Dilated cardiomyopathy in the postgenomic era

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Dilated cardiomyopathy (DCM) is a disease with heterogeneous aetiology. The term refers not only to familial forms present in 20-35% of patients and caused by mutation(s) in one out of at least 20 genes but also to non-familial cases, which are most frequent and in which viral, autoimmune and toxic causes are likely to play a causative role [1]. Familial DCM is in the vast majority a monogenic disorder transmitted in an autosomal dominant fashion. In the non-familial form genetic predis-position is extensively studied with regard to myocarditis and its progression to DCM. In this setting, a polygenic pattern is most frequently recognised. It is likely that the combined effect of polymorphisms in several genes coding especially for proteins involved in the innate immune system can confer susceptibility for the development/progression of an autoimmune form of DCM.

Spiroska et al. reported an analysis of distribution of an extensive panel of single nucleotide polymorphisms (SNP) in cytokine genes among patients with DCM and controls. Whereas the number of cases studied is relatively small making conclusions preliminary, the approach taken by authors is worth commenting.

Recent advances, which were possible due to elucidation of the sequence of *homo sapiens* genome, revealed that virtually all human genes are polymorphic with numerous SNP located in particular in promoters and introns (http://hapmap.ncbi.nlm.nih.gov/index.html.en). Although at first this variation was regarded as mainly silent, recent data indicate that unexpectedly extensive correlations exist between SNPs and gene function [2]. This knowledge makes it possible to test hypotheses about primary pathogenic pathway(s) of a disease through analysis of an association with polymorphisms in selected panels of genes.

Indeed, numerous variants from the extensive panel studied by Spiroska et al. have already documented functional effects.

The *IL1A* -889 T (rs1800587) allele has been consistently shown to increase the risk of periodontal disease although its effect is most likely caused by an absolute linkage disequilibrium with a nearby SNP (rs17561) which changes Ala 114 into Ser, increasing the processing of pre-IL-1α and subsequent release of mature IL1A [3-5]. The *IL1B* -511 C>T (rs16944) probably does not have a direct functional significance but is in strong linkage disequilibrium with -31 T>C (rs1143627) polymorphism whose T allele increases promoter activity [6]. The *IL4R* +1902 variant (rs1801275) changes Gln into Arg at position 576 of the protein enhancing the receptor signalling. The functional relevance of this polymorphism is underscored by numerous associations to asthma and related traits [7-9].

The variation in the 3' UTR, the *IL12B* (position 1188, rs3212227) may influence the mRNA level of the cytokine and has been convincingly associated with an increased risk of psoriasis and Crohn disease in genome-wide studies [10, 11]. The *TGFB* Leu10Pro (rs1982037) variant present in the signal peptide affects the production of a mature protein [12].

The *TNF* promoter variants, i.e. *TNF*-308 A>G (rs1800629) and *TNF*-238 A>G (rs361525) have not been consistently shown to have a functional significance but their relevance stems from their location in the HLA complex – a region harbouring a high number of immunologically relevant genes in exceptionally strong linkage disequilibrium. The *IL2* -330 T>G (rs2069762) promoter variation has been associated with up to threefold differences in production of the cytokine by peripheral blood lymphocytes in vitro [13].

The -590 *IL4* C>T (rs2243250) polymorphism increases transcription of the gene [14] and in a number of reports the *IL4* -590 T allele has been associated with inflammatory and allergic conditions as well as strokes [15]. Interestingly, in the case of myocardial infarction the same variant appears to confer protection, especially in young people [16].

Among the *IL6* variants, the *IL6* -174 G>C (rs1800795) polymorphism has been most extensively studied after the initial suggestion that it reduces expression of the cytokine. However, recent work indicated that a polymorphism located even further up-stream (-6331 T>C or rs10499563) may be more relevant functionally [17].

The SNPs in the *IL10* promoter, i.e. -1082 G>A (rs1800896), -819 C>T (rs1800871) and -592 C>A (rs1800872), are well known markers which in Caucasians define three common haplotypes: GCC, ACC and ATA.

Although the contributions of individual SNPs are debated, the most prevalent GCC haplotype has been associated with relatively high *IL10* production [18].

By analysing this extensive panel what did the authors find? After stringent correction for the large number of comparisons performed in the study, Spiroska et al. observed a statistically significant association between DCM and variants of *IL4* as well as trends suggesting associations with *TNF, IL1B* and *IL2*. The association with *IL4* polymorphisms may be particularly interesting since this cytokine is important for development of humoral (TH2) immune responses and autoantibodies have been linked with pathogenesis of both non-familial and familial DCM [19, 20]. On the other hand, it should be noted that the *IL4* SNPs were not in Hardy–Weinberg equilibrium (HWE) among controls used by the authors. Lack of HWE is usually taken as an indication of erroneous typing which of course may invalidate the results.

In conclusion, whereas results of the study by Spiroska et al. await confirmation, the authors are commended for a comprehensive 'quasi-genomic' approach to the important question of the role of the immune system in DCM.

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