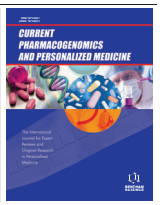
Current Pharmacogenomics and Personalized Medicine, 2020, *17*, 7-10

EDITORIAL



HLA-B27 is a Risk Factor for Rheumatoid Arthritis: Suggestion for an Evidence-based Update

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ARTICLE HISTORY

Received: December 20, 2018
Revised: February 08, 2019
Accepted: March 08, 2019

DOI:
10.2174/1875692117666190408113012

Abstract: Previously, the association of human leukocyte antigen (HLA)-B27 with ankylosing spondylitis has been investigated as original and meta-analysis studies. However, the association of HLA-B27 with rheumatoid arthritis is not currently investigated as a meta-analysis. Hence, in this letter, a brief meta-analysis on this association will be performed. Although there were some studies on the association of RA and HLA-B27, however, there was not a pooled odds ratio reported in textbooks. Based on this brief meta-analysis, number 2.687 can be reported as the odds ratio of this association. It shows that this association is neither sensitive nor specific, but can be an idea for pharmacogenomics and personalized medicine as a potential risk factor. Such other associations should be reported numerically and updated in textbooks.

Keywords: HLA-B27, rheumatoid arthritis, meta-analysis, personalized medicine, human leukocyte antigen, immunogenic peptides.

1. INTRODUCTION

Rheumatoid Arthritis (RA) is an autoimmune disease which is observed in many people all over the world. RA leads to joint damage and reduces the quality of life and finally results in disability [1, 2]. RA initiation and progression are associated with genetic and environmental factors. Human leukocyte antigen (HLA) diversity has the strongest association with rheumatoid arthritis among other genetic factors [3]. Among environmental factors, smoking plays a crucial role in RA development [4].

HLA-B27 is a member of the HLA class I family which is identified on chromosome 6. Today, more than 100 subtypes of HLA class I have been identified [5-7]. HLA-B27 acts as an antigen presenter which presents endogenous antigens for cytotoxic T-cells. Moreover, it has been reported that HLA-B27 and HLA class I in general can present antigen to natural killer (NK) cells *via* interaction with Killer-cell Immunoglobulin-like Receptors (KIR) [7]. HLA-B27 is associated with a series of disorders such as reactive arthritis, uveitis, psoriatic arthritis, Inflammatory Bowel Disease (IBD)-associated arthritis and Ankylosing Spondylitis (AS) [8]. About the pathogenesis of HLA-B27, there are different hypotheses such as its misfolding and presentation of specific immunogenic peptides [9].

Previously, the association of HLA-B27 and its polymorphism with AS has been investigated as original and meta-analysis studies. However, the association of HLA-B27 with rheumatoid arthritis is not currently investigated as a meta-analysis. Hence, a brief meta-analysis on this association will be performed.

In order to find relevant papers, databases PubMed, Science Direct and Web of Science (WOS) will be searched. After screening and applying eligibility

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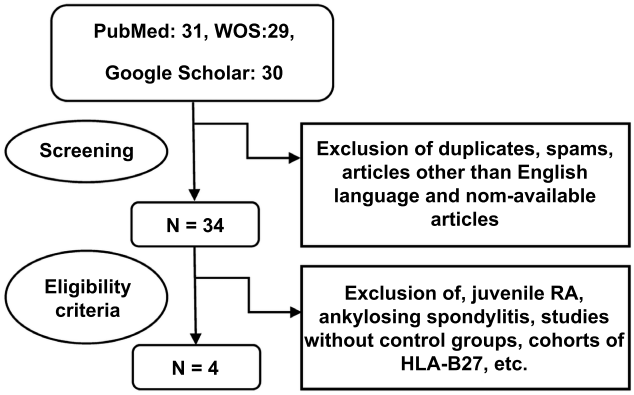

Fig. (1). Flowchart of study selection.

Table 1. Summary of the data from previous articles. * Calculated with Yate's correction.

Study ID	Country	Method of Evaluation	Positive in RA	Positive in Control	Negative in RA	Negative in Control	OR*	Lower Limit	Upper Limit	Fixed Weight	Random Weight
Pasternack, 1977	Finland	Serology	9	19	35	101	1.234	0.505	3.010	4.829	3.999
Khan, 1987	US	Unknown	15	29	90	446	2.419	1.240	4.719	8.608	6.283
Yazici, 1987	Netherland	Unknown	7	8	43	260	4.561	1.563	13.306	3.351	2.929
Paimela, 1993	Finland	Serology	29	130	58	770	2.872	1.769	4.664	16.354	9.602

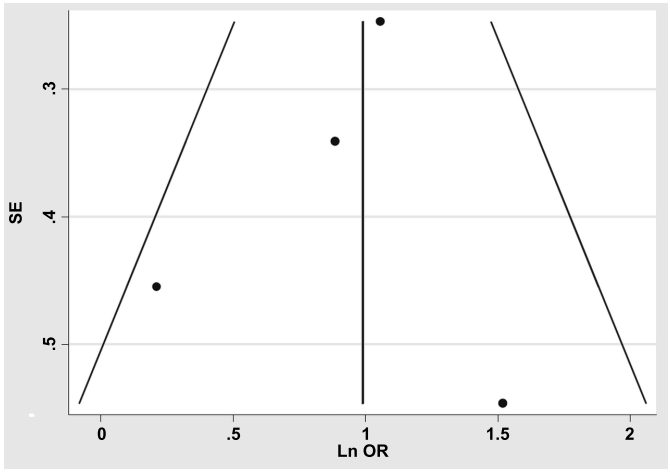

Fig. (2). Funnel plot of the imported studies shows no publication bias.

criteria, 4 papers imported for meta-analysis (Fig. **1**). To analyze and graph the collected data, Excel 2013 (Microsoft, US) and STATA 14 (StataCorp LLC, US) through manual analysis will be used. Data were collected and sorted as 2 by 2 contingency tables. The odds ratios (OR) were corrected with Yate's correction and were reported with 95% confidence interval (CI), and thereafter the pooled result was analyzed based on Woolf's rule and inverse variance weighting. The application of Yate's correction in meta-analysis has been previously reported [10]. A funnel plot was used to investigate publication bias.

Among the four eligible studies, all of them were for the previous century [11-14]. A total number of patients was 286 and a total number of controls was 1763. The data of each study are summarized (Table **1**). Merely case-control studies on the association of HLA-B27 positivity with susceptibility to RA were eligible. The funnel plot showed no publication bias (Fig. **2**). The fixed effect model of pooled result showed a significant association between HLA-B27 and rheumatoid arthritis (OR=2.687 with 95% CI: 1.342-5.379) as well as the random effect model (OR=2.677 with 95% CI: 1.243-5.767**)** (Fig. **3**).

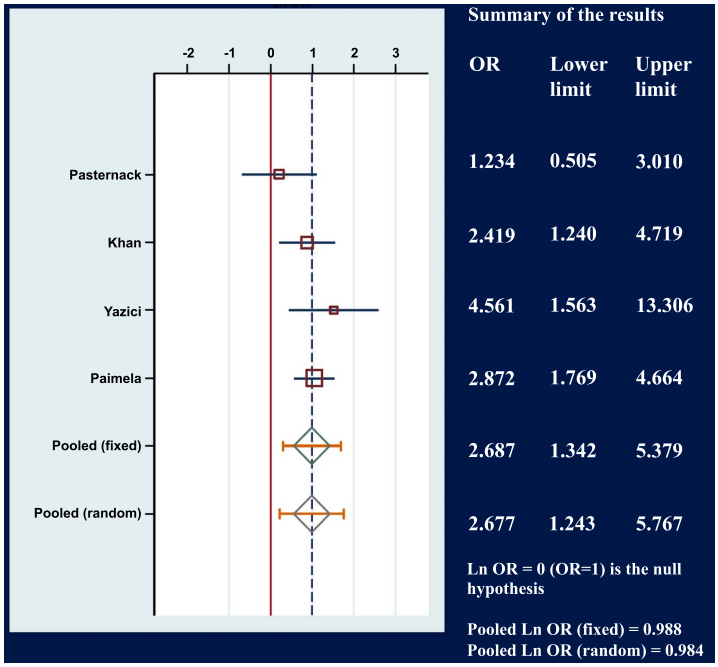

Fig. (3). Forest plot of the imported studies and the pooled results.

Although there were some studies on the association of RA and HLA-B27, however, there was not a pooled odds ratio reported in textbooks. Interestingly, the case-control studies on this association were rare. However, evidence from the existed literature will be extracted. Based on this brief meta-analysis, number 2.687 will be reported as the odds ratio of this association. Of course, the ethnicities were limited to Finland, US and Netherland. Therefore, this odds ratio may not be able to be generalized. However, some current commonplace statistics in medical sciences are based on single original studies. The obtained odds ratio shows that this association is neither sensitive nor specific, but can be an idea for pharmacogenomics and personalized medicine as a potential risk factor. Our suggestions for future studies are (1) investigating the role of HLA-B27 as an independent risk factor using adjusting models, (2) investigation of its causation role using Mendelian randomization studies, and (3) investigation of the role HLA-B27 positivity on response to treatment as pharmacogenomics studies. Such other associations should be reported numerically and updated in textbooks.

LIST OF ABBREVIATIONS

AS = Ankylosing Spondylitis

HLA = Human Leukocyte Antigen

IBD = Inflammatory Bowel Disease

KIR = Killer-cell Immunoglobulin-like Receptors

NK = Natural Killer

RA = Rheumatoid Arthritis

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

This letter is a part of a rheumatology project supported by Lorestan University of Medical Sciences with ethics code IR.LUMS.REC.1396.375. We also thank Mr. Bijan Ansari-moghaddam for his help on the occasion of his MSc thesis.

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