

Review

Genetics of rheumatic disease

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Published: 14 October 2009
This article is online at <http://arthritis-research.com/content/11/5/248>
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Arthritis Research & Therapy 2009, **11**:248 (doi:10.1186/ar2781)

Abstract

Many of the chronic inflammatory and degenerative disorders that present to clinical rheumatologists have a complex genetic aetiology. Over the past decade a dramatic improvement in technology and methodology has accelerated the pace of gene discovery in complex disorders in an exponential fashion. In this review, we focus on rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis and describe some of the recently described genes that underlie these conditions and the extent to which they overlap. The next decade will witness a full account of the main disease susceptibility genes in these diseases and progress in establishing the molecular basis by which genetic variation contributes to pathogenesis.

Genetics of rheumatic disease

The spectrum of rheumatic disease is wide and includes conditions with diverse pathology, although most have in common a heritable risk with a complex genetic basis. There has therefore been intense effort to understand the contribution of genotype to the expression of disease in terms of both basic pathogenesis and clinical characteristics. Recent technical advances in genotyping and statistical analysis and international collaborations assembling large cohorts of patients have led to a wealth of new data. In this review we describe insights gained into the pathogenesis of autoimmune rheumatic disease by the techniques of modern genetics, in particular evidence from genome-wide association (GWA) studies, which provide support for the existence of a common genetic risk basis to several diseases. To reflect the new data from GWA studies, our discussion will be confined to rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and ankylosing spondylitis (AS), which in some cases share a common autoimmune pathogenesis. Osteoarthritis and osteoporosis are also complex genetic traits but limitations of space are such that these two conditions will not be considered in this review.

The concept of a systematic, GWA study became practical with the cataloguing of libraries of common polymorphisms. Currently, over 20 million single nucleotide polymorphisms (SNPs) have been identified [1] and platforms are available to type up to 1 million of these in a single reaction. Although not all SNPs are currently genotyped, as the human genome is arranged into haplotype blocks in linkage disequilibrium, it is only necessary to type so-called tag SNPs, which identify these areas of limited variability [2], to achieve good representation of the total amount of genetic variation. Most typed SNPs are relatively common (minor allele frequency of >5%) and if associated with disease are likely, therefore, to have only modest pathogenic effects (odds ratios (ORs) usually between 1.2 and 2), as otherwise they would become depleted in a population due to natural selection. It is necessary, therefore, to invoke the 'common-disease common-variant' (CD-CV) model [3], which assumes an accumulation of risk caused by the carriage of multiple deleterious alleles, to explain current experimental findings.

One of the revolutionary advantages of the GWA study is the freedom from a required gene-centric hypothesis, which provides an unprecedentedly effective technique for risk gene discovery. Many disease-associated genes identified by GWA studies were completely unsuspected to be relevant - for example, the autophagy system in Crohn's disease [4]. However, because in essence up to 1 million independent hypotheses are being tested in each genotyping reaction, sample sizes powered to detect even the stronger associations must be large, and criteria for significance stringent. The general consensus is that significance can be defined as a P -value smaller than 5×10^{-7} , which in a cohort such as the Wellcome Trust Case Control Consortium (WTCCC) of 2,000 cases, for example, approximates to a power of 43% rising to 80% to detect alleles with ORs of 1.3

AS = ankylosing spondylitis; BCR = B cell receptor; CNV = copy number variation; GWA = genome-wide association; HLA = human leukocyte antigen; IFN = interferon; IL = interleukin; IRF = interferon regulatory factor; MHC = major histocompatibility complex; NF = nuclear factor; OR = odds ratio; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SNP = single nucleotide polymorphism; STAT = signal transducer and activation of transcription factor; TLR = toll-like receptor; TNF = tumour necrosis factor; TNFAIP = TNF α -induced protein-3; TRAF = TNF receptor associated factor; WTCCC = Wellcome Trust Case Control Consortium.

and 1.5, respectively [5]. However, the genome is subject to variation at more than the SNP level, and individuals also differ in the copy number of sections of DNA of greater than several kilobases in size, so called copy number variation (CNV), which in fact accounts for more total nucleotide difference between individuals than SNPs [6,7]. CNV can affect gene expression levels [8] and has been linked to autoimmune disease [9,10], including SLE [11]. Whilst the latest genotyping platforms include assessment of CNV, earlier products actively excluded SNPs within regions of the most variation as they were more likely to fail quality control steps. Association studies based on CNV are, therefore, in their relative infancy. Finally, the genome is subject to modification without a change in DNA sequence; epigenetic mechanisms can have profound effects on gene expression. These include DNA methylation and changes in chromatin structure [12].

It has become apparent that SLE, RA, and AS, which have divergent clinical features, may share a common genetic risk framework, and we aim in our review to illustrate this.

The MHC region and antigen processing

The major histocompatibility complex (MHC) region on chromosome 6 contributes to the risk of almost all autoimmune diseases, and its role in immunity in mice was recognized over 60 years ago. In humans, the MHC locus is also known as the *HLA* (human leukocyte antigen) region, reflecting the initial identification of MHC gene products on the surface of white blood cells. The classical MHC extends over around 4 megabases, and comprises three clusters: class I, II, and III. Class I and II regions include genes that encode the α - and β -chains of the MHC I and II complexes, and flank the class III region, which contains an assortment of immunologically relevant genes. Despite extensive study, the mechanisms that link the MHC to disease are largely unknown, although it is supposed that variation in the MHC peptide binding cleft facilitates presentation of self-antigen to autoreactive lymphocytes.

These difficulties in understanding the MHC are not without reason; it contains some of the most polymorphic loci described in the genome, and has a highly complicated genetic architecture, with some regions exhibiting extended linkage disequilibrium [13].

In RA, the MHC accounts for around a third of the genetic liability [14]. Alleles at *HLA-DRB1* contribute much of this risk - for example, *DRB1*0401* carries an OR of 3. GWA studies confirm the strong association with MHC variants; risk alleles confer an OR of around 2 to 3 in homozygotes [15], with very high statistical significance ($P < 10^{-100}$). Additional loci contributing to the risk of RA identified by high-density genotyping include *HLA-DP* in patients with anti-cyclic citrullinated peptide antibodies [16]. SLE not only has strongly associated alleles in the class II region, *HLA-DR2*

(*DRB1*1501*) and *DR3* (*DRB1*0301*) [14], with ORs of 2 [17], but also risk variants in the class III cluster, which encodes genes such as *TNF* and the complement components *C2*, *C4A* and *C4B*. *C4* is crucial in the classical and mannose-binding lectin pathways of complement activation, and complete deficiency of *C4* or indeed other components of the classical pathway are rare, but strong, risk factors for SLE [18]. The *C4* gene is subject to CNV and is of two isotypes, *C4A* and *C4B*. It is an attractive hypothesis that CNV at *C4* affects expression and contributes to SLE risk. However, it remains to be established whether haplotypes carrying partial *C4* deficiency exert their risk via an influence on complement or through other genetic variants that are in linkage disequilibrium. Other loci in the class III region have been implicated in SLE, including the *SKIV2L* gene, SNPs in which carry an OR of 2 in a family-based analysis [19]. *SKIV2L* encodes superkiller viralicidal activity 2-like, the human homologue of which is a DEAD box protein that may have nucleic acid processing activity. The second MHC III signal for SLE we will consider was identified in the International Consortium on the Genetics of Systemic Lupus Erythematosus (SLEGEM) GWA study [17,20]. The SNP rs3131379 in *mutS* homologue 5 (*MSH5*) has an OR of 1.82. There is evidence that *MSH5* has a role in immunoglobulin class switch variation [21]. Again, further work is required to definitively implicate this gene rather than variants in linkage disequilibrium, which include *HLA-DRB1*0301* and *C4A* deletions.

Clearly, *HLA-B27* is the overwhelming association in AS, with an OR of 200 to 300. In the MHC, other genetic risk variants have been identified, including *HLA-B60* (OR 3.6) [22] and various *HLA-DR* genes with relatively minor contributions [23]. The pathogenic mechanism for these risk alleles is unknown. Outside of the MHC, two significant genes have so far been identified in AS: *ARTS1* and *IL-23R* [24], the latter of which will be discussed below and has been associated with several different autoimmune diseases. *ARTS1* has two identified functions. Its first is in the processing of peptide for presentation via MHC I. It is localised in the endoplasmic reticulum, and is upregulated by $\text{IFN}\gamma$. It acts as an amino-terminal aminopeptidase and in mice is essential for the display of the normal peptide repertoire. In its absence, many unstable and highly immunogenic MHC-peptide complexes are presented [25]. A hypothetical connection with *HLA-B27* can thus be drawn. Its other function is to downregulate signalling by IL-1, IL-6, and $\text{TNF}\alpha$ through surface receptor cleavage [26-28]. The most associated SNP rs30187 risk allele has an OR of 1.4, and is of unknown functional significance.

Innate-adaptive interface

Interferon signalling: *IRF5*

It is clear that type 1 interferons ($\text{IFN}\alpha$ and $\text{IFN}\beta$) are of great importance in the pathogenesis of SLE. Patients with active disease have high levels of $\text{IFN}\alpha$, which has multiple immuno-

modulatory actions [29], including the induction of dendritic cell differentiation, the upregulation of innate immune receptors such as toll-like receptors (TLRs), the polarization of T cells towards a T_H1 phenotype, and the activation of B cells. Type I interferons are produced by all cells in response to viral infection, but particularly by plasmacytoid dendritic cells in response to unmethylated CpG oligonucleotides binding to TLR-9, or RNA to TLR-7. Using a candidate gene approach targeting the IFN signalling pathway, the SNP rs2004640 in *IRF5* (interferon regulatory factor 5) was found to be significantly associated with SLE (OR 1.6) [30], a risk gene confirmed in several other studies [17,31-35]. The functional consequences for IRF5 of the identified mutations are variable, but include the creation of a 5' donor splice site in an alternative exon 1, allowing the expression of several isoforms [35], a 30 base-pair in-frame insertion/deletion variant of exon 6, a change in the 3' untranslated region, and a CGGGG insertion-deletion (indel) polymorphism, the latter two affecting mRNA stability [32,36]. Interestingly, these mutations may occur together in a haplotype, with varying degrees of associated risk. The exact role of IRF5 in IFN signalling has not been fully elucidated, but it is also critical for the gene induction programme activated by TLRs [37], providing further biological plausibility for its importance in the pathogenesis of SLE. Haplotypes of IRF5 are also implicated in RA, and may confer either protection (OR 0.76) or predisposition (OR 1.8) [38]. The same CGGGG indel allele described above also carries risk for multiple sclerosis and inflammatory bowel disease [36].

TNF-associated signalling pathway: *TNFAIP3* and *TRAF1-C5*

TNF-associated signalling pathway genes play a prominent role in the risk for both SLE and RA, and associations with variants in *TNFAIP3*, and the *TRAF1-C5* locus have been identified [39,40]. TNF α -induced protein-3 (TNFAIP3; also known as A20) is a ubiquitin editing enzyme that acts as a negative regulator of NF κ B. A20 can disassemble Lys63-linked polyubiquitin chains from targets such as TRAF6 and RIP1. A second region of A20 catalyses Lys48-linked ubiquitination that targets the molecule for degradation by the proteasome [41]. A20 modifies key mediators in the downstream signalling of TLRs that use MyD88, TNF receptors, the IL-1 receptor family, and nucleotide-oligomerization domain protein 2 (NOD2) [42]. *Tnfaip3* knockout mice develop severe multi-organ inflammatory disease, and the phenotype is lethal [43]. The SNP rs10499194 in *TNFAIP3* carries an OR of 1.33 for RA, and rs5029939 an OR of 2.29 for SLE [44], the latter also conferring an increased risk of haematologic or renal complications [45].

On chromosome 9, the region containing *TRAF1* (TNF receptor associated factor 1) and *C5* (complement component 5) genes is associated with significant risk for RA (risk SNP OR of approximately 1.3) in most [15,40,46-48], but not all [5], studies. Due to linkage disequilibrium, the functional

variant remains elusive. TRAF1 is principally expressed in lymphocytes, and inhibits NF κ B signalling by TNF. This pathway is blocked in TRAF1 overexpression [49] whilst, conversely, *Traf1*^{-/-} mice are sensitized to TNF and have exaggerated TNF-induced skin necrosis [50].

The complement system has long been known to be involved in the pathogenesis of RA. In the collagen-induced arthritis model of RA, C5 deficiency prevents disease *de novo* and ameliorates existing symptoms and signs [51,52]. Interestingly, GG homozygotes at the *TRAF1-C5* SNP rs3761847 with RA have a significantly increased risk of death (hazard ratio 3.96, 95% confidence interval 1.24 to 12.6, $P = 0.02$) from malignancy or sepsis, potentially allowing identification of patients for appropriate screening [53].

Immunomodulatory adhesion molecule: *ITGAM*

Integrin- α -M (ITGAM), variants of which are strongly associated with SLE, forms a heterodimer with integrin- β -2 to produce $\alpha_M\beta_2$ -integrin (also known as CD11b, Mac-1, or complement receptor-3), which mediates the adhesion of myeloid cells to the endothelium via ICAM-1 (Intercellular adhesion molecule-1) and recognizes the complement component iC3b. It not only has a role in cell trafficking and phagocytosis [54], but also has other immunomodulatory functions. Antigen-presenting cells produce tolerogenic IL-10 and transforming growth factor- β on iC3b binding to CD11b [55], and mice deficient in this receptor upregulate expression of IL-6, favouring a pro-inflammatory T_H17 response [56]. Despite its implication in defective immune complex clearance in SLE, experimental evidence for a role was lacking. GWA studies, however, demonstrate a strong and significant association [17,33,44], with an OR of 1.83 ($P = 7 \times 10^{-50}$) in meta-analysis [57]. The implicated SNP rs1143679 is non-synonymous, causing the substitution of histidine for arginine at amino acid 77, although this change does not affect the iC3b binding site [58]. Furthermore, although this SNP is disease associated in European and Hispanic patients, it is monomorphic in Japanese and Korean populations [59]; an explanation of its effect is therefore outstanding. It has been mentioned that CNV is important in C4 expression; the same is true for the Fc γ receptor IIIb (FCGR3B) [60], which relies on CD11b for function. Fc γ receptor IIIb is principally present on neutrophils and is important in the binding and clearance of immune complexes, therefore marking itself as a potential SLE risk gene. There is a significant association between low *FCGR3B* copy number and SLE. Patients with two or fewer copies of *FCGR3B* have an OR of 2.43 for SLE with nephritis, and 2.21 for SLE without nephritis [61].

Lymphocyte differentiation

T cell receptor signalling: *PTPN22*

Outside the HLA region, the first reproducible genetic association for RA came with the implication of *PTPN22* from a candidate gene approach [62] based on linkage analysis

identification of a susceptibility locus at 1p13 [63]. It has remained the strongest and most consistent association mapped by GWA studies in RA. A role in SLE has also been identified [17]. The OR for the risk allele is around 1.75 in RA, and 1.5 in SLE. However, it should be noted that this allele (encoding the R620W mutation) is monomorphic or not disease associated in Korean or Japanese patients [64,65]. *PTPN22* encodes lymphoid tyrosine phosphatase (LYP), a protein tyrosine phosphatase that inhibits T cell receptor signalling, decreasing IL-2 production. The disease associated SNP is responsible for a change from arginine to tryptophan at position 620, which inhibits binding to the SH3 domain of carboxy-terminal Src kinase. This in turn appears to enhance dephosphorylation of tyrosine residues in the Src family kinases Lck, FynT, and ZAP-70 [66,67]. The overall effect of the mutation is a reduction in T cell receptor signalling. The pathogenic effect of this is unclear, but may relate to impaired negative selection in the thymus, or lead to a reduction in regulatory T cells [68]. Conversely, the R623Q variant of *PTPN22*, which is a loss-of-function mutation affecting the phosphatase activity of LYP, is protective against SLE [69]. *PTPN22* does not appear to be a risk gene for AS [70].

Polarization towards T_H1 and T_H17 phenotypes: *STAT4* and *IL23R*

STAT4 encodes signal transducer and activation of transcription factor-4, responsible for signalling by IL-12, IL-23, and type 1 IFNs [71]. *STAT4* polarizes T cells towards T_H1 and T_H17 phenotypes, which has the potential to promote autoimmunity [72]. In RA the OR for the risk allele of SNP rs7574865 is 1.32 in one case-control study [73], with a less strong disease association at rs11893432 in a meta-analysis of GWA studies (OR 1.14) [15]. There is convincing evidence that *STAT4* is a risk locus for SLE in multiple racial groups [33,74], and it may be theorized that interference in type I IFN signalling may be the underlying pathogenic mechanism in this case. Distinctive disease pathways could, therefore, emerge from mutations in a single gene. The WTCCC AS study identified *IL23R* as a risk gene in AS [24]. IL-23 is instrumental in the development of T cells with the pro-inflammatory T_H17 phenotype [75], and *IL23R* has been linked to psoriasis, ulcerative colitis, and Crohn's disease in GWA studies [5,76,77]. An interesting connection between these conditions, all of which may share common clinical features, is thus made. In AS the risk SNP rs11209032 confers an OR of 1.3.

B cell activation

B cells are a population long suspected to be important in autoimmune rheumatic disease, and the benefits of their depletion in RA and SLE has resurrected interest in their pathogenic role. The risk genes identified so far are involved in signalling from the B cell receptor (BCR). *BLK* encodes a Src family tyrosine kinase restricted to the B cell lineage and is poorly understood. Risk alleles in the region upstream of

the transcription initiation site are associated with SLE (OR 1.39, $P=1 \times 10^{-10}$) and reduce levels of *BLK* mRNA [33]. *BANK1* (B cell scaffold protein with ankyrin repeats-1) undergoes tyrosine phosphorylation upon B cell activation by the BCR, leading to an increase in intracellular calcium through the inositol trisphosphate mechanism [78]. The non-synonymous SNP rs10516487 in *BANK1*, which substitutes histidine for arginine at amino acid 61, also has disease association (OR 1.38) [79]. The functional consequence of this may be higher affinity for the inositol trisphosphate receptor, as the substitution is located in the binding site.

Lyn, another Src tyrosine kinase, is important in determining signalling thresholds for myeloid and B cells. On BCR ligation, it phosphorylates tyrosine residues of Syk, an activating tyrosine kinase, CD19, and the immunoreceptor tyrosine-based activation motifs (ITAMs) of the Ig α /Ig β subunits of the BCR. However, it also has a critical regulatory role, mediated by phosphorylation of the inhibitory motifs of CD22 and Fc γ R1IB, which in turn activate SH2-domain containing phosphatases, leading to dephosphorylation and deactivation of a number of signalling intermediaries [80]. *Lyn*^{-/-} mice develop severe autoimmunity associated with glomerulonephritis [81]. An association between SNPs in *LYN* and SLE, identified initially in the SLEGEN GWA study [17], has been recently confirmed in a case-control study [82]. The most associated SNP, rs6983130, is near the primary transcription initiation site.

OX40L, a member of the TNF super-family encoded by *TNFSF4* (TNF superfamily 4), is associated with SLE. The cross-talk between B lymphocytes and dendritic cells expressing OX40L, and T cells that express its receptor, OX40, serves to enhance the adaptive immune response [83]. An upstream *TNFSF4* haplotype, associated with SLE, enhances gene expression *in vitro* [84,85], although the mechanism responsible for the deleterious effects observed remains to be established.

Despite the importance of B cells in the pathogenesis of RA, none of the gene effects described above have been identified in the current generation of GWA studies. However, variants at *CD40* in European patients do carry risk [15]. *CD40* expressed on B cells, via interaction with its ligand *CD154* on CD4⁺ T cells, promotes immunoglobulin class switching, and germinal centre formation. B cells, however, also have a regulatory role, likely to be mediated by IL-10, and disruption of this function may be another route to autoimmune disease [86].

Post-translational modification: *PADI4*

Peptidyl arginine deiminase-4 (*PADI4*) is a member of the enzyme family responsible for the post-translational citrullination of arginine residues in RA synovium, subsequently recognized by anti-cyclic citrullinated protein antibodies. In Japanese [87] and Korean patients [88], case-control asso-

ciation studies have identified functional haplotypes of *PADI4* conferring risk of RA. However, in Caucasian populations this association is inconsistent [89-91].

Conclusion

Even with the proliferation of new genetic associations discovered in the past few years by GWA studies, only around 10 to 15% of the inherited risk for SLE and RA can be currently explained. This may be accounted for, in part, by a number of factors, some related to limitations of recent study design. As mentioned above, even the largest current GWA cohorts have limited power to detect associations with ORs <1.3, potentially losing multiple risk genes. By definition, most genotyped SNPs are common, and so rare but causal variants have a tendency to be missed. These rarer SNPs may be either those with a low minor allele frequency (<5%), or occur *de novo*, of which 200 to 500 non-synonymous SNPs are expected per individual [92]. In many cases, it is far from certain if the associated SNP is functional, or in linkage disequilibrium with the true cause. Finally, the great majority of GWA studies have been conducted on European populations, thereby excluding carriers of many potential risk variants from analysis. However, it is unfortunately the case that current genotyping platforms often have poor coverage of tagging SNPs within populations that exhibit low levels of genomic linkage disequilibrium, such as those of African ancestry [93]. For example, the latest high-density genotyping chips from Affymetrix (6.0) and Illumina (1M) may capture fewer than half the SNPs identified through re-sequencing in Yoruban Nigerians [94]. Given that clear differences exist in the risk of autoimmune disease according to ethnicity, and that not all disease risk alleles are in common, it is imperative that full account of this variation is made. Structural genetic differences have only recently begun to be assessed by modern genotyping platforms, and the contribution of, for example, CNV to inherited disease risk is largely unquantified. Even more difficult to appreciate is the influence of heritable epigenetic factors, and the exact relationship between genotype and phenotype. Nevertheless, although it will probably not be possible to explain all the observed genetic

risk in the near future, we are rapidly moving towards the ability to quickly and cheaply fully sequence individual genomes [95], with all the advantages that brings [96]. In the meantime, understanding the functional basis of the disease risk variants so far identified presents an outstanding challenge. Integration of genotypic with RNA and protein expression data in a systems biologic approach represents one potentially valuable methodology [97]. Exploring and therapeutically utilizing the genetic differences between individuals is axiomatic to personalized medicine, and will undoubtedly lead to better outcomes in the management of autoimmune disease.

Competing interests

The authors declare that they have no competing interests.

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The Scientific Basis of Rheumatology: A Decade of Progress

This article is part of a special collection of reviews, *The Scientific Basis of Rheumatology: A Decade of Progress*, published to mark *Arthritis Research & Therapy's* 10th anniversary.

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