ∗ 51 : 01 and HLA – B ∗ 51 : 02 alleles (Table 1). Moreover, in our set of Europeans, the HLA – B ∗ 51 : 08 variant showed a 11.25 OR (Table 2).

Our results are in line with the work by Guasp and colleagues where high-resolution HLA – B ∗ 51 alleles were associated with epistasis with Hap10, a low-activity variant of ERAP1 (endoplasmic reticulum aminopeptidase 1), although its pathogenic role in BS is still unclear. In particular, the authors studied the effects of Hap10 on the HLA – B ∗ 51 peptidome aiming at distinguishing the different effects of this epistasis with high-resolution HLA – B ∗ 51 polymorphisms in BS [47]. The HLA – B ∗ 51 : 08 BS-associated peptidome expressed in a Hap10-positive cell line was compared with the HLA – B ∗ 51 : 01 peptidome from cells expressing more active ERAP1 variants. The authors

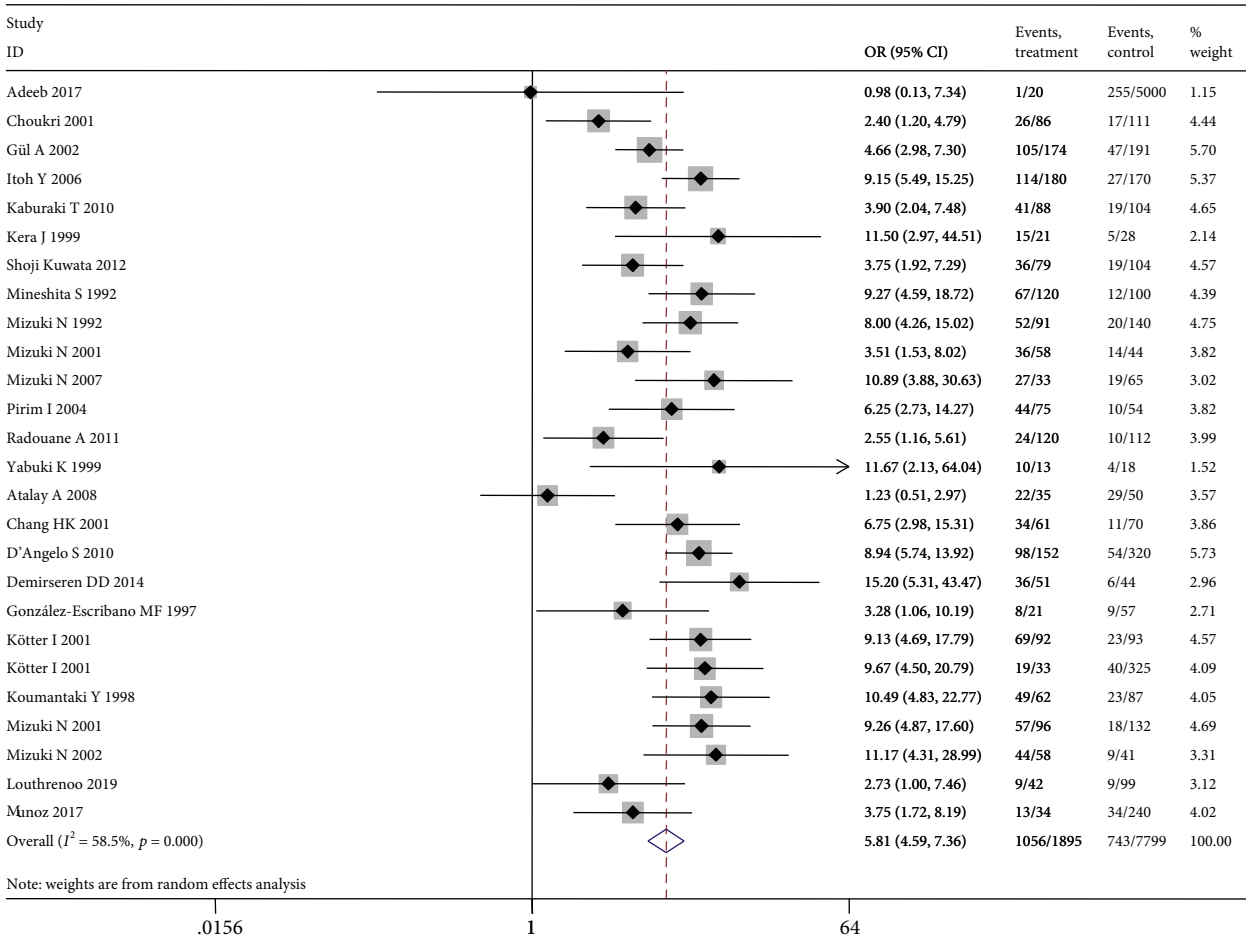

Figure 3: Forest plot from the meta-analysis for the HLA – B ∗ 51 allele.

Table 2: Meta-analysis for ethnic subgroups. Values are odds ratio (OR) and confidence interval (CI) in parentheses.

	Overall	Asia	Europe	Middle East	Morocco	Turkey	Japan
A ∗ 26 : 01	2.48 (1.8-3.5)	1.89 (1.2-2.8)					3.50 (2.1-5.8)
B ∗ 15	1.79 (1.2-2.7)		2.53 (0.8-7.6)		1.92 (1.0-3.5)	1.51 (0.8-2.7)	
B ∗ 51	6.07 (4.8-7.8)	5.99 (3.1-12)	8.22 (5.6-12)	5.03 (1.7-15)	2.46 (1.5-4.1)	5.97 (3.2-11)	6.44 (4.3-9.6)
B ∗ 51 : 01	5.57 (4.5-6.8)		5.16 (3.7-7.2)			5.98 (3.7-9.8)	6.12 (4.5-8.3)
B ∗ 51 : 02	3.14 (1.3-7.3)					2.91 (1.0-8.2)	5.39 (0.6-47)
B ∗ 51 : 08	7.00 (3.8-13)		11.25 (4.9-26)			3.96 (1.6-9.9)	
B ∗ 52	0.58 (0.4-0.9)	0.69 (0.2-2.7)	0.25 (0.1-5.4)	1.01 (0.2-4.8)	0.93 (0.2-4.7)	0.63 (0.3-1.5)	0.51 (0.3-0.9)
B ∗ 54	0.36 (0.2-0.6)					0.36 (0.1-9.0)	0.36 (0.2-0.6)

estimated that peptide-binding affinity and the HLA – B ∗ 51 : 08 peptidome generated longer peptides. They concluded that the BS-associated Hap10 haplotype induces changes in the repertoire of peptides presented to HLA – B ∗ 51 altering its antigen-presenting specificity and generating a lower affinity peptidome [45].

In our analysis we also observed an association with BS with the HLA – A ∗ 26 : 01 allele (HLA class I), the HLA

– Cw ∗ 14, HLA – Cw ∗ 15, and HLA – Cw ∗ 16 alleles (HLA class I) and with HLA – DQB1 ∗ 03 allele (HLA class II) (Table 1).

As to HLA – A ∗ 26 risk allele, our real-world data are a confirmation of the results imputed by Ombrello and colleagues, who inferred in 2014 the independent role of HLA-B51 and HLA-A26 in BS susceptibility by imputed MHC-region SNPs and also found HLA – B ∗ 15 to be an independent BS risk [48]. Moreover, we observed in a sample of 600 healthy subjects (personal unpublished data) that the HLA – A ∗ 26;B ∗ 51 haplotype was not the most frequent among HLA-A;B haplotypes (seventh place), thus further confirming with our real-world data the results by Ombrello and colleagues [48].

Regarding the association between BS and HLA-C alleles, Hughes and colleagues genotyped 8572 SNPs to infer classical HLA alleles in the HLA-A, HLA-B, HLA-C, HLA-DQA1, HLA-DQB1, and HLA-DRB1 genes from 2 ancestry groups, and they imputed data suggesting a robust HLA – B ∗ 51 association with BS and an additional independent genetic association with HLA – Cw ∗ 16 : 02 [49]. In agreement with imputed data by Hughes and colleagues, in our sample of 600 healthy Caucasian subjects (personal unpublished data), we observed that the HLA – B ∗ 51;Cw ∗ 15 and HLA – B ∗ 51;Cw ∗ 14 haplotypes were the second and third most frequent haplotypes, while the HLA – B ∗ 51 ;Cw ∗ 16 haplotype was the sixth place, thus supporting an independent role of HLA – B ∗ 51 and HLA – Cw ∗ 16 in BS.

Finally, we found that the HLA – DQB1 ∗ 03 was a BS risk allele (Table 1). To take into account all possible bias due to some linkage, we also observed in the same sample of 600 healthy subjects (personal unpublished data) that the frequency of the B ∗ 51;DQB1 ∗ 03 haplotype was the second place.

Piga and colleagues found the HLA-A2; Cw2; B ∗ 5101; DRB1 ∗ 11; DQA1 ∗ 05; DQB1 ∗ 03 haplotype in a subset of BS patients; however, the authors also found that the HLA-A2; Cw2; B ∗ 5101; DRB1 ∗ 04; DQA1 ∗ 03; DQB1 ∗ 03 haplotype was not associated with BS, thus highlighting the importance of studying extended HLA haplotypes rather than single alleles [50].

Finally, we considered populations from Europe (Greece, Spain, Italy, Germany, and Ireland), Asia (Korea, China, China Han, and Thailand), Middle-East (Israel, Saudi Arabia, and Iran), and Morocco (as no other North-African population was included), and we separately considered studies from Japanese and Turkish samples due to their higher frequency of BS.

In our study, the most remarkable result was that the most frequent HLA – B ∗ 51 two-digit alleles associated with BS were different in different populations: in Europe, the HLA – B ∗ 51 : 08 (OR 11.25 C.I. 4.9-26), in Turkey the HLA – B ∗ 51 : 01 (OR 5.98 C.I. 3.7-9.8), and in Japan the HLA – B ∗ 51 : 02 (OR 5.39 C.I. 0.6-47) (Table 2).

On the whole, HLA – B ∗ 51 is no more the only flag tagging a genetic marker to BS susceptibility; in fact, we observed that HLA-A and HLA-C variants also play an independent role in BS risk.

Beyond the distribution of HLA variants related to different ethnicities, we suggest that a further study ought to be focused on the correlation between these HLA – B ∗ 51 two-digit variants (in particular HLA – B ∗ 51 : 08) and clinical signs.

5. Conclusion

Despite remarkable different results on the distribution of the two-digit HLA – B ∗ 51 alleles associated with BS among populations, unfortunately, we could not find sufficient data on the association between HLA alleles and different clinical features. This comparison should be a further goal in order to find also clinically relevant differences in treatment response.

Data Availability

Data is available at http://www.crd.york.ac.uk/PROSPEROCRD42019130390

Conflicts of Interest

The authors declare no conflict of interests.

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Review Article

The Role of HLA in the Association between IgA Deficiency and Celiac Disease

Dimitri Poddighe[1,2] **and Cristina Capittini**[3]

[1]*School of Medicine, Nazarbayev University, Nur-Sultan, Kazakhstan*
[2]*Clinical Academic Department of Pediatrics, National Research Institute for Maternal and Child Health, University Medical Center, Nur-Sultan, Kazakhstan*
[3]*Clinical Epidemiology and Biometric Unit, Scientific Direction, IRCCS Policlinico San Matteo Foundation, Pavia, Italy*

Correspondence should be addressed to Dimitri Poddighe; dimitri.poddighe@nu.edu.kz

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Selective IgA deficiency (SIgAD) is the most frequent primary immune defect. Since SIgAD is not characterized by relevant infectious issues in most cases, it is often diagnosed during the diagnostic work up of several and different autoimmune disorders, which are associated with this primary immune defect. The genetic background of SIgAD is complex and three HLA haplotypes resulted to be more frequently associated with it; in detail, two of them include HLA-DQB1*02 allelic variants, which are essential predisposing factors to develop Celiac Disease (CD). Here, we discuss the evidence regarding the role of HLA in the etiopathogenesis of SIgAD and its association with CD. Actually, the HLA region seems to play a modest role in the genetic predisposition to SIgAD and we may speculate that the association with the HLA-DQB1*02 alleles (or haplotypes including them) could derive from its link with CD. Indeed, SIgAD and some related immunological alterations are likely to predispose to several autoimmune diseases (with and despite different HLA backgrounds), including CD, which is relatively common and directly associated with the HLA-DQB1*02 allelic variants coding the DQ2 heterodimer. Further and specific studies are needed to make final conclusions in this regard.

1. Introduction

Celiac disease (CD) is a gluten-related systemic immune-mediated disorder characterized by a very variable clinical expression, including both gastrointestinal and extra-gastrointestinal manifestations. It is diagnosed by the demonstration of specific autoantibodies, such as anti-tissue transglutaminase antibody and anti-endomysium antibody (which mainly belongs to the IgA isotype), along with the presence of atrophic (small bowel) enteropathy at the histopathological level [1–2].

Selective IgA deficiency (SIgAD) is the most common primary immune deficiency worldwide [3]. Notably, SIgAD is significantly associated with CD [1], which can make the diagnosis of the latter disease be more difficult, since the main serological markers are IgA autoantibodies. Indeed, the assessment of total serum IgA concomitantly to the serological screening for CD is a mandatory test in the suspicion of CD [4–5].

The HLA (human leukocyte antigen) system represents a relevant component of the genetic predisposition to autoimmunity in general, even if the implicated loci and allelic variants are different according to the specific autoimmune disorder [6]. Notably, several studies described a significant association between SIgAD and a few HLA haplotypes [7].

In general, primary immune deficiencies and autoimmunity are linked: several autoimmune diseases may complicate the same immune deficit [8]; moreover, the diagnosis of one autoimmune disorder increases the risk of developing other autoimmune diseases and/or different autoantibodies, as it happens in CD as well [9–10].

In this review, we discuss SIgAD and CD in the perspective of the HLA system, in order to analyze and assess the specific contribution of these loci in the etiology and

pathogenesis of the epidemiological association between these diseases.

2. Selective IgA Deficiency

Immunoglobulin A (IgA) is the most abundant antibody isotype in the human body, overall. Indeed, even though IgG have the highest blood concentration by far, IgA is also present in the mucosal surfaces of respiratory, intestinal, and genitourinary systems and then account for >70% of the total immunoglobulin pool [11]. Secretory IgA is dimeric and contributes to limit the epithelial adherence and penetration of endogenous bacteria through the mucosal surfaces, in addition to preventing infections by pathogenic microorganisms [12–13]. Serum IgA actually circulates in monomeric form, and its function in the systemic immune response has not been completely elucidated; however, it may have an immunomodulatory role, and form immune complexes with foreign antigens and clear them through the phagocytic system, but without activating the complement cascade [14–15]. However, it is clear that IgA plays a fundamental role in maintaining the homeostasis at the mucosal surfaces. In detail, secretory IgA is supposed to promote an immune exclusion by entrapping dietary antigens and microorganisms in the mucus, downregulate the expression of proinflammatory bacterial epitopes on commensal bacteria, and maintain the appropriate bacterial communities, especially in the gut [16].

Serum IgA levels are age-related: IgA is basically absent at birth and its concentration gradually increases during the pediatric age until reaching the adult levels during the adolescence (with normal levels ranging between 61 and 365 mg/dl) [17]. Total IgA deficiency is defined by serum IgA levels < 7 mg/dl. IgA deficiency is defined as partial when serum IgA levels are >7 mg/dl, but below the lower limit of the normal range according to the age [3, 17–18].

In infants and young children, low levels of serum IgA can be observed in the general context of transient hypogammaglobulinemia of infancy or their level can be selectively reduced due to delayed ontogeny of the immune system after birth in terms of IgA production. Therefore, a threshold of 4 years of age is commonly accepted to make a final diagnosis of SIgAD, which is then diagnosed in children older than 4 years, who show low IgA levels, but normal levels of IgG and IgM (in addition to normal vaccine responses and, importantly, after exclusion of secondary causes of hypogammaglobulinemia and T cell defects), even if it may be associated with IgG subclasses deficiency. Indeed, additional immunological abnormalities indicate different disorders, such as common variable immunodeficiency, secondary hypogammaglobulinemia, and unclassified antibody deficiencies [3, 19]. SIgAD is the most common immunodeficiency: worldwide, its prevalence is estimated to be around 1 : 400, despite significant variations according to the ethnicity. Indeed, it is considered more common in Caucasian populations (1 : 134–1 : 875), whereas the lowest prevalence is described in (East) Asian populations (China, 1 : 4100; Japan, 1 : 18500) [3, 20].

However, SIgAD prevalence studies are still lacking in many countries and, importantly, almost 90% of individuals with IgA deficiency have no specific symptoms or are completely asymptomatic. Overall, less than 30% of patients present with overt clinical manifestations of immunodeficiency, such as recurrent respiratory or gastrointestinal tract infections. Moreover, most patients with evident sinopulmonary infections (caused by encapsulated bacteria, such as *Haemophilus influenzae* and *Streptococcus pneumoniae*) are more likely to also have IgG subclass deficiency, especially IgG2 and IgG3 [3, 20–21]. However, an important clinical characteristic of SIgAD is its frequent association with allergy and autoimmunity, which may be the only "clinical manifestation" of this primary immune defect [19].

3. Allergy and Autoimmunity in Selective IgA Deficiency

A wide range of allergic disorders (including allergic conjunctivitis, rhinitis, urticaria, eczema, food allergy, and asthma) are often diagnosed in SIgAD patients [3, 22]. In a recent report, allergy was evidenced in 84% of patients with SIgAD (age range: 4–32 years) [23]. However, although a significant epidemiological association is supported by most studies on this topic, the actual prevalence of allergy among SIgAD patients is debated and may vary according to several factors, including the ethnical background [24]. In practice, allergic manifestations are the presenting symptoms in at least 25–50% of SIgAD patients [18, 21]. It is speculated that IgA deficiency by itself may bring to an increased prevalence of allergic disorders. Indeed, IgE concentrations are often increased in patients with SIgAD (and, in detail, atopic children), which may be due to a compensatory mechanism for a low secretory IgA level. Conversely, reduced IgA to gastrointestinal antigens were described in the mucosa of atopic children, which led to the hypothesis that gut luminal IgA deficiency may promote eczema and food allergy [25–27].

Similarly, a number of autoimmune diseases are associated with SIgAD. Indeed, according to different studies, at least 5–30% of SIgAD patients are diagnosed with concomitant autoimmune disorders, including idiopathic thrombocytopenic purpura, Graves' disease, autoimmune hemolytic anemia, type 1 diabetes mellitus, rheumatoid arthritis, thyroiditis, systemic lupus erythematosus (SLE), autoimmune hepatitis, and CD [21, 28–29].

The pathogenesis of this relationship between SIgAD and autoimmunity is not completely understood. However, considering the number of different autoimmune disorders linked to SIgAD, multiple mechanisms could be variably implicated to explain this link. Odineal et al. recently summarized the potential mechanisms involved in SIgAD-related autoimmunity [30]. As mentioned, serum IgA can bind antigens and clear them without activating the complement and, thus, limiting the inflammatory responses: accordingly, IgA deficit may predispose the immune system to become sensitized to autoantigens through mechanisms of molecular mimicry [7, 31]. In this regard, the concomitant deficit of mucosal IgA can expose the adaptive immune system to some pathogenic or commensal microorganisms,

promoting cellular and humoral responses that may cross-react with self-antigens [3, 30].

Moreover, SIgAD definitely recognizes a background of genetic predisposition, which is heterogenous and not well defined, yet. Mutations in transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI, TNFRSF13B) have been found in a subset of patients with IgA deficiency, but also in patients with common variable immunodeficiency (CVID). Even though the pathogenic role TACI mutations in SIgAD is controversial, it is clear that SIgAD can be associated with B cell, T cell, or cytokine abnormalities, which in turn may be implicated in the susceptibility to autoimmunity [30, 32–34].

Finally, the potential role of the HLA system was also considered, which may favor the development of SIgAD and concomitantly predispose to autoimmunity. As discussed later, specific HLA haplotypes resulted to be associated with SIgAD, and some HLA allelic variants also appeared to be independently associated with several autoimmune diseases, including SLE, CD and dermatitis herpetiformis, type I insulin-dependent diabetes, myasthenia gravis, and scleroderma [27, 30].

4. The HLA System in Selective IgA Deficiency

SIgAD usually occurs sporadically, but familial cases are described, even though no Mendelian inheritance pattern can be clearly defined. Indeed, the pedigrees of IgA-deficient-related individuals can be both autosomal recessive and autosomal dominant [18]. However, the genetic component appears to be relevant: the risk of developing SIgAD can be up to 50-fold higher in first-degree family members of patients with SIgAD compared to the general population. Moreover, this risk is 4-fold greater when the affected parent is the mother compared to the father [34–35]. In summary, SIgAD is likely to recognize a multifactorial etiology with a multigenic inheritance, where epigenetic aspects also play a role.

In such a not well-defined genetic background, the HLA loci have been investigated to understand if they could play a direct role in the pathogenesis of the SIgAD. Indeed, specific HLA haplotypes, including both class I and II HLA genes, were found to be more frequently represented in patients with SIgAD [3]. In detail, three major haplotypes resulted to be associated with SIgAD. HLA-B*0801/DRB1*03/DQB1*0201 was strongly associated with SIgAD in Caucasian populations, especially in Northern Europe (Sweden, Norway, Iceland, Finland, and Germany) [36–37]. Indeed, a 13% prevalence of SIgAD was initially reported in individuals who are homozygous for the HLA B8/DR3 haplotype, corresponding to an extremely high relative risk (RR = 77.8) [38]. However, eventual and larger studies evidenced a much more modest effect (RR = 11.1 for homozygosity, RR = 3.4 for heterozygosity) of this haplotype on the risk for SIgAD than what was previously suggested [39]. Interestingly, some authors suggested that the SIgAD association with this haplotype could have been actually due to a class III HLA region allele, based on a study comparing this haplotype across SIgAD patients from Sardinia (Italy), North Europe, Australia, and USA [38, 40–42]. A second haplotype (HLA-DRB1*0701/DQB1*0202) has been associated with SIgAD, again in Northern Europe, whereas a third haplotype (HLA-DRB1*0102, DQB1*0501) has been described more frequently in Southern Europe (Spain and Italy) and in Southwest Asia (in detail, Iran) [37, 43–45]. Conversely, some authors explained the low prevalence of SIgAD in Chinese population with the lower frequency of these disease-related haplotypes/alleles in China [46].

Despite the number of studies describing the increased frequency of these haplotypes in SIgAD patients, a recent genetic analysis showed that the influence of HLA in SIgAD genetics is likely to be modest, and suggested that other non-HLA genes and/or other epigenetic influences from environmental factors may be more relevant for the development of SIgAD. However, at the same time, these researchers observed that some specific HLA allelic variants may have some influence on the IgA serum levels. For instance, HLA-A*01 and HLA-B*14 alleles were associated with an increased IgAD risk and carriers resulted to have a significantly lower mean serum IgA concentration; conversely, HLA alleles B*07 and DRB1*15 were found to confer protection against SIgAD and, accordingly, carriers showed a significantly increased mean serum IgA concentration [47].

Notably, a recent study proposed an "epigenetic" role for the HLA region. A specific micro-RNA (miR-6891-5p), which is encoded by an intronic sequence inside HLA-B, resulted to regulate the expression of the immunoglobulin heavy chain alpha 1 and 2 (IGHA1 and IGHA2) genes at the post-transcriptional level, thus potentially affect IgA levels and contribute to the development of SIgAD [48].

Therefore, non-HLA loci seem to be as important as—or actually more than—HLA genes in the determination of the genetic susceptibility to SIgAD. Recent studies proposed associations with several non-HLA loci (e.g., CLEC16A, CTLA4, ICOS, FAS, IL6, and IL10), but conclusive evidence for their role in the pathogenesis of SIgAD is still lacking [49].

5. HLA-DQ Genes in Selective IgA Deficiency and Celiac Disease

The prevalence of SIgAD in CD patients is estimated to be around 1 : 40 (2–2.5%). Indeed, IgA levels should be systematically measured in patients diagnosed with CD and, even earlier, during the diagnostic work up for CD, considering the implication of low serum IgA levels for the reliability of CD serological tests based on the detection of specific IgA autoantibodies, such as anti-tTG, EMA, anti-gliadin antibody, and antibody to deamidated gliadin peptides [5, 50–51].

Similarly, CD is more frequent in children with SIgAD than in the general population and, actually, their association looks even stronger in this direction. Meini et al. reported a 7.7% prevalence in children affected with SIgAD [52]. In other studies, CD prevalence reached values of 15–30%, when SIgAD patients had been already diagnosed with other autoimmune disorders [53–54]. Another study by Lenhardt et al. confirmed a similar prevalence of CD (8.7%, $n = 11$ CD patients) in their cohort of 126 patients

with SIgAD (age range: 2–20 years). Additionally, these authors also described the HLA-DQ genetic background of these patients (DQ2 : $n = 9$, DQ8 : $n = 2$) [55].

As mentioned, the necessary environmental trigger for CD is well known, namely, the dietary exposure to gluten. Indeed, the pathogenesis of CD can be summarized as a gluten-induced activation of the adaptive immune response: gluten-reactive T lymphocytes are found in the lamina propria, which display a Th1 phenotype with a cytokine production dominated by IFN-γ, even though gliadin-specific Th17 cells and CD8+ T cells have been described, too [56].

A key finding supporting the central role of the adaptive immune response in CD pathogenesis is the constant association with specific HLA class II molecules. Indeed, CD is strongly associated with the carriage of DQ2 and/or DQ8 MHC heterodimers. In detail, almost 100% of CD patients carry the specific HLA alleles DQA1*0501-DQB1*02 (coding the DQ2 MHC heterodimer) and/or DQA1*0301-DQB1*0302 (coding the DQ8 MHC heterodimer) [1–2]. Among these HLA-DQ genes, recent studies showed the epidemiological importance of HLA-DQB1*02 alleles in the pediatric CD population [57–58]. In detail, our group highlighted that around or >95% of CD patients (and especially children) carry at least one copy of HLA-DQB1*02 variants [59–61]. However, such an HLA immunogenetic predisposition to CD is quite common in the general population (since 30%–40% of the individuals in Europe, North America, and other populations have been demonstrated to carry HLA-DQB1*02 alleles) and, thus, it is not sufficient for developing CD: indeed, only a minority of these MHC DQ2/DQ8 carriers (around 3%) actually develop CD during life, despite a comparable dietary exposure to gluten [62–64].

Interestingly, the main SIgAD-associated HLA haplotypes (HLA-B*0801/DRB1*03/DQB1*0201 and HLA-DRB1*0701/DQB1*0202) included the allelic variants coding for the MHC-DQ2 heterodimer. In detail, 45% of SIgAD patients have the haplotype 8.1 (HLA-A1, B8, DR3, and DQ2) compared to 16% of the general population [39, 65]. These HLA-DQ genes may concomitantly favor the development of SIgAD and predispose to CD. Even though the most recent evidence seems to reappraise the role of HLA in the pathogenesis of SIgAD, some correlations between a few HLA alleles and the level of serum IgA were actually observed, as previously explained [47].

Moreover, SIgAD could be a risk factor for CD regardless of the common HLA genetic background, through a series of immunopathogenic mechanisms. In detail, the low levels of secretory IgA to protect mucosal barriers could increase the exposure to pathogens and foreign antigens. Also, IgA may also play a regulatory role in the general homeostasis of the immune system: T regulatory cell deficiency was evidenced in 64% of SIgAD patients, and a number of alterations of (memory) B cells were described in these patients, all of which may potentially contribute to autoimmunity [66–69]. In this sense, SIgAD may favor the gluten sensitization in patients who are HLA-predisposed to mount an immune response against gluten-derived peptides. Then, the association between SIgAD and HLA haplotypes, including DQB1*02 alleles, may indirectly result from the pathogenetic role of SIgAD by itself in CD development, considering the greater prevalence of CD compared to other autoimmune disorders and its strong and direct association with HLA-DQB1*02 alleles.

Actually, the concept of SIgAD itself as a risk factor for CD and, in general, for autoimmune diseases, appears to be more likely than a general association between SIgAD and autoimmunity based on a common HLA genetic background, which should concomitantly promote both SIgAD and CD or other autoimmune disorders. Indeed, SIgAD has been described in numerous and very diverse autoimmune diseases, which differ in terms of immunopathogenic mechanisms and HLA predisposition [7, 30]. For instance, the prevalence of SIgAD among children with juvenile idiopathic arthritis (JIA), which is one of the most frequent rheumatic disorders in children, was reported to range from 1 to 4.35% (weighted average of 2.7%) [30], which is as significant as the frequency of SIgAD in CD patients. However, the HLA genetic predisposition in JIA is variable and not much linked to HLA-DQ alleles [70–71].

Moreover, the recent advances in the understanding of the interplay between gut microbiota and immune system suggested that IgA may contribute to the establishment and maintenance of beneficial interactions with the microbiota [72]. Therefore, SIgAD may affect the microbiota composition in the gut, and that may be an additional mechanism for such a strong association between SIgAD and CD, considering the growing evidence that supports the role of microbiota in the pathogenesis of several autoimmune disorders [30]. Very recently, spontaneous inflammation in the ileum (but not the other parts of the gastrointestinal tract) was described in IgA−/− mice, which was also associated with skewed intestinal microbiota composition [73]. In the human counterpart, Moll et al. described a perturbed microbiota in individuals affected with SIgAD, which resulted to be enriched of species with increased proinflammatory potential [74]. Previously, other studies suggested a critical and nonredundant role of IgA in controlling gut microbiota composition in humans and maintaining a diverse and stable gut microbial community, even though there were differences in terms of phyla-relative abundance and diversity in SIgAD patients across these studies [75–77].

Even though no clear "celiac" signature has been identified in the microbiome of CD patients, the lack of secretory IgA is likely to alter the mucosal homeostasis of the local microbiota along the gastrointestinal tract [78–80]. In the small bowel, the alterations of the gut microbiota could perturb the mucosal barrier, impair its permeability to antigens, and finally promote immunological phenomena of cross-reactivity [81–82]. Modifications of the salivary and gut microbiome could affect the digestion of nutrients (including gluten proteins) and, thus, their ability to be recognized by the immune system and trigger the immunopathological events leading to CD [83–84].

In this regard, it is also worth to mention that several studies highlighted the potential and direct role of HLA-DQB1 in driving the gut microbial colonization process. De Palma et al. first investigated a cohort of newborns and infants being first-degree relatives of CD patients: they were

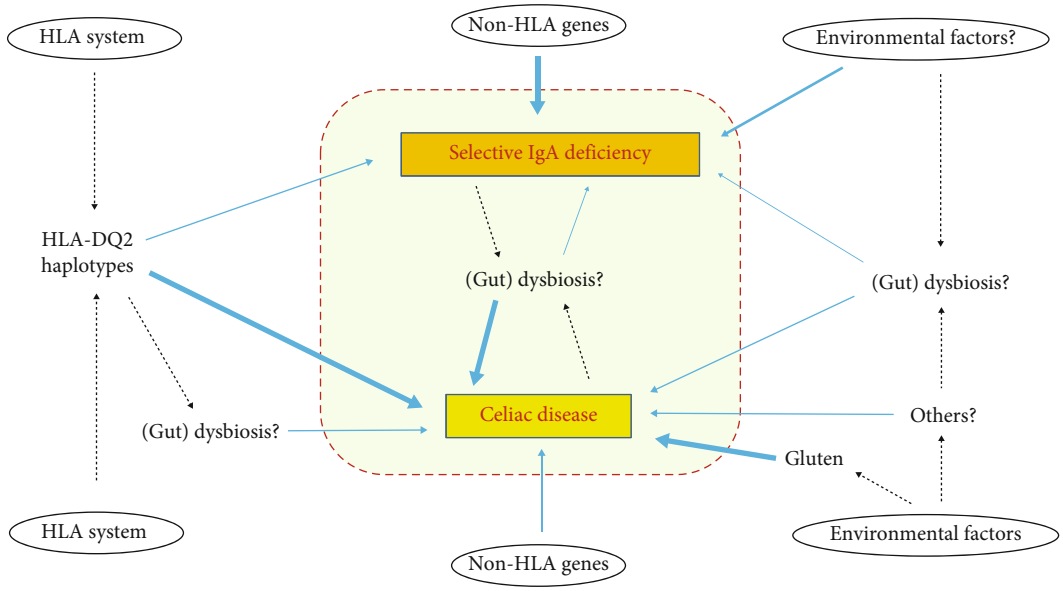

Figure 1: Schematic overview of the etiologic factors and aspects that are implicated in the pathogenesis of SIgAD and CD and may variably interplay to explain the association between these two diseases. HLA-DQ2 allelic variants are the necessary genetic background in CD patients and are also associated in part of SIgAD patients. Non-HLA genes (such as TACI, TNFRSF13B, CLEC16A, CTLA4, ICOS, FAS, IL-6, and IL-10) seems to mainly contribute to the genetic predisposition to SIgAD. A number of environmental factors are supposed to be implicated in both diseases; however, these are not well defined, except for dietary gluten exposure, which is a mandatory condition for developing CD. In addition to a direct role, all these factors might impact on the risk of developing CD and/or SIgAD by affecting (gut) microbiome; the potential dysbiosis associated with each disease might also contribute to pathogenesis of the other one.

analyzed for their HLA class II (DQA1 and DQB1) genotype. They found an association between higher proportions of the *Bacteroides-Prevotella* group and the high genetic risk group, basically represented by those individuals being DQB1*02 homozygous or double heterozygous for DQB1*02 and DQB1*0301. Total Gram-negative bacteria and *E. coli*, *Streptococcus-Lactococcus* spp., the *E. rectale-C. coccoides* group, *C. lituseburense*, and the *C. histolyticum* group proportions followed a similar trend when comparing the high- versus the low-genetic risk groups [85].

The larger PROFICEL study further supported this concept, in addition to investigating the concomitant contribution of breastfeeding. Indeed, specific features of fecal microbiota were associated with the genetic risk of developing CD, based on the HLA-DQ genotype, regardless of the milk-feeding type. In detail, the authors here described an increased number of *Bifidobacterium* spp. and *B. longum* in the microbiota of infants with the lowest genetic risk, whereas increased numbers of bacteria belonging to the *Staphylococcus* spp. and *B. fragilis* group were observed in infants with the highest genetic CD risk [86].

A more recent study also supported the hypothesis that a reduced abundance of *B. longum*, dependent on both genetic (also HLA-related) and environmental factors, may favor CD development. Additionally, this study evidenced a faster reduction in secretory IgA fecal levels in children who developed CD over time compared to healthy ones: this might suggest that a premature reduction of secretory IgA levels in the group of CD children could be related to shifts in bacterial community development, which in turn may affect the maturation of the mucosal immune functions, possibly increasing the risk for autoimmune dysfunctions as well [87]. Indeed, in a previous study, reduced IgA-coated bacteria in CD patients were associated with intestinal dysbiosis [88].

6. Conclusion

Several aspects and mechanisms can be theoretically implicated in the association between CD and SIgAD, including the HLA system (in detail, HLA-DQ2-related allelic variants), non-HLA genes, and environmental factors, as schematically summarized in Figure 1.

Despite a number of studies describing the association between a few HLA haplotypes and SIgAD, the most recent evidence suggested that the direct influence of HLA genes in its pathogenesis is likely to be modest, supporting a heterogeneous genetic background in the context of an etiologic and pathogenic picture where non-HLA genes and/or epigenetic influences from environmental factors play a relevant role for the development of SIgAD.

The two main haplotypes associated with SIgAD both include HLA-DQB1*02 alleles, which are known to be the genetic predisposing factor to CD in >90% of patients. The prevalence of SIgAD in CD patients is around 2–2.5%, whereas pediatric studies show up to 10% prevalence of CD in SIgAD patients. We may speculate that such an association between SIgAD and HLA-DQB1*02 could be driven by the higher population prevalence of CD compared to other SIgAD-associated immune diseases, all of which may recognize a direct pathogenic contribution from low blood/mucosal levels of IgA. However, some influence of HLA genes and, in detail, HLA-DQB1*02 alleles on the development of SIgAD

(maybe through microbiome alterations and related epigenetic/immunological mechanisms) cannot be definitely ruled out. Further and specific studies are needed to make final conclusions in this regard.

Conflicts of Interest

The authors have no conflict of interest to declare.

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