

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

5,400

Open access books available

133,000

International authors and editors

165M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Genetics of Sarcoidosis

Nabeel Y. Hamzeh and Lisa A. Maier

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/55332>

1. Introduction

Sarcoidosis is a multi-system, T-helper 1 (Th1) cell biased granulomatous disorder. The current hypothesis is that sarcoidosis develops in a genetically predisposed individual who is exposed to a yet unknown environmental trigger(s) [1]. Antigen presentation in the context of major histocompatibility complex II (MHC-II) activates Th1 cells with subsequent production of various cytokines and chemokines including but not limited to IFN- γ , TNF- α , TGF- β , IL-2, IL-12 and others leading to further immune cell recruitment and activation [2]. The immune response ultimately leads to the formation of granulomas which consist of a central core of mononuclear cells surrounded by CD4+ cells and a small number of CD8+ and B-cells [2]. A role for regulatory T-cells has been proposed but their exact role in sarcoidosis is yet unknown [3].

The disparity in prevalence and variability of organ involvement between ethnic groups [1] and the familial clustering of sarcoidosis strongly support a genetic basis for sarcoidosis [4]. Several genome wide associations studies (GWAS) have identified potential association between specific genetic loci and sarcoidosis [5-11] and several studies have also associated various human leukocyte antigen (HLA) markers and gene-specific single nucleotide polymorphisms (SNP) with the risk, disease course and organ involvement with sarcoidosis indicating that sarcoidosis is a polygenic disease. Adding to this complexity, certain genetic markers have shown an association based on ethnicity and gender and some have shown differential associations based on gender and ethnicity [34]. Genetic polymorphisms that are functional can potentially influence the immune system's recognition of an antigen and the subsequent immune response to the antigen thus dictating disease phenotype (Figure 1).

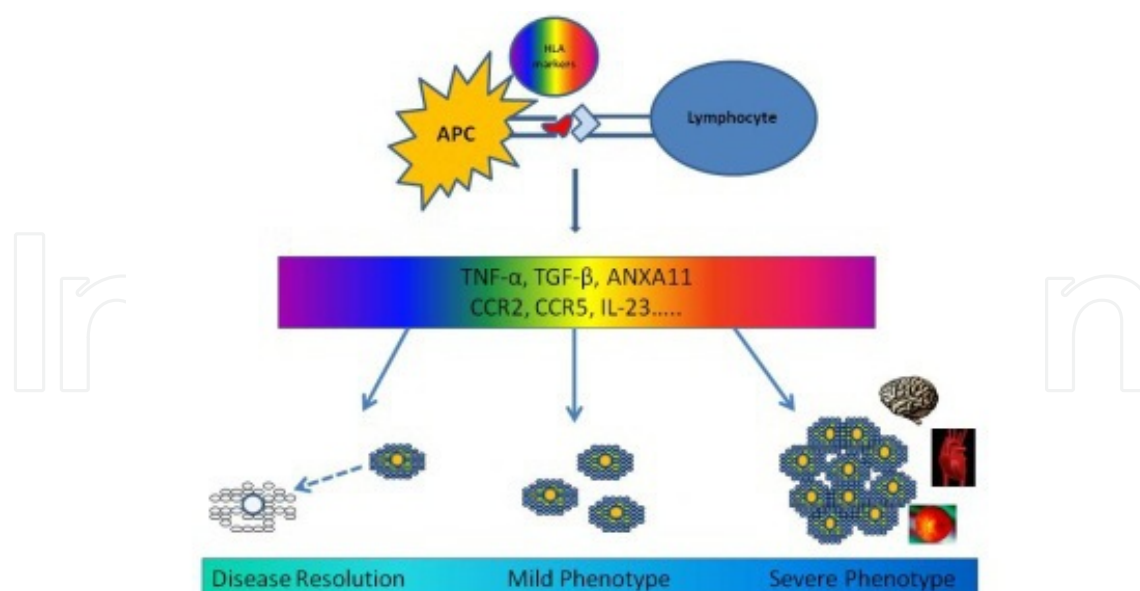


Figure 1. Functional genetic polymorphisms dictate immune response and disease phenotype

Genetic studies have played an important role in revealing new pathways and mechanisms involved in the pathogenesis of immune mediated diseases such as rheumatoid arthritis, inflammatory bowel disease, psoriasis, systemic lupus erythematosus, type 1 diabetes and others [12]. Genome-wide association studies investigate the potential association of a disease with genetic markers across the entire genome without a mechanistic hypothesis [13]. Thousands of representative SNPs (tagging SNPs) that span the whole genome are assayed for potential association with a specific disease. In contrast, a candidate-gene approach is hypothesis driven and investigates the potential association of disease with polymorphisms in a specific gene(s) that encode molecule(s) (receptor, cytokine, signal transduction...) that are involved in the pathogenesis of a disease [13]. Familial-genetic studies investigate the association of genetic markers with a rare disease. Family members of an affected individual are studied for genetic markers that are present in affected members but absent in others [13].

Several environmental and infectious agents have been proposed to be associated with sarcoidosis but none proven yet. The ACCESS (A Case Controlled Etiological Study in Sarcoidosis) study group identified 5 occupations and 5 exposures that were more prevalent in sarcoidosis patients [14]. These exposures included agricultural employment, physicians, jobs raising birds, jobs in automotive manufacturing and middle/secondary school teachers, insecticides, employment in pesticide-using industries, occupational exposure to mold and mildew, occupational exposure to musty odors and use of home central air-conditioning [14]. In contrast, smoking appears to be protective against sarcoidosis [14, 15]. Infectious agents, particularly Mycobacteria, are re-emerging as a potential antigen in sarcoidosis with studies detecting Mycobacteria proteins in tissues from sarcoidosis patients and T-cells from sarcoidosis patients responding to stimulation by Mycobacterial antigens [16-23]. Recent studies have also demonstrated an interaction between genetic markers and in vitro immune responses to Mycobacterial antigens further supporting the gene-environment interaction theory. [22]

In this review, we will attempt to summarize the current literature on the association of genetic markers with sarcoidosis from a functional perspective and highlight differences that might exist between different racial groups.

Genetic markers and risk of disease (Table 1):

Gene	Polymorphism	Population	OR	CI	p	Ref	
Lofgren's Syndrome	HLA	DRB1*03	White UK/Dutch	7.97	4.16-15.26	<0.0001	[26]
		DRB1*0301	White Spanish	3.52	1.83-6.79	0.0004	[27]
		DRB1*0301	White Swedish	7.71	4.63-12.84	<0.0001	[27]
		DRB1*03	White Swedish	6.71	NR	<0.0001	[28]
		DRB1*03-DQB1*0201	White Dutch	12.5	5.69-27.52	<0.0001	[29]
		DRB1*0301	Finnish	2.46	1.11-5.45	0.044	[33]
		DRB1*1501	Finnish	2.16	1.06-4.41	0.037	[33]
MHC2TA	rs3087456G	White Swedish	1.31†	1.04-1.65†	.019	[31]	
	rs11074932C	White Swedish	1.27†	1.02-1.58†	.026	[31]	
BTNL2	rs3117099T	White UK/Dutch	3.05	2.01-4.62	<0.0001	[26]	
CCR2	Haplotype 2*	White Dutch	4.4	1.9-9.7	<0.0001	[41]	
	Haplotype 2*	Spanish	2.03	1.11-3.73	0.041	[27]	
	Haplotype 2*	Swedish	3.02	1.65-5.52	0.0027	[27]	
CCR5	rs2040388A	German/Female	1.93	1.35-2.77	0.0003	[53]	
	rs2856757C	German/Female	1.65	1.17-2.33	0.004	[53]	
TNF [#]	TNF-α 308AA rs1800629	US White	8.182	2.45-27.34	0.027	[73]	
	TNF-α 308A rs1800629	Polish	2.3	1.23-4.32	<0.01	[77]	
	TNF-α 308A	UK/Dutch	3.1†	1.33-7.20†	0.006	[78]	
	TNF-α 308A	German	NR	NR	0.0078	[79]	
	LTA-252G rs909253	Polish	2.98	1.67-5.29	<0.001	[77]	
	LTA-252GG rs909253	US White females	11.33	3.18-40.37	0.027	[73]	
ANXA11	rs1049550TT	Czech	0.31	0.11-0.84	0.02	[95]	
Increased risk of non-Lofgren's							
HLA	DQB1*0602-DRB1*15	White Dutch	2.27	1.46-3.54†	0.0032	[32]	
	DRB1*12	White UK/Dutch	2.5	1.26-4.96	0.003	[26]	
	DRB1*12	UK	3.7	1.73-7.94	0.001	[29]	
	DRB1*12	Japanese	2.5	1.17-5.21	0.03	[29]	
	DRB1*1201	US White/AA	2.13	1.14-4.12	0.015	[34]	
	DRB1*10	White UK/Dutch	2.4	1.00-5.88	0.01	[26]	
	DRB1*14	White UK/Dutch	3.1	1.7-5.57	0.0003	[26]	
	DRB1*14	White Swedish	1.79	NR	0.017	[28]	
	DRB1*1401	US White/AA	2.29	1.21-4.34	0.011	[34]	

Gene	Polymorphism	Population	OR	CI	p	Ref
	DRB1*14	UK	2.54	1.47-4.41	0.001	[29]
	DQB1*0503/4	Dutch	2.4	1.11-5.18	0.04	[29]
	DRB1*15	Finnish	1.67	1.12-2.5	0.011	[33]
	DRB1*1501	US White/AA	1.7	1.18-2.46	0.003	[34]
	DRB1*1101	US White/AA	1.98	1.37-2.9	<0.001	[34]
	DRB3*0101	US White/AA	1.6	1.16-2.2	0.004	[34]
	DRB1*1201	US AA	2.67	1.2-6.52	0.014	[34]
	DPB1*0101	US AA	1.72	1.14-2.62	0.008	[34]
	DRB1*0402	US white	2.57	1.02-7.28	0.043	[34]
	DRB1*1501	US White	2.08	1.39-3.15	<0.001	[34]
	DRB1*13	Czech	2.4	1.43-4.03	<0.02	[74]
BTNL-2	rs2076530A	German	2.31	1.27-4.23	<0.006	[37]
	rs2076530A	White UK/Dutch	1.49	1.20-1.86	0.002	[26]
	rs2076530A	White Dutch	1.85	1.19-2.88	0.007	[38]
	rs2076530A	White US	2.03	1.32-3.12	NR	[39]
	rs2294878C	White UK/Dutch	1.54	1.24-1.92	0.001	[26]
TNF	LTA-252G rs909253	Czech	2.63	1.63-4.25	<0.00001	[74]
	TNF- α 308A rs1800629	Polish	2.167	1.17-4.01	<0.05	[77]
	TNF- α -857T	UK/Dutch	NR	NR	0.002	[78]
TLR						
TLR-10	rs1109695C	Dutch	NR	NR	0.002	[68]
	rs7658893A	Dutch	NR	NR	0.001	[68]
TLR-1	rs5743604G	Dutch	NR	NR	0.003	[68]
	rs5743594G	Dutch	NR	NR	0.049	[68]
SLC11A1						
	Allele 2 ^f	US AA	0.48	0.28-0.81	0.014	[69]
	Allele 3 ^y	Polish	1.68	1.01-2.81	0.04	[71]
	Allele 3 ^y	Turkish	2.69	1.61-4.47	<0.001	[70]
	Allele 3 ^y	Greek	1.52	1.08-4.52	0.015	[72]
	INT4	Turkish	2.75	1.68-4.52	<0.001	[70]
ANXA11	rs1049550C	German	1.54	1.23-1.92	0.00014	[94]
	rs1049550T	Czech	0.77	NR	0.04	[95]
	rs2573346C	German	1.55	1.24-1.92	0.00008	[94]
Decreased risk						
HLA	DRB1*01	White Swedish	0.61	NR	0.003	[28]
	DRB1*01	White UK/Dutch	0.5	0.35-0.82	0.001	[26]
	DRB1*01	UK	0.5	0.34-0.76	0.001	[29]
	DRB1*01	Dutch	0.4	0.23-0.76	0.006	[29]
	DRB1*01	Japanese	0.12	0.03-0.52	0.001	[29]
	DRB1*01	Finnish	0.43	0.26-0.72	0.001	[109]
	DRB1*04	White UK/Dutch	0.6	0.46-0.92	0.02	[26]

Gene	Polymorphism	Population	OR	CI	p	Ref
	DRB1*0401	US White/AA	0.48	0.28-0.8	0.003	[34]
	DRB1*04	UK	0.54	0.35-0.84	0.008	[29]
	DQB1*0301	UK	0.69	0.51-0.94	0.02	[29]
	DQB1*0603	US Males	0.5	NR	NR	[34]
	DRB1*1503	US AA	0.56	0.3-0.99	0.44	[34]
	DRB1*0401	Us white	0.44	0.25-0.77	0.003	[34]
	DRB1*07	Czech	0.40†	0.21-0.76†	0.0031	[74]
CCR2						
	CCR2-64I	Japanese	0.37	0.21-0.67	0.0007	[43]

US: United States of America

UK: United Kingdom

AA: African American.

HLA: Human Leukocyte Antigen.

TLR: Toll-like receptor

NR: Not reported.

£Allele 2: T(GT)₅AC(GT)₅AC(GT)₁₀

¥Allele 3: T(GT)₅AC(GT)₅AC(GT)₉

*haplotype 2: (A at -6752, A at 3000, T at 3547 and T at 4385)

#TNF association with erythema nodosum

† Values calculated by authors from raw data provided in original manuscript.

Table 1. Association of genetic markers with risk of developing sarcoidosis.

Numerous studies have been published investigating the association of genetic markers with the risk of developing sarcoidosis or the risk of disease severity, disease course or specific organ involvement [5-11]. Genetic polymorphisms, that are functional, can influence the immune system's response or function leading to active, progressive disease or self-resolving, limited disease. Although it is yet unknown if, and how, many of the genetic polymorphisms detected can influence the immune response, they do provide new insight on pathways that are potentially involved in the pathogenesis of sarcoidosis and provide new potential therapeutic targets.

2. Receptors

2.1. HLA region

The HLA system plays an important role in the immune response and has been associated with various autoimmune diseases [24]. The HLA genes are encoded on chromosome 6 and

consist of over 200 genes [25]. HLA class I molecules, HLA-A, B and C, are expressed by most somatic cells and are important in the immune response [25]. They are composed of an α polypeptide chain, which is coded by the class I genes, and a β chain which is coded by the β_2 -microglobulin gene on chromosome 15 [25]. The HLA class II genes code for the α and β polypeptides of the class II molecule [25]. The HLA class II molecules are designated by 3 letters, the first (D) represents the class, the second (M,O,P,Q or R) represent the family and the third (A or B) represent the α or β chains [25]. The numbers that precedes the asterisk indicates the gene and the numbers following the asterisk represent the allelic variant of that gene [25]. HLA class II molecules are primarily expressed on immune cells. The HLA class II molecules play an important role in the immune response presenting antigens to the effector cells and induce activation of the immune cells [25].

Sarcoidosis can present insidiously (non-Lofgren's syndrome) or present acutely with systemic symptoms, acute arthritis, erythema nodosum and bilateral hilar lymphadenopathy, more commonly known as Lofgren's syndrome (LS) [1]. Several HLA alleles have been associated with LS. HLA-DRB1 is the most common and has been reported in a white Dutch and UK cohorts [26], Spanish and Swedish cohorts (HLA-DRB1*0301) [27], a Scandinavian cohort (HLA-DRB1*03) [28] and a Dutch cohort (HLA-DRB1*03-DQB1*0201) [29]. In addition, HLA-DQB1*0201 has been reported in White UK and Dutch cohorts [30]. HLA-DRB1*03 and HLA-DQB1*02 are in strong LD [30]. In addition, 2 SNPs (rs3087456 and rs11074932) in the major histocompatibility complex class II transactivator (MHC2TA) gene, which acts as a master regulator for the expression of MHC class II molecules, were found to be associated with LS independent of HLA-DRB1*03 [31].

Several HLA alleles have also been associated with increased risk of developing non-LS sarcoidosis. HLA-DQB1*0602 has been associated with increased risk of non-LS sarcoidosis in a Dutch cohort [32]. HLA-DRB1*14, *12 and *10 have been associated with increased risk of sarcoidosis in a white Dutch and British cohort [26], and HLA-DRB1*12 and DRB1*14 in cohorts from the UK, Netherlands and Japan [29] whereas HLA-DRB1*1501 was associated with risk of sarcoidosis in a Finnish cohort [33]. HLA-DRB1*1201, *1401, *1501, *1101 and HLA-DRB3*0101 were associated with sarcoidosis in the ACCESS cohort in the USA [34].

In contrast, HLA alleles that have been associated with decreased risk (protective) for sarcoidosis included HLA-DRB1*01 and *04 in white Dutch and UK cohorts [26] and HLA-DRB1*01 in cohorts from the UK, Netherlands and Japan [29] and HLA-DRB1*0101 was protective in a Finnish cohort [33]. In the ACCESS cohort, HLA-DRB1*0401 was protective for the overall cohort (African Americans and Caucasians) [34].

Some HLA markers are gender or ethnic specific in their association with sarcoidosis. In the ACCESS cohort, HLA-DRB1*1101 was associated with increased risk more in males than females whereas HLA-DRB1*0401 was associated with decreased risk more in males than females, [34] HLA-DQB1*0603 was a risk factor for females but a protective factor for males. [34] For blacks in the ACCESS cohort, HLA-DRB1*1201 and HLA-DPB1*1503 were associated with increased risk of sarcoidosis and HLA-DRB1*1503 was associated with decreased risk of sarcoidosis [34] whereas in whites, HLA-DRB1*0402 and DRB1*1501 were associated with increased risk whereas HLA-DRB1*0401 was protective against sarcoidosis [34].

Overall, HLA-DRB1 molecules appear to play an important role in the pathogenesis of sarcoidosis either by recognizing specific antigen(s) or mounting different immune responses to different antigen(s). A better understanding of the role of HLA molecules in the pathogenesis of sarcoidosis could move us a step closer to potentially identifying the antigen(s) that trigger sarcoidosis [35].

2.2. BTNL2

The butyrophilin like 2 gene (BTNL2) belongs to the immunoglobulin gene superfamily and is related to the CD80 and CD86 co-stimulatory receptors. [7] In a mouse model, it was shown that BTNL2 binds to activated T-cells and inhibits their proliferation. [36] BTNL-2 was first linked to sarcoidosis when a GWAS in 63 German families with sarcoidosis identified a linkage to chromosome 6p21. [5] Further investigation found an association between SNP rs2076530A in the BTNL2 gene and sarcoidosis. [7] rs2076530A produces an alternative splice site that results in an early stop codon and a truncated, non-functional protein as a final product. [7] These findings were replicated in another German sarcoidosis cohort [37]. In a white British and Dutch cohorts, the SNPs rs2076530A and rs2294878C both showed an association with increased risk of sarcoidosis whereas haplotype 4 (which included rs2076530G and rs2294878A) had a protective association [26]. The SNP rs2076530A was associated with non-Lofgren's sarcoidosis and a gene dose effect was detected (AG vs GG OR 1.98, AA vs GG OR 2.63) [26]. There was strong linkage disequilibrium (LD) between BTNL2 haplotype 2 and HLA-DRB1*03 and between BTNL2 haplotype 4 and HLA-DRB1*01. [26] When the association of rs2076530A with the risk of sarcoidosis was analyzed in the context of HLA-DRB1, the rs2076530A association no longer held whereas the association of HLA-DRB1*12 and *14 with the risk of sarcoidosis persisted. [26] In a Dutch cohort, BTNL2 rs2076530A was associated with increased risk of sarcoidosis and a strong LD was found with HLA-DRB1*15. [38] rs2076530A was also associated with an increased risk of sarcoidosis in an American Caucasian cohort whereas in an African American cohort, the BTNL2 gene risk and the HLA-DRB1 gene risk negated each other. [39] In the same cohort, BTNL2 rs3117099T was associated with Lofgren's syndrome, similar but stronger association was also detected for haplotype 2 which contains rs3117099T. [26] The association of both haplotype 2 and HLA-DRB1*03 with Lofgren's syndrome remained significant after adjusting for each other and was stronger when both were present and protective against sarcoidosis when both were absent [26].

2.3. CCR2

CCR2 is a receptor for the chemokines CCL5, CCL2 and CCL3 that play an important role in recruiting monocytes, T-cells and other inflammatory cells. [40, 41] The association of 8 SNPs in the CCR2 gene with sarcoidosis was investigated in a white Dutch sarcoidosis population, a haplotype that consisted of 4 unique alleles (A at -6752, A at 3000, T at 3547 and T at 4385) was associated with LS, this association remained significant after adjustment for HLA-DRB1*0301-DQB1*0201 and female gender (both of which have been associated with LS). [41] No difference was seen between non-LS and controls. [41] This association and independence from HLA-DRB1 was confirmed in Swedish and Spanish sarcoidosis cohorts. [27] Similar

findings were found in a Czech cohort although the difference did not reach statistical significance. [40] No association was detected between 3 SNPs in CCR2 and sarcoidosis in a German cohort. [42] CCR2-64I mutation (A substitution mutation where isoleucine replaces valine in the transmembrane region) was found it to be protective against sarcoidosis in a Japanese cohort. [43]

2.4. CCR5

The CCR5 gene is located on the short arm of chromosome 3 [44] and codes for a receptor for several chemokines including CCL3, CCL4, CCL5 and CCL8. [45] These chemokines play an important role in lymphocyte and monocyte recruitment and activation in sarcoidosis. [46, 47] In Sarcoidosis, CCR5 expression is up-regulated in Bronchoalveolar lavage (BAL) macrophages and lymphocytes [48, 49] and levels of the CCR5 ligands, CCL3 and CCL5, correlate with risk of disease progression. [50-52] The CCR5 Δ 32 null allele results a 32bp deletion in the CCR5 gene and produces a non-functional receptor that is unable to bind to its ligand [53]. The A allele at position -5663 (rs2040388) and the C allele at position -3900 (rs2856757), both of which are part of the HHC haplotype, were associated with LS in a German cohort, particularly in females [53]. No association between 8 SNPs in the CCR5 gene and risk of sarcoidosis was detected in a white Dutch and UK cohorts but an association was noted with severity of lung disease. [54]

2.5. CARD15

CARD15/NOD2 is an intracellular molecule that is part of the innate immunity which recognizes muramyl dipeptide, a component of gram-positive and gram-negative bacteria cell wall [55]. It was first identified in association with the risk of Crohn's disease. [55] No significant association was detected between CARD15 polymorphisms and risk of sarcoidosis in German [56, 57], Japanese [58], Danish [59, 60] cohorts. In contrast, an association was noted with risk of disease in a Greek cohort [61].

2.6. Toll-Like receptors

Toll-like receptors (TLR) are transmembrane proteins that are critical in the innate immune system. [62] They are also known as pattern recognition receptors as they recognize specific microbial structures. [62] So far, 11 TLRs have been recognized. [62] Several studies in German and Dutch cohorts have investigated the potential association of polymorphisms in the TLR4, TLR2 and TLR9 genes with sarcoidosis but found no association with the risk of sarcoidosis. [63-67] One study in a German cohort suggested an association with chronic sarcoidosis. [63] In a Dutch cohort, SNPs rs1109695 and rs7658893 in the TLR-10 gene and rs57436004 and rs5743594 in the TLR-1 gene were associated with the risk of sarcoidosis. [68] None of the 4 SNPs were significantly different between remitting and chronic disease but they did differ significantly between healthy controls and sarcoidosis patients with chronic/progressive disease. [68]

2.7. SLC11A1 (NRAMP1, Natural Resistance-Associated Macrophage Protein Gene)

The SLC11A1 gene encodes a macrophage-specific, membrane protein whose function involves transport and appears to be important in the early stages of macrophage activation. [69] In US African Americans, a repeat polymorphism in 5' region (allele 2) of the gene was protective against sarcoidosis. [69] This finding was replicated in Polish, Turkish and Greek cohorts where the opposite polymorphism (allele 3) was associated with increased risk of sarcoidosis. [70-72] In the Turkish cohort, polymorphism in INT4 was also associated with increased risk of sarcoidosis but this association was not noted in the other cohorts. [70]

3. Cytokines/Chemokines

3.1. TNF- α and lymphotoxin-A (LTA, TNF- β)

TNF- α and LTA genes are located within the MHC class III region on chromosome 6p21.3 [73-75]. TNF- α plays a pivotal role in sarcoidosis [76]. It is produced by alveolar macrophages and high levels of spontaneous and stimulated release of TNF- α by macrophages from sarcoidosis patients correlates with disease severity. [76] Several Loci in the TNF- α gene have been studied including -307 (previously mislabeled as -308), -857, -863.

LTA-252G (rs909253) allele was associated with sarcoidosis in Czech and Polish cohorts [77] and TNF- α -308A (rs1800629) allele was associated with sarcoidosis in Polish and Czech sarcoidosis cohorts [77]. There was a strong LD between the TNF- α 308A, LTA252G alleles and HLA-DRB1*03 which has been associated with LS [74]. An association between TNF- α 308A (rs1800629) allele and LS and between TNF- α -857T allele and non-LS sarcoidosis was also found in a British and Dutch cohort [78] and German cohorts [79-81]. An association was found between the TNF- α -308 (rs1800629) and LTA252G(rs909253) SNPs and erythema nodosum in US white women [73] but no association between polymorphisms in the TNF- α gene and sarcoidosis in African Americans was detected. [82] There was also an increased frequency of the -857T allele in British and Dutch sarcoidosis patients compared to controls. [78]

The relationship between serum TNF- α levels and genotypes is unclear, one study found an increased serum TNF- α levels with the TNF- α -307(8)G and the TNF- α -238A alleles in a sarcoidosis population but not normal controls, [83] whereas another study did not detect any association in the spontaneous or stimulated release of TNF- α from BAL and PBMC cells with the TNF- α 308 and TNF- β (intron 1) genotypes. [84]

The TNF- α -863 position lies further upstream in the promoter region. It influences the binding of NF- κ B p50-p50 to the promoter region and inhibiting TNF- α production. The A allele variant inhibits the binding of NF- κ B p50-p50 and thus leading to a higher production of TNF- α . [85] There was a marginal association of the allele TNF-1031A with the risk of sarcoidosis and an association of TNF-1031A and TNF- α -863A with chronic disease in an Indian cohort. [83]

3.2. TGF- β

TGF- β is a growth factor with 3 isoforms: TGF- β 1, TGF- β 2 and TGF- β 3. They have nearly identical biological properties but the functional properties are usually attributed to TGF- β 1. [86] TGF- β induces the synthesis of extracellular matrix and decreases matrix degradation, has immunomodulatory properties acting as a mediator regulating chemotaxis and fibroblasts and has been implicated in pulmonary fibrosis. [86, 87] The variant allele C of -509T/C and C of codon 10 are associated with higher TGF- β 1 protein levels in the serum and the codon 10 variant is associated with increased mRNA levels in PBMC. [88, 89] TGF- β 1 levels in the BAL and alveolar macrophage supernatant are higher in patients with active sarcoidosis and especially in those with pulmonary function changes, [90] there was also a positive correlation with BAL lymphocytosis. [90]

No association was found between sarcoidosis and 2 polymorphisms (codon 10, T869C) in the TGF- β 1 gene in a Japanese sarcoidosis cohort and no relationship with Scadding chest x-ray stage was found either. [91] Codon 10 was also not associated with sarcoidosis in a German cohort [92]. No association between polymorphisms in the TGF- β 1, TGF- β 2 and TGF- β 3 genes and sarcoidosis was detected in a white Dutch cohort. [93]

4. Signaling molecules

4.1. Annexin A11

The ANXA11 gene plays a role in the apoptosis pathway and depletion or dysfunction of the Annexin A11 protein may impair cell apoptosis and the down-regulation of the immune response [8]. A GWAS analysis in a German sarcoidosis cohort found a strong association between several SNPs in the annexin A11 (ANXA11) gene on chromosome 10 (10q22.3) and the risk of sarcoidosis. [8] This association was confirmed in a separate German cohort where the C allele of both rs1049550 and rs2573346 were associated with the development of sarcoidosis. [94] The association of rs1049550 with risk of sarcoidosis was also confirmed in a Czech cohort [95].

5. Others

5.1. Angiotensin Converting Enzyme (ACE)

Serum ACE is one of the biochemical markers that reflect disease activity in sarcoidosis. [1] Serum ACE levels do correlate with ACE genotype, with genotype D/D having the highest levels and I/I the lowest. [96-100] Several studies have investigated the association of ACE genotypes with sarcoidosis. In an African American cohort, the DD genotype was associated with increased risk of sarcoidosis, but not extent or severity, and the association was stronger when a family history of sarcoidosis was taken into account. [101] This association was not noted in a later study in African Americans. [82] In a Japanese cohort, the DD genotype was

associated with increased risk of sarcoidosis in their female patients. [96] No association was detected in a US Caucasian cohort [101]. Otherwise, no association between polymorphisms in the ACE gene and risk of sarcoidosis was detected in German, Dutch, Italian, British, Finnish and Czech sarcoidosis cohorts. [97-100, 102, 103]

The angiotensin II receptor 1 genotype AA and CC potentially increase the risk of sarcoidosis in males in a German cohort but these findings were not replicated in a Dutch cohort. [97, 98] No association existed between the angiotensin II receptor 1 and 2 genotypes and sarcoidosis in a Japanese cohort. [104]

5.2. IL-10 and CD40

No association between polymorphisms in the IL-10 or the CD40 gene and risk of sarcoidosis in Japanese cohorts was detected. [105, 106]

Genetic markers and disease course / organ involvement (Table 2):

Gene	Polymorphism	Population	OR	CI	p	Ref
Progressive Pulmonary disease						
HLA	DQB1*0602	AA	NR	NR	0.032	[107]
	DRB1*07	Scandinavian	0.44	NR	0.009	[28]
	DRB1*14	Scandinavian	2.14	NR	0.005	[28]
	DRB1*15	Scandinavian	1.55	NR	0.011	[28]
	DRB1*01	Scandinavian	0.41	NR	<0.001	[28]
	DRB1*03	Scandinavian	5.42	NR	<0.001	[28]
	DRB1*03	Finnish	2.22	1.20-4.1	0.011	[33]
BTNL 2	rs2076530	Dutch	1.84	1.06-3.21	0.03	[38]
CCR5	HHC haplotype	British	6.8*	2.5-18.0	0.0045	[54]
	HHC haplotype	Dutch	9*	3.5-23.1	0.0009	[54]
CARD15/NOD2	rs2066844T	British	4.1	1.0-15.5	0.04	[110]
IL23	Rs11209026A	German	0.63	0.5-0.79	<0.001	[117]
TNF						
	TNF- α 308A	Dutch	0.43	0.31-0.61	<0.001	[75]

Gene	Polymorphism	Population	OR	CI	p	Ref
	TNF- α 308T	Italian	3.53	1.66-7.5	<0.001	[77]
TGF- β						
TGF- β 1	rs1800469	US white	2.5	1.3-4.5	0.005	[118]
TGF- β 3	rs3917165A	US White	7.9	2.1-30.9	P=0.01	[118]
TGF- β 3	rs3917200C	US White	5.1	1.6-17.7	P=0.05	[118]
GREM1	rs1919364CC	Dutch	6.37	2.89-14.1	<0.001	[120]
ANXA11	rs1049550T	Czech	0.61	0.41-0.89	0.01	[95]
Ophthalmic						
HLA	DRB1*0401	AA/White	3.49	1.62-7.54	<0.0008	[34]
	DRB1*0401-DQB10301	UK	3.4	1.64-7.08	0.001	[29]
	DRB1*03-DQB1*0201	UK	0.21	0.08-0.54	<0.0001	[29]
Hypercalcemia	PBB1-0101	US white	4.28	1.45-12.6	0.005	[34]

* OR at 4 years

HLA : Human Leukocyte Antigen

Table 2. Association of genetic markers with sarcoidosis disease course, severity and/or organ involvement.

6. Receptors

6.1. HLA region

HLA genetic markers were also investigated for their association with sarcoidosis disease course, severity and/or organ involvement. HLA-DQB1*0602 was associated with radiographic progression in an African American cohort [107], advanced pulmonary disease and uveitis in Dutch cohorts [30, 108] whereas in a Scandinavian cohort, HLA-DRB1*07,*14 and *15 were associated with progressive pulmonary disease whereas *01 and *03 were associated with non-progressive disease [28]. In a Finnish cohort, HLA-DRB1*03 was associated with resolving disease [109].

6.2. BTNL-2

In a Dutch cohort, BTNL2 16071A variant was associated with increased risk of progressive or persistent pulmonary sarcoidosis [38].

6.3. CCR5

CCR5 Δ 32 null allele was associated with the need for immunosuppressive therapy in a Czech cohort [40]. The haplotype HHC (-5663A, -3900C, -3458T, -2459G, -2135T, -2086G, -1835C, Δ 32 wt) was strongly associated with the presence of parenchymal disease in British and Dutch cohorts at presentation, 2 and 4 years of follow up [54]. The haplotype HHC was also associated with lower forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), bronchoalveolar lavage neutrophilia (>4%) but not other organ involvement with Sarcoidosis [54].

6.4. CARD15/NOD2

In a British cohort, there was an association between allele T at loci 2104 (rs2066844) and the risk of radiographic Scadding stage IV at year 4 of follow up and an association between the allele G at loci 1761 with better lung function, defined by DLCO, at presentation, 2 and 4 years of follow up. [110] Interestingly, in a study in Crohn's disease patients, variants in loci 2104, 2722 and 3020 were associated with decreased number of T-regulatory cells in the lamina propria. [111] T-regulatory cells have been implicated to have a role in the immune pathogenesis of sarcoidosis but their exact role is yet unknown. [3, 112, 113]

7. Cytokines/Chemokines

7.1. TNF- α 308, LTA252 (TNF- β)

A higher representation of the TNF- α 308A allele was found in a Dutch cohort with non-persistent disease compared to persistent disease. [75] In a Polish cohort, TNF- α 308 A/A was associated with disease remission. [77]

7.2. TGF β

In a white Dutch cohort, there was an increased frequency of the A allele in rs3917165 in the TGF- β 3 gene in the fibrotic group compared to the acute/chronic groups [93], in addition, the C allele in rs3917200 was more frequent in the fibrotic group compared to the acute/chronic groups. [93] In another study, white American sarcoidosis patients who had CC homozygosity at position -509 (rs1800469) were more likely to have parenchymal disease [118].

7.3. IL-23

IL-23 is a pro-inflammatory cytokine that stimulate Th-17 cells to produce IL-17 and other cytokines and has a role in a number of autoimmune diseases [114, 115]. Polymorphisms in rs11209026 can affect serum IL-17A levels in rheumatoid arthritis patients [116]. In a German cohort, rs11209026A was protective against chronic sarcoidosis [117].

8. Signaling

8.1. GREM1

Gremlin, encoded by GREM1, is a secreted glycoprotein and antagonizes bone morphogenetic protein (BMP) by forming heterodimers with BMP-2, BMP-4 and BMP-7 preventing BMP from interacting with its ligand and subsequent downstream signaling. [119] Dutch sarcoidosis patients with the CC genotype for rs1919364 in GREM1 had a 6 fold increased risk of developing fibrotic lung disease. [120]

8.2. Annexin A11

In a Czech cohort, rs1049550 T-allele was protective against parenchymal disease (Scadding stages II-IV) [95].

9. Other

9.1. COX2

In a Spanish cohort, there was an association between the CC genotype of the COX2.8473 polymorphism and increased risk of sarcoidosis [121] and an association of the C-allele of the COX2.3050 with systemic sarcoidosis versus non-systemic sarcoidosis [122].

9.2. IL-10 and CD40

There were no associations between polymorphisms in the IL-10 and CD40 gene in Japanese cohorts and the risk of sarcoidosis. [105, 106]

10. Organ involvement

A few genetic markers have also been associated with organ involvement in sarcoidosis. In the ACCESS study, HLA-DRB3 was associated with bone marrow involvement in blacks, HLA-DPB1*0101 with hypercalcemia in whites, HLA-DRB1*0401 with parotid and salivary gland involvement in blacks and HLA-DRB1*0401 was found to have possible association with eye involvement [34]. In a cohort from the UK, HLA-DRB1*0401-DQB1*0301 was associated with increased risk of uveitis whereas HLA-DRB1*03 and DQB1*0201 were protective for uveitis. [29] In a Japanese cohort, HLA-DRB1*15 and DQB1*0602 were associated with skin disease and HLA-DRB1*0803 with neurosarcoidosis. [29] In a Japanese cohort, polymorphisms in the CTLA-4 gene were associated with BAL lymphocytosis, ocular involvement and multi-organ involvement. [123, 124]

11. Conclusions

Sarcoidosis is a complex disease with variable presentations, course and organ involvement, as such, it is no surprise that research into the genetic basis of the disease yields complex and variable results. This is supported by the variability in presentation, course and organ involvement between various ethnic groups. To add to this complexity, linkage disequilibrium (LD) occurs when alleles at two loci are not independent of each other. As such, when one genetic marker is identified as associated with a disease or trait, then any allele in strong LD with that marker could be the actual link to the disease. For example, BTNL-2 has been associated with increased risk of sarcoidosis [5, 7, 8, 26, 37] but has also been shown to be in strong LD with HLA markers [26].

HLA molecules play an important role in antigen presentation and immune stimulation [24, 25]. The association of HLA markers with increased risk of sarcoidosis or specific organ involvement could potentially lead to identification of a causative agent(s), as seen in chronic beryllium disease [125], and a recent study has shown an interaction between genetics and immune response to certain environmental antigens [22]. Chronic beryllium disease, a granulomatous disorder that is caused by exposure to beryllium and resembles sarcoidosis, has been associated with HLA-DP- β Glu69 as a genetic risk factor [126]. Studies have shown that HLA-DP- β Glu69 interacts with beryllium with subsequent stimulation of the immune response [125]. In addition, the identification of genetic markers that are associated with sarcoidosis might uncover novel pathways not previously identified or suspected as contributors to disease pathogenesis, which could subsequently lead to identification of new therapeutic targets.

Further research is still needed to clarify the associations of the various genetic markers with risk and prognosis of disease and large validation studies will be needed to confirm these associations. Proper phenotyping of cases and stratification according to ethnicity and gender when analyzing genetic studies is extremely important. Several studies have shown opposite associations between gender and/or ethnicity and genetic markers when the analysis was stratified by gender and/or ethnicity [53]. In addition, the interaction between two or more distinct SNPs or haplotypes in sarcoidosis has yet to be studied [127].

So what role does genetic testing have in the clinical care of sarcoidosis patients? At this stage, genetic testing has no identifiable role in the clinical arena. The odds of a first or second degree relative of a sarcoidosis patient also having sarcoidosis are 4.6 and the familial relative risk was larger in sibs than in parents and higher in Whites than African Americans [4]. This said, the absolute risk and attributable risk for a sib or parent of a sarcoidosis patients is approximately 1% and as such, screening family members, clinically or genetically, is not recommended [4].

Potential future applications of genetic testing in the clinical arena include prognostication on disease course which will aid in determining intensity of follow up, prognostication on potential organ involvement which will influence frequency and intensity of screening for sarcoidosis involvement, and potentially a role for pharmacogenetics in guiding immunomodulatory therapy.

Author details

Nabeel Y. Hamzeh^{1,2} and Lisa A. Maier^{1,2}

1 Division of Environmental and Occupational Health Sciences, National Jewish Health, Denver, CO, USA

2 Division of Pulmonary and Critical Care Sciences, Department of Medicine, School of Medicine, University of Colorado, Aurora, CO, USA

References

- [1] Statement on Sarcoidosis. *Am J Respir Crit Care Med.* 1999 August 1, 1999;160(2):736-55.
- [2] Gerke AK, Hunninghake G. The immunology of sarcoidosis. *Clin Chest Med.* 2008 Sep;29(3):379-90, vii.
- [3] Miyara M, Amoura Z, Parizot C, Badoual C, Dorgham K, Trad S, et al. The immune paradox of sarcoidosis and regulatory T cells. *The Journal of experimental medicine.* 2006 Feb 20;203(2):359-70.
- [4] Rybicki BA, Iannuzzi MC, Frederick MM, Thompson BW, Rossman MD, Bresnitz EA, et al. Familial aggregation of sarcoidosis. A case-control etiologic study of sarcoidosis (ACCESS). *American journal of respiratory and critical care medicine.* 2001 Dec 1;164(11):2085-91.
- [5] Schurmann M, Reichel P, Muller-Myhsok B, Schlaak M, Muller-Quernheim J, Schwinger E. Results from a genome-wide search for predisposing genes in sarcoidosis. *American journal of respiratory and critical care medicine.* 2001 Sep 1;164(5):840-6.
- [6] Iannuzzi MC, Iyengar SK, Gray-McGuire C, Elston RC, Baughman RP, Donohue JF, et al. Genome-wide search for sarcoidosis susceptibility genes in African Americans. *Genes and immunity.* 2005 Sep;6(6):509-18.
- [7] Valentonyte R, Hampe J, Huse K, Rosenstiel P, Albrecht M, Stenzel A, et al. Sarcoidosis is associated with a truncating splice site mutation in BTNL2. *Nat Genet.* 2005 Apr;37(4):357-64.
- [8] Hofmann S, Franke A, Fischer A, Jacobs G, Nothnagel M, Gaede KI, et al. Genome-wide association study identifies ANXA11 as a new susceptibility locus for sarcoidosis. *Nat Genet.* 2008;40(9):1103-6.

- [9] Franke A, Fischer A, Nothnagel M, Becker C, Grabe N, Till A, et al. Genome-wide association analysis in sarcoidosis and Crohn's disease unravels a common susceptibility locus on 10p12.2. *Gastroenterology*. 2008 Oct;135(4):1207-15.
- [10] Rybicki BA, Levin AM, McKeigue P, Datta I, Gray-McGuire C, Colombo M, et al. A genome-wide admixture scan for ancestry-linked genes predisposing to sarcoidosis in African-Americans. *Genes and immunity*. 2010.
- [11] Hofmann S, Fischer A, Till A, MÃ¼ller-Quernheim J, HÃ¤sler R, Franke A, et al. A genome-wide association study reveals evidence of association with sarcoidosis at 6p12.1. *European Respiratory Journal*. 2011 November 1, 2011;38(5):1127-35.
- [12] Cho JH, Gregersen PK. Genomics and the multifactorial nature of human autoimmune disease. *The New England journal of medicine*. 2011 Oct 27;365(17):1612-23.
- [13] Attia J, Ioannidis JP, Thakkinstian A, McEvoy M, Scott RJ, Minelli C, et al. How to use an article about genetic association: A: Background concepts. *Jama*. 2009 Jan 7;301(1):74-81.
- [14] Newman LS, Rose CS, Bresnitz EA, Rossman MD, Barnard J, Frederick M, et al. A Case Control Etiologic Study of Sarcoidosis: Environmental and Occupational Risk Factors. *Am J Respir Crit Care Med*. 2004 December 15, 2004;170(12):1324-30.
- [15] Gerke AK, van Beek E, Hunninghake GW. Smoking Inhibits the Frequency of Bronchovascular Bundle Thickening in Sarcoidosis. *Academic Radiology*. 2011;18(7):885-91.
- [16] Song Z, Marzilli L, Greenlee BM, Chen ES, Silver RF, Askin FB, et al. Mycobacterial catalase-peroxidase is a tissue antigen and target of the adaptive immune response in systemic sarcoidosis. *The Journal of Experimental Medicine*. 2005 March 7, 2005;201(5):755-67.
- [17] Dubaniewicz A, Dubaniewicz-Wybieralska M, Sternau A, Zwolska Z, Izycka-Swieszewska E, Augustynowicz-Kopec E, et al. Mycobacterium tuberculosis Complex and Mycobacterial Heat Shock Proteins in Lymph Node Tissue from Patients with Pulmonary Sarcoidosis. *J Clin Microbiol*. 2006;44:3448 - 51.
- [18] Carlisle J, Evans W, Hajizadeh R, Nadaf M, Shepherd B, Ott RD, et al. Multiple Mycobacterium antigens induce interferon-gamma production from sarcoidosis peripheral blood mononuclear cells. *Clinical & Experimental Immunology*. 2007;150(3):460-8.
- [19] Carlisle J, Evans W, Hajizadeh R, Richter K, Drake WP. "Immune recognition of multiple mycobacterial antigens by sarcoidosis subjects." *J Clin Exp Immunol*. 2007;150:460 - 8.

- [20] Drake WP, Dhason MS, Nadaf M, Shepherd BE, Vadivelu S, Hajizadeh R, et al. Cellular Recognition of Mycobacterium tuberculosis ESAT-6 and KatG Peptides in Systemic Sarcoidosis. *Infect Immun*. 2007 January 1, 2007;75(1):527-30.
- [21] Allen S, Evans W, Carlisle J, Hajizadeh R, Nadaf M, Shepherd B, et al. Superoxide dismutase A antigens derived from molecular analysis of sarcoidosis granulomas elicit systemic Th-1 immune responses. *Respiratory Research*. 2008;9(1):36.
- [22] Chen ES, Wahlstrom J, Song Z, Willett MH, Wiken M, Yung RC, et al. T Cell Responses to Mycobacterial Catalase-Peroxidase Profile a Pathogenic Antigen in Systemic Sarcoidosis. *J Immunol*. 2008 December 15, 2008;181(12):8784-96.
- [23] Oswald-Richter KA, Culver DA, Hawkins C, Hajizadeh R, Abraham S, Shepherd BE, et al. Cellular Responses to Mycobacterial Antigens Are Present in Bronchoalveolar Lavage Fluid Used in the Diagnosis of Sarcoidosis. *Infect Immun*. 2009 September 1, 2009;77(9):3740-8.
- [24] Klein J, Sato A. The HLA system. Second of two parts. *The New England journal of medicine*. 2000 Sep 14;343(11):782-6.
- [25] Klein J, Sato A. The HLA system. First of two parts. *The New England journal of medicine*. 2000 Sep 7;343(10):702-9.
- [26] Spagnolo P, Sato H, Grutters JC, Renzoni EA, Marshall SE, Ruven HJ, et al. Analysis of BTNL2 genetic polymorphisms in British and Dutch patients with sarcoidosis. *Tissue Antigens*. 2007 Sep;70(3):219-27.
- [27] Spagnolo P, Sato H, Grunewald J, Brynedal B, Hillert J, Mana J, et al. A common haplotype of the C-C chemokine receptor 2 gene and HLA-DRB1*0301 are independent genetic risk factors for Lofgren's syndrome. *J Intern Med*. 2008 Nov;264(5):433-41.
- [28] Grunewald J, Brynedal B, Darlington P, Nisell M, Cederlund K, Hillert J, et al. Different HLA-DRB1 allele distributions in distinct clinical subgroups of sarcoidosis patients. *Respiratory research*. 2010;11(26):25.
- [29] Sato H, Woodhead FA, Ahmad T, Grutters JC, Spagnolo P, van den Bosch JM, et al. Sarcoidosis HLA class II genotyping distinguishes differences of clinical phenotype across ethnic groups. *Human molecular genetics*. 2010 Oct 15;19(20):4100-11.
- [30] Sato H, Grutters JC, Pantelidis P, Mizzon AN, Ahmad T, Van Houte AJ, et al. HLA-DQB1*0201: a marker for good prognosis in British and Dutch patients with sarcoidosis. *American journal of respiratory cell and molecular biology*. 2002 Oct;27(4):406-12.
- [31] Grunewald J, Idali F, Kockum I, Seddighzadeh M, Nisell M, Eklund A, et al. Major histocompatibility complex class II transactivator gene polymorphism: associations with Löfgren's syndrome. *Tissue Antigens*. 2010;76(2):96-101.

- [32] Voortter CEM, Drent M, van den Berg-Loonen EM. Severe Pulmonary Sarcoidosis Is Strongly Associated With the Haplotype HLA-DQB1*0602-DRB1*150101. *Human immunology*. 2005;66(7):826-35.
- [33] Wennerstrom A, Pietinalho A, Vauhkonen H, Lahtela L, Palikhe A, Hedman J, et al. HLA-DRB1 allele frequencies and C4 copy number variation in Finnish sarcoidosis patients and associations with disease prognosis. *Human immunology*. 2012;73(1):93-100.
- [34] Rossman MD, Thompson B, Frederick M, Maliarik M, Iannuzzi MC, Rybicki BA, et al. HLA-DRB1*1101: A Significant Risk Factor for Sarcoidosis in Blacks and Whites. *Am J Hum Genet*. 2003 Aug 20;73(4).
- [35] Dai S, Murphy GA, Crawford F, Mack DG, Falta MT, Marrack P, et al. Crystal structure of HLA-DP2 and implications for chronic beryllium disease. *Proceedings of the National Academy of Sciences of the United States of America*. 2010 Apr 20;107(16):7425-30.
- [36] Nguyen T, Liu XK, Zhang Y, Dong C. BTNL2, a Butyrophilin-Like Molecule That Functions to Inhibit T Cell Activation. *J Immunol*. 2006 June 15, 2006;176(12):7354-60.
- [37] Li Y, Wollnik B, Pabst S, Lennarz M, Rohmann E, Gillissen A, et al. BTNL2 gene variant and sarcoidosis. *Thorax*. 2006 Mar;61(3):273-4.
- [38] Wijnen PA, Voortter CE, Nelemans PJ, Verschakelen JA, Bekers O, Drent M. Butyrophilin-like 2 in pulmonary sarcoidosis: a factor for susceptibility and progression? *Human immunology*. 2011 Jan 20.
- [39] Rybicki BA, Walewski JL, Maliarik MJ, Kian H, Iannuzzi MC. The BTNL2 gene and sarcoidosis susceptibility in African Americans and Whites. *Am J Hum Genet*. 2005 Sep;77(3):491-9.
- [40] Petrek M, Drabek J, Kolek V, Zlamal J, Welsh KI, Bunce M, et al. CC chemokine receptor gene polymorphisms in Czech patients with pulmonary sarcoidosis. *American journal of respiratory and critical care medicine*. 2000 Sep;162(3 Pt 1):1000-3.
- [41] Spagnolo P, Renzoni EA, Wells AU, Sato H, Grutters JC, Sestini P, et al. C-C Chemokine Receptor 2 and Sarcoidosis: Association with Lofgren's Syndrome. *Am J Respir Crit Care Med*. 2003 November 15, 2003;168(10):1162-6.
- [42] Valentonyte R, Hampe J, Croucher PJP, Muller-Quernheim J, Schwinger E, Schreiber S, et al. Study of C-C Chemokine Receptor 2 Alleles in Sarcoidosis, with Emphasis on Family-based Analysis. *Am J Respir Crit Care Med*. 2005 May 15, 2005;171(10):1136-41.
- [43] Hizawa N, Yamaguchi E, Furuya KEN, Jinushi E, Ito A, Kawakami Y. The Role of the C-C Chemokine Receptor 2 Gene Polymorphism V64I (CCR2-64I) in Sarcoidosis in a Japanese Population. *Am J Respir Crit Care Med*. 1999 June 1, 1999;159(6):2021-3.

- [44] Samson M, Soularue P, Vassart G, Parmentier M. The genes encoding the human CC-chemokine receptors CC-CCR1 to CC-CCR5 (CMKBR1-CMKBR5) are clustered in the p21.3-p24 region of chromosome 3. *Genomics*. 1996 Sep 15;36(3):522-6.
- [45] Blanpain C, Migeotte I, Lee B, Vakili J, Doranz BJ, Govaerts C, et al. CCR5 binds multiple CC-chemokines: MCP-3 acts as a natural antagonist. *Blood*. 1999 Sep 15;94(6):1899-905.
- [46] Baggiolini M, Loetscher P. Chemokines in inflammation and immunity. *Immunology today*. 2000 Sep;21(9):418-20.
- [47] Ziegenhagen MW, Schrum S, Zissel G, Zipfel PF, Schlaak M, Muller-Quernheim J. Increased expression of proinflammatory chemokines in bronchoalveolar lavage cells of patients with progressing idiopathic pulmonary fibrosis and sarcoidosis. *J Investig Med*. 1998 Jun;46(5):223-31.
- [48] Capelli A, Di Stefano A, Lusuardi M, Gnemmi I, Donner CF. Increased macrophage inflammatory protein-1alpha and macrophage inflammatory protein-1beta levels in bronchoalveolar lavage fluid of patients affected by different stages of pulmonary sarcoidosis. *American journal of respiratory and critical care medicine*. 2002 Jan 15;165(2):236-41.
- [49] Katchar K, Eklund A, Grunewald J. Expression of Th1 markers by lung accumulated T cells in pulmonary sarcoidosis. *J Intern Med*. 2003 Dec;254(6):564-71.
- [50] Iida K, Kadota J, Kawakami K, Matsubara Y, Shirai R, Kohno S. Analysis of T cell subsets and beta chemokines in patients with pulmonary sarcoidosis. *Thorax*. 1997 May;52(5):431-7.
- [51] Keane MP, Standiford TJ, Strieter RM. Chemokines are important cytokines in the pathogenesis of interstitial lung disease. *Eur Respir J*. 1997 Jun;10(6):1199-202.
- [52] Petrek M, Pantelidis P, Southcott AM, Lympany P, Safranek P, Black CM, et al. The source and role of RANTES in interstitial lung disease. *Eur Respir J*. 1997 Jun;10(6):1207-16.
- [53] Fischer A, Valentonyte R, Nebel A, Nothnagel M, Muller-Quernheim J, Schurmann M, et al. Female-specific association of C-C chemokine receptor 5 gene polymorphisms with Lofgren's syndrome. *Journal of molecular medicine (Berlin, Germany)*. 2008 May;86(5):553-61.
- [54] Spagnolo P, Renzoni EA, Wells AU, Copley SJ, Desai SR, Sato H, et al. C-C chemokine receptor 5 gene variants in relation to lung disease in sarcoidosis. *American journal of respiratory and critical care medicine*. 2005 Sep 15;172(6):721-8.
- [55] Hugot JP, Chamaillard M, Zouali H, Lesage S, Cezard JP, Belaiche J, et al. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. *Nature*. 2001 May 31;411(6837):599-603.

- [56] Schurmann M, Valentonyte R, Hampe J, Muller-Quernheim J, Schwinger E, Schreiber S. CARD15 gene mutations in sarcoidosis. *Eur Respir J*. 2003 Nov;22(5):748-54.
- [57] Pabst S, Golebiewski M, Herms S, Karpushova A, Díaz-Lacava A, Walier M, et al. Caspase recruitment domain 15 gene haplotypes in sarcoidosis. *Tissue Antigens*. 2011;77(4):333-7.
- [58] Akahoshi M, Ishihara M, Namba K, Kitaichi N, Ando Y, Takenaka S, et al. Mutation screening of the CARD15 gene in sarcoidosis. *Tissue Antigens*. 2008;71(6):564-7.
- [59] Milman N, Nielsen FC, Hviid TV, Hansen TO. Blau syndrome-associated mutations in exon 4 of the caspase activating recruitment domain 15 (CARD 15) gene are not found in ethnic Danes with sarcoidosis. *The clinical respiratory journal*. 2007 Dec; 1(2):74-9.
- [60] Milman N, Nielsen OH, Hviid TV, Fenger K. CARD15 single nucleotide polymorphisms 8, 12 and 13 are not increased in ethnic Danes with sarcoidosis. *Respiration; international review of thoracic diseases*. 2007;74(1):76-9.
- [61] Gazouli M, Koundourakis A, Ikonopoulou J, Gialafos EJ, Rapti A, Gorgoulis VG, et al. CARD15/NOD2, CD14, and toll-like receptor 4 gene polymorphisms in Greek patients with sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2006 Mar;23(1):23-9.
- [62] West AP, Koblansky AA, Ghosh S. Recognition and signaling by toll-like receptors. *Annual review of cell and developmental biology*. 2006;22:409-37.
- [63] Pabst S, Baumgarten G, Stremmel A, Lennarz M, Knufermann P, Gillissen A, et al. Toll-like receptor (TLR) 4 polymorphisms are associated with a chronic course of sarcoidosis. *Clinical and experimental immunology*. 2006 Mar;143(3):420-6.
- [64] Schurmann M, Kwiatkowski R, Albrecht M, Fischer A, Hampe J, Muller-Quernheim J, et al. Study of Toll-like receptor gene loci in sarcoidosis. *Clinical and experimental immunology*. 2008 Jun;152(3):423-31.
- [65] Veltkamp M, Grutters JC, van Moorsel CH, Ruven HJ, van den Bosch JM. Toll-like receptor (TLR) 4 polymorphism Asp299Gly is not associated with disease course in Dutch sarcoidosis patients. *Clinical and experimental immunology*. 2006 Aug;145(2): 215-8.
- [66] Veltkamp M, Van Moorsel CH, Rijkers GT, Ruven HJ, Van Den Bosch JM, Grutters JC. Toll-like receptor (TLR)-9 genetics and function in sarcoidosis. *Clinical and experimental immunology*. 2010 Oct;162(1):68-74.
- [67] Veltkamp M, Wijnen PA, van Moorsel CH, Rijkers GT, Ruven HJ, Heron M, et al. Linkage between Toll-like receptor (TLR) 2 promotor and intron polymorphisms: functional effects and relevance to sarcoidosis. *Clinical and experimental immunology*. 2007 Sep;149(3):453-62.

- [68] Veltkamp M, van Moorsel CH, Rijkers GT, Ruven HJ, Grutters JC. Genetic variation in the Toll-like receptor gene cluster (TLR10-TLR1-TLR6) influences disease course in sarcoidosis. *Tissue Antigens*. 2011 Jan;79(1):25-32.
- [69] Maliarik MJ, Chen KM, Sheffer RG, Rybicki BA, Major ML, Popovich J, et al. The Natural Resistance-Associated Macrophage Protein Gene in African Americans with Sarcoidosis. *American journal of respiratory cell and molecular biology*. 2000 June 1, 2000;22(6):672-5.
- [70] Akcakaya P, Azeroglu B, Even I, Ates O, Turker H, Ongen G, et al. The functional SLC11A1 gene polymorphisms are associated with sarcoidosis in Turkish population. *Molecular biology reports*. 2012 Apr;39(4):5009-16.
- [71] Dubaniewicz A, Jamieson SE, Dubaniewicz-Wybieralska M, Fakiola M, Nancy Miller E, Blackwell JM. Association between SLC11A1 (formerly NRAMP1) and the risk of sarcoidosis in Poland. *Eur J Hum Genet*. 2005;13(7):829-34.
- [72] Gazouli M, Koundourakis A, Ikonopoulou J, Gialafos EJ, Papaconstantinou I, Natsioulas G, et al. The functional polymorphisms of NRAMP1 gene in Greeks with sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2007 Sep;24(2):153-4.
- [73] McDougal KE, Fallin MD, Moller DR, Song Z, Cutler DJ, Steiner LL, et al. Variation in the lymphotoxin-alpha/tumor necrosis factor locus modifies risk of erythema nodosum in sarcoidosis. *The Journal of investigative dermatology*. 2009 Aug;129(8):1921-6.
- [74] Mrazek F, Holla LI, Hutyrova B, Znojil V, Vasku A, Kolek V, et al. Association of tumour necrosis factor-alpha, lymphotoxin-alpha and HLA-DRB1 gene polymorphisms with Lofgren's syndrome in Czech patients with sarcoidosis. *Tissue Antigens*. 2005 Feb;65(2):163-71.
- [75] Wijnen PA, Nelemans PJ, Verschakelen JA, Bekers O, Voorter CE, Drent M. The role of tumor necrosis factor alpha G-308A polymorphisms in the course of pulmonary sarcoidosis. *Tissue Antigens*. 9999(9999).
- [76] Ziegenhagen MW, Benner UK, Zissel G, Zabel P, Schlaak M, Muller-Quernheim J. Sarcoidosis: TNF-alpha release from alveolar macrophages and serum level of sIL-2R are prognostic markers. *Am J Respir Crit Care Med*. 1997 Nov;156(5):1586-92.
- [77] Kieszko R, Krawczyk P, Chocholska S, Dmoszynska A, Milanowski J. TNF-alpha and TNF-beta gene polymorphisms in Polish patients with sarcoidosis. Connection with the susceptibility and prognosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2010 Jul;27(2):131-7.
- [78] Grutters JC, Sato H, Pantelidis P, Lagan AL, McGrath DS, Lammers J-WJ, et al. Increased Frequency of the Uncommon Tumor Necrosis Factor -857T Allele in British and Dutch Patients with Sarcoidosis. *Am J Respir Crit Care Med*. 2002 April 15, 2002;165(8):1119-24.

- [79] Seitzer U, Swider C, Stuber F, Suchnicki K, Lange A, Richter E, et al. Tumour necrosis factor alpha promoter gene polymorphism in sarcoidosis. *Cytokine*. 1997 Oct;9(10):787-90.
- [80] Swider C, Schnittger L, Bogunia-Kubik K, Gerdes J, Flad H, Lange A, et al. TNF-alpha and HLA-DR genotyping as potential prognostic markers in pulmonary sarcoidosis. *European cytokine network*. 1999 Jun;10(2):143-6.
- [81] Labunski S, Posern G, Ludwig S, Kundt G, BrÄcker E-B, Kunz M. Tumour Necrosis Factor-alpha Promoter Polymorphism in Erythema Nodosum. *Acta Dermato-Venereologica*. 2001;81(1):18 - 21.
- [82] Rybicki BA, Maliarik MJ, Poisson LM, Iannuzzi MC. Sarcoidosis and granuloma genes: a family-based study in African-Americans. *Eur Respir J*. 2004 Aug;24(2):251-7.
- [83] Sharma S, Ghosh B, Sharma SK. Association of TNF polymorphisms with sarcoidosis, its prognosis and tumour necrosis factor (TNF)-alpha levels in Asian Indians. *Clinical & Experimental Immunology*. 2008;151(2):251-9.
- [84] Somoskovi A, Zissel G, Seitzer U, Gerdes J, Schlaak M, Muller Quernheim J. Polymorphisms at position -308 in the promoter region of the TNF-alpha and in the first intron of the TNF-beta genes and spontaneous and lipopolysaccharide-induced TNF-alpha release in sarcoidosis. *Cytokine*. 1999 Nov;11(11):882-7.
- [85] Udalova IA, Richardson A, Denys A, Smith C, Ackerman H, Foxwell B, et al. Functional consequences of a polymorphism affecting NF-kappaB p50-p50 binding to the TNF promoter region. *Molecular and cellular biology*. 2000 Dec;20(24):9113-9.
- [86] Border WA, Noble NA. Transforming growth factor beta in tissue fibrosis. *The New England journal of medicine*. 1994 Nov 10;331(19):1286-92.
- [87] Moses HL, Yang EY, Pietenpol JA. TGF-beta stimulation and inhibition of cell proliferation: new mechanistic insights. *Cell*. 1990 Oct 19;63(2):245-7.
- [88] Grainger DJ, Heathcote K, Chiano M, Snieder H, Kemp PR, Metcalfe JC, et al. Genetic control of the circulating concentration of transforming growth factor type beta1. *Human molecular genetics*. 1999 Jan;8(1):93-7.
- [89] Yamada Y, Miyauchi A, Goto J, Takagi Y, Okuizumi H, Kanematsu M, et al. Association of a polymorphism of the transforming growth factor-beta1 gene with genetic susceptibility to osteoporosis in postmenopausal Japanese women. *J Bone Miner Res*. 1998 Oct;13(10):1569-76.
- [90] Salez F, Gosset P, Copin MC, Lamblin Degros C, Tonnel AB, Wallaert B. Transforming growth factor-beta1 in sarcoidosis. *Eur Respir J*. 1998 October 1, 1998;12(4):913-9.

- [91] Niimi T, Sato S, Sugiura Y, Yoshinouchi T, Akita K, Maeda H, et al. Transforming growth factor-beta gene polymorphism in sarcoidosis and tuberculosis patients. *The International Journal of Tuberculosis and Lung Disease*. 2002;6:510-5.
- [92] Murakozy G, Gaede KI, Zissel G, Schlaak M, Muller-Quernheim J. Analysis of gene polymorphisms in interleukin-10 and transforming growth factor-beta 1 in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2001 Jun;18(2):165-9.
- [93] Kruit A, Grutters JC, Ruven HJT, van Moorsel CHM, Weiskirchen R, Mengsteab S, et al. Transforming Growth Factor- β^2 Gene Polymorphisms in Sarcoidosis Patients With and Without Fibrosis*. *Chest*. 2006 June 2006;129(6):1584-91.
- [94] Liu Y, Helms C, Liao W, Zaba LC, Duan S, Gardner J, et al. A genome-wide association study of psoriasis and psoriatic arthritis identifies new disease loci. *PLoS Genet*. 2008;4:e1000041.
- [95] Mrazek F, Stahelova A, Kriegova E, Fillerova R, Zurkova M, Kolek V, et al. Functional variant ANXA11 R230C: true marker of protection and candidate disease modifier in sarcoidosis. *Genes and immunity*. 2011;12(6):490-4.
- [96] Furuya K, Yamaguchi E, Itoh A, Hizawa N, Ohnuma N, Kojima J, et al. Deletion polymorphism in the angiotensin I converting enzyme (ACE) gene as a genetic risk factor for sarcoidosis. *Thorax*. 1996 Aug;51(8):777-80.
- [97] A. Kruit HJTR, J.C. Grutters, J.M.M. van den Bosch. Angiotensin II Receptor Type 1 1166 A/C and Angiotensin Converting Enzyme I/D gene polymorphisms in a Dutch sarcoidosis cohort. *SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES*. 2010;27(2):147-52.
- [98] Biller H, Ruprecht B, Gaede KI, Muller-Quernheim J, Zissel G. Gene polymorphisms of ACE and the angiotensin receptor AT2R1 influence serum ACE levels in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2009 Jul;26(2):139-46.
- [99] Arbustini E, Grasso M, Leo G, Tinelli C, Fasani R, Diegoli M, et al. Polymorphism of angiotensin-converting enzyme gene in sarcoidosis. *American journal of respiratory and critical care medicine*. 1996 Feb;153(2):851-4.
- [100] Tomita H, Ina Y, Sugiura Y, Sato S, Kawaguchi H, Morishita M, et al. Polymorphism in the angiotensin-converting enzyme (ACE) gene and sarcoidosis. *American journal of respiratory and critical care medicine*. 1997 Jul;156(1):255-9.
- [101] Maliarik MJ, Rybicki BA, Malvitz E, Sheffer RG, Major M, Popovich J, Jr., et al. Angiotensin-converting enzyme gene polymorphism and risk of sarcoidosis. *American journal of respiratory and critical care medicine*. 1998 Nov;158(5 Pt 1):1566-70.
- [102] McGrath DS, Foley PJ, Petrek M, Izakovicova-Holla L, Kolek V, Veeraraghavan S, et al. Ace gene I/D polymorphism and sarcoidosis pulmonary disease severity. *American journal of respiratory and critical care medicine*. 2001 Jul 15;164(2):197-201.

- [103] Pietinalho A, Furuya K, Yamaguchi E, Kawakami Y, Selroos O. The angiotensin-converting enzyme DD gene is associated with poor prognosis in Finnish sarcoidosis patients. *Eur Respir J*. 1999 Apr;13(4):723-6.
- [104] Takemoto Y, Sakatani M, Takami S, Tachibana T, Higaki J, Ogihara T, et al. Association between angiotensin II receptor gene polymorphism and serum angiotensin converting enzyme (SACE) activity in patients with sarcoidosis. *Thorax*. 1998 Jun;53(6):459-62.
- [105] Sakuyama K, Meguro A, Ota M, Ishihara M, Uemoto R, Ito H, et al. Lack of association between IL10 polymorphisms and sarcoidosis in Japanese patients. *Molecular vision*. 2012;18:512-8.
- [106] Tanizawa K, Handa T, Nagai S, Ito I, Kubo T, Ito Y, et al. A CD40 single-nucleotide polymorphism affects the lymphocyte profiles in the bronchoalveolar lavage of Japanese patients with sarcoidosis. *Tissue Antigens*. 2011 Dec;78(6):442-5.
- [107] Iannuzzi MC, Maliarik MJ, Poisson LM, Rybicki BA. Sarcoidosis susceptibility and resistance HLA-DQB1 alleles in African Americans. *American journal of respiratory and critical care medicine*. 2003 May 1;167(9):1225-31.
- [108] van den Berg-Loonen EM, Voorter CEM, Drent M. Strong association of severe pulmonary sarcoidosis with HLA DQB1*0602. *Human immunology*. 2004;65(9-10, Supplement 1):S34-S.
- [109] Wennerstrom A, Pietinalho A, Vauhkonen H, Lahtela L, Palikhe A, Hedman J, et al. HLA-DRB1 allele frequencies and C4 copy number variation in Finnish sarcoidosis patients and associations with disease prognosis. *Human immunology*. 2011(0).
- [110] Sato H, Williams HRT, Spagnolo P, Abdallah A, Ahmad T, Orchard TR, et al. CARD15/NOD2 polymorphisms are associated with severe pulmonary sarcoidosis. *Eur Respir J*. 2009 August 13, 2009:09031936.0010209.
- [111] Rahman MK, Midtling EH, Svingen PA, Xiong Y, Bell MP, Tung J, et al. The pathogen recognition receptor NOD2 regulates human FOXP3+ T cell survival. *J Immunol*. Jun 15;184(12):7247-56.
- [112] Idali F, Wahlstrom J, Muller-Suur C, Eklund A, Grunewald J. Analysis of regulatory T cell associated forkhead box P3 expression in the lungs of patients with sarcoidosis. *Clinical and experimental immunology*. 2008 Apr;152(1):127-37.
- [113] Taflin C, Miyara M, Nochy D, Valeyre D, Naccache J-M, Altare F, et al. FoxP3+ Regulatory T Cells Suppress Early Stages of Granuloma Formation but Have Little Impact on Sarcoidosis Lesions. *Am J Pathol*. 2009 January 15, 2009:ajpath.2009.080580.
- [114] Weaver CT, Harrington LE, Mangan PR, Gavrieli M, Murphy KM. Th17: an effector CD4 T cell lineage with regulatory T cell ties. *Immunity*. 2006 Jun;24(6):677-88.

- [115] Marieke A. Hoeve Nigel DLSTdBDennis MLLRde Waal MTom HMOFrank AWV. Divergent effects of IL-12 and IL-23 on the production of IL-17 by human T cells. *European Journal of Immunology*. 2006;36(3):661-70.
- [116] Hazlett J, Stamp LK, Merriman T, Highton J, Hessian PA. IL-23R rs11209026 polymorphism modulates IL-17A expression in patients with rheumatoid arthritis. *Genes and immunity*. 2012 Apr;13(3):282-7.
- [117] Fischer A, Nothnagel M, Franke A, Jacobs G, Saadati HR, Gaede KI, et al. Association of inflammatory bowel disease risk loci with sarcoidosis, and its acute and chronic subphenotypes. *Eur Respir J*. 2011 Mar;37(3):610-6.
- [118] Jonth AC, Silveira L, Fingerlin TE, Sato H, Luby JC, Welsh KI, et al. TGF-beta1 Variants in Chronic Beryllium Disease and Sarcoidosis. *J Immunol*. 2007 September 15, 2007;179(6):4255-62.
- [119] Hsu DR, Economides AN, Wang X, Eimon PM, Harland RM. The *Xenopus* dorsalizing factor Gremlin identifies a novel family of secreted proteins that antagonize BMP activities. *Molecular cell*. 1998 Apr;1(5):673-83.
- [120] Heron M, van Moorsel CHM, Grutters JC, Huizinga TWJ, van der Helm-van Mil AHM, Nagtegaal MM, et al. Genetic variation in *GREM1* is a risk factor for fibrosis in pulmonary sarcoidosis. *Tissue Antigens*. 2010;77(2):112-7.
- [121] Lopez-Campos JL, Rodriguez-Rodriguez D, Rodriguez-Becerra E, Alfageme Michavila I, Guerra JF, Hernandez FJ, et al. Cyclooxygenase-2 polymorphisms confer susceptibility to sarcoidosis but are not related to prognosis. *Respir Med*. 2009 Mar;103(3):427-33.
- [122] Lopez-Campos JL, Rodriguez-Rodriguez D, Rodriguez-Becerra E, Michavila IA, Guerra JF, Hernandez FJ, et al. Association of the 3050G>C polymorphism in the cyclooxygenase 2 gene with systemic sarcoidosis. *Archives of medical research*. 2008 Jul;39(5):525-30.
- [123] Handa T, Nagai S, Ito I, Shigematsu M, Hamada K, Kitaichi M, et al. Cytotoxic T-lymphocyte antigen-4 (CTLA-4) exon 1 polymorphism affects lymphocyte profiles in bronchoalveolar lavage of patients with sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2003 Oct;20(3):190-6.
- [124] Hattori N, Niimi T, Sato S, Achiwa H, Maeda H, Oguri T, et al. Cytotoxic T-lymphocyte antigen 4 gene polymorphisms in sarcoidosis patients. *Sarcoidosis Vasc Diffuse Lung Dis*. 2005 Mar;22(1):27-32.
- [125] Falta MT, Bowerman NA, Dai S, Kappler JW, Fontenot AP. Linking Genetic Susceptibility and T Cell Activation in Beryllium-induced Disease. *Proc Am Thorac Soc*. May 1, 2010;7(2):126-9.
- [126] Newman LS. Beryllium disease and sarcoidosis: clinical and laboratory links. *Sarcoidosis*. 1995 Mar;12(1):7-19.

- [127] Zhang L, Liu R, wang z, Culver D, Wu R. Modeling Haplotype-Haplotype Interactions in Case-Control Genetic Association Studies. *Frontiers in Genetics*. 2012 2012-January-18;3.

IntechOpen

IntechOpen

