Genetic Studies in the Rheumatic Diseases: Present Status and Implications for the Future

JOHN D. REVEILLE

ABSTRACT. Recent breakthroughs in genetic methodology have greatly augmented our understanding of the contribution of genetics to susceptibility to the rheumatic diseases. Disorders in which familial aggregation has been best documented include rheumatoid arthritis (RA), ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc). Much of the genetic contribution to these diseases lies in the MHC, including HLA-DR4 (RA), HLA-B27 (AS), HLA-DRB1*0301, DRB1*1501/*1503, DRB1*08, and C4 null alleles (SLE), and HLA-DRB1*11 and DRB1*1502 (SSc). Genome-wide scans have provided inconsistent data in RA, although consistent regions have been observed in scans from different groups in AS and SLE. No consistent non-MHC candidate gene has been identified in RA. There is active investigation in AS in this area. In SLE the FcγRIIa and FcγIIIa genes have been most thoroughly described, and in SSc fibrillin and SPARC. Newer techniques being developed presently, such as high density single nucleotide polymorphism genome-wide scanning, show promise to bring these analyses to the next level, which will hopefully result not only in better screening of individuals at highest risk, but also in novel treatments. (J Rheumatol 2005;32 Suppl 72:10-13)

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Breakthroughs in technology have greatly accelerated elucidation of the pathogenesis of the rheumatic diseases. Many of these show a significant hereditary predisposition, which is rapidly being better understood. This brief article summarizes the status of studies in the pathogenesis of 4 of the rheumatic diseases most extensively studied (Table 1), particularly in underscoring the successful collaborations between groups in the US and Canada.

RHEUMATOID ARTHRITIS

It has been known for some time that first-degree relatives of patients with rheumatoid arthritis (RA) are at increased risk for developing RA, and this risk is highest in those with most severe disease. Moreover, monozygotic twins have a concordance rate of 12–15%, compared to a 3–4% frequency in dizygotic twins. The association of RA with genes of the major histocompatibility complex (MHC), specifically HLA-DR4, has been apparent for nearly 30 years (reviewed in[1]). However, it has become clear that MHC genes contribute only part of the genetic risk. Yet genome-wide scans from Europe and North America have provided inconsistent data, with the only common genetic factor in RA susceptibility being the MHC[2-4]. A recent update of the North American Rheumatoid Arthritis Consortium (NARAC) genetic studies examining 256 new multicase RA families recruited from across the US and Canada[4] confirmed previous linkage chromosomes 1p13, 6p21.3 (the MHC), and 18q21. The combined analysis of both data sets from this group (512 families) showed that the inclusion of *HLA-DRB1*04* as a covariate significantly increased the probability of linkage on chromosome 6. In addition, some linkages on chromosome 1 showed improved significance when modeling *HLA-DRB1*04* or rheumatoid factor (RF) positivity as covariates[4].

A related study of 1097 individuals with RA from these 512 multicase NARAC families[5] found several disease characteristics to exhibit significant familial clustering, including seropositivity for RF, nodules, and age at RA diagnosis. Despite a number of promising candidates, a non-MHC gene has not been definitively identified in RA susceptibility.

The presence and gene dosage of HLA-DRB1 alleles encoding the shared epitope (SE) has been associated with the presence of rheumatoid nodules, a more rapid rate of developing radiographic erosions, vasculitis, Felty's syndrome, and the need for joint surgery in the US, Britain, France, and Spain. Similar findings have been reported from Japan, Singapore, China, and Korea (reviewed in[1]). These findings have not been universally confirmed, with other studies from England, Switzerland, Sweden, Edmonton, Canada, and Japan showing a marginal effect. Moreover, studies in other ethnic groups have not confirmed an effect of the SE on prognosis. Neither Teller, *et al*[6], examining Hispanic

From the Division of Rheumatology and Clinical Immunogenetics, the University of Texas-Houston Health Science Center, Houston, Texas, USA.

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J. Reveille, MD.

Address reprint requests to Dr. J. Reveille, University of Texas, MSB 5.270, 6431 Fannion, Houston, TX 77030, USA. E-mail: john.d.reveille@uth.tmc.edu

Table 1. A summary of genetic studies in 4 rheumatic diseases.

Disease	MHC Contribution	Chromosomal Regions	Non-MHC Candidate Genes
Rheumatoid arthritis	HLA-DR4 (DR1, DR10, DRB1*1402)	1p13, 18q21	None consistently identified
Ankylosing spondylitis	HLA-B27, DR1, DR4, DR8	1q,2q (OX), 6p21 (MHC), 6q (NA), 10q, 11q (NA), 16q, 17q, 19q	CYP2D6, ANKH, IL-1/IL1RN
Systemic lupus erythematosus	HLA-DRB1*0301, *1501, *1503, *08	1q22-23 (OK, UCLA), 1q42, 2q37 (UP), 6p21,16q13	FcγRIIa, FcγRIIIa, PCDC1
Systemic sclerosis	HLA-DRB1*11, DQB1*0301	1p21, 1q42, 5q31-33, 6p21 (MHC),6q23-27	Fibrillin-1, SPARC, topoisomerase I

Regions identified in specific genome-wide scans but not in others. OX: Oxford; NA: NASC; OK: Oklahoma City; UCLA: University of California-Los Angeles; UP: Uppsala.

American RA patients, nor McDaniel, *et al*[7], examining African American RA patients, could observe any such effect.

ANKYLOSING SPONDYLITIS

Studies from Oxford, England, and elsewhere have suggested that susceptibility to AS is largely genetically determined, with a sibling recurrence risk ratio ~60–80 and heritability of 97% (reviewed in[8]). The concordance in identical twins is 63%, compared to 23% in non-identical twins. It is abundantly clear that the MHC is the major locus, with HLA-B27 the major gene, although it is likely that more than one MHC gene is probably involved. However, less than 5% of HLA-B27-positive people in the general population develop a spondyloarthropathy (SpA), compared to 20% of HLA-B27 positive relatives of AS patients. Family studies, in fact, have suggested that HLA-B27 forms only about 40% of the overall risk for SpA, and that the entire effect of the MHC, on the other hand, is about 50%. Genome-wide scans from Oxford have most strongly implicated, in addition to the MHC, regions on chromosomes 2q and 16q.

The North American Spondylitis Consortium (NASC) is a collaboration of 6 sites in US cities (Houston, Los Angeles, Portland, Oregon, Cleveland, Minneapolis, and Philadelphia) as well as the Spondylitis Association of America; and 2 sites in Canada (Toronto and Edmonton) examining multicase families with AS. To date, NASC has collected over 317 sibling pairs concordant for AS from 272 families. A genome-wide scan in 244 sib pairs in 231 families has been completed[9], most strongly implicating, in addition to the MHC on chromosome 6p, regions on chromosomes 6q and 11q. Other regions suggested by both the Oxford and the NASC scans were seen on chromosomes 1q, 3q, 5q, 10q, 16q, 17p, and 19q.

CANDIDATE GENE ANALYSES COMPLETED BY NASC AND OTHERS

Interleukin 1 receptor antagonist. In 2 studies from Scotland and The Netherlands[10,11], a weak association of AS was found with a variable number of tandem repeats (VNTR) in intron 2 of interleukin 1 receptor antagonist (*IL1RN*). Further, an association of 2 synonymous single nucleotide polymorphisms (SNP) in exon 6 of IL1RN and their haplotypes with a large Canadian cohort of AS patients has recently been described[12]. However, in the NASC, no evidence for linkage of AS to IL1RN was seen examining the same SNP[13].

Matrix metalloproteinase III. Although high levels of matrix metalloproteinase III (MMP3) expression in synovial biopsies predicted greater disease activity in patients with AS, no association or linkage of MMP3 SNP could be demonstrated in the NASC families, despite the location of this gene in one of the regions identified in the genome-wide scan[14].

ANKH. ANKH is a multipass transmembrane protein encoded on chromosome 5p that exports inorganic pyrophosphate from intracellular to extracellular compartments. Examination in 112 unrelated Canadian AS patients and in 124 NASC family individuals found both association and linkage of SNP in *ANKH* to AS. However, the overall contribution (ls) of *ANKH* to AS susceptibility was relatively small: 1.9[15]. This has not been confirmed in another British family study, however, where no linkage or association was seen[16].

CYP2D6. *CYP2D6*, a gene found on chromosome 22q, encodes a protein involved in the metabolism of xenobiotics, which are promoters of inflammation via T cells. The "*pm*" (poor metabolizer) genotype is weakly associated with AS in German and British patients[17,18].

SYSTEMIC LUPUS ERYTHEMATOSUS

*HLA-DRB1*0301* has been associated with systemic lupus erythematosus (SLE) in Caucasians in most studies (reviewed in[19]). *HLA-DRB1*1501/*1503* has been implicated in Africans, Chinese, Japanese, and some Caucasian cohorts. *HLA-DRB1*08* has been described in

Hispanics[20]. HLA-DQA1, DQB1 genes are associated primarily with autoantibody subsets of SLE. C4 null alleles (*C4A*Q0*, *C4BQ*0*) have similarly been associated with SLE in most ethnic groups[19]. A recent study using a dense map of polymorphic microsatellites across the HLA region in a large collection of families with SLE identified 3 distinct haplotypes that encompassed the MHC class II region that exhibited transmission distortion, specifically *HLA-DRB1*1501*/*DQB1*0602*, *DRB1*0801*/*DQB1*0402*, and *DRB1*0301*/*DQB1*0201* alleles[21].

Genome-wide scans in SLE have been conducted in several locations (reviewed in[19]). The first scan, from the University of California at Los Angeles (UCLA), implicated a region on chromosome 1q42. This region was confirmed in all subsequent groups: one from Minneapolis, USA, that examined mostly Caucasian multiplex families, another from Oklahoma City, USA (including a number of African American families), and one from Uppsala, Sweden, that included families from Scandinavia, Iceland and Mexico City, and also a separate group from Los Angeles, USA. Linkage to the MHC was confirmed in the Minneapolis and UCLA cohorts. Other sites implicated included chromosome 6q13 (Minneapolis and Los Angeles), chromosome 1q23 (Oklahoma City and Los Angeles), and chromosome 2q37 (Uppsala), among others.

Outside of MHC genes, the most intensely studied in SLE susceptibility have been FcγRIIa and FcγIIIa, genes located at chromosome 1q23[19]. Other than this, a mutation disrupting a RUNX1 binding site of the programmed cell death 1 (*PDCD-1*) gene (located at chromosome 2q37) that can lead to dysregulated self-tolerance and to the chronic lymphocyte hyperactivity characteristic of SLE has recently been described in Swedish SLE patients and may provide additional clues in the pathogenesis of SLE[22].

SCLERODERMA (SYSTEMIC SCLEROSIS) Until recently, genetic factors were believed to play a lesser role in the pathogenesis of scleroderma (systemic sclerosis, SSc) (reviewed in[23]). However, recent data have suggested that familial aggregation does occur in about 2% of SSc patients, and that a positive family history confers a relative risk of ~10–16. Still, the absolute risk is very small. Studies of 24 monozygotic and 18 dizygotic twin pairs have shown a disease concordance of only 4.2% in the monozygotic compared to 5.6% in dizygotic twins. However, a positive antinuclear antibody was seen in 71% of the monozygotic compared to 40% of dizygotic twins. The most consistent theory of heredity and SSc susceptibility is that inherited factors predispose to autoimmunity, whereas other triggers may provide costimulation for specific phenotypes.

MHC genes have long been implicated in SSc susceptibility. *HLA-DRB1*11* has been most consistently implicated in Caucasians, African Americans, and Hispanics, and *HLA-DRB1*1502* in Asians with SSc. In collaborative studies between the US and Canada, as well as elsewhere, HLA-DQA1, DQB1, and DPB1 genes have been shown to also play a role, particularly in determining autoantibody subsets.

Non-MHC genes have also been implicated, particularly fibrillin genes, which are located on chromosome 15[23], SPARC (chromosome 5)[24], and topoisomerase I (chromosome 20). Independent of this, a recent genome-wide association study in Choctaw Native Americans has confirmed associations of microsatellite markers located near the chromosomal regions where these genes lie[25].

CONCLUSIONS - THE FUTURE

Without question, the MHC plays a major role in susceptibility to rheumatic diseases such as RA, AS, SLE, and SSc. However, the biggest challenge lies in identifying the non-MHC contribution to the pathogenesis of these diseases. Success in this area will increase chances in both screening individuals at highest risk and identifying novel treatments. Although some useful data have emerged, the results of genome-wide scans using microsatellite markers have largely been disappointing. Future efforts should focus on using dense SNP screening of the genome in these diseases. Much has been learned, but much more progress is needed.

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