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Review

Genetic basis of rheumatoid arthritis: A current review

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ABSTRACT

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases. As with other complex traits, genome-wide association studies (GWASs) have tremendously enhanced our understanding of the complex etiology of RA. In this review, we describe the genetic architecture of RA as determined through GWASs and meta-analyses. In addition, we discuss the pathologic mechanism of the disease by examining the combined findings of genetic and functional studies of individual RA-associated genes, including *HLA-DRB1*, *PADI4*, *PTPN22*, *TNFAIP3*, *STAT4*, and *CCR6*. Moreover, we briefly examine the potential use of genetic data in clinical practice in RA treatment, which represents a challenge in medical genetics in the post-GWAS era.

Contents

1. Genetic aspects of rheumatoid arthritis . . . 00
2. *HLA-DRB1* gene . . . 00
3. Insights from GWASs . . . 00
4. RA risk genes and pathogenesis . . . 00
   4.1. PADI4 . . . 00
   4.2. PTPN22 . . . 00
   4.3. TNFAIP3 . . . 00
   4.4. STAT4 . . . 00
   4.5. CCR6 . . . 00
5. Missing heritability . . . 00
6. Clinical use of genetic data in RA . . . 00
   Acknowledgments . . . 00
   References . . . 00

1. Genetic aspects of rheumatoid arthritis

Rheumatoid arthritis (RA) is one of the most common forms of autoimmune arthritis, affecting approximately 0.5–1.0% of the world's population. The serum of most RA patients contains autoantibodies, such as rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPAs), the presence of which constitutes one of the new classification criteria for RA revised in 2010 [1]. Although RF is also present in other autoimmune diseases and immunological conditions, such as chronic infection and inflammation, ACPAs have a higher specificity, suggesting a central role for citrulline as an antigenic determinant in this disease [2] (Fig. 1). This suggests that autoimmunity to citrullinated proteins may be the hallmark of RA pathogenesis. However, the rest of RA patients lack these autoantibodies, suggesting a heterogeneity in the disease etiology. In clinical practice, the appearance of biologics that target inflammatory cytokines has dramatically improved the outcome of RA, although some patients still suffer destructive arthritis that leads to disability. The limitations of current RA therapies underscore the need for further investigation of disease pathogenesis and identification of new therapeutic targets.

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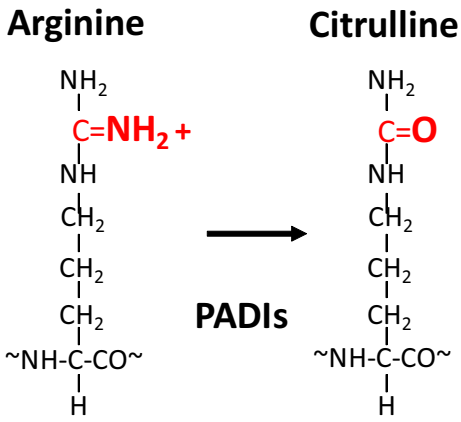

Fig. 1. Citrullination of arginine residues by PADI enzymes.

As with other complex traits, evidence from familial studies suggests that RA is caused by a combination of genetic and environmental factors. For instance, a recent population-based epidemiologic study in Sweden demonstrated that the familial odds ratio for RA is approximately 3 in first-degree relatives of RA patients and 2 in second-degree relatives [3]. In addition, higher concordance rates in monozygotic twins over dizygotic twins suggest the involvement of genetic factors [4–6]. The heritability of a disease, which is defined as the contribution of genetic variation to variation in the liability of that disease, has been estimated at around 60% in RA by the above-mentioned studies.

The establishment of a comprehensive catalog of common genetic variants in human populations by the HapMap project [7], as well as significant recent advances in genotyping technology, now enable searching of the entire genome at once for risk loci for complex diseases. This methodologic approach, now broadly known as the "genome-wide association study (GWAS)," has greatly advanced understanding of the genetic background of complex traits such as RA. In contrast, with a few exceptions, such as cigarette smoking, infections, and diet, little is known about the role of environmental factors in the development of RA. Although environmental aspects of RA are beyond the topic of this review, readers are referred to other excellent articles [8,9].

2. *HLA-DRB1* gene

Since the first evidence suggesting the involvement of human leukocyte antigens (HLAs) in RA was reported in 1969 [10], polymorphisms in the *HLA* region have been at the center of genetic studies of RA. That study demonstrated reduced lymphocyte responses in autologous mixed cultures of cells from RA patients, suggesting that polymorphisms in *HLA* genes (which encode the major histocompatibility complex [MHC] molecules that present antigens to T cells) are shared among patients [10]. Subsequently, serologic studies showed that the frequency of the HLA-DR4 serotype is higher in RA patients compared with control subjects [11,12]. Other serotypes, such as DR1, are also associated with increased risk for RA, although the increase in risk is moderate compared with that of DR4 [13]. Sequencing of *HLA-DRB1*, which encodes the polymorphic β-chain of the DR molecule, revealed that the prominent subtypes of DR4 differ between populations. For example, Europeans harbor the *04:01 and *04:04 *DRB1* alleles and East Asians harbor the *04:05 allele. In addition, several subtypes of the *DR4* allele, such as *04:02 and *04:03, were shown to protect against the disease. These observations led to the hypothesis that a conserved epitope (i.e., QKRAA/QRRAA/RRRAA) spanning amino acid residues 70–74 in the third hypervariable region of the β chain (which is now referred to as a "shared epitope [SE]") is associated with RA susceptibility [14]. Although this SE hypothesis is generally accepted, there have been several attempts to reclassify or refine it. Recently, two studies demonstrated that the amino acids at residues 11 and 13 are also independently associated with the disease, which may explain the higher risk associated with *DR4* (*04:01/*04:04/*04:05) compared with *DR1* (*01:01) [15,16].

As the importance of ACPAs in RA has become apparent over the last decade, the strong association between SE alleles and the appearance of ACPAs in RA patients has been demonstrated in multiple populations [17–20], suggesting that DR molecules encoded by SE alleles are involved in the presentation of citrullinated peptides to T cells (Fig. 2). This hypothesis is supported by the observation in human *DR4*-transgenic mice that the conversion of arginine (positively charged) to citrulline (neutral) leads to a substantial increase in HLA-peptide affinity and subsequent activation of CD4 T cells [21]. The molecular basis of these observations was determined in a recent crystal structure analysis showing that citrulline residues of peptides are accommodated within the electropositive P4 pocket of *DRB1**04:01/04, whereas the electronegative P4 pocket of the non-risk allele product *04:02 are not accommodated [22]. As the amino acid residues at positions 13 and 71 comprise the P4 pocket and directly contact the citrulline residue, the nature of these residues may be crucial in the presentation of citrullinated peptides and may explain the genetic association between *HLA-DRB1* and RA.

The primary citrullinated autoantigens that directly cause RA are poorly defined because clinical laboratory testing of serum samples from RA patients typically involves an artificial cyclic-citrullinated peptide that reacts with multiple citrullinated self proteins. However, fibrinogen, α-enolase, vimentin, immunoglobulin binding protein (BiP), and type II collagen, all of which are expressed in the synovial joint tissues, are potential candidates [23]. The primary autoantigen may differ between individuals, as a study examining patient serum samples showed that epitope spreading with an increase in the recognition of citrullinated antigens occurs before the onset of RA [24]. Differences in antibody profile between patients could depend on other genetic and environmental factors. Cigarette smoking is an environmental factor that substantially increases the risk of ACPA appearance. Intriguingly, gene-environment interactions (defined as a departure from a multiplicative model) between the *HLA-DRB1* SE allele and smoking have been reported [25–27]. Another study demonstrated that the combination of smoking and genetic factors, including *HLA-DRB1*, may determine the specificity of ACPAs in RA patients [28,29].

The association between *HLA-DRB1* and ACPA-negative RA has been relatively understudied due to the higher prevalence of APCA-positive RA. In Europeans, *HLA-DR3* (*DRB1**03:01) is associated with ACPA-negative RA [30,31]. A study of Japanese populations (in which the *DRB1**03:01 allele is rare) indicated that both ACPA- and RF-negative RA are associated with *DR14* and the *HLA-DR8* homozygote [32]. These observations suggest that the contribution of *HLA-DRB1* alleles is distinctly different in ACPA-negative RA. However, the lack of a specific serologic test for ACPA-negative RA could result in heterogeneity in studies of different cohorts. To overcome this problem, a recent study of ACPA-negative patients that statistically adjusted for the clinical heterogeneity of ACPA-negative RA identified two independent association signals in the *HLA-DRB1* and *HLA-B* gene products: serine 11 (encoded by *DRB1**03) and aspartate 9 (encoded by *HLA-B**08), respectively, providing additional evidence that ACPA-positive and -negative RA are genetically distinct [33].

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