Genetic studies in rheumatoid arthritis

Kurreeman, F.

Propositions

1. The *Tumour Necrosis Factor (TNF) Receptor Associated Factor 1 – Complement component 5* locus on chromosome 9 is not only a risk factor for rheumatoid arthritis but also predisposes to juvenile arthritis and systemic lupus erythematosus implying its possible role in a common underlying pathway across several autoimmune diseases (this thesis).

2. Allelic imbalance at the transcriptional level at the Interleukin 10 gene can be responsible for the aberrant production of the protein in individuals with certain haplotypes (this thesis).

3. Despite years of research into the role of *TNF-alpha* polymorphisms in predisposing to the development and severity of rheumatoid arthritis, no significant and reproducible associations have been found so far (this thesis).

4. The identification of the CD40 as a gene locus involved in rheumatoid arthritis along with potential candidates like *TNF Receptor Associated Factor* 1 and *TNF alpha-induced protein*, strongly suggest a role for the CD40 signalling cascade in rheumatoid arthritis (this thesis).

5. In 2007, the journal science announced human genetic variation as the scientific breakthrough of the year appraising the cataloguing of over 3 million genetic variants from the HapMap initiative (Science, 2007) which has now lead to the identification of hundreds of loci involved in complex diseases.

6. Genetic mapping is a double-edged sword: Local correlation of genetic variants facilitates the initial identification of a region but makes it difficult to distinguish causal mutation(s). (Altshuler D et al. Genetic mapping in human disease. Science. 2008 Nov 7; 322(5903):881-8.)

7. The case of missing heritability in common diseases may not only be attributed to an incomplete catalogue of variants in the human genome but also a lack of profound understanding of complex biological mechanisms that underlie diseases.

8. Recent insight into the human genome suggests that a large proportion of our DNA is transcribed and implies that intergenic sequences are unlikely to be “junk-DNA” and may harbor regulatory elements relevant to human disease. (Henikoff S. et al, Nature genetics 2007 Jul;39(7):817-8)