




# The opposite effect of human leukocyte antigen genotypes in sarcoidosis and tuberculosis: a narrative review of the literature

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**ABSTRACT** Sarcoidosis and tuberculosis share several similar clinical and pathogenic characteristics that make some researchers consider a common pathogenesis for these diseases. Human leukocyte antigen (HLA) genotypes are studied both in sarcoidosis and tuberculosis patients, but to our knowledge, there are no comparative studies of genetic predisposition for sarcoidosis and tuberculosis development.

The aim of this review was to analyse the relationship between HLA genotypes and the development of sarcoidosis and tuberculosis. Original and review articles published in various online databases from 1960 to 2019 were studied.

The search results showed opposite effects of the HLA genotypes on predisposition to sarcoidosis or tuberculosis. It was revealed that the genotypes predisposing to the development of sarcoidosis (HLA-DRB1\*03/07/15) have protective properties against the development of tuberculosis. Moreover, genotypes causing the development of tuberculosis (HLA-DRB1\*04) have a protective effect on the development of sarcoidosis.

The results of this narrative review of the literature may allude to the existence of genetic predispositions that lead to the development of an antibacterial or autoimmune response to mycobacteria.



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**The HLA-DRB1\*03/07/15 genotypes predispose to the development of sarcoidosis and have protective properties against the development of tuberculosis, while the HLA-DRB1\*04 genotype has an opposite effect on the development of these diseases** <https://bit.ly/2Tl2rj1>

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## Introduction

Sarcoidosis and tuberculosis (TB) are granulomatous diseases that affect various organs and share some clinical and pathogenic similarities, and because of this, doctors and scientists have long suggested the possibility of a common pathogenic mechanism for these diseases [1].

It is recognised that sarcoidosis is an autoimmune disease triggered by different inorganic (dust, paint, vaccinations) and infection factors (viruses, bacteria, fungi), among which the greatest attention is paid to mycobacterial infections [2]. The signs of mycobacterial infection, such as structural cell wall elements and nucleic acids, have been repeatedly described in sarcoid granulomas [3, 4]. Also, antibodies against bacterial proteins and mononuclear cell activation after incubation with bacterial antigens have been observed in patients with sarcoidosis [5, 6]. Because of the absence of active TB infection in these patients, these findings can indicate a possible previous mycobacterial infection, which was suggested by SCADDING [7] in 1960. The ability of bacteria to cause autoimmune inflammation is explained by a possible mimicry of bacterial proteins (p36 proteins, heat shock proteins HSP65, and HSP7, ESAT-6 and KatG enzymes) with human autoantigens (tubulin, desmin, vimentin) [8]. The cross-reactivity of anti-TB antibodies and anti-DNA autoantibodies obtained in patients with systemic lupus erythematosus was also shown by SHOENFELD *et al.* [9]. Anti-TB antibodies were found to react with ssDNA, dsDNA, and other polynucleotides, whereas anti-DNA autoantibodies bound to three glycolipids shared among all mycobacteria and derived from the mycobacterial cell wall.

A similar clinical, radiological picture, as well as similar pathogenic pathways, can indicate a relationship between sarcoidosis and TB. *Mycoplasma tuberculosis* initiates the processes of productive inflammation in TB, which causes the formation of granulomatous inflammation in affected organs [1]. In sarcoidosis, granuloma formation is also described, induced by the influence of trigger factors and various microorganisms, including *M. tuberculosis*. However, sarcoid granulomas are lacking severe caseous necrosis, which is a specific criterion for the differential diagnosis of diseases [10]. Unfortunately, this difference in the histological picture leads to a large number of errors in the differentiation of diagnoses [11, 12]. A variety of immunological studies that have determined the activity of *M. tuberculosis* have also provided estimations of the diagnosis. The significant difference in the results of immunological tests (ELISPOT, QuantiFERON TB test, Diaskintest) has been described, with 80–94% negative results in sarcoidosis and predominantly positive results in TB, even without bacterial excretion [13]. It can be assumed, that *M. tuberculosis*, being an aetiological factor of TB, might also be one of the infectious triggers in sarcoidosis. The severity of inflammation depends on the immunogenetic characteristics of the macro-organism and the human leukocyte antigen (HLA) system is the main coordinator of the development of both autoimmune and infectious types of inflammation [14]. Gene polymorphisms of the HLA system are the most studied risk factors [15]. These genes encode major histocompatibility complex (MHC) molecules presenting antigens on the cell surface to T-lymphocytes. The HLA system is one of the first to come into contact with foreign antigens, which explains its influence on the development of the subsequent immune response, particularly in autoimmune processes [16].

This review aims to summarise recent genetic and immunological literature, describing the relationship between HLA genotypes and the development of sarcoidosis and TB.

## Methods

Original and review articles indexed in the online databases Medline/PubMed, Scopus and ResearchGate from 1970 to 2019 were studied.

The initial selection of articles was based on the keywords: sarcoidosis, Löfgren's syndrome, TB, pulmonary TB, HLA genes, genetic predisposition. The inclusion criteria for the original articles were publications describing the study design and the results of HLA genotyping of adults and children aged 0–18 years without HIV infection, with an active/chronic form of sarcoidosis and pulmonary TB.

In total, 388 publications were selected by keywords, of which 288 described the immunogenetic studies of TB and 100 publications described sarcoidosis (figure 1).

Literature reviews (n=73) and publications prior to 1995 (n=141) were excluded from the analysis because of the serological methods of HLA-DR/DQ genotyping. Among several publications from one group of authors, articles with the most complete information and a large number of analysed parameters were selected. Articles used in meta-analyses were excluded. In total, data were subsequently analysed in 28 publications (14 for TB and 15 for sarcoidosis).

According to the data presented in the publications, the examination of TB patients included: analysis of clinical symptoms, radiography, laboratory, and bacteriological examination. If necessary, in order to verify

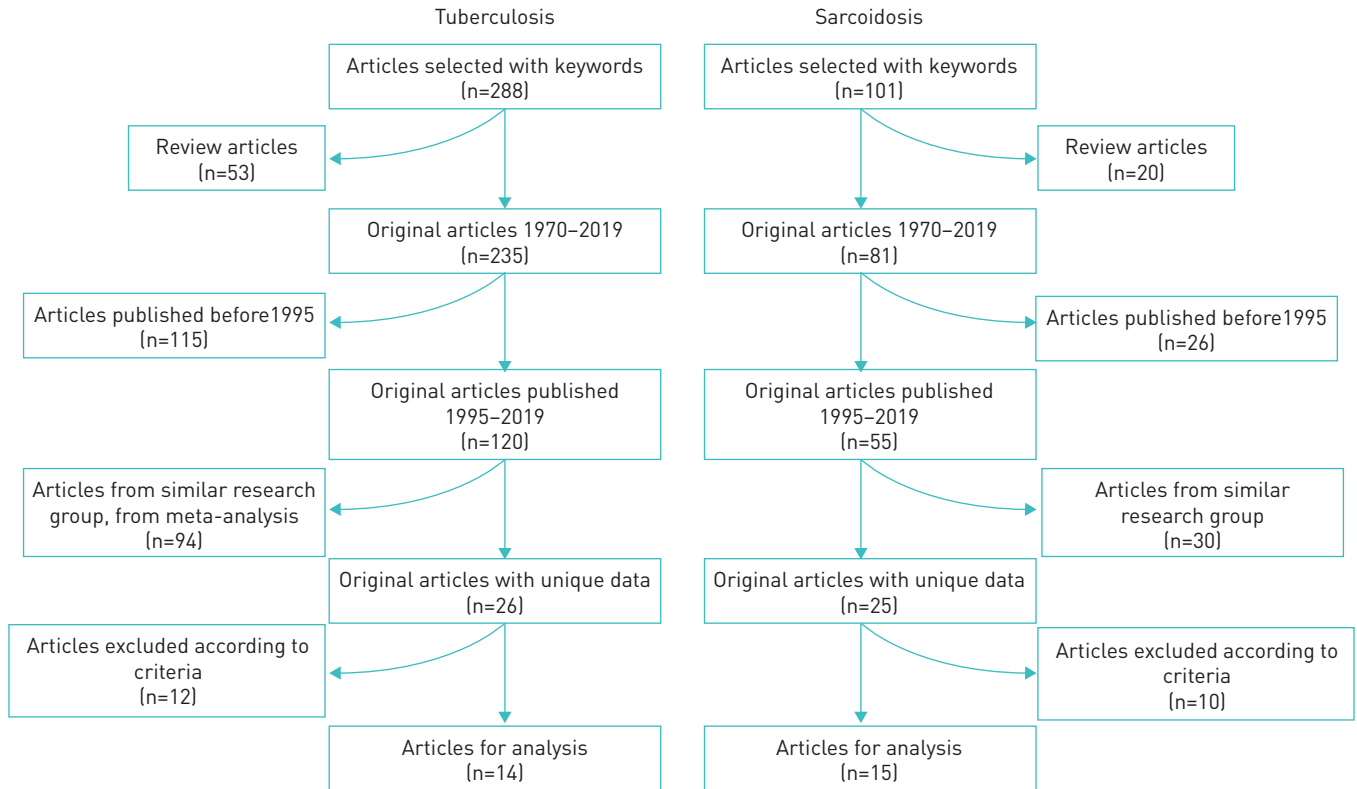


FIGURE 1 Study design diagram.

the diagnosis and conduct differential diagnosis, a histological method for examining diagnostic material was used.

Statistical analysis of the data was not performed due to the small number of studies.

### The results of the analysis

According to the studied sources and several meta-analyses, the presence of the HLA-DRB1\*04 and HLA-DRB1\*08 genotypes is most typical for TB, while a protective function was particularly noted with the HLA-DRB1\*03 and HLA-DRB1\*07 genotypes [17, 18]. It is important to stress the point that genotype distribution strongly varies among different ethnic groups. Thus, the HLA-DRB1\*16 genotype is a predisposing factor for TB development in Polish people, but a protective effect was found in people from Central India [19].

Several studies have established the relationship of different HLA genotypes with the development of active or chronic forms of TB. For the active form of TB, the presence of the HLA-DRB1\*01.04 genotypes are more typical, whereas for the chronic form, the combinations of HLA-DRB1\*16 with HLA-DQB1\*05/03 and HLA-DRB1\*04 with HLA-DQB1\*02 are more prevalent [20].

The results of HLA-DRB1, DQB1-genotyping in studied publications are presented in table 1.

In sarcoidosis, a relationship between the development of the disease and HLA genotypes of classes I, II, and III was detected. The carrying of the HLA-DRB1 and HLA-DQB1 genotypes also turned out to be most significant (table 2). In addition, an association between a genotype and the form of the disease was found. For Löfgren's syndrome, the presence of the HLA-DRB1\*01.03 or HLA-DQB1\*02.01 genotypes was more typical, whereas for the chronic form, HLA-DRB1\*07/14/15 or HLA-DQB1\*06.02 was found. A protective effect has been stated for the HLA-DRB1\*01/04 genotypes.

The results of HLA-DRB1, DQ1 genotyping in studied publications are presented in table 3.

There are several studies revealing genetic predisposition for sarcoid granuloma formation in various organs. Thus, HLA-DRB1\*04/15 alleles carriers are more prone to developing sarcoidosis of the cardiovascular system, and the HLA-DRB1\*04 alleles are more likely to cause uveitis [49].

TABLE 1 HLA-DRB1, DQB1 genotypes in various forms of tuberculosis

First author, year [ref.]	Patients with lung TB	Method of genotyping	The statistically approved HLA genotypes		Country
			Of predisposition	Protective	
ARCHAKOVA, 2008 [20]	Adults (307)	PCR-SSP	DRB1*04/ 16	DRB1*03/07/15	Russia
PAVLOVA, 2003 [21]	Adults (114)	PCR-SSP	DRB1*04/16	DQB1*03	Russia
DUARTE, 2011 [22]	Adults (92)	PCR-SSP	DRB1*14	-	Portugal
AMIRZARGAR, 2004 [19]	Adults (40)	PCR-SSP	DRB1*07	DRB1*03/05/15	Iran
DUBANIEWICZ, 2005 [23]	Adults (61)	PCR-SSP	DRB1*14/16	DQB1*02	Poland
KIM, 2005 [24]	Adults (160)	PCR-SSO, PCR-SSP	DRB1*08.03	DRB1*10	Korea
TERÁN-ESCADÓN, 1999 [25]	Adults (50)	PCR-SSP	DRB1*15/01	DRB1*08/44	Mexico
VEJBAESYA, 2002 [26]	Adults (82)	PCR-SSO	DRB1*16.02	DRB1*07.01	Thailand
STARSHINOVA, 2018 [27]	Children (n=98)	PCR-SSP	DRB1*04	DRB1*07	Russia
WAMALA, 2016 [28]	Adults (n=43)	PCR-SSP	-	DQB1*03.03	Uganda
TOYO-OKA, 2017 [29]	Adults (n=682)	PCR-SSP	DRB1*09.01	-	Thailand
WU, 2013 [31]	Adults (n=231)	PCR-SSP	DRB1*04	-	China
DE LIMA, 2016 [31]	Adults (n=316)	PCR-SSP	DRB1*04	-	Brazil
WANG, 2001 [32]	Adults (n=74)	PCR-SSP	DRB1*15	DRB1*11	China

TB: tuberculosis; HLA: human leukocyte antigen; PCR-SSP: single specific primer PCR; PCR-SSO: sequence-specific oligonucleotide PCR.

Also, the association between ethnicity and sarcoidosis is worth mentioning (among ethnic groups, such as African-American and European people with a high prevalence of sarcoidosis, various HLA genotypes were found) [48, 49].

The presence of the HLA-DRB1\*11.01 genotype increased the disease risk in both races, whereas the HLA-DRB1\*12.01/15.03 genotypes were more typical for African-American people, and HLA-DRB1\*15.01/04.01 for white people. Moreover, the HLA-DRB1\*03.01 genotype is a predisposing factor for the development of sarcoidosis for European people; for African-American people, this genotype is of protective value [38].

## Discussion

The study on the HLA genotypes distribution in patients with TB and sarcoidosis showed that the acute form of TB most often occurs with the HLA-DRB1\*04 genotypes; the chronic form is associated with a combination of HLA-DRB1\*16 with HLA-DQB1\*05/03, or HLA -DRB1\*04 with HLA-DQB1\*02. A protective effect was characteristic for the HLA-DRB1\*3/7/15 genotypes. The most significant genotypes affecting the development of sarcoidosis were HLA-DRB1 and HLA-DQB1. Many studies have shown that the development of Löfgren's syndrome is associated with the HLA-DRB1\*01.03 or HLA-DQB1\*02.01 genotypes, and the development of a chronic form is associated with genotypes HLA-DRB1\*07/14/15 or HLA-DQB1\*06.02. The HLA-DRB1\*01/04 genotype has a protective effect.

Similar results were obtained by a group of researchers from Poland. According to their data, HLA-DRB1\*15 is statistically more common in sarcoidosis than in TB, whereas relatively healthy individuals among patients with sarcoidosis were more often found to have HLA-DRB1\*3/11 genotypes. The HLA-DRB1\*04/08 and 16 genotypes were determined much less frequently in comparison to the

TABLE 2 HLA genotypes in sarcoidosis

<b>HLA genes</b>		
<b>HLA I</b>	HLA-B*07/08, HLA-A3	
<b>HLA II</b>	Löfgren's syndrome	HLA-DRB1*01/03, HLA-DQB1*02.01
	Chronic form	HLA-DQB1*06.02, HLA-DRB1*07/14/15
	Protective effect	HLA-DRB1*01/04
<b>HLA III</b>	BTNL2, C4, C6orf10, HSPA1L, LTA, NOTCH4, TAP2, TNF, VEGF	

HLA: human leukocyte antigen.

TABLE 3 HLA-DRB1, DQB1 genotypes in various forms of sarcoidosis

First author, year [ref.]	Patients with sarcoidosis and Löfgren's syndrome	Method of genotyping	The statistically approved HLA genotypes		Country
			Of predisposition	Protective	
<b>BERLIN, 1997 [33]</b>	Sarcoidosis (n=122) Löfgren's syndrome (n=34) Chronic form (n=57)	PCR-SSP	DRB1*03/17 DRB1*17 DR B1*14/15	- - -	Scandinavia
<b>BOGUNIA-KUBIK, 2001 [32]</b>	Sarcoidosis (n=53)	PCR-SSP	DRB1*03	DRB1*11	Poland
<b>PLANCK, 2002 [35]</b>	Löfgren's syndrome (n=19)	PCR-SSP	DR B1*17	-	Scandinavia
<b>FOLEY, 2001 [36]</b>	Sarcoidosis (n=345)	PCR-SSP	DRB1*03	DRB1*01/04	UK, Poland, Czech Republic
<b>GRUNEWALD, 2010 [37]</b>	Sarcoidosis (n=724)	PCR-SSP	DRB1*03/14/15	DRB1*01/03/07	Scandinavia
<b>ROSSMAN, 2003 [38]</b>	Sarcoidosis (n= 948)  black white	PCR-SSP	DRB1*11.01/15.01/ 12.01 DRB1*11.01/1201 DRB1*11.01/04.02/ 15.01	DRB1*04.01/04.04/ 04.07/15.03 DRB1*15.03 DRB1*04.01	USA
<b>DARLINGTON, 2011 [39]</b>	Patients with sarcoidosis (n=1000) out of whom had symptoms associated with HS (Heerfordt's syndrome) (n=83)	PCR-SSP	DRB1*04 - uveitis	DRB1*04 - system sarcoidosis	Sweden
<b>LEVIN, 2015 [40]</b>	Sarcoidosis (n=1277)	Illumina HumanOmni1-Quad	DRB1*12/11	DRB1*03	African Americans
<b>DA COSTA, 2013 [41]</b>	Sarcoidosis (n=63)	QuantiGene Plex assay	DRB1*14	DRB1*15/16	Brazil
<b>MORTAZ, 2015 [42]</b>	Pulmonary sarcoidosis (n=51), Extrapulmonary sarcoidosis (n=39)	PCR-SSP	DRB1 *7 - pulmonary, DRB1 *12 - Extrapulmonary	-	Iran
<b>OZYILMAZ, 2014 [43]</b>	Pulmonary sarcoidosis (n=86), Extrapulmonary sarcoidosis (n=46)	PCR-SSP	DRB1*15	DRB1*11 - extrapulmonary	
<b>SHARMA, 2003 [44]</b>	Sarcoidosis (n=56)	PCR-SSP	DRB1*11/14 (chronic form)	DRB1*07	India
<b>VOORTER, 2005 [45]</b>	Sarcoidosis (n=149)	PCR-SSP	DRB1*15.01/01 - severe form	-	Netherlands
<b>YANARDAG, 2017 [46]</b>	Sarcoidosis (n=74)	PCR-SSP	DRB1*07/14/15	-	Turkey
<b>PAPADOPOULOS, 2006 [47]</b>	Sarcoidosis (n=66)	PCR-SSP	DRB1*02/14	-	Germany

HLA: human leukocyte antigen; PCR-SSP: single specific primer PCR.

control group and the HLA-DRB1\*14 genotype, in comparison with TB patients. Analysis of the genotypes associated with a predisposition to TB showed a positive association with HLA-DRB1\*14 and 16 alleles and a negative association with HLA-DRB1\*04 genotype in comparison with healthy individuals. A comprehensive analysis of the results revealed that for the Polish population, the HLA-DRB1\*11 genotype predisposes to the development of sarcoidosis and is protective for the development of TB, whereas the HLA-DRB1\*14 genotype has the opposite effect [50, 51].

Despite conflicting and ambiguous results derived from the studies on the genetic predisposition to TB and sarcoidosis, our data analysis revealed another genotype distribution pattern for these diseases. The HLA-DRB1\*03/07/15 genotypes are predisposing risk factors for the development of sarcoidosis, whereas the protective effect of these genotypes is revealed in TB. As for the HLA-DRB1\*04 genotype, this was associated with the development of TB, whereas a protective effect was revealed for sarcoidosis (table 4).

The differences observed when comparing the data shown in table 4 may be associated with the molecular structure of the HLA proteins. According to some studies of binding activity based on the silicate analysis in the HLA-DRB1\*04 genotype, MHC molecules have a weak affinity for mycobacterial antigens, whereas in the HLA-DRB1\*03.01 genotype, there was a high affinity of MHC proteins for bacterial antigens [31].

TABLE 4 HLA-DRB1 genotypes in sarcoidosis and tuberculosis

Disease	Susceptibility	Protective effect
Sarcoidosis	HLA-DRB1*03/07/15	HLA-DRB1*04
Tuberculosis	HLA-DRB1*04	HLA-DRB1*03/07/15

A previous *in silico* analysis found that patients with Löfgren's syndrome express HLA-DR alleles capable of binding a significantly higher number of bacterial epitopes than other HLA-DR alleles [52].

Interestingly, DRB1\*03.01, shows the highest predicted binding to *M. tuberculosis* epitopes [53]. According to silicate binding analysis, The HLA-DRB1\*03.01 allele consistently demonstrated the highest binding affinities for all six peptides, while HLA-DRB1\*03.02 had relatively strong binding affinities for the proteins SodA (*M. tuberculosis*). The authors suggested that this difference in binding may be due to the difference in amino acid residues 28 and 86, which determined the ability to bind HSP 3–13 and HSP 4–15 [54, 55].

CONTINI *et al.* [56] revealed a relationship between the affinity for mycobacterial proteins and the type HLA-DRB1. It turned out that with genotypes characteristic of the development of TB (HLA-DRB1\*08.01, \*08.02, \*14.01, \*15.01 and \*15.02), the affinity for proteins is lower than with other genotypes HLA-DRB1 \*03.01, \*07.01, \*11.01, \*11.02, \*13.01 and \*13.02, among which one can distinguish genotype characteristics for the development of sarcoidosis.

Moreover, studies of the activation of T-lymphocytes by mycobacterial proteins showed that the culture filtrate protein of 10 mycobacteria induces the release of interferon (IFN) and cytotoxic reactions in CD4<sup>+</sup> T-lymphocytes with DRB1\*04 molecules [57].

Interesting results were obtained by SELVARAJ *et al.* [58]. In response to live *M. tuberculosis* and culture filtrate antigen in patients with TB, the level of pro-inflammatory cytokine interleukin (IL)-6 increased with the DRB1\*04 genotype, the level of IFN- $\gamma$  decreased with the HLA-DRB1\*15 genotype, whereas among the group in HLA-DRB1\*03 representatives, IFN- $\gamma$  levels increased. However, researchers find it difficult to explain the results.

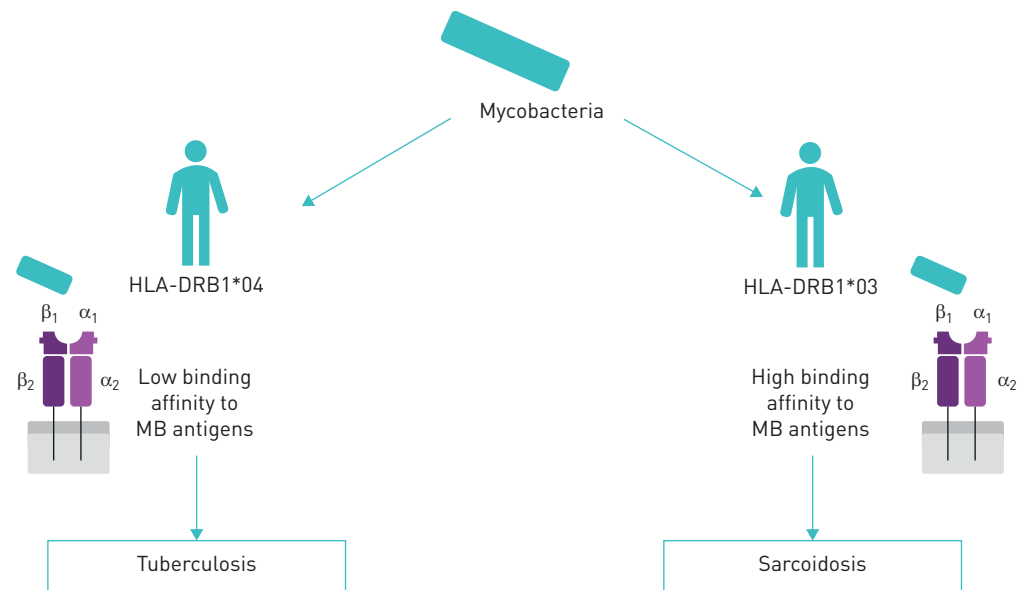
Perhaps the HLA-DRB1\*03 molecule, having a greater affinity for proteins, triggers a stronger immune response, which leads to auto-inflammatory processes, while the HLA-DRB1\*04 molecule with moderate affinity properties activates the antimicrobial immune response. Such hyperactivation can be seen in the pathogenesis of coeliac disease, a chronic autoimmune disease that affects the small intestine. In representatives of the HLA-DQ2/8 genotypes, the molecules have high affinity for gliadin, which leads to hyperactivation of the immune response and the development of autoimmune reactions [59].

Thus, it can be assumed that depending on the HLA-DRB1 genotypes the antibacterial inflammation and/or autoimmune processes may characterise the immune response in mycobacterial infection.

However, it is worth noting that autoimmune reactions occur in TB patients. For example, there are autoimmune reactions, such as granulomatosis with polyangiitis, arthritis, and uveitis, which are also detected in TB [60]. The presence of an autoimmune process in TB may be confirmed by studies showing the presence of autoantibodies in patients with TB. Antibodies to anti-cardiolipin IgG, anti-b2 glycoprotein IgG, anti-prothrombin, anti-proteinase 3 and anti-neutrophil cytoplasmic antibodies decreased after anti-TB treatment [61]. Unfortunately, there are no data on the immunogenetic characteristics of TB patients who showed signs of autoimmune inflammation, which could help to determine the role of various genotypes in the development of the immune response in contact with the *M. tuberculosis*.

According to our point of view, mycobacterial antigens of the HLA-DRB1\*03/07/15 genotypes carriers are triggers developing sarcoid reactions with an autoimmune component, while the HLA-DRB1\*04 genotype is associated with a high risk of developing TB, as presented in schematic form in figure 2.

Similar results were found when studying the role of the Epstein–Barr virus (EBV) in the development of autoimmune diseases in individuals with different alleles of the HLA-DRB1 genotype. It is considered that antigens of the EBV can cause the development of autoimmune reactions by the mechanism of molecular mimicry. For example, an autoimmune reaction in multiple sclerosis was detected in HLA-DRB1\*15 genotype carriers against myelin basic protein, which has a structure similar to the EBNA-1 virus protein [62]. For carriers of HLA-DRB1\*04 an increased risk of developing rheumatoid arthritis with EBV infection was found, which is associated with the molecular similarity of the virus glycoprotein-110 and



**FIGURE 2** Predisposition to sarcoidosis or tuberculosis development according to HLA-DRB1 genotypes. MB: mycobacterial.

the QKRAA sequence located in DRB1\*04.01 [63] The HLA-DRB1\*04.05 genotype has a protective effect on the development of typhoid fever caused by *Salmonella enterica*, but it is a predisposing factor for the development of rheumatoid arthritis in the Asian population [64].

### Conclusion

Thus, the HLA system and specific properties of external factors, determine the development of the immune response when a person comes in contact with this factor. Determining HLA genotypes may result in assessing a risk degree for developing TB or sarcoidosis in the foci of mycobacterial infection and forecasting a possible course of the disease, thus providing more effective preventive measures and future prospects for differential diagnosis.

The study of immunogenetic characteristics, with respect to the development of TB or sarcoidosis, is a very promising area and needs further investigation to obtain more accurate data necessary for making practical recommendations.

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