International Journal of Pharmacy Research and Technology
2014, Volume 4, Issue 1, 01-06
ISSN 2250 – 0944 (Online)
ISSN 2250 – 1150 (Print)

Review Article

Sarcoidosis: Involvement of Genetic Factors

Sengupta S.[a*], Soni G.[b], Shandilya S.[a]

[a] NIMS Institute of Pharmacy, Shobha Nagar, Jaipur – 303001, Rajasthan

[b] Kuchaman College Pharmaceutical Sciences Nagaur – 341508, Rajasthan

***Corresponding Author** Email: sandipan.sengupta72@gmail.com*

Received: 27/07/2013, Revised: 05/10/2013 Accepted: 17/12/2013

ABSTRACT

Sarcoidosis affects people of all racial and ethnic groups and occurs at all ages, although it usually develops before the age of 50 years, with the incidence peaking at 20 to 39 years. The incidence of Sarcoidosis varies widely throughout the world. The modern history of Sarcoidosis disease goes back to 1899 when the pioneering Norwegian dermatologist coined the term to describe skin nodules characterized by compact, sharply defined foci of epithelioid cells with large pale nuclei and also a few giant cells. Thinking this resembled sarcoma, he called the condition "multiple benign sarcoid of the skin". This review article has focused on the underlaying mechanism which is responsible for occurance of Sarcoidosis. It also involved the genetic factors (genes) that are responsible for Sarcoidosis. Sarcoidosis has no known cause; although none of potential causes has been definitely confirmed, there is increasing evidence to support that one or more infectious agents may cause Sarcoidosis, although this organism may no longer be viable in the patient. The diagnosis of Sarcoidosis has been significantly aided by new technology. This includes the endobronchial ultrasound, which has been shown to increase the yield of needle aspiration of mediastinal and hilar lymph nodes. The positive emission tomography scan has proven useful for selecting possible biopsy sites by identifying organ involvement not appreciated by routine methodology. Emerging technologies and advances in genomics and proteomics will help to find the causes of Sarcoidosis in future, with the better understanding of pathogenesis of Sarcoidosis and to test new therapy for it.

Keywords: Sarcoidosis, Genes, Diagnosis

INTRODUCTION

Sarcoidosis is a disease that causes inflammation of the body's tissues. It affects multiple systems and is characterized by the formation of granulomas that can be either inside the body or on the body's exterior. The earliest step in the immunological events leading to granuloma formation is the accumulation of T-lymphocytes and mononuclear phagocytes in the affected organs, activated CD45R0+ve T-helper (Th) 1-type T-cells being central to this infiltration. Such a phenomenon is up-regulated at sites of inflammation by two mechanisms:

a) The expansion of CD4+ve memory cells, following a redistribution from blood flow, under the influence of several chemokine's.
b) Interleukin (IL)-2 mediated proliferation [1].

Sarcoidosis is shared by many other pulmonary disorders, such as asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), primary pulmonary hypertension, pulmonary alveolar proteinosis, all conditions in which biochemistry, cell biology, and molecular biology techniques have yielded pathogenesis breakthrough. Sarcoidosis predominantly affects the lung and the lymphatic system, but virtually any organ can be involved. Involvement of genetic factors in Sarcoidosis is supported by familial clustering, increased concordance in monozygotic twins and varying incidence and disease presentation among different ethnic groups. Studies have revealed several human leukocyte antigen (HLA) and non-HLA alleles consistently associated with Sarcoidosis susceptibility. Two genome scans have been reported in Sarcoidosis one in African reporting linkage to chromosome 5 and the other in German families reporting linkage to chromosome 6. Recent genome-wide association studies have found annexin A11 and RAB23 genes associated with Sarcoidosis.

Etiology

The cause of Sarcoidosis is still remaining obscure. Most researchers agree that Sarcoidosis involves an altered immune system but they do not know the source of the problem. Some investigators believe that Sarcoidosis results from a respiratory infection caused by a virus, bacteria, or an unidentified environmental toxin. There is also some evidence of a genetic basis for Sarcoidosis. Current theories are that Sarcoidosis develops from an interaction between a preexisting genetic risk for it and a triggering event, such as an infection or environmental exposure. More research is needed to determine the exact cause for this disease [2].

Symptoms

In most of cases, Sarcoidosis affects the lungs. Respiratory symptoms are present in one-third to half of cases, such as shortness of breath, dry cough, and chest pain. Other common symptoms include fatigue, lymph node swelling or soreness, weight loss, and reddened, watery, or sore eyes. In some cases, symptoms can also appear outside of the lungs, such as lumps, ulcers, discolored skin or skin sores on the back, arms, legs, scalp and face [3].

Diagnosis

Diagnosing Sarcoidosis is a process of elimination. Many other respiratory diseases must be ruled out first. X-rays and other scans are often used to check the lungs and other organs for granulomas. A sample of tissue from the affected area (biopsy) is usually required to confirm the disease. When the lungs are involved, a bronchoscopy is used to acquire the tissue sample. In this procedure, a long, thin tube is inserted through the nose or mouth and down the throat to the lungs [4]. The diagnosis of Sarcoidosis has

been significantly aided by new technology. This includes the endobronchial ultrasound, which has been shown to increase the yield of needle aspiration of mediastinal and hilar lymph nodes. The positive emission tomography scan has proven useful for selecting possible biopsy sites by identifying organ involvement not appreciated by routine methodology.

Treatment

Treatment for Sarcoidosis varies for each individual patient. In over half of the cases, Sarcoidosis only lasts for 12 to 36 months. In cases that do not involve certain organs or that have no additional problems from the disease, treatment is not always necessary. However, 10 to 20 percent of Sarcoidosis patients are left with permanent effects from the disease. Among those whose lungs are impacted, 20 to 30 percent end up with permanent lung damage. For a small percentage of patients, their Sarcoidosis can become chronic, lasting for many years. For those patients, therapy primarily targets ways to keep the lungs and any other affected organs working and to relieve the symptoms. Steroids are commonly prescribed to reduce inflammation. Frequent check-ups are also important so that doctors can monitor the illness and if necessary, adjust treatment. Most people with Sarcoidosis can lead normal lives. Patients need to follow instructions from their physician and take all medication diligently. It is also particularly important that Sarcoidosis patients do not smoke, and avoid exposure to dust and chemicals that can harm the lungs [5].

Deaths

Although uncommon, death from Sarcoidosis can occur if the disease causes serious damage to a vital organ. The most common cause of mortality associated with Sarcoidosis is pulmonary fibrosis resulting from the disease. In the United States, there were 924 deaths due to Sarcoidosis in 2006, an age-adjusted death rate of 0.32 per 100,000. Both of these numbers are higher than the average number of deaths (about 821 per year) and the age-adjusted death rate (0.30 per 100,000) for 1999 through 2012 [5].

Evidence for Genetic Predisposition

Familial Sarcoidosis was first noted in Germany in 1923 by Martenstein, who reported two affected sisters. After that several familial cases were reported across Europe and USA. Worldwide surveys revealed that familial Sarcoidosis occurred in 10.3% cases from the Netherlands [6], 7.5% from Germany [7], 5.9% from the United Kingdom [8], 4.7% from Finland [9], 4.3% from Japan [9], 9.6% from Ireland and 6.9 % from Sweden. A family history survey of Detroit clinic–based population in USA showed that 17% of African Americans and 3.8% of white American reported a family history in first- and second degree relatives. In African Americans, the sibling recurrence risk ratio, which compares disease risk among siblings with the disease prevalence in the general population, is about 2.2 [10]. A registry-based twin study in the Danish and the Finnish population showed an 80-fold increased risk of developing Sarcoidosis in monozygotic co-twins and 7-fold increased risk in dizygotic twins [11]. Differences in disease incidence among different ethnic and racial groups exist worldwide. In the United States, African Americans have about a threefold higher age-adjusted annual incidence; 35.5 per 100,000 compared with Caucasians, 10.9 per 100,000. African American females aged 30 to 39 years were found at greatest risk at 107/100,000.The lifetime risk was calculated to be 2.4% for African Americans and 0.85% for Caucasian Americans [12]. In the United Kingdom, prevalence of Sarcoidosis was found to be three times higher in the Irish living in London than in native Londoners [13]. It was eight time more common in natives of Martinique living in France than in the indigenous French populations [13].

Genetic Attachment Studies in Sarcoidosis

Genetic studies in Sarcoidosis have gone through three phases – candidate gene studies, genome scanning using affected sib pair (ASP) linkage analysis and most recently, genome wide association studies (GWAS).

Candidate Gene

The search for Sarcoidosis susceptibility genes has generally relied on the candidate gene approach. Investigators have selected genes for study that fit into the prevailing disease model. Sarcoidosis is thought to be a deregulated response to an inhaled antigen that involves antigen-presenting cells, T cells (primarily a helper T-cell type 1 polar response), and cytokine and chemokine release resulting in cell recruitment and the formation of granulomas in involved organs.

Table 1 Summary of different subtypes of Human Leukocytes Antigens (HLA)

HLA gene	HLA class	Chromosome location	Risk Alleles	Putative Functional Significance
HLA-A	Class I	30,018, 309-30, 021, 041 bp	A*1	Susceptibility
HLA-B	Class I	31, 431, 922-31, 432, 914 bp	B*8	Susceptibilityin several population
HLA-DQB1	Class II	32, 735, 918-32, 742, 420 bp	*0201 *0602	Susceptibility / disease progression in several groups
HLA-DRB1	Class II	32, 654, 526-32, 665, 559 bp	*0301 *01, *04 *1101	Susceptibility in whites and African Americans. Stage II/III chest X-ray
HLA-DRB3	Class II	32, 654, 526-32, 665, 540 bp	*1501 *0101	Susceptibility/disease progression in whites
BTNL2	Class II	32, 470, 490-32, 482, 878 bp	rs2076530	*BTNL2* rs2076530 G → A is associated with sarcoidosis risk in white patients but not in black patients.

Entanglement with Human Leukocyte Antigens (HLA)

HLA genes have been the best studied candidate genes in Sarcoidosis. HLA genes are involved in presenting antigen to T cells and are grouped into three classes: class I, II and III. HLA association studies in Sarcoidosis began over thirty years ago. A summary of the most consistent HLA associations in Sarcoidosis is shown below. In 1977 Brewerton and colleague [14] first revealed an association of acute Sarcoidosis with the HLA class I antigen HLA-B8 which was later confirmed by other groups. Hedfors and co-workers also noted that HLA-B8/DR3 genes were inherited as a Sarcoidosis risk haplotype in whites. In white HLA-B8/DR3 haplotype is associated with wide variety of autoimmune diseases. These earlier studies of class I HLA antigens directed to the studies focused on HLA class II. A recent report by Grunewald and colleagues [15] suggests that HLA class I and II genes work together in Sarcoidosis pathophysiology.

Among the HLA class II antigens, HLA-DRB1 have been the most studied antigen associated with Sarcoidosis. The variation in the HLA-DRB1 gene affects both susceptibility and prognosis in Sarcoidosis [16]. In the ACCESS study, the HLA-DRB1* 1101 allele was associated with Sarcoidosis both in blacks and whites ($p<0.01$) and had a population attributable risk of 16% in blacks and 9% in whites [16]. In addition susceptibility markers, the ACCESS study also found that HLA class II alleles might be markers for different phenotypes of Sarcoidosis such as RB1*0401 for eye involvement in blacks and whites, DRB3 for bone marrow involvement in blacks, and DPB1*0101 for hypercalcaemia in whites [16]. Another consistent finding across populations has been the HLA-DQB1*0201 allele association with decreased risk and lack of disease progression [17]. Other reports strongly support the notion that several different HLA class II genes acting either in concert or independently predispose to Sarcoidosis [17]. Linkage disequilibrium (LD) within the major histocompatibility complex (MHC) region limits the ability to precisely identify the involved HLA genes. LD exists when alleles at two distinctive loci occur in gametes more frequently than expected. Grunewald and colleagues showed that the HLA-DRB1*03 associated with resolved disease and HLA-DRB1*15 with persistent disease were synonymous with HLA-DQB1*0201 with resolved disease and HLA DQB1*0602 with persistent disease. Consequently, determining the effects of HLA-DQB1 on Sarcoidosis risk apart from DRB1 or dissecting out other gene effects from closely linked haplotypes in the MHC region may be an intractable problem in whites. In African Americans, HLA-DRB1/DQB1 LD may not be as strong as in Caucasians [18].

Entanglement with Non-HLA candidate genes

Genes that influence antigen processing, antigen presentation, macrophage and T-cell activation, and cell recruitment and injury repair may be considered Sarcoidosis candidate genes.

Angiotensin-Converting Enzyme

Angiotensin-converting enzyme (ACE) is produced by sarcoid granulomas and its serum level can be elevated in Sarcoidosis. Serum ACE levels are thought to reflect granuloma burden. The ACE gene insertion (I)/deletion (D) polymorphism partially accounts for the serum ACE level variation, and investigators have proposed that this genotype should be used to adjust serum ACE reference values. Studies to support a role for ACE gene polymorphisms in susceptibility or severity have been inconsistent. While only a few case control studies have suggested that ACE gene polymorphism is associated with Sarcoidosis susceptibility and disease severity, most of the studies does not support that finding [19-21].

CC-Chemokine Receptor 2 (CCR2)

CCR 2, a receptor for monocyte chemoattractant protein, plays an important role in recruiting monocytes, T-cells, natural killer cells and dendritic cells. CCR2 knockout mice die rapidly when challenged with mycobacteria and display decreased IFN-γ production when challenged with *Leishmania donovani* or *Cryptococcus neoformans.* A single nucleotide polymorphism (SNP) in CCR2 gene (G190A, Val64Ile) is associated with protection in Japanese patients. Evaluation of eight SNPs in the CCR2 gene in 304 Dutch patients showed that haplotype 2 was associated with Lofgren's syndrome. Underrepresentation of the Val64Ile variant was observed in 65 Czech patients and in 80 control subjects but did not achieve statistical significance [22-23].

C-C Chemokine Receptor 5 (CCR5)

CCR5 serves as a receptor for CCL3 (macrophage inflammatory protein 1-α), CCL4 (macrophage inflammatory protein 1-β), CCL5 [regulated upon activation, T-cell expressedand secreted], and CCL8 (monocyte chemotactic protein 2) . A 32 bp deletion in the CCR5 gene results in a non-functional receptor unable to bind its ligands .Petrek and colleagues reported that 32-bp deletion in CCR5 gene was significantly increased in Czech patients. Whereas Spagnolo and colleagues, using haplotype analysis, found no association in evaluating 106 white British patients and 142 control subjects and 112 Dutch patients and 169 control subjects [24].

Complement receptor 1

Complement receptor 1 (CR1; CD35) is present on polymophonuclear leukocytes, macrophages, B lymphocytes, some T lymphocytes, dendritic cells, and erythrocytes. Immune complexes bound to CR1 are transferred to phagocytes as erythrocytes traverse the liver and spleen [25]. Immune complex clearance rates correlate with CR1 density. Low expression of erythrocyte CR1 is associated with impaired immune complex clearance and deposition outside the reticuloendothelial system. These extra reticuloendothelial immune complexes deposits incite local inflammatory responses and presumably granuloma formation. That immune complexes may be involved in Sarcoidosis was suggested in the early 1970s.

Cystic fibrosis transmembrane conductance regulator

The R75Q mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) occurs in high frequency in patients with atypical mild cystic fibrosis, bronchiectasis, and allergic bronchopulmonary aspergillosis. Bombieri and colleagues reported a R75Q association with Sarcoidosis, but in follow-up using complete cystic fibrosis gene mutation screening they could not replicate their findings. Schurmann and colleagues could not demonstrate a CFTR association with Sarcoidosis [26].

Heat shock protein A1L

Heat shock proteins (HSPs) comprise a conserved group of proteins with an average weight of 70 kD. Intracellular HSPs serve as molecular chaperones, whereas extracellular HSPs induce cellular immune responses [83]. HSPs may also act as carrier molecules for the immunogenic peptides presented on antigen-presenting cells. Polymorphisms in the HSPA1L (alias HSP70-hom) have been associated with susceptibility to rheumatoid arthritis. Antibodies to HSP70 in Sarcoidosis have been reported. To further evaluate the role of HSPs in Sarcoidosis, the HSP70 +2437 C allele was evaluated and found to be associated with Sarcoidosis and Lofgren's syndrome in Polish patients but not in Japanese patients [27].

Inhibitor κB-α

Inhibitor κB (IκB) masks the nuclear factor (NF)- κB nuclear localization sequence, thus retaining NF-κB in the cytoplasm and preventing DNA binding. On phosphorylation, IκB Degrades, allowing NF-kB's nuclear localization and initiation of transcription. Terminating the NF-κB response requires IκB-α. IκB-α knockout mice die 7 to 10 days after birth with increased levels of TNF-α mRNA in the skin and severe dermatitis. NF-κB–dependent signaling in alveolar macrophage makes NF-κB and thus IκB central to sarcoid pathophysiology. Abdullah and colleagues found the promoter -297T allele associated with Sarcoidosis. No other IκB studies in Sarcoidosis have been reported [28].

Interlukin-1(IL-1)

IL-1β produced mainly by macrophages maintains T-cell alveolitis and granuloma formation. Hunninghake and colleagues also demonstrated higher IL-1β activity in the BALF of patients with Sarcoidosis compared with normal subjects. Mikuniya and colleagues suggested thatthe ratio of IL-1 receptor antagonist to IL-1β in sarcoidal alveolar macrophage culture supernatants could predict disease chronicity. The IL-1α 5' flanking –889 C allele was found nearly two times more commonly among Czech patients with Sarcoidosis compared with control subjects [29].

Genome scanning: Affected sib pair linkage analysis

Sarcoidosis genome scan in Germans

The first genome scan study related to Sarcoidosis was conducted by Schurmann and colleagues, in which they used 225 microsatellite markers spanning the genome in 63 German families to identify a linkage signal (D6S1666) on chromosome 6p21. This group then used a three-stage single-nucleotide polymorphism (SNP) scan of the 16-MB region surrounding D6S1666 [30] and identified a single SNP, rs2076530, in the BTNL2 gene associated with Sarcoidosis. This SNP (G/A) was found at the 3' boundary of the exon 5 coding region. The A allele at this position has been proposed to introduce an alternative splice site at the exon 5–3' intron boundary of the BTNL2 transcript that results in a premature truncation of the protein. BTNL2, also known as "butyrophilin-like 2" and "BTL-2," is a butyrophilin gene that belongs to the immunoglobulin gene superfamily related to the B7 family [31]. Butyrophilin was initially cloned from cattle mammary epithelial cells. This gene was localized to the MHC class II region in humans. To determine the consistency of the BTNL2 gene as a Sarcoidosis risk factor across different populations, Rybicki and colleagues characterized variation in the BTNL2 exon/intron 5 region in an African-American family sample that consisted of 219 nuclear families (686 individuals) and in 2 case–control samples (295 African-American matched pairs and 366 white American matched pairs) [32]. They confirmed that BTNL2 somewhat was less associated with Sarcoidosis in African Americans compared with whites.

Sarcoidosis genome scan in African Americans

Eleven centers joined together in an NHLBI-sponsored effort (Sarcoidosis Genetic Analysis Consortium [SAGA] to perform a genome scan in African American siblings. This group performed a 380-microsatellite genomewide scan across 22 autosomes in 519 African American sib pairs. The significant findings included 15 markers with p values < 0.05 with the strongest linkage signal on chromosome 5 [33]. Fine mapping studies indicated a Sarcoidosis susceptibility gene on chromosome 5q11.2 and a gene protective effect for Sarcoidosis on 5p15.2 [34]. The reason why African Americans were chosen to uncover Sarcoidosis susceptibility genes was that African Americans are more commonly and severely affected and have affected family members more often than whites. But the disadvantage of doing so is that AfricanAmericans are admixed with white and other populations to varying degrees with possible admixture among their participating centers ranging from 12% in South Carolina to 20% in New York. To address the possibility that admixed subpopulations existed in the SAGA sample and affected the power to detect linkage, the sample was stratified by genetically determined ancestry using the data from the 380 microsatellite markers genotyped in the genome scan. The African-American families were clustered into subpopulations based on ancestry similarity. Evidence of two genetically distinct groups was found: Stratified linkage results suggest that one subpopulation of families contributed to previously identified linkage signals at 1p22, 3p21-14, 11p15, and 17q21 and that a second subpopulation of families contributed to those found at 5p15-13 and 20q13 [35]. These findings support the presence of Sarcoidosis susceptibility genes.

Genome-Wide Association Studies (GWAS)

In genome-wide association study high throughput genotyping methods are used to genotype a dense set of SNPs across the genome. A significant advantage of this approach is that association studies are more powerful than affected sib pair methods of linkage analysis. Hofmann and colleagues [36] conducted a genomewide association study of 499 German patients with Sarcoidosis and 490 control subjects. The strongest signal mapped to the annexin A11 gene on chromosome 10q22.3. Validation in an independent sample confirmed the association. Annexin A11 has regulatory functions in calcium signaling, cell division, vesicle trafficking, and apoptosis. Depletion or dysfunction of annexin A11 may affect the apoptosis pathway in Sarcoidosis. Later the same group reported another associated locus 6p12.1 that comprises several genes, a likely candidate being RAB23. RAB23 is proposed to be involved in antibacterial defense processes and regulation of the sonic hedgehog signaling pathway [37].

CONCLUSION

The cause of Sarcoidosis remains unknown. It is thought to be caused by interaction between environmental and genetic factors. Genetic studies have revealed the HLA

and other candidate genes associated with Sarcoidosis susceptibility. Unfortunately, many of the reported associations have not been replicated. Two genome scans have been reported and one has yielded a likely candidate gene, BTNL2 that has been replicated in large studies. Emerging technologies and advances in genomics and proteomics will help to find the causes of Sarcoidosis, better understanding of pathogenesis of Sarcoidosis and to test new therapy. Gene expression profiling in BALF and blood carried out at the time of presentation will likely help to better predict disease resolution or progression in future.

REFERENCES

1. M Luisetti , A Beretta , L Casali, " Genetic aspects in sarcoidosis" , Eur. Respir. J. 16, 768-780, (2000).
2. National Heart, Lung and Blood Institute. Diseases and Conditions Index. Sarcoidosis: Causes. (February 2009) http://www.nhlbi.nih.gov/health/dci/Diseases/sarc/sar_causes.html, accessed Nov. 9, 2009.
3. National Heart, Lung and Blood Institute. Diseases and Conditions Index. Sarcoidosis: Signs & Symptoms. (February 2009), http://www.nhlbi.nih.gov/health/dci/Diseases/sarc/sar_signs and symptoms.html, accessed November 9, 2009.
4. National Heart, Lung and Blood Institute. Diseases and Conditions Index. Sarcoidosis: Diagnosis. (February2009), http://www.nhlbi.nih.gov/health/dci/Diseases/sarc/sar_diagnosis.html, accessed December 8, 2009.
5. H Nunes, D Bouvry, P Soler, D Valeyre, "Sarcoidosis", Orphanet Journal of Rare Diseases. 2(46), (2007).
6. R M Wirnsberger, J De Vries, E F Wouters, and M Drent, "Clinical presentation of sarcoidosis in The Netherlands an epidemiological study", Neth J Med. 53(2), 53-60 (1998).
7. D Kristen, "Sarcoidosis in Germany. Analysis of a questionnaire survey in 1992 of patients of the German Sarcoidosis Group", Pneumologie. 49(6), 378-82 (1999).
8. D Mcgrath, S, Z Daniil, and P Foley, JL du Bois, PA Lympany, P Cullinan,RM du Bois, "Epidemiology of familial sarcoidosis in the UK", Thorax. 55(9), 751-754, (2000).
9. A Pietinalho, M Ohmichi, M Hirasawa, Y Hiraga, A Lofroos, and O Selroos, "Familial sarcoidosis in Finland and Hokkaido, Japan-a comparative study", Respir Med, 93, 408-412, (1999).
10. B Rybicki, K L Kirkey, M Major, & M Maliarik, GA Chase, MC Iannuzzi, "Familial risk ratio of sarcoidosis inAfrican-American sibs and parents", Am J Epidemiol. 153, 188-193, (2001).
11. A Sverrild, V Backer, K O Kyvik, J Kaprio, N Milman, C Svendsen, & S F Thomsen, "Heredity in sarcoidosis: a registry-based twin study", Thorax. 63(10), 894-896, (2008).
12. B A Rybicki, & M Major, J Popovich Jr, MJ Maliarik, MC Iannuzzi, "Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization", Am J Epidemiol. 145, 234-241, (1999).
13. B A Rybicki, M Maliarik, & M Major, J Popovich Jr, MC Iannuzzi, "Epidemiology, demographics, and genetics of sarcoidosis", Sem Respir Infect. 3, 166-173, (1998).
14. D A Brewerton, C Cockburn, D James, D G James, & E Neville, HLA antigens in sarcoidosis", Clin Exp Immunol. 27, 227-229, (1977).
15. J Grunewald, A Eklund, & O Olerup, "Human leukocyte antigen class I alleles and the disease course in sarcoidosis patients", Am J Respir Crit Care Med. 169, 696-702, (2004).
16. M D Rossman, B Thompson, M Frederick, M Maliarik, M C Iannuzzi, B A Rybicki, J Pandey, L S Newman, E Magira, & Beznik-cizman, "a 68 Sarcoidosis significant risk factor for sarcoidosis in blacks and whites", Am J Hum Genet . 73, 720-735, (2003).
17. M C Iannuzzi, M J Maliarik, L M Poisson, & B A Rybicki, "Sarcoidosis susceptibility and resistance HLA-DQB1 alleles in African Americans", Am J Respir Crit Care Med. 167, 1225-1231, (2003).
18. A A Zachary, W B Bias, A R Johnson, & M S Leffell, "Antigen, allele, and haplotype frequencies report of the ASHI minority antigens workshops: part 1, African-Americans", Hum Immunol. 62, 1127-1136, (2001).
19. A Planck, A Eklund, E Yamaguchi, & J Grunewald, "Angiotensin-converting enzymegene polymorphism in relation to HLA-DR in sarcoidosis", J Intern Med. 251(3), 217-22. (2002).
20. D S Mcgrath, P. J Foley, M Petrek, & Izakovicova-holla, L Du Bois, "Ace gene I/D polymorphism and sarcoidosis pulmonary disease severity", Am J Respir Crit Care Med. 164(2), 197-201, (2001).
21. M Schürmann, P Reichel, B Müller-myhsok & E Schwinger, "Angiotensin-converting enzyme (ACE) gene polymorphisms and familial occurrence of sarcoidosis", J Intern Med. 249(1), 77-83, (2001).
22. P Spagnolo, E A Renzoni, A U Wells, et al. "C-C chemokine receptor 2 and sarcoidosis: association with Lofgren's syndrome", Am J Respir Crit Care Med. 168, 1162-1166, (2003).
23. R Valentonyte, J Hampe, P. J Croucher, J Muller-quernheim, E Schwinger, "Study of C-C chemokine receptor 2 alleles in sarcoidosis, with emphasis on family-based analysis", Am J Respir Crit Care Med . 171, 1136-1141, (2005).
24. P Spagnolo, E Renzoni, A Wells, S J Copley, S R Desai, H Sato, J C Grutters, et al. "C-C chemokine receptor 5 gene variants in relation to lung disease in sarcoidosis", Am J Respir Crit Care Med . 172, 721-728, (2005).
25. R Janssen, H Sato, J C Grutters, & H J Ruven, et al. "The Clara cell10 adenine38 guanine polymorphism and sarcoidosis susceptibility in Dutch and Japanese subjects", Am J Respir Crit Care Med . 170, 1185-1187, (2004).
26. M Luisetti, & P F Pignatti, "Genetics of idiopathic disseminated bronchiectasis". Semin Respir Crit Care Med. 24, 179-184, (2003).
27. K Bogunia-kubik, K Koscinska, K Suchnicki, & A Lange, "HSP70-hom gene single nucleotide (-2763 G/A and-2437 C/T) polymorphisms in sarcoidosis", Int J Immunogenet.. 33, 135-140. (2006).
28. A Abdallah, H Sato, J. C Grutters, S Veeraraghavan, P. A Lympany, & H. J. Ruven, "Inhibitor kappa B-alpha (IkappaB- alpha) promoter polymorphisms in UK and Dutch sarcoidosis". Genes Immun. 4, 450-454. (2003).
29. B Hutyrova, P Pantelidis, J Drabek, M Zurkova, "Interleukin-1 gene cluster polymorphisms in

sarcoidosis and idiopathic pulmonary fibrosis", Am J Respir Crit Care Med. 165, 148-151, (2002).
30. R Valentonyte, J Hampe, K Huse, P Rosenstiel, M Albrecht, A Stenzel, "Sarcoidosis is associated with a truncating splice site mutation in BTNL2", Nat Genet. 37, 357-364, (2005).
31. A Sharpe, G J Freeman, "CD28 superfamily", Nat Rev Immunol. 2, 116-126, (2002).
32. B A Rybicki, J L Walewski, M J Maliarik, "The BTNL2 gene and sarcoidosis susceptibility in African Americans and whites", Am J Hum Genet. 77, 491-499, (2005).
33. M C Iannuzzi, & S K Iyengar, et al. "Genome-wide search for sarcoidosis susceptibility genes in African Americans". Genes Immun. 6, 509-518. (2005).
34. C Gray-McGuire, R Sinha, SK Iyengar, C Millard, BA Rybicki, RC Elston, "Genetic characterization and fine mapping of susceptibility genes for sarcoidosis in African Americans on chromosome 5", Hum Genet. 120, 420-430, (2006).
35. C L Thompson, R C Elston, & S K Iyengar, "Stratified linkage analysis based on population substructure in a population of African-American sarcoidosis families". Am J Hum Genet. 79, 603-613, (2006).
36. S Hofmann, A Franke, A Fischer, et al. "Genome-wide association study identifies ANXA11 as a new susceptibility locus for sarcoidosis", Nat Genet. 40(9), 1103-1106. (2008).
37. S Hofmann, A Fischer, et al. "A genome-wide association study reveals evidence of association with sarcoidosis", Eur Respir J . 12, (2011).