Editorial

Complex genetic association of 6q23 with autoimmune rheumatic conditions

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Published: 27 April 2009
This article is online at http://arthritis-research.com/content/11/2/107

Arthritis Research & Therapy 2009, **11:**107 (doi:10.1186/ar2663)

Abstract

In the paper by Dieguez-Gonzalez and colleagues in the present issue of *Arthritis Research & Therapy*, the results of a detailed genetic investigation of the recently identified rheumatoid arthritis and systemic lupus erythematosus susceptibility region at 6q23 containing the *TNFAIP3* gene are reported. Their data confirm the complex nature of the association involving both the *TNFAIP3* locus and a region >150 kb upstream that does not encode any known gene. These data are consistent with recent studies of systemic lupus erythematosus susceptibility confirming the presence of several independent genetic contributions to autoimmune rheumatic diseases arising from 6q23.

In the present issue of *Arthritis Research & Therapy*, Dieguez-Gonzalez and colleagues report the results of a large case–control genetic study of the 6q23 region that contains the *TNFAIP3* gene [1]. Their study reveals a complex association involving interactions between the *TNFAIP3* locus and an intergenic region >150 kb upstream.

The upstream region was initially implicated in rheumatoid arthritis (RA) susceptibility in the Wellcome Trust Case Control Consortium study [2], and was subsequently replicated in large European and American populations [3,4]. The biological explanation was not clear as the associated SNPs (rs6920220 and rs10499194) are located in a 60 kb linkage disequilibrium block not encoding any known genes or transcripts other than a pseudogene of PTPN11. The region is flanked by the *OLIG3* and *TNFAIP3* loci. The former encodes a protein involved in neuronal development and does not seem to be a plausible susceptibility gene for RA; however, the *TNFAIP3* gene encodes a potent inhibitor of NF-κB signalling, resulting in downregulation of production of proinflammatory cytokines including TNF, IL-1 and IL-6, and mice with targeted deletion of *TNFAIP3* develop cachexia widespread organ inflammation, including a destructive arthritis [5]. Additional loci encoding immune relevant proteins (IL22RA and IFNGR1) are also located within 1 Mb.

Recent genetic studies of 6q23 in systemic lupus erythematosus (SLE) have revealed a more complex pattern of associations than was initially reported for RA. A genome scan reported three independent associations arising from the upstream region (rs6920220) and two signals near the *TNFAIP3* gene including a missense polymorphism in exon 3 (rs2230926), resulting in a phenylalanine to cysteine switch at amino acid 127 of *TNFAIP3* [6]. These findings have been replicated in a case–control study that typed 129 SNPs spanning *TNFAIP3*; furthermore, examination of the functional effects of the lupus-associated Cys127 variant revealed reduced effectiveness at inhibiting TNF-induced NF-κB activity, suggesting a biological mechanism of association [7].

The study by Dieguez-Gonzalez and colleagues involved the use of haplotype tagging SNPs centred on two regions identified in the SLE studies. Surprisingly, only modest associations with RA were detected at both the *TNFAIP3* and intergenic regions. This is a common finding in replication studies reflecting winner curse. On further analysis, however, strong evidence of interaction (epistasis) between the two regions with RA susceptibility was detected.

We can therefore conclude that the 6q23 region contains at least two RA susceptibility effects and perhaps three effects for SLE. The biological mechanism for the associations of the intergenic region is unclear since it is only known to contain the pseudogene for PTPN11. Intriguingly, however, the parent *PTPN11* gene – located at 12q24.13 – lies within a region associated with susceptibility to RA, type 1 diabetes

IL = interleukin; NF = nuclear factor; RA = rheumatoid arthritis; siRNA = small interfering RNA; SLE = systemic lupus erythematosus; SNP = single nucleotide polymorphism; TNF = tumour necrosis factor; TNFAIP3 = tumour necrosis factor alpha-induced protein 3.

and inflammatory bowel disease [2]. Approximately 20% of pseudogenes are transcribed, and some generate siRNAs that target homologous genes [8]. Sequence variability in the sequence of the pseudogene could potentially affect expression of *PTPN11*, leading to autoimmune disease. Determining whether the pseudogene is transcribed and whether sequence variants of the transcript are present on disease-associated haplotypes will therefore be required as initial steps in determining its potential role in modulating *PTPN11* expression. An alternative explanation is that a polymorphism within an enhancer sequence in the intergenic region may alter *TNFAIP3* expression. The most plausible disease susceptibility variant identified so far is rs2230926, with experimental evidence that the SLE-associated variant is less biologically active [6].

The identification of the primary disease-related variants at 6q23 is likely to initially involve high-throughput DNA sequencing in a large number of patients and controls to more fully characterise the genetic structure of the region. This will be followed by well-powered genetic studies in both RA and SLE that will hopefully lead to the identification of the primary disease-related variants, some of which may arise from low-frequency alleles. Complementary functional studies should lead to a full understanding of the biological basis of the genetic associations of this region with autoimmune rheumatic diseases.

Competing interests

The authors declare that they have no competing interests.

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