

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/315719350>

The Frequency of HLA-B27 in a Colombian Population with Signs of Spondyloarthritis

Article in *Current Rheumatology Reviews* · March 2017

DOI: 10.2174/1573397113666170329121552

CITATIONS

2

READS

167

10 authors, including:



Consuelo Romero-Sánchez

Hospital Militar Central, - UIBO Institute (Oral Basic ResearchUnit), Scholl of Dentistr...

83 PUBLICATIONS 711 CITATIONS

SEE PROFILE



Lorena Chila

Hospital Militar Central -Universidad El Boque

20 PUBLICATIONS 17 CITATIONS

SEE PROFILE



Alberto Gomez

Pontificia Universidad Javeriana (Bogotá, Colombia)

96 PUBLICATIONS 558 CITATIONS

SEE PROFILE



Wilson Bautista-Molano

Fundación Santa Fe de Bogotá

84 PUBLICATIONS 547 CITATIONS

SEE PROFILE

Some of the authors of this publication are also working on these related projects:



Chikungunya-Related Inflammatory Arthropaties Guideline in LA [View project](#)



Immunopathology of Rheumatic Disease [View project](#)

The frequency of HLA-B27 in a Colombian population with signs of spondyloarthritis

Consuelo Romero-Sánchez^{*a,b,c,f}, Lorena Chila M², Alberto Gómez^{c,e}, María Consuelo Casas G^c, Wilson Bautista-Molano^f, Ignacio Briceño^{e,g}, Juan C. Rueda^g, Juliette de Ávila^b, John Londoño^{d,g}, Rafael Valle-Oñate^{a,f}

^aSpondyloarthropathy Group, Division of Rheumatology, Hospital Militar Central, Bogotá, Colombia, ^bUIBO Institute (Oral Basic Research Unit), Universidad El Bosque, Bogotá, Colombia, ^cInstituto de Referencia Andino, Bogotá, Colombia, ^dSpondyloarthropathy Group, Universidad de la Sabana-Division of Rheumatology and Immunology, Hospital Militar Central, Bogotá, Colombia, ^eInstitute of Human Genetics, Faculty of Medicine, Pontificia Universidad Javeriana, Bogotá, Colombia, ^fFaculty of Medicine, Universidad Militar Nueva Granada, Bogotá, Colombia, ^gFaculty of Medicine, Universidad de la Sabana, Bogotá, Colombia

Abstract: The strong association between HLA-B27 and spondyloarthritis (SpA) has demonstrated that typing the HLA-B27 antigen is a crucial step in diagnosis and aids in defining the progression and severity of disease.

Objective: To describe the frequency of HLA-B27 in Colombian individuals with clinical manifestations associated with SpA.

Materials and Methodology: We retrospectively analyzed 4109 HLA-B27 typing requests to the Hospital Militar Central and the Instituto de Referencia Andino from Colombian individuals with clinical signs suggestive of SpA between 2009 and 2012. We used basic digital cytometry followed by Polymerase Chain Reaction with sequence specific primers when confirmation was needed. We determined the frequency of HLA-B27 in the population and levels of association of HLA-B27 with SpA.

Results: Our population included 1585 men (36.8%) and 2524 women (61.4%). The predominant age range was between 19 and 45 years (49.9%). The majority (95.4%) of the study population came from the Andean region and eastern plains. Only a small fraction (12.1%) of the 497 subjects were HLA-B27 positive, among whom 56.9% were male, and 62.5% were between 19 and 45 years old ($p < 0.0001$). Women constituted 43.1% of the sample, with 7.8% under 18 years old and 37.4% above 45 years old. The most frequent clinical manifestations were peripheral: synovitis, polyarthralgias, musculoskeletal pain and heel pain.

Conclusion: The frequency of the HLA-B27 allele in individuals with clinical signs suggestive of SpA was low, in accordance with the lower prevalence found in Colombian patients diagnosed with SpA compared to American and European population. **Keywords:** 6 to 8 keywords must be provided.

1. INTRODUCTION

In 1973, a strong association between HLA-B27 and Spondyloarthritis was documented, making this membrane antigen useful for diagnosing and predicting the progress and severity of the disease. The HLA-B27 antigen is used as a prognostic marker and has been included in the current classification criteria [1]. HLA-B27 is one of the genetic variants of the human leukocyte antigen (HLA), which is part of the Major Histocompatibility Complex I (MHC-I) and is present in up to 90% of patients with Ankylosing Spondylitis (AS) [2]. HLA-B27 positive patients develop rheumatic inflammatory disorders at earlier ages, with a tendency to chronicity, than HLA-B27 negative patients [3].

Timely and accurate determination of HLA-B27 provides an important aid for diagnosis and long-term prognosis.

The prevalence of SpA in Colombia has not been established nor are there official statistics on the incidence. However, data from some studies provide a preliminary overview of these entities in the country [4]. In 1999, Martínez, Caraballo et al. studied the distribution of HLA-B27 subtypes in patients with AS from two ethnic Colombian groups: mulatos and mestizos [5]. Additional studies from Londoño et al. [3] and Velásquez et al. [6] in a series of patients with established diagnoses of SpA found a 50% frequency for HLA-B27, which is similar to two reports from Romero et al. [7, 8], where HLA-B27 frequency was 41.9 and 42.6%, respectively. These data differ from those reported by

Márquez et al. [9], where the frequency for HLA-B27 was 18% in a SpA group [9], unlike in a healthy population where the HLA-B27 rate was close to 4% [3].

The aim of this study was to determine the frequency of HLA-B27 in Colombian subjects initially suspected of SpA according to their clinical characteristics. We analyzed 4109 HLA-B27 applications from subjects referred to the Hospital Militar Central and the Instituto de Referencia Andino between 2009 and 2012

* Corresponding author: Cra. 3 n° 49-00 at the Department of Rheumatology, Hospital Militar Central, Bogotá, Colombia., Tel/Fax: 3486868 Ext 5050, E-mails: spacolomba@gmail.com

MATERIALS AND METHOD

PATIENTS

We performed a retrospective, descriptive, non-experimental study. We included patients with a presumptive diagnosis of spa who were referred to the immunology laboratory of the Hospital Militar Central and the Instituto de Referencia Andino (IRA) with a HLA-B27 request between 2009 and 2012. Four thousand one hundred and nine (4109) applications were selected.

STATISTICAL METHODS

Demographic characteristics, age, gender, and the most important clinical manifestations were analyzed using a chi-squared test (X^2) to determine frequencies and levels of association. The data were analyzed using spss v18 for windows with a confidence interval (CI) of 95%. The study was approved by the Hospital Militar Central ethics and research committees (n° c-2012-084).

Serum samples were processed in the Hospital Militar Immunology laboratory and the IRA within a 3-year period between 2009 and 2012. The presence of HLA-B27 in each patient was determined from peripheral blood samples by flow cytometry and was confirmed by polymerase chain reaction with sequence specific primers (PCR-SSP).

ETHICAL APPROVAL

This project was approved by the research committee of the Hospital Militar Central (code 2012-084).

EXPERIMENTAL:

Flow Cytometry

A FACSCanto II® was used to measure the expression of HLA-B27. Conjugated detection antibodies directed against the HLA-B27 molecule coupled to a fluorochrome were incubated with the cell samples from patients and healthy controls according to the manufacturer's instructions (Becton Dickinson, San Diego, CA, USA). Data were acquired with FACSCanto software, and the results were based on 15000

measured events from a CD3 lymphocyte population. HLA-B27 was scored as positive or negative based on a threshold defined by the suppliers of the monoclonal antibodies (10, 11).

PCR SSP

Positive HLA-B27 results by flow cytometry were confirmed by molecular PCR SSP (Biotest, Landsteimerstrasse, Dreieich). The amplified alleles were separated on a 2% agarose gel, stained with ethidium bromide (handled under biosafety protocols) and visualized in a UV transilluminator [12].

RESULTS

Of the 4109 HLA-B27 applications of patients with suggestive manifestations of spa, 36.8% were men, and 61.4% women. The predominant age range was 19 to 45 years (49%), followed by those over 45 years (43.3%), and those 0 to 18 years of age (6.7%). Internal medicine was the service with the most applications for HLA-B27 (46.8%), followed by the sum of others such as general medicine, physical medicine and rehabilitation, pediatrics, orthopedics, endocrinology (28.9%). Ophthalmology and rheumatology requested HLA-B27 in 12.4% and 11.9% of the cases, respectively (table 1).

Table 1. Demographic Analysis

	N (%)
GENDER	
Female	2524(61,4%)
Mele	1585 (36,8%)
AGE	
0-18	277(6,7%)
19-45	2051(49,9%)
> 45	1781(43,3%)
ORIGIN	
Group 1♦	0(0,0%)
Group 2♦	3921(95,4%)
Group 3♦	82(2,0%)
Group 4♦	106(2,6%)
HLA-B27	
Negative	3612(87,9%)
Positive	497(12,1%)
Specialties	
Rheumatology	(11,9%)
Ophthalmology	(12,4%)
Internal Medicine	(46,8%)
Other*	(28,9%)
Total	4109(100%)

♦ Group 1: North Pacific Coast and San Andrés Island, Group 2: Andean Region, Amazon and Orinoquia Region, Group 3: Southwest of Andean Region, Group 4: Caribbean Coast.

*Other: General Medicine, Physical medicine and Rehabilitation, Pediatrics, Orthopedics, Endocrinology

The most frequent clinical manifestations were peripheral osteoarticular and muscular symptoms such as arthralgia, talalgia, and peripheral arthritis in the shoulders, hands and knees, or polyarthralgias (48.8%), followed by axial symptoms such as spine pain, stiffness, buttock pain, back pain, hip pain and sacroiliitis (27.9%). Extra-articular symptoms such as dry eyes, eye pain, xerophthalmia, xerostomia were present in 28.4% of the HLA-B27 applications (table 2).

Table 2. Frequencies of Clinical Manifestations

CLINICAL MANIFESTATIONS	(%)
Peripheral: talalgia, arthralgia and peripheral arthritis: shoulders, hands, knees, polyarthralgias	43,8%
Extra-articular: dry eye, eye pain, xerophthalmia, xerostomia and other extra-articular organs	28,4%
Axial: spine pain, stiffness, buttock pain, back pain, hip pain, sacroiliitis	27,9%

Frequencies in Percentage

Geographical distribution of HLA-B27 in colombian population

We used the following geographical distribution proposed by paredes et al in 2003 (13): 1. North pacific coast and san andrés island; 2. Andean, amazon and orinoco; 3. Southwest andean; 4. Caribbean coast.

Ninety five percent (95.4%) of the applications came from the second group, corresponding to the regions of valle del cauca, antioquia, santander, boyacá, risaralda, cundinamarca, tolima, norte de santander, quindío, huila, caldas, arauca, meta, vichada, casanare, caquetá, and amazonas. Approximately 3% (2.6%) of the applications came from the caribbean coast (córdoba, sucre, bolívar, cesar, guajira, magdalena, atlántico), and 2% came from the southwest andean region (cauca, nariño). Subjects from san andres island and the pacific coast region (choco) were not included (table 1).

HLA-B27 frequency

Of the 4019 applications, only 497 (12.1%) were HLA-B27 positive. A male tendency was observed (males: 56.9%; female: 43.1%), (table 3).

Table 3. Frequency of HLA-B27

	N (%)
HLA-B27	497(12,1%)
0-18 years	39 (7,80%)
19-45 years	272 (54,70%)
> 45 years	186 (37,40%)
Females	214 (43,1%)
Males	283 (56,9%)

The frequency of HLA-B27 in age range includes female and male sex

DISCUSSION

The aim of this study was to describe the frequency of HLA-B27 in colombian subjects with an initial suspicion of spa based on clinical characteristics. The frequency of the HLA-B27 allele in patients with spa can reach up to 90% in different populations and has been reported to be 41.9% in the colombian population [14-17]. However, when patients with suggestive manifestations of spa were analyzed, only 10% were HLA-B27 positive. This result suggests an overestimation of this parameter in primary care consultations.

It is also possible that HLA-B27 positive subjects with spa in the colombian population are less common than in other populations. In a healthy population, the frequency of the HLA-B27 allele is approximately 4%, and in spa patients, its frequency may vary between 50 and 65% [3, 6, 14]. Compared to american and european caucasian populations, where the HLA-B27 is present in nearly 8% of the healthy population and in more than 90% of spa patients [15, 16], it seems that the studied population may have a lower association or that the molecular mechanisms of spa could be different.

Regarding the data presented according to geographical distribution, it is important to mention that the distribution described does not correspond to the frequency of the disease in different regions. The data correlates with a higher request rate for the HLA-B27 test in more densely populated areas.

Our study shows a predominance of positive HLA-B27 alleles in male patients with suspicion of spa. Although most HLA-B27 requests were from females (61.4%), HLA-B27 was positive in a higher percentage of men, coinciding with previous studies in which a higher frequency was reported (63 to 70%) [9, 14] and reflecting an approximately 3:1 male to female ratio.

The fact that the test was requested more often in female subjects reflects a more frequent consultation for osteoarticular and muscular symptoms by women; a situation familiar to clinicians. However, our data show a higher frequency of HLA-B27 in males, which matches with the predominantly male clinical presentation of spa. Our data

may also reflect the difficulty in differentiating the clinical characteristics of spa with other rheumatic diseases such as fibromyalgia in primary care, especially in women.

To our knowledge, there are no published studies on the colombian population that determine the incidence, prevalence or demographics of spa. Additionally, there are no prior reports on the presence of HLA-B27 in individuals with clinical suspicion of spa. Previous studies in patients with confirmed spa compared with healthy individuals provide a preview of the frequency of HLA-B27 in colombia [4].

The most frequent age range of subjects with spa suspicion in our study was 19 to 45 years (54%), mainly young economically active individuals. Similar results were reported by londoño et al. (14) in 2012, where the mean age was 31.9 ±(9.9 years, and by marquez et al. [9] in 2010, where the mean age was 42 years.

Equally noteworthy was the prevalence of peripheral manifestations (arthritis, arthralgia of hands, knees and hips), found in nearly 43% of the patients. This percentage is similar to that presented by citera et al. [17], who reported 39% of patients having peripheral compromise, and carpeta et al. (54% knees, and 35% hips) in patients with as. In this subgroup of patients, even though axial symptoms predominate, peripheral arthritis of the hands, knees and ankles could also be found. We explain the prevalence of axial symptoms in the context of our population because the requests for HLA-B27 typing were made by individuals suspected of spa in general. This group included not only predominantly axial spondylitis but also reactive arthritis, undifferentiated spondylitis and psoriatic arthritis. Therefore, in this context, the spectrum of peripheral symptoms is wider, as reported by the patients. Similarly, the colombian population has more genotypic and phenotypic heterogeneity, which explains the greater diversity from a clinical point of view.

Finally, the fact that HLA-B27 requests were more frequent in internal medicine and other departments (general medicine, physical medicine and rehabilitation pediatrics, orthopedics, endocrinology) and that HLA-B27 positivity was low in subjects with suggestive manifestations of spa, suggests that the requests are being over-prescribed in primary care and reflects a lack of knowledge about spa and its clinical manifestations.

STANDARD PROTOCOL ON APPROVALS, REGISTRATIONS, PATIENT CONSENTS & ANIMAL PROTECTION:

This article does not contain any studies with animals performed by any of the authors. this retrospective study was approved by the research committee of the Hospital Militar Central (code 2012-084).

CONCLUSION

Our data showed a higher frequency of positive HLA-B27 in males, which matches with the predominantly male clinical

presentation of spa. The most frequent age range of subjects with spa suspicion in our study was 19 to 45 years. The frequency of HLA-B27 in individuals with clinical signs suggestive of spa was low, in accordance with the lower rate found in colombian patients fully diagnosed with spa than in american and european populations.

LIST OF ABBREVIATIONS

HLA = Human leukocyte antigen

MHC-I = Major Histocompatibility Complex I

PCR-SSP = Polymerase chain reaction with sequence specific primers

SpA = Spondyloarthritis

CONFLICT OF INTEREST

The authors confirm that this article has no financial contributions and any conflict of interest.

ACKNOWLEDGEMENTS

All individuals listed as authors ζ have contributed substantially to the design, performance, analysis, or reporting of the work and are required to indicate their specific contribution. Anyone (individual/company/institution) who has substantially contributed to the study for important intellectual content, or who was involved in the article's drafting the manuscript or revising must also be acknowledged.

Guest or honorary authorship based solely on position (e.g. research supervisor, departmental head) is discouraged.

SUPPLEMENTARY MATERIAL

Supportive/Supplementary material intended for publication must be numbered and referred to in the manuscript but should not be a part of the submitted paper. List all Supportive/Supplementary Material and include a brief caption line for each file describing its contents.

REFERENCES

- [1] Bautista-Molano W, Londoño J, Romero C, Ávila M, Valle R . Espondiloarthritis y su Asociación con el Complejo Mayor de Histocompatibilidad. *Rev Col Reumatol* 2011;18:34-41.
- [2] Khan M, Kellner H . Immunogenetics of Spondyloarthropathies. *Rheum Dis Clin North Am* 1992;18: 837- 4.
- [3] Londoño J, González L, Ramírez L, et al .Caracterización de las Espondiloartropatías y Determinación de Factores de Mal Pronóstico en una Población de Pacientes Colombianos. *Rev Col Reum* 2005;12:95-207.
- [4] Valle-Oñate R, Candia L, Romero-Sánchez C, et al .Epidemiology of Spondyloarthritis in Colombia. *Am J Med Sci* 2011;341: 293-4.

- [5] Martínez B, Caraballo L, Hernández M, et al .HLA-B27 Subtypes in Patients with Ankylosing Spondylitis (AS) in Colombia. *Rev Invest Clin* 1999;51: 221-6
- [6] Velásquez E, Quintero J, Aristizábal B, et al .Frequency of HLA Alleles Class I and II in a Cohort of Northwestern Colombian Patients with Spondyloarthritis. *Biomedica* 2012; 32:43-51.
- [7] Romero-Sánchez C, Jaimes D, Londoño J, et al .Association between Th-17 cytokine profile and clinical features in patients with spondyloarthritis. *Clin Exp Rheumatol* 2011; 29: 828-34.
- [8] Romero-Sánchez C, Londoño J, Delgado G, et al Association of tumor necrosis factor alpha-308 promoter polymorphism with spondyloarthritis patients in Colombia. *Rheum Int* 2012; 32: 2195-7.
- [9] Márquez J, Pinto L, Candia D, et al. Espondiloartritis en el Hospital Pablo Tobón Uribe. Descripción de una Cohorte. *Rev Col Reum* 2010;17: 80-5.
- [10] Beckman Coulter Company. IOTest®OHLA-B27-FITC/HLA-B7-PE.
[www.beckmancoulter.com/wsrportal/page/itemDetails?itemNumber=A07739#2]
- [11] Dako (2006) Dako Flow Cytometry Educational Guide©. 2nd ed.Colorado, USA. Dako Fort Collins
- [12] Texas BioGene Inc. Morgan™ HLA SSP B27 Typing. http://www.texasbiogene.com/product/product_detail.php?id=91
- [13] Paredes M, Galindo A, Bernal M, et al .Analysis of the CODIS Autosomal STR Loci in Four Main Colombian Regions. *Forensic Sci Int* 2003; 137: 67-73.
- [14] Londoño J, Romero C , Torres V, et al .The Association Between Serum Levels of Potential Biomarkers with the Presence of Factors Related to the Clinical Activity and Poor Prognosis in Spondyloarthritis. *Rev Bras Reumatol* 2012; 52: 536-44.
- [15] Vergara M . Patogenia de las Artropatías Seronegativas. *Rev Chil Reumatol* 2009;25: 88-9.
- [16] Brown M . Genetics and the Pathogenesis of Ankylosing Spondylitis. *Curr Op Rheumatol* 2009; 21: 318–23.
- [17] Citera G, Schneeberger E, Maldonado-Cocco J, et al . Caracterización Inmunogénica de Pacientes con Espondilitis Anquilosante en Argentina. *Rev Arg Reumatol* 2009; 20: 26-33

Received: March 20, 2014

Revised: April 16, 2014

Accepted: April 20, 2014