

# Human histocompatibility antigens and Dermatology: from research to clinical practice\*

## *Antígenos de histocompatibilidade humanos e dermatologia: da pesquisa para a prática clínica\**

Crésio Alves<sup>1</sup>  
Cândida Oliveira Alves<sup>4</sup>

Nara Vieira<sup>2</sup>  
Maria Betânia P. Toralles<sup>5</sup>

Isadora Meyer<sup>3</sup>  
Maria de Fátima S. P. Oliveira<sup>6</sup>

**Abstract:** The participation of the human histocompatibility system (HLA: human leukocyte antigens) in the pathogenesis of autoimmune diseases is well known. Situated on the short arm of chromosome 6, the HLA system is very polymorphic and has the capacity to confer susceptibility or resistance to different diseases. In Dermatology, this system has an important participation in the pathogenesis and natural course of various diseases. The strength and type of association differ with conditions and sometimes with the ethnic-racial group studied. The discovery of molecular methods to typify HLA alleles and recent updates in its nomenclature has contributed to a better understanding of this system. Unfortunately, this information has not been adequately transmitted in the literature, hindering identification of the association of the HLA with skin diseases. In this review, some aspects of the HLA system are discussed, such as methods of detection, nomenclature and association with vitiligo, pemphigus, psoriasis, lupus erythematosus, scabies, cutaneous leishmaniasis, leprosy, paracoccidioidomycosis and atopic dermatitis.

**Keywords:** HLA antigens; Major histocompatibility complex; Skin diseases

**Resumo:** A participação do sistema de histocompatibilidade humano (HLA: human leukocyte antigens) na patogênese das doenças auto-imunes é bem conhecida. Situado no braço curto do cromossomo 6, o sistema HLA se destaca por seu polimorfismo e por sua capacidade de conferir susceptibilidade ou proteção a diferentes enfermidades. Em Dermatologia, esse sistema desempenha papel importante na patogenia e história natural de várias doenças. A força e o tipo de associação variam com a dermatose e, algumas vezes, com o grupo étnico-racial estudado. O surgimento de métodos moleculares para tipificação dos alelos HLA e as recentes atualizações de sua nomenclatura têm contribuído para o melhor entendimento desse sistema. Infelizmente, essas informações não têm sido veiculadas de maneira adequada na literatura clínica, o que dificulta o entendimento da associação do HLA com as doenças cutâneas. Nesta revisão, são discutidos alguns aspectos do sistema HLA, métodos de detecção, nomenclatura e sua associação com vitiligo, pênfigo, psoríase, lúpus eritematoso, escabiose, leishmaniose cutânea, hanseníase, paracoccidioidomicose e dermatite atópica.

**Palavras-chave:** Antígenos HLA; Complexo principal de histocompatibilidade; Dermatopatias

\* Work done at Faculdade de Medicina, Universidade Federal da Bahia - UFBA - Salvador (BA), Brazil.  
Conflict of interests: None

<sup>1</sup> Lecturer of Pediatrics, Faculdade de Medicina, Universidade Federal da Bahia – UFBA. Coordinator of the Specialized Endocrinology Laboratory, Hospital Universitário Professor Edgard Santos - Salvador (BA), Brazil.

<sup>2</sup> Medical student, Escola Bahiana de Medicina e Saúde Pública – EBMS - Salvador (BA), Brazil.

<sup>3</sup> Medical student, Universidade Federal da Bahia – UFBA - Salvador (BA), Brazil.

<sup>4</sup> Medical student, Universidade Federal da Bahia – UFBA - Salvador (BA), Brazil.

<sup>5</sup> Lecturer of Genetics, Faculdade de Medicina, Universidade Federal da Bahia – UFBA. Director of the Medical Genetics Laboratory, Hospital Universitário Professor Edgard Santos - Salvador (BA), Brazil.

<sup>6</sup> Master's degree in Internal Medicine, Faculdade de Medicina, Universidade Federal da Bahia – UFBA. M.D., Dermatology Service, Hospital Universitário Professor Edgard Santos - Salvador (BA), Brazil.

## INTRODUCTION

Major histocompatibility complex (MHC) represents a gene region that codifies the histocompatibility molecules responsible for antigen presentation to the immune system.<sup>1</sup> In humans, MHC is located in the short arm of chromosome 6 and it is called HLA (human leukocyte antigens) system.<sup>1,3</sup> The genes in the HLA system have been classified into three regions: class I, II and III.<sup>1,2,4,5</sup> Class I comprises HLA-A, -B and -C loci which codify the classical histocompatibility molecules expressed on the surface of all nucleated cells. Class II region is composed by HLA-DR, -DQ and -DP loci, which codify the histocompatibility molecules found on the surface of antigen presenting cells. Class III region does not codify histocompatibility molecules but other molecules such as tumor necrosis factor, proteins C4, C2 and factor B of the complement system, heat shock protein and 21-hydroxylase enzymes.

The main function of HLA molecules is the presentation of antigenic peptides to T lymphocytes, which is necessary to trigger the adaptive immune response.<sup>4,6</sup> Class I and II HLA antigens and alleles have been commonly associated with susceptibility, protection and clinical manifestation of several diseases, with an emphasis on autoimmune diseases, infectious, neoplastic and idiopathic diseases.<sup>2,5,7</sup> Various mechanisms have been suggested to explain these findings,<sup>2,4</sup> and the following stand out: (a) molecular mimetism between certain peptides in the pathogen and host-derived peptides; (b) unbalanced binding among histocompatibility molecules and other MHC genes or outside the MHC system which are also involved with the disease; (c) HLA molecules acting as receptors for some etiological agents; (d) selection of the peptide to be presented by the HLA molecule to the immune system; (e) induced expression of class II HLA antigens in tissue cells that normally do not perform it.

This review discusses some aspects of the HLA system, methods of detection, nomenclature and its association as a pathogenesis mediator of some skin diseases.

## METHODS TO DETECT HLA ANTIGENS AND ALLELES

Detection of HLA polymorphism can be carried out by cellular or molecular methods.<sup>1,2</sup> The former typifies the histocompatibility antigens expressed in cellular surfaces. This method employs the cellular microlymphocytotoxicity mediated by antibodies and complement-dependent (serologic method of Terasaki) or by mixed lymphocyte culture, in which cells with known phenotypes are used to define HLA specificities.<sup>1,2</sup> In the molecular method, HLA allele

typing is performed by means of DNA amplification through the polymerase chain reaction (PCR), using either the method called sequence specific primers (SSP) or sequence specific oligonucleotide probes (SSOP).<sup>1,2</sup>

## HLA SYSTEM NOMENCLATURE

HLA system nomenclature is periodically revised and defined by an International Committee to assign names to the newly discovered alleles or to change the existing nomenclature.<sup>1,2</sup> Before the emergence of Molecular Biology techniques, HLA typing was serologically performed only through antigen identification. When this method is used, the result is reported by the acronym HLA followed by one or two capital letters representing the gene locus and by one or two numbers representing the gene (*e.g.*, HLA-A1, HLA-DR4, HLA-B2).<sup>8</sup> The development of typing by means of Molecular Biology methods has allowed the detection of a specific allele rather than only the antigen that could represent a wide variety of alleles. For example, HLA-B27 antigen is now named HLA-B\*27 and it encompasses at least 23 variants of the HLA-B27 molecule (HLA-\*2701 a -B\*2723). Alleles are represented by the locus letter followed by an asterisk and by two to eight digits (*e.g.*, HLA-DRB1\*1501, -DQA1\*0102, -A\*0101).<sup>9</sup> The first two digits define the serological family the allele belongs to; the third and fourth digits are the variation code, *i.e.*, they specify the allele within the family; the fifth and sixth digits describe variations of that allele; and the seventh and eighth digits describe variations in introns (regions 5' or 3' in the gene).<sup>10</sup>

The nomenclature of Class II HLA alleles of loci -DQ and -DP also expresses the type of heterodimer chain of its molecules ( $\alpha$  ou  $\beta$ ), which are named with letters "A" or "B", respectively (*e.g.*, HLA-DQB1\*1101, -DQA\*0102).<sup>1</sup> In HLA-DR molecules, polymorphism occurs only in domain  $\beta$ 1 of  $\beta$  chains, since the  $\alpha$  is not polymorphic. Therefore, in HLA-DR, only the letter "B" is added. The nomenclature employed for Class I HLA alleles does not contain this specification since they only present polymorphism in the  $\alpha$  chain and they are named only as HLA-A, HLA-B and HLA-C.<sup>2</sup> Previous standardization rules have introduced the optional suffix "N" or "L" to indicate null or low expression of an allele.

## ASSOCIATION OF HLA WITH SKIN DISEASES

Some studies have shown genetic predisposition and association of the HLA system with different dermatological diseases.<sup>11</sup> These findings, added to participation of autoantibodies and cellular immunity mediated by T cells in the pathogenesis of some der-

matoses and by the association of HLA genes with the immune system suggest an autoimmune character for these conditions.<sup>12</sup> Although the altered expression of HLA antigens was very much demonstrated in tissues affected by autoimmune diseases, the reason why the immune system is abnormally activated against certain cells is still unknown.<sup>8,13</sup>

Given the polymorphism of the HLA system, its association with skin diseases is highly variable. As a result, depending on the genetic load, an individual may present a higher or lower risk of developing a certain condition. In many cases, the presence of an allele suggestive of susceptibility is not enough to justify the emergence of dermatosis, which suggests the participation of other factors in its pathogenesis.<sup>11</sup>

Additionally, due to the genetic variability seen in different ethnicities, the combination of alleles responsible for the manifestation of dermatoses vary according to the population studied, although some alleles are more prevalent independently of the group ethnic basis.<sup>14</sup> Hence, it is recommended that racial groups be individually analyzed so that their particularities are noticed.

Although the participation of MHC markers was established in the pathogenesis of some skin diseases, the etiology of some conditions is still unknown and the actual meaning of the association between HLA and these diseases has not been determined.<sup>14</sup>

The main dermatological diseases associated with HLA system are vitiligo, pemphigus, psoriasis, lupus erythematosus, scabies, cutaneous leishmaniasis, leprosy, paracoccidioidomycosis and atopic dermatitis.

## VITILIGO

Vitiligo is a polygenic autoimmune disease of unknown etiology characterized by loss of epidermal melanocytes and consequent progressive cutaneous depigmentation.<sup>15,16</sup>

There are reports in literature about positive association of vitiligo with HLA-DR4 antigen and negative association with HLA-DR3 antigen.<sup>17</sup> Because of HLA gene polymorphism, the results of these reports may vary according to the population studied.<sup>18</sup>

A high incidence of HLA-DRw12 and -A2 antigens was detected in a population of Caucasian Germans.<sup>19</sup> Hungary, Poloy et al. showed the association with HLA-DRI.<sup>20</sup> Orecchia et al. studied Italian individuals and observed a high frequency of HLA-A30, -Cw6 and -DQw3 antigens.<sup>21</sup> Zamani et al. reported an increased frequency of HLA-DRB4\*0101 and -DQB1\*0303 alleles in the Dutch population.<sup>22</sup> In black patients there was a higher frequency of HLA-DR4 and -DQw3 antigens.<sup>23</sup> In Turkey, HLA-DRB1\*03, -DRB1\*04 and -DRB1\*07 alleles were considered risk markers.<sup>18</sup>

Other researches showed differences in the association of HLA and vitiligo in terms of age at onset, presence of family history and clinical manifestations. HLA-DR4 antigen is more frequent in individuals with early manifestation (less than 20 years old), while HLA-DRw6 antigen is associated with late development.<sup>23</sup> HLA-DQw3 and -DR4 antigens seem to be more frequent in patients with a positive family history for autoimmune diseases, whereas HLA-DRw6, -A30 and -DQw3 antigens occur more frequently in those with a negative family history for these diseases.<sup>21,23</sup>

As to the clinical spectrum, Orecchia et al. demonstrated that individuals with extensive lesions had a higher frequency of HLA-A30 and -Cw6 antigens.<sup>21</sup> Venkataram et al. suggested the association of HLA-DR7 antigen with the acrofacial involvement.<sup>24</sup>

Since it is an autoimmune condition associated with the HLA system, differences in the results of distinct studies are expected, especially because they cover populations with diverse ethnical backgrounds.

## PEMPHIGUS

Pemphigus is a group of autoimmune diseases characterized by the formation of intraepidermal blisters affecting the skin and sometimes the mucosae, as a result of acantholysis and action of T cells and immunoglobulins G against desmosomal glycoproteins of keratinocytes. It can present as three different types: pemphigus vulgaris (PV), pemphigus foliaceus (PF) and the endemic form, the endemic pemphigus foliaceus (EPF), also known as fogo selvagem [wild fire] (FS).<sup>25,26</sup> HLA alleles seem to be the most important predisposing genetic factors.<sup>26,27</sup>

As to the association with class I HLA system, Glorio et al. did not find an association of PV with HLA-A, -B or -C antigens in Caucasian Argentinians.<sup>27</sup> Miyagawa et al. found a high prevalence of HLA-B15 antigen, specifically of HLA-B\*1507 allele in the Japanese population with PV,<sup>28</sup> and Abroobaker et al., in South Africa, reported positive HLA-B8 antigen.<sup>29</sup> An increased frequency of HLA-B16 antigen was seen in Caucasian Brazilians with FS.<sup>30</sup>

As to the Class II HLA, the HLA-DRB1\*04 and -DRB1\*14 alleles are associated with PV, regardless of the ethnic profile of the sample studied.<sup>28</sup> In Caucasian Argentinians with PV, Glorio et al. reported an increased frequency of HLA-DR3 and -DR4 antigens, of HLA-DRB1\*0402, -DQB1\*0302, -DRB1\*1401 and -DQB1\*0503 alleles.<sup>27,31</sup> In Italy, a high frequency of HLA-DRB1\*04 and -DRB1\*1401 alleles was seen both in individuals with PV and PF, with protection being associated with the HLA-DRB1\*07 allele.<sup>11</sup> In Japanese individuals with PV there was a positive association with HLA-DQB1\*0503 and -DRB1\*1405

alleles and a negative association with HLA-DQA1\*0103 and -DQB1\*0601 alleles.<sup>32</sup> In Caucasian Brazilians with FS, Petzl-Erler & Santamaría found a higher incidence of HLA-DR1 and -DR4 antigens.<sup>30</sup> In a study carried out by Moraes et al. the HLA-DRB1\*0102 allele was pointed out as a marker of susceptibility for FS in Brazilians, whereas the HLA-DQw2 antigen was associated with protection.<sup>33</sup> The HLA-DRB1\*0404, -DRB1\*1402 and -DRB1\*1406 alleles were associated with FS in Indians from Terena and Xavante tribes.<sup>34,35</sup> Also in Brazilians, Pavoni et al. reported increased frequency of HLA-DRB1\*0101, -DRB1\*0102, -DRB1\*0103, -DRB1\*0404, -DRB1\*0406, -DRB1\*0410, -DRB1\*1406 and -DRB1\*1601 alleles in patients with FS, and a negative association with HLA-DRB1\*0301, -DRB1\*0701, -DRB1\*0801, -DRB1\*1101, DRB1\*1104 and -DRB1\*1402 alleles.<sup>36</sup>

From the analysis of these results it is possible to suggest an association of HLA-DRB1\*04 and -DRB1\*14 alleles with pemphigus, since they were associated with this disease in all the ethnicities studied. The alleles HLA-DQB1\*0302 and -DQB1\*0503 also stood out. As to protection, few studies detected alleles negatively associated with pemphigus and, among those with a positive correlation, there was no consensus. For example, according to Niizeriki et al., the protective alleles were HLA-DQA1\*0103 and -DQB1\*0601,<sup>32</sup> on the other hand, according to Lombardi et al. this protection was associated with the HLA-DRB1\*07 allele.<sup>11</sup>

## PSORIASIS

Psoriasis is a chronic and recurrent inflammatory disease that affects mainly the skin and joints, and is characterized by abnormal cellular differentiation and exacerbated proliferation of the epidermis and keratinocytes.<sup>37-39</sup> These changes are mediated by activated T lymphocytes, and CD4<sup>+</sup> and CD8<sup>+</sup> lymphocytes actively participate in triggering and maintaining the process.<sup>40</sup> The pathogenesis of psoriasis involves genetic and constitutional factors, especially the major histocompatibility complex.<sup>41</sup>

Psoriasis can be classified into two types: type I, which is associated with early manifestation of the disease and a positive family history, and type II, which is related to late manifestation and a negative family history.<sup>42</sup>

The association with the HLA system varies according to the ethnical group, type of psoriasis and clinical manifestations of the disease.<sup>12,42</sup> Despite this diversity, there is a strong association of the HLA-Cw\*0602 allele in different ethnical groups.<sup>43</sup> In spite of the association of HLA-Cw\*0602, only 10% of the individuals with this allele developed psoriasis, suggesting the participation of other genes in the patho-

genesis of the disease.<sup>44</sup>

In Caucasians, the presence of HLA-Cw\*0602 allele poses a 10-fold higher risk of developing psoriasis.<sup>45</sup> In Chinese individuals there was an association with HLA-Cw\*0602, -A\*26, -B\*27, -DQA1\*0201, -DQB1\*0303, -DQB1\*0201 and -DQA1\*0104 alleles.<sup>14,40,42</sup> In Brazilians, Gonzaga et al. reported an association with HLA-Cw6, -B13 and -B17 antigens.<sup>46</sup> Corroborating the findings of Gonzaga et al., Vignale & Paciel found an increased frequency of HLA-B13 antigen in the molecular membrane of circulating lymphocytes in cases of psoriasis vulgaris.<sup>47</sup>

Zangh et al. reported an association of HLA-DQA1\*0104, -DQA1\*0201 and -DQA1\*0501 alleles with type I psoriasis.<sup>14</sup> In Croatians, there was an association of HLA-DRB1\*0701, -DQA1\*0201, -DQB1\*0201 and -DQB1\*0303 alleles with type I psoriasis and no association with type II psoriasis.<sup>48</sup> There were no differences in severity and clinical manifestations of psoriasis (distribution of plaques, nail abnormalities) between individuals who were homozygous or heterozygous for HLA-Cw\*0602 allele.<sup>45</sup>

## LUPUS ERYTHEMATOSUS

Lupus erythematosus is an autoimmune disorder with a wide spectrum of clinical manifestations ranging from the cutaneous forms (CLE) to the multi-systemic disease.<sup>49</sup> Discoid lupus erythematosus (DLE) and subacute cutaneous lupus erythematosus (SCLE) are the clinical forms that affect primarily the skin.<sup>49</sup> In SCLE there are two patterns: psoriasiform or papulosquamous and an annular form with patchy and papular lesions.

Multiple factors are involved in the development of CLE.<sup>50,51</sup> Experimental studies suggest a strong association with polymorphic genes codifying immunoregulatory molecules (e.g., HLA, TNF- $\alpha$  complement), especially in patients anti-Ro-positive.<sup>50</sup> The variation of disease expression can be attributed to a genetic predisposition that is probably conferred by certain genetic polymorphisms, such as those of HLA system.<sup>50,52</sup>

HLA-B8 and -DR3 antigens were associated with the development of SCLE.<sup>33,54</sup> In some studies, HLA-DR3 antigen was detected in more than 50% of patients with SCLE.<sup>53</sup> HLA-DR3 antigen showed an association especially with the annular subtype and with the presence of anti-Ro-SSA antibodies.<sup>53</sup> Neonatal lupus erythematosus was also related with maternal HLA-DR3 antigen.<sup>55</sup>

As to the association between HLA and DLE, HLA-A1, -B8, -DR3, -B7 and -DR2 antigens are found in Caucasian patients.<sup>50</sup>

Associations of HLA-DR2 and -DR3 antigens with susceptibility for systemic lupus erythematosus

(SLE) are found in different ethnical groups, particularly in Caucasian Europeans.<sup>56,57</sup> A strong association of HLA-DR and -DQ antigens with autoantibodies related with SLE was also described.<sup>56,57</sup>

### SCABIES

Scabies is a dermatozoonosis caused by *Sarcoptes scabiei*. This mite causes a dermatitis, with skin rash and pruritus, which are consequent of the body immune response against the parasite.<sup>58</sup>

The immune response can help in limiting the amount of *Sarcoptes scabiei* mites in the human skin, thus offering susceptibility or protection against the disease.<sup>58</sup>

There are few reports in literature about the association between HLA and scabies. HLA-A11 antigen was associated with increased susceptibility.<sup>59,60</sup>

In patients resistant to the treatment for scabies who developed multiple papular nodular lesions despite the appropriate use of medications, intense perivascular infiltration of lymphocytic cells compatible with Langerhans cells positive for HLA-DR antigens was seen.<sup>61</sup>

### CUTANEOUS LEISHMANIASIS

Leishmaniasis is a zoonosis caused by a protozoon of the genus *Leishmania*. The infection may result in four different syndromes: localized cutaneous leishmaniasis (LCL), diffuse cutaneous leishmaniasis (DCL), mucocutaneous leishmaniasis (MCL) and visceral leishmaniasis (VL). The type of syndrome developed depends on the interaction between the protozoon species of *Leishmania* and the host immune and genetic status.<sup>62,63</sup>

Regarding the association of cutaneous leishmaniasis with class I HLA antigens, Barbier et al. reported a low frequency of HLA-Cw7 antigen.<sup>64</sup> In the Egyptian population, a significant association was found between Class I HLA-A11, -B5 and -B7 antigens and DCL.<sup>60,65</sup>

Evaluating Classes I and II of HLA antigens, Lara et al. suggested that HLA-Bw22 and -DQw3 antigens were positively associated with LCL in the Venezuelan population.<sup>66</sup>

A study in Mexican mestizos showed that HLA-DQ3 antigen and HLA-DRB1\*0407, -DQA1\*3011, -DPA1\*0401 and -DPB1\*0101 alleles were associated with susceptibility for LCL, whereas the HLA-DR2 group (-DRB1\*1500, -DRB1\*1600) and HLA-DPB1\*0401 allele was associated with protection.<sup>63</sup> A previous study in this same population showed a significant increase of HLA-DQ3 antigen and a decrease of -DPw4 antigen in patients affected with LCL.<sup>67</sup>

In Brazilians, Petzl-Erler et al. investigated the association of MCL with Classes I and II HLA mole-

cules in Caucasians and mulattos; no significant difference was found for Class I HLA antigens between patients and controls.<sup>68</sup> However, for Class II HLA antigens an important association was found. HLA-DQw3 antigen was associated with susceptibility to MCL, whereas HLA-DR2 antigen was associated with protection.<sup>68</sup> Pirmez et al. studied the expression of HLA-DR, -DQ and -DP antigens in lesions found in Brazilian patients affected with tegumentary American leishmaniasis; these authors noticed an abnormal expression of HLA-DR molecules in keratinocytes in the active lesions with reversal after antimonial therapy or spontaneous formation of sores.<sup>69</sup> This result suggested that the abnormal expression of HLA-DR molecules in keratinocytes is restricted to the active lesions and it may be involved with the disease immunopathology.

Despite the ethnic variations and different parasite/host relations, HLA-DQw3 antigen was associated with susceptibility in Venezuelan Mestizos affected with LCL,<sup>66</sup> in Mexican Mestizos with LCL,<sup>67</sup> in Brazilian Caucasians and Mulattos with MCL.<sup>68</sup> HLA-DR2 antigen is associated with protection in Mexicans<sup>65</sup> and in Brazilians.<sup>68</sup> HLA-DQw3 and -DR2 antigens may be probable markers of risk and genetic protection, respectively, for cutaneous leishmaniasis.

### LEPROSY

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. Its clinical manifestations depend on the host cellular immune response.<sup>70,71</sup> The disease initial stage presents the indeterminate group (IL, indeterminate leprosy) which can spontaneously regress or evolve to one of the main presentations of the disease: tuberculoid leprosy (TL), virchowian (lepromatous) leprosy (VL) and dysmorphic leprosy (DL).<sup>72</sup> TL and VL are the two stable types.<sup>71,72</sup> The first is related with a strong cellular immune response and the second is related with a deficient cellular immune response.<sup>71,72</sup> DL is an unstable clinical type in which patients present mixed characteristics of the two stable types.<sup>72,73</sup>

Genetic factors of the host have been pointed as the main responsible elements for susceptibility to leprosy.<sup>74,75</sup> Immunogenetics and the studies in humans suggest that the HLA system is associated with the development of several types of the disease.<sup>70,72,73</sup>

The associations with Class I HLA molecules have been inconsistent.<sup>74,76</sup> On the other hand, the associations between Class II HLA molecules and TL and VL were well established in several ethnic groups, particularly with HLA-DR2, -DR3 and -DQ1 antigens.<sup>72,74, 76,77</sup> In most studies, HLA-DR2 and -DR3 antigens were associated with TL, and the HLA-DQ1

antigen was associated with VL.<sup>74,78</sup> In a population in the south of Brazil, HLA-DR2 antigen was significantly associated with the tuberculoid type of leprosy.<sup>73</sup>

### PARACOCCIDIOIDOMYCOSIS

Paracoccidioidomycosis (PCM) is a chronic granulomatous disease caused by the fungus *Paracoccidioides brasiliensis*. It is believed that a defect in the phagocytosis process of the fungus by neutrophils associated with class I HLA molecules in the membranes of such cells is involved in the development of PCM.<sup>78</sup>

In Brazilian patients, Lacerda et al. reported an association of HLA-B40 antigen with the development of PCM.<sup>79</sup> Goldani et al. showed an association of HLA-B40 and -Cw1 antigens with susceptibility to PCM.<sup>80</sup> This study also established an association with HLA-A2, -B7 and -B21 antigens and with HLA-B40-Cw1 and -A2-B40 haplotypes. Visentainer et al. found a positive association with HLA-A1, -A3, -B8, -Cw7, -DQw2 and -DQw3 antigens, and a negative association with HLA-Cw3, -DR1 and -DQw1 antigens.<sup>81</sup> However, when the *p* value was corrected, no statistically significant association was shown. Dias et al. observed an increased frequency of HLA-A1 antigen in patients with PCM although it was not statistically significant.<sup>78</sup>

The lack of uniform results may be attributed to variability in frequency of HLA antigens in the Brazilian population; more comprehensive studies are necessary to better define the type and strength of the association.<sup>78</sup>

### ATOPIC DERMATITIS

Atopic dermatitis (AD) is a skin chronic inflammatory disease that is highly pruriginous and recurrent, and frequently associated with the development of allergic rhinitis or asthma.<sup>82,83</sup>

Some agreement studies with twins pointed to a strong influence of genetic factors in atopy and atopic disease.<sup>83</sup> Since HLA molecules participate in the presentation and recognition of allergens in the immune response, class I and II HLA antigens are presumed to be involved with the pathogenesis of dermatitis and other atopic disorders.<sup>84,85</sup> Based on these data, several studies were performed seeking associa-

tions between atopies and the HLA system.<sup>85</sup>

Some studies suggested an association with HLA genes. Lee et al. studied Korean patients and showed an association with HLA-A24 antigen.<sup>84</sup> Saeki et al., in Japan, verified a high frequency, although not significant, of HLA-A24, -A33, -Cwblank, -B44, -DR13 antigens and HLA-DRB1\*1302, -DQB1\*0604 and -DPB1\*0301 and reduced frequency of HLA-Cw1, -Bw6, -DR4, and -DR53 antigens and of HLA-DQ1\*0302 allele.<sup>86</sup> In another study, this same group showed the association between amino acid epitopes in class II HLA molecules and severe AD accompanied by high serum levels of IgE.<sup>87</sup>

### CONCLUSION

The association between some dermatological diseases and the HLA system draws attention to participation of immune mechanisms and genetic predisposition in the pathogenesis of these conditions. However, this association is not enough to explain the complete pathogenesis of these disorders, suggesting the contribution of other factors (e.g., environmental, infectious) in its development. It is important to emphasize that, although susceptibility is associated with some alleles, and protection with others, the condition of bearing a certain type of allele or susceptibility antigen does not necessarily mean that the individual will develop the disease; likewise, the presence of an allele or protective antigen does not assure that the disease will not develop.

Since the genes in the HLA system are extremely polymorphic, the allele differences among diverse populations imply that the markers established for a certain ethnic group may not be possible to be extrapolated to another. Therefore, studies in ethnically distinct populations, mainly in mixed populations such as the Brazilian population are recommended to check if susceptibility or protection is associated with the alleles described in literature.

As foreseen in this journal almost 10 years ago by Santamaría et al. (1996),<sup>8</sup> enhanced knowledge of the association between HLA and skin diseases contributed to diagnosis, prognosis, characterization of type and clinical course, and anatomical predilection in certain dermatoses. □

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## MAILING ADDRESS:

*Crésio Alves**Rua Plínio Moscoso, 222/601**40157-190 - Salvador – BA**Tel.: (71) 9975-8220**E-mail: cresio.alves@uol.com.br*