Genetics of Sarcoidosis

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ABSTRACT

Sarcoidosis likely results from an interplay of environmental and genetic factors. Despite a recent large multicenter study, A Case-Control Etiologic Study of Sarcoidosis (ACCESS), no single causative environmental agent has been identified. Family clustering and differences in racial incidence of sarcoidosis support an inherited susceptibility to sarcoidosis. Siblings of patients with sarcoidosis have about a fivefold increased risk of developing sarcoidosis. Certain human leukocyte antigen (HLA) alleles have been consistently associated with sarcoidosis susceptibility. Furthermore, HLA-DRB1*0301/DQB1*0201 has been associated with good prognosis in Löfgren's syndrome. Many candidate genes studied based on their potential function in immunopathogenesis have been evaluated in case-control studies, but few have been consistently associated with sarcoidosis across populations. Two genome scans have been reported in sarcoidosis. One in African Americans reporting linkage to chromosome 5 and the other in German families reporting linkage to chromosome 6. Follow-up studies on chromosome 6 identified the *BTNL2* gene, a B7 family costimulatory molecule to be associated with sarcoidosis. Advances in genotyping and statistical analysis are helping to elucidate the genetics of sarcoidosis.

KEYWORDS: Sarcoidosis, genetics, *BTNL2*, linkage

Genetic polymorphisms likely affect every pathophysiological step in sarcoidosis, beginning with antigen presentation through granuloma accumulation and in some cases to fibrosis. That genetic polymorphisms play a role in sarcoidosis is most strongly supported by the observed familial clustering and ethnic differences in incidence and disease severity.

Familial sarcoidosis was first noted in Germany in 1923 by Martenstein, who reported two affected sisters.[1] Although several cases were then noted across Europe, familial sarcoidosis was not reported in the United States until 1947, when Robinson and Hahn reported two sets of brothers.[2] Worldwide surveys revealed that familial sarcoidosis occurred in 10.3% cases from the Netherlands,[3] 7.5% from Germany,[4] 5.9% from the United Kingdom,[5] 4.7% from Finland,[6] and 0.8% from Spain.[7] In a Detroit clinic–based population, 19% of African Americans reported a family history in first- and second-degree relatives.[8] In African Americans, the sibling recurrence-risk ratio (λs), which compares disease risk among siblings to the disease prevalence in the general population, is $\sim$2.2 (CI 1.03 to 3.68).[9] The ACCESS study (A Case-Control Etiologic Study of Sarcoidosis) found that cases were five times more likely than controls to report a sibling or parent as affected.[10]

Ethnic variation in sarcoidosis incidence also occurs worldwide.[11] 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

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39 years are at greatest risk at 107/100,000.[12] The lifetime risk is 2.4% for African Americans and 0.85% for Caucasian Americans.[12]

HUMAN LEUKOCYTE ANTIGEN GENES IN SARCOIDOSIS

Human leukocyte antigen (HLA) genes are central to antigen presentation and are expected to play a role in sarcoidosis. The search for HLA associations with sarcoidosis began over 30 years ago with the HLA class I antigen HLA-B8 reported to be associated with acute sarcoidosis.[13] Other groups[14,15] confirmed the HLA-B8 association and noted that HLA-B8/DR3 genes were inherited as a sarcoidosis risk haplotype.[14] These earlier studies of class I HLA antigens gave way to HLA class II studies. However a recent report by Grunewald et al suggests that HLA class I and II genes may work together in sarcoidosis pathophysiology.[16]

For the class II HLA genes, the HLA-DRB1 association predominates in the literature, with variation in the HLA-DRB1 gene affecting both sarcoidosis susceptibility and prognosis (Table 1).[17,18] The ACCESS study reported that the HLA-DRB1*1101 allele was associated ($p < .01$) with sarcoidosis in blacks and whites and had a population attributable risk of 16% in blacks and 9% in whites. HLA-DRB1-F47 was the amino acid residue most associated with sarcoidosis and independently associated with sarcoidosis in whites. HLA-DRB1*1501 was differentially associated with sarcoidosis in whites ($p < .003$).

An HLA allele of interest is HLA-DPB1 Glu-69, which has been reported to be strongly associated with chronic beryllium disease.[19,20] The immunopathologic and clinical similarities between chronic beryllium disease and sarcoidosis suggest that the same immune response genes could be involved in both diseases. Three studies were unable to confirm that HLA-DPB1 Glu-69 is associated with sarcoidosis.[21–23]

Table 1 Consistent Human Leukocyte Antigen Associations

HLA Allele	Association
B*8	Susceptibility
DQB1*0201	Protection, good prognosis, Löfgren's syndrome
DRB1*0301	Acute onset, good prognosis, Löfgren's syndrome
DRB1*04	Protection
DRB1*1101	Susceptibility in Caucasians and African Americans
DRB3*0101	Susceptibility, disease progression in Caucasians
DRB3*1501	Löfgren's syndrome

A consistent finding across populations has been the HLA-DQB1*0201 allele association with decreased risk and lack of disease progression (Table 1).[24] One caveat is that linkage disequilibrium (LD) within the major histocompatibility complex (MHC) region may limit precisely identifying the involved HLA genes. LD exists when alleles at two distinctive loci are transmitted together more frequently than expected. For example, whereas HLA-DQB1*0201 is associated with a good prognosis, it is in tight LD with HLA-DRB1*0301, which has also been associated with a good prognosis.[25]

FAMILIAL GRANULOMATOUS DISEASES

Two more commonly recognized familial granulomatous diseases are Blau syndrome and Crohn's disease. Blau syndrome, an autosomal dominant granulomatous disease of childhood, consists of acute anterior uveitis, arthritis, and skin rash. The main difference between Blau syndrome and sarcoidosis is that Blau syndrome patients do not have lung involvement or a positive Kveim skin test.[26] Crohn's disease may also present with uveitis, arthritis, and skin rash. Although lung involvement may occur in Crohn's disease, the pattern is distinguishable from that of sarcoidosis.

The susceptibility locus for these two familial granulomatous inflammatory disorders was localized to a 40 centimorgan (cM) region spanning the chromosome 16 centromere (16p12-q21).[27,28] The gene responsible for the linkage signal is the nucleotide oligomerization domain *(NOD)2* gene.[29,30]*NOD2* was renamed caspase activating recruitment domain (CARD) 15. CARD15, a 1040 amino acid protein, is expressed in monocytes and epithelial cells and is a member of the family of nucleotide binding site and leucine rich repeat (NBS-LRR) proteins that recognize microbes.

Mutations found in Blau syndrome, located in the region encoding the nucleotide binding domain, are associated with constitutive NF-κ B activation (approximately fourfold increase in basal activity) independent of any exogenous stimulation.[31] Mutations in Crohn's located in the LRR domain result in defective peptidoglycan sensing. Impaired sensing is thought to trigger diffuse activation of NF kB through CARD15 independent mechanisms.[32] Alternatively deficient NOD2 signaling might lead to inappropriate induction of costimulatory signals for T cells.[32]

No evidence for genetic linkage between the IBD (inflammatory bowel disease) -Blau syndrome locus and sarcoidosis could be found.[33–35] Further, refuting CARD15 as a sarcoidosis susceptibility gene, Schurmann et al, using both case-control and family-based samples, evaluated four coding CARD15 polymorphisms associated with increased risk of Crohn's

Table 2 Candidate Genes Evaluated in Sarcoidosis

Candidate Gene	Comment	References
Angiotensin converting enzyme (ACE)	Increased risk for ID and DD genotypes; moderate association between II genotype and radiographic progression	38–42
C-C chemokine receptor 2	Associated with protection/Löfgren's syndrome	43–46
C-C chemokine receptor 5	CCR5Delta32 allele more common in patients treated with corticosteroid; refuted with haplotype analysis and larger sample	45,47
CD80, CD86	No association detected	48
Clara cell 10KD protein	A allele associated with sarcoidosis and with progressive disease at 3 years follow-up	49
Complement receptor 1	Association with the GG genotype for the Pro1827Arg (C(5507)G) polymorphism	50
Cystic fibrosis transmembrane regulator	R75Q increases risk	51,52
Heat shock protein 70 like	HSP(+2437)CC associated with susceptibility/Löfgren's syndrome	53
Inhibitor kappa B α	Associated with -297T allele; allele -827T in stage II	54
IL-1 α	The IL-1α -889 1.1 genotype increased risk	55
IL-4 receptor	No association detected	56
IL-18	Genotype -607CA increased risk over AA	57–60
Interferon gamma	IFNA17 polymorphism (551T→G) and IFNA10 [60A]-IFNA17 [551G] haplotype increased risk	61
Natural resistance associated macrophage protein	Protective effect of (CA)(n) repeat in the immediate 5′ region of the NRAMP1 gene.	62
Toll-like receptor 4	Asp299Gly and Thre399Ile mutations associated with chronic disease	63
Transforming growth factor	TGF β2 59941 allele, TGFβ3 4875 A and 17369 C alleles were associated with fibrosis on chest x-ray	64
Tumor necrosis factor α	Genotype -307A allele associated with erythema nodosum/Löfgren's syndrome and -857T allele with sarcoidosis; -307A not associated in African Americans	38,65–68
Vascular endothelial growth factor	+813 CT and TT genotypes associated with protection	69
Vitamin D receptor (VDR)	BsmI allele associated with sarcoidosis	38,70,71

disease and concluded that CARD15 mutations play no role in sarcoidosis susceptibility.[36] Kanazawa et al, however, reported an association in 10 early-onset sarcoidosis patients who had disease onset ranging from 6 months to 4 years of age.[37] Although CARD15 is not a candidate gene for disease susceptibility it may affect phenotype.

Several non-MHC candidate genes have been evaluated in sarcoidosis. In general these candidates were chosen based on their known function in antigen presentation or T cell response (Table 2).[38–71] Unlike HLA, these non-MHC candidate gene associations detected in case-control studies have not been consistently found across populations and for many of these genes, when evaluated in family-based studies, have not been confirmed as sarcoidosis susceptibility genes.[38,72–75]

LINKAGE STUDIES

An alternative approach to choosing candidate genes based on their possible functional role is to identify candidates in chromosomally linked regions. Two affected sib pair linkage studies in sarcoidosis have been reported, one in German families and the other in African American families. On the basis of 225 microsatellite markers tested in 63 German families (Caucasians) with affected sib pairs, linkage at the MHC on chromosome 6p was found with additional suggested linkage to markers on chromosomes 1, 3, 9, and X.[35] For the African American linkage study, 380 markers on 22 autosomes were genotyped in 229 families with 519 pairs consisting of 338 affected sib pairs, 116 discordantly affected pairs where one sib had sarcoidosis and the other was healthy, and 15 unaffected sib pairs. This differed from the German study that only included affected full sibs. The Sarcoidosis Genetic Analysis (SAGA) study in African Americans allowed analysis of decreased allele sharing among the discordantly affected pairs as well as increased sharing among the concordantly affected sib pairs.[76] Peaks with p values less than .05 were identified on chromosomes 1p22, 2p25, 5p15–13, 5q11, 5q35, 9q34, 11p15, and 20q13, with the most prominent peak at D5S2500 on

chromosome 5q11 ($p = .0005$). Agreement for linkage between the scans performed in the German and African American populations were found at chromosomes 1p, 3p, and 9q.[34]

FINE MAPPING STUDIES

In follow-up to the African American genome scan, additional microsatellite markers were used to examine regions with suggestive linkage.[77] Of the nine regions that were fine mapped, support was found for the presence of a sarcoidosis susceptibility allele on chromosome 5p15.2 and a protective allele on chromosome 5q11.2.

A limitation to linkage analysis is confounding due to admixture. For example, it is known that African Americans are admixed with European Americans and other populations to varying degrees. Parra et al[78] showed that African Americans sampled from different geographic regions show different amounts of European admixture, from 6.8% in a Jamaican sample to 22.5% in a sample from New Orleans. Thompson et al further analyzed the SAGA sample using linkage analysis stratified by genetically determined ancestry; they confirmed the signals on chromosome 5 and found evidence of a additional susceptibility locus at 2q37.[79]

In the follow-up to the scan performed in Caucasians, Schurmann et al went on to use a three-stage single nucleotide polymorphism (SNP) scan of the 16 MB region surrounding D6S1666, the marker with the highest evidence of linkage. This regions was screened using 69 SNPs and an association with butyrophilin like 2 (BTNL2) detected. Typing an additional 48 SNPs across a 440 kb region surrounding BTNL2 narrowed the association to a single SNP, rs2076530, in BTNL2.[80] This SNP (G/A) was found at the 3′ boundary of the exon 5 coding region. The A allele at this position introduces an alternate splice site at the transcript's exon 5 -3′ intron that results in a premature truncation of the protein. Cellular localization studies showed that the rs2076530 G encoded transcript BTNL2-L (long) localized to the membrane, whereas the truncated rs2076530 A encoded a transcript BTNL2-S (short) that remained in the cytoplasm.[80]

BTNL2 (aliases "butyrophilinlike 2" and "BTL-2") is a butyrophilin gene that belongs to the B7 family.[81,82] Butyrophilin was initially cloned from cattle mammary epithelial cells[83] and is a member of a family of genes located in the MHC class II region.[81] In evaluating the BTNL2 gene as a sarcoidosis risk factor in both Caucasians and African Americans, Rybicki et al also found that BTNL2 moderately influences disease risk (OR of 1.6 in heterozygotes and 2.8 in homozygotes) and appears somewhat less associated with sarcoidosis in African Americans compared with Caucasians.[84] An association between sarcoidosis and BTNL2 has also been reported in a second study in Germans.[85]

One question regarding BTNL2 as a sarcoidosis risk factor is whether it is independent of HLA-DRB1 risk alleles. As noted earlier for other genes in the MHC region, HLA-DRB1 and BTNL2 are also in LD. HLA-DRB lies ~180 kb centromeric to BTNL2. Based on regression models, BTNL2 appears to be an independent risk factor in sarcoidosis.[80,85] In the case of African Americans where the BTNL2 conferred sarcoidosis risk is less significant than for Caucasians, a negative interaction with HLA-DR appears to exist.[85] When association of rs2076530 was studied in a large UK population with multiple sclerosis and one with Graves' disease, the association of rs2076530 was reported to be secondary to a preestablished DRB1association.[86,87] BTNL2 was *not* associated with Wegener's granulomatosis, type I diabetes, rheumatoid arthritis, or systemic lupus erythematosis.[88,89]

To test the hypothesis that sibling pairs might have similar phenotypic expression, Judson et al search for concordance in organ system involvement among 509 affected African American siblings that participated in the SAGA study.[90] This was the first study to examine whether phenotypic expression of sarcoidosis is more similar within families with multiple affected family members compared with unrelated cases. Minimal concordance was found with the exception that the second sibling with sarcoidosis was three times more likely to have ocular (OR: 3.02; CI: 1.7 to 5.4) or liver involvement (OR: 3.31; CI: 1.5 to 7.4) if the first sibling had involvement of these organs, although concordance of these phenotypes was relatively weak. There was virtually no concordance between members of sibling pairs in terms of clinical course or degree of pulmonary involvement.[90] These results support that, although affected siblings may share disease-predisposing genes, differences in genes and exposures may still exist between sibling pairs that determine phenotype.

CONCLUSION

Although it has been 130 years since Sir Jonathan Hutchinson published the first case report of sarcoidosis, the etiology remains unknown. We do know that sarcoidosis clusters in families and that certain ethnic groups are more commonly affected. Investigators began in the 1970s searching for sarcoidosis susceptibility genes using case-control studies and serologically testing for HLA alleles. More recently, several HLA alleles detected by DNA analysis have been consistently associated with sarcoidosis. Although many non-MHC candidate gene associations have been reported, few have been consistently identified across populations. Advancements in high-throughput genotyping and

more sophisticated statistical methods are fueling more thorough genetic analyses. Two genome scans have so far been reported. The SAGA study points to susceptibility and protective alleles on chromosome 5. One candidate gene identified by linkage analysis, BTNL2, a B7 family member, has been consistently associated with sarcoidosis and we await more detailed studies on defining its precise role.

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