allergic disorders, such as asthma,[50] urticaria,[51] and food allergy.[52] Finally, HLA-DRB1*04/HLA-DRB1*04, HLA-DRB1*04/HLA-DRB1*14, and HLA-DRB1*04/HLA-DRB1*15 genotypes increase the risk of non-NMO MS, probably by interaction with DRB1*15 allele.[39]

In contrast, researches in Caucasian populations have come to the conclusion that the HLA-DRB1*03 allele is highly frequent in the NMO-IgG positive patients, while DPB1*05:01 is quite rare both in patients and healthy controls.[37] We should also highlight the negative association between HLA-DRB1*15:01 and NMO, which indicates a possible protective role.[53,54] In this point, the observation that NMO-IgG-positive and negative patients differ mostly in terms of gender and the association of other autoimmune diseases, could imply that HLA-DRB1*03 is associated with the NMO-IgG presence, but not with NMO *per se* and raise the question of whether NMO-IgG is epiphenomenon or pathogenic.[37] In reply to this, Arellano *et al*.[55] found that hAQP4281-330 is the dominant linear immunogenic determinant of hAQP4 in the context of HLADRB1*03:01. Within hAQP4281-330 are two dominant immunogenic determinants that induce differential Th phenotypes. In recent times, Asgari *et al*.[27,53] reported a high frequency of HLA-DQB1*04:02 in NMO patients, an allele described to be associated with autoimmune diseases such as primary biliary cirrhosis, type-1 diabetes and juvenile idiopathic arthritis, but he didn't show any correlation with HLA-DRB1*03.

In Brazilian cohorts, NMO patients present a high frequency of the HLA-DRB1*03 allele and extremely low frequency of the HLA-DRB1*15. In addition to this, the same study showed that HLA-DRB1*01 allele is associated with NMO and benign MS, a correlation that indicates that this allele may influence the outcome of these demyelinating disorders.[56] We would like to emphasize once more that HLA-DRB1*01 has a protective effect in anti-AQP4-negative MS patients in Japanese and Caucasians.[47,48] In African-Americans, none OSMS patient carries the HLA-DRB1*1501 allele,[57] while in Afro-Carribeans, NMO has been associated with the HLA-DRB1*03 allele [Table 2].[58]

DISCUSSION

To the best of our knowledge, this is the first review aiming at summarizing all the results concerning HLA allelic frequencies in NMO and NMOSD, worldwide. Apart from a detailed description of HLA allelic frequencies in all genotyped NMO ethnic groups, we created a workable table including all this information, for an easier reader's approach.

As a conclusion, it is clear that quite different HLA-alleles are correlated to NMO/NMOSD compared to MS patients, reflecting different underlying immunopathogenic mechanisms. Particularly, the well-established and most frequent HLA-DRB1*15:01 allele, associated with MS, plays rather a protective role for NMO. In addition, rare alleles, HLA-DRB1*12, like HLA-DRB1*01 and especially HLA-DRB1*09, play a core role in NMO risk or protection respectively and obviously in immonopathogenesis, in some ethnic groups. On the other hand, it is clear that different HLA alleles are associated with different ethnic groups, like Eastern NMO (association with the HLA-DPB1*05:01), which in turn are specifically associated with certain clinical/paraclinical features.

Moreover, the comorbidity of NMO with other autoimmune diseases is still under further investigation, although it seems that so far this comorbidity is highly reflected in HLA profile and anti-AQP4 antibody presence, suggesting common pathways in their immunopathogenesis.

In MS there is also comorbidity with other autoimmune diseases, like SLE, Hashimoto's thyroiditis, *etc*., However, this co-existence presumes rarer than in NMO, although more investigation studies are warranted to prove this notion.

In this paper, we tried to focus only on the HLA-immunogenetics of NMO, since the HLA molecule is a core component of the trimolecular complex, which is involved in antigen-presentation, as the first step of the immune response. However, as in MS, similarly in NMO, many non-MHC genes are candidates for the overall genetic burden. First, genes correlated to immune system and immunogenetics, namely IL-7 receptor polymorphisms,[59] IL-2 receptor a chain gene polymorphisms[60] and CD6, interferon regulatory factor 8 and tumor necrosis factor receptor superfamily[61] polymorphisms and secondly, the polymorphisms of the promoter region of cytochrome-P450-7A1 gene[62,63] and AQP4 genetic variations[64] are involved.

Regarding MS, it has been shown that specific alleles, in particular HLA-DRB1*04:01, HLA-DRB1*04:08 and HLA-DRB1*16:01, are associated with an increased risk of antiinterferon beta antibody development.[65] As a result, the poorer therapeutical outcome highligths the importance of the stratification of patients to responders and nonresponders, according to HLA-genotyping.[1] Similarly, Warabi *et al*.[66] concluded that patients carrying the NMO-specific HLA allele DPB1*05:01 showed a poor prognosis following interferon beta-1b treatment. The crucial role of the AQP4-antibodies in the pathogenesis of NMO has been

Table 2: The distribution of HLA alleles in different ethnic groups

Ethnic group	HLA	Alleles	Findings	References
Caucasians	HLA class I		No correlations found	[37]
	HLA-DR	HLA-DRB1*01	High frequency in NMO-IgG positive patients	[37]
		HLA-DRB1*0301	High frequency in NMO-IgG positive patients Not demonstrated association	[27,37,53]
		HLA-DRB1*1501	Not associated with NMO	[37,54]
	HLA-DQ	HLA-DQB1*0402	Higher frequency in NMO compared to HCs Increased in NMO	[27,53]
		HLA-DQA1*0102	High frequency in NMO-IgG negative patients No significant differences noticed	[37,53]
	HLA-DP	HLA-DPB1*0501	Rare allele in Caucasians. No correlations found	[37]
Japanese-Chinese	HLA class I		No data	No data
	HLA-DR	HLA-DRB1*01	Protective effect on anti-AQP4 negative MS patients	[39]
		HLA-DRB1*04	Increases the risk of non-NMO MS, especially HLA-DRB1*04/04, 04/14, 04/15	[39]
		HLA-DRB1*09	Protective factor for anti-AQP4 negative MS, especially HLA-DRB1*09/15. Decreased the risk of anti-AQP4 positive MS in monovariate studies NMO/NMOSD patients showed a significantly lower frequency	[39,40]
		HLA-DRB1*12	Increased frequency in anti-AQP4 positive MS, especially HLA-DRB1*12/15	[39]
		HLA-DRB1*15	Common in MS patients. Probable in correlation with *04, *09, *12 alleles Association with common MS	[12,38,39]
		HLA-DRB1*1602	Higher frequency in anti-AQP4 positive patients in Han Chinese Risk factor only for anti-AQP4 positive NMO/NMOSD	[40,41]
	HLA-DP	HLA-DPB1*0501	Strong positive association with OSMS Associated with opticospinal MS Increased frequency in anti-AQP4 positive patients Risk factor only for anti-AQP4 positive NMO/NMOSD patients Susceptibility in anti-AQP4 positive NMO in Han Chinese Important role in the development of MS in general, but not in OSMS. The strong association of DPB1*0501 with OSMS may be due to the over-representation of the DPB1*0301 allele among individuals in the non-OSMS	[12,38,40-46]
		HLA-DPB1*0301	The most strongly associated allele with conventional MS, complete lack in OSMS Possible protection against the development of OSMS	[38,44]
Brazilians	HLA-class I		No data	No data
	HLA-DR	HLA-DRB1*01	High frequency in NMO	[56]
		HLA-DRB1*03	High frequency in NMO	[56]
		HLA-DRB1*15	Low frequency in NMO, possible protective role	[56]
African-Americans and Afro-Caribbeans	HLA class I		No data	No data
	HLA-DR	HLA-DRB1*1501	None OSMS African-American patient	[57,58]
		HLA-DRB1*03	Highly noticed in NMO Afro-Caribbean patients	

HLA: human leukocyte antigens; NMO: neuromyelitis optica; IgG: immunoglobulin G; MS: multiple sclerosis; OSMS: opticospinal multiple sclerosis; AQP4: aquaporin-4; NMOSD: NMO-spectrum diseases

in our consideration for a few years only, in contrast to the 30 years of worldwide research regarding MS and HLA. We expect this to be the new field of extensive future research, in correlation with the accumulated knowledge on the pathogenesis of NMO.

Finally, the HLA profile in a patient with a CNS demyelinating disease tends to highlight different backgrounds in immunopathogenesis and clinical phenotype, components which are very important in the diagnosis and disease therapeutic decision making, which is strongly requested. To this direction and in order to use HLA alleles, as a biomarker, in patients' early stratification, more HLA-genotyping studies are needed, in different ethnic groups, in order to clarify, replicate or even expand the already existed results.

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