Role of HLA-DR Alleles to Increase Genetic Susceptibility to Onychomycosis in Nail Psoriasis

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Key Words

Psoriasis · Nail psoriasis · Onychomycosis · HLA class II allele · Nail fungus · Genetic predisposition

Conclusion: HLA-DR*08 and HLA-DR*01 probably increase the susceptibility to fungal infection in psoriasis-affected nails, but larger studies are required to confirm this observation.

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Abstract

Background: Patients with nail psoriasis have an increased risk of onychomycosis. Previous studies suggest it may be due to structural changes of the nails. However, a genetic predisposition seems to be also at play. **Objective:** To determine a genetic susceptibility for onychomycosis in nails with changes of psoriasis. **Methods:** This is a prospective case-control study of patients with suggestive changes of nail psoriasis with onychomycosis (cases) and without onychomycosis (controls) confirmed by mycological tests. HLA typing was performed in all of them by sequence-specific primers. **Results:** Twenty-five patients and 20 controls with a mean age of 50 years (range 37–72 years) were studied. HLA-DRB1*08 was found in 12 cases (48%) and only 3 controls (15%) [$p < 0.033$, odds ratio (OR) = 3.8, 95% confidence interval (CI): 0.9–19]. HLA-DR1 was found in 9 cases (36%) and only 1 control (5%) ($p < 0.023$, OR = 8.5, 95% CI: 1–188). **Con-**

Introduction

Psoriasis is a chronic inflammatory disease that primarily affects the skin, but can also involve the nails [1]. It is more common in Caucasian populations in men as well as women [2]. In Mexicans, it represents 2% of dermatological outpatients [3]. Etiology is multifactorial, including a hereditary component, which is associated with both class I and class II human leukocyte antigen (HLA), and it also influences clinical features, course and severity of the disease [1–3].

The early onset of psoriasis is associated with HLA-Cw6 and HLA-B*57, whereas patients with psoriatic arthritis show a high frequency of HLA-B*27 (30–60%) [4, 5]. On the other hand, the HLA-DR*07 has been found in 38.8% of patients with psoriatic arthritis and in 41.5% of

patients with psoriasis [5]. Both HLA alleles HLA-B*27 and HLA-DR*07 have been found to be associated with nail psoriasis [6].

The lifetime incidence of nail involvement in psoriatic patients is up to 80% [7, 8–13]. The main changes are pitting, oil drop discoloration, red spotted lunula, splinter hemorrhages, subungual hyperkeratosis and onycholysis [7, 14]. Onychomycosis is the main differential diagnosis and may coexist in up to 30% of these patients [15, 16]. It is believed that the structural alterations caused by the inflammation at the nail matrix may facilitate fungal infection [17, 18].

Recent studies have shown an autosomal dominant inheritance pattern in onychomycosis [19, 20]. Asz-Sigall et al. [21] demonstrated that HLA-DR*06 was associated with resistance to nail infection with *T. rubrum* in Mexican Mestizos.

García-Romero et al. [22] conducted an analysis of the genetic polymorphism of the HLA-B and HLA-DR loci in Mexican patients with dermatophyte onychomycosis and first-degree relatives and found susceptibility genes, namely the HLA-DR*08 allele.

However, we are not aware of studies of HLA in patients with nail psoriasis and onychomycosis. The aim of this case-control study is to determine whether there is a genetic susceptibility marker for onychomycosis in these patients.

Methods

Cases and Controls

Both cases and controls were prospectively selected at the Department of Dermatology at 'Dr. Manuel Gea González' General Hospital in Mexico City. All cases and controls were Mexican Mestizos, as well as their parents and grandparents.

Cases of suspected onychomycosis in nail psoriasis had a mean age of 45 years (between 37 and 72 years old). They were examined by experienced dermatologists and mycologists. After obtaining ethical approval and informed consent, the patients underwent mycological study (KOH direct microscopy and culture in Sabouraud dextrose agar and BBL Mycosel agar, Becton Dickinson and Company, Sparks, Md., USA). The control group were patients with nail psoriasis without onychomycosis confirmed by mycological study. Blood samples were taken from all cases and controls for HLA-DR genotyping.

Total genomic deoxyribonucleic acid (DNA) was extracted from peripheral blood mononuclear cells by using the salting out technique, and purification by the phenol chloroform method.

Identification of Polymorphisms for the HLA-DR Locus

This was accomplished by using the sequence-specific primers method, after amplification of HLA-DR beta 1 chain, using the polymerase chain reaction technique. Gene frequencies were de-

Table 1. Demographic

	n	%
Gender		
Female	11	44
Male	14	56
Age		
30–40 years	2	8
40–50 years	3	12
50–60 years	12	48
>60 years	8	32
Psoriasis features		
Plaque	22	88
Guttate	1	4
Inverse	2	8

termined in cases and compared to those of controls, significant differences were tested by nonparametric statistics that included the χ^2 analysis and Fisher's exact test by using the StatCalc within the EPIINFO program.

Results

Twenty-five patients and twenty controls with a mean age of 50 years (range 37–72 years) were recruited. The proportion of men to women was 56–44%, in cases as well as controls; 88% had plaque psoriasis (table 1). Table 2 displays the gene frequencies of HLA-DR alleles in each study group. It is readily seen that the HLA-DR*08 allele is increased in the group of patients (48%) as compared to only 15% in controls, which was statistically significant [$p < 0.033$, odds ratio (OR) = 3.8, 95% confidence interval (CI): 0.9–19]. Likewise, the HLA-DR*01 allele was found in 9 cases (36%) and only 1 control (5%) ($p < 0.023$, OR = 8.5, 95% CI: 1–188).

Discussion

These results show the association of the HLA-DR*08 with the genetic susceptibility to develop onychomycosis in nail psoriatic patients. Interestingly, there is also the possible association of the HLA-DR*01 in the genetic predisposition to develop onychomycosis; nevertheless, the small sample size of this study suggest further confirmation in a larger cohort of patients and repeating the study design in distinct genetic population.

These results confirm the role of HLA-DR*08 locus in the pathogenesis of the onychomycosis study by García-

Table 2. Determination of gene frequencies of the alleles of the HLA-DR locus in nail psoriasis patients with onychomycosis compared to nail psoriasis patients without onychomycosis

HLA alleles	Cases (n = 50)		Controls (n = 40)		p value	OR	95% CI
	n	allele frequency	n	allele frequency			
DR1	9	0.180	1	0.025	0.02	8.5	1–188
DR3	2	0.040	3	0.075	0.47	0.51	0.06–4.06
DR4	12	0.240	13	0.325	0.15	0.52	0.19–1.42
DR7	4	0.080	3	0.075	0.90	1.07	0.19–6.53
DR8	12	0.240	3	0.075	0.03	3.8	0.9–19
DR11	1	0.020	3	0.075	0.21	0.25	0.01–2.9
DR13	4	0.080	6	0.150	0.29	0.49	0.11–2.19
DR14	4	0.080	1	0.025	0.10	4.33	0.42–106.8
DR15	0	–	3	0.075	0.10	0.19	0.01–1.89
DR16	2	0.040	4	0.100	0.20	0.38	0.4–2.58

Romero et al. [22]; it should be noted that this study only analyzed patients with onychomycosis and their families, whereas the present study analyzed patients with nail psoriasis and onychomycosis compared with patients with nail psoriasis without onychomycosis.

The mechanism by which the HLA-DR*08 or HLA-DR*01 confer susceptibility for onychomycosis is multifactorial; nonetheless, the genetic factor seems to be primarily relevant, probably contributing with other gene and environmental factors in the development of onychomycosis in nail psoriasis.

According to these observations, we conclude that the HLA-DR locus has a role in the pathogenesis of nail psoriasis with onychomycosis and suggest that it might be useful to include the immunogenic profile along with mycological study in order to determine the susceptibility to develop onychomycosis in nail psoriasis.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to disclose.

References

- 1 Wolf K, Goldsmith L, Katz S: Fitzpatrick's Dermatology in General Medicine, ed 7a. New York, McGraw-Hill, 2008, pp 169–193.
- 2 Van de Kerkhof P, Schalkwijk J: Psoriasis; in Bologna JL, Jorizzo JL, Rapini RP (eds): Dermatology, ed 2. London, Mosby, 2008, pp 115–135.
- 3 Arenas R: Dermatología. Atlas, diagnóstico y tratamiento, ed 5. México, McGraw-Hill, 2012, 594–605.
- 4 Torre-Alonso JC, Rodríguez-Pérez A, Arribas-Castillo JM: Psoriatic arthritis (PA): a clinical, immunological and radiological study of 180 patients. *Br J Rheumatol* 1991;30: 245–250.
- 5 al-Fouzan AS, Nanda A: A survey of childhood psoriasis in Kuwait. *Pediatr Dermatol* 1994;11:116–119.
- 6 Duran-McKinster C, Ortiz-Solis D, Grana-dos J, Tamayo L, Orozco-Covarrubias L, Ruiz-Maldonado R: Juvenile psoriatic arthritis with nail psoriasis in the absence of cutaneous lesions. *Int J Dermatol* 2000;39: 30–40.
- 7 Jiaravuthisan M, Sasseville D, Vender R, Murphy F, Muhn CY: Psoriasis of the nail: anatomy, pathology, clinical presentation, and a review of the literature on therapy. *J Am Acad Dermatol* 2007;57:1–27.
- 8 Guenther L, Ortonne J: Pathophysiology of psoriasis: science behind therapy. *J Cutan Med Surg* 2002;6:2–7.
- 9 Langley RG, Dauden E: Treatment and management of psoriasis with nail involvement: a focus on biologic therapy. *Dermatology* 2010; 221:29–42.
- 10 De Jong EMGJ, Seegers BAMPA, Gulinck MK, Boezeman JBM, Van de Kerkhof PCM: Psoriasis of the nails associated with disability in a large number of patients: results of a recent interview with 1,728 patients. *Dermatology* 1996;193:300–303.
- 11 Baran R: The burden of nail psoriasis: an introduction. *Dermatology* 2010;221(suppl): 1–5.
- 12 Armesto S, Esteve A, Coto-Segura P, Drake M, Galache C, Martinez-Borra J, Santos-Juanes J: Nail psoriasis in individuals with psoriasis vulgaris: a study of 661 patients. *Actas Dermosifiliogr* 2011;102:365–372.
- 13 Zaia N: Psoriasis of the nail: a clinical-pathologic study. *Arch Dermatol* 1969;99:567–579.
- 14 Kaur I, Sarawat A, Kumar B: Nail changes in psoriasis: a study of 167 patients. *Int J Dermatol* 2001;40:597–604.

- 15 Muñoz H, Leyva J, Arenas R: Onicomicosis. Su frecuencia en pacientes con psoriasis. *Dermatología Rev Mex* 1999;43:41–44.
- 16 Gupta AK, Lynde CW, Jain HC, Sibbald RG, Elewski BE, Daniel CR 3rd, Watteel GN, Summerbell RC: A higher prevalence of onychomycosis in psoriatics compared with non-psoriatics: a multicentre study. *Br J Dermatol* 1997;136:786–789.
- 17 Szepietowski JC, Salomon J: Do fungi play a role in psoriatic nails? *Mycoses* 2007;50:437–442.
- 18 Larsen GK, Haedersdal M, Svejgaard EL: The prevalence of onychomycosis in patients with psoriasis and other skin diseases. *Acta Derm Venereol* 2003;83:206–209.
- 19 Zaias N, Tosti A, Rebell G, Morelli R, Bardazzi F, Bielely H, Zaiac M, Glick B, Paley B, Allevato M, Baran R: Autosomal dominant pattern of distal subungueal onychomycosis caused by *Trichophyton rubrum*. *J Am Acad Dermatol* 1996;34:302–304.
- 20 Adahiro A, Feresin-Moraes JR, Hue-Moraes ME, Romero M, Alves de Lima Gouvea H, Gouvea CJ, et al: HLA in Brazilian ashkenazic jews with chronic dermatophytosis caused by *T. rubrum*. *Braz J Microbiol* 2004;35:69–73.
- 21 Asz-Sigall D, López-García L, Vega-Memije ME, Lacy-Niebla RM, García-Corona C, Ramírez-Rentería C, Granados J, Villa A, Ameen M, Arenas R: HLA-DR6 association confers increased resistance to *T. rubrum* onychomycosis in Mexican Mestizos. *Int J Dermatol* 2010;49:1406–1409.
- 22 García Romero MT, Granados J, Vega Memije ME, Arenas R: Análisis del polimorfismo genético de los loci HLA-B y HLA-DR en pacientes con onicomicosis dermatofítica y familiares en primer grado. *Actas Dermosifiliogr* 2012;103:59–62.