

Are ANCA-associated vasculitides inherited?

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While direct DNA diagnostics nowadays is feasible for nearly all known monogenetic disorders, common and complex diseases are far from being understood – even in the most general terms. In this special issue of *Clinical and Experimental Rheumatology* dedicated to vasculitis, Stefan Borgmann and Marion Haubitz review the current knowledge of the role of genetic factors for the pathogenesis of ANCA-associated vasculitides (AAV) (1). Epidemiological studies and analyses of single nucleotide polymorphisms (SNPs) in candidate gene association studies had previously revealed initial data on the meaning of genetics for AAV.

Regionally differing incidence rates for AAV imply genetic and environmental factors in the pathogenesis of AAV (2, 3). Comparison of data from large European vasculitis registries showed that *e.g.* Wegener's granulomatosis (WG) is more common in northern Europe compared to southern Europe (4, 5). As Borgmann and Haubitz point out, AAV are rarely observed in non-Caucasian populations, a finding which makes an influence of the genetic background likely.

Despite indications for genetic factors, AAV are not typical monogenic diseases with disease clusters in certain families. Due to the extremely low prevalence of familial AAV cases, whole genome linkage screens for defining genetic predisposition factors have not been reported so far. To date no mutations in specific genes have been identified to induce AAV in most of its carriers. Unlike for other diseases with a strong correlation of genotype and phenotype, like mutations of the *huntingtin* gene causing Huntington disease, a specific mutation or a defined combination of specific genetic variations leading ultimately to the induction of the disease are not to be expected in AAV.

The relevance of many of the published genetic variations in AAV is unclear. Genetic research in AAV has mainly focused on the analysis of variations in candidate genes which code for proteins that are thought to be more or less relevant for the pathogenesis of vasculitis. There is general consensus that in order to demonstrate a useful link between polymorphisms and disease, certain criteria must be met (6). One criterion is the plausibility of the candidate gene studied. A mutation in a “good” candidate gene should cause a relevant alteration in the activity or sequence of the encoded protein and this protein should be somehow relevant for the pathogenesis of the disease. This criterion is not met by a number of studies summarized by Borgmann and Haubitz in this issue. For many SNPs, like for some SNPs of the promoter region of certain cytokines, it is unclear whether they alter the effects of the gene product at all. Another requirement for the pathogenetic relevance of SNPs is that the allele be associated with a particular phenotype in a large number of cases (6). Evidently, in most of the studies on AAV, this number is far from “convincing”. A typical example is the increased carrier frequency of an allele encoding a defective proteinase inhibitor (PI*Z) in patients with WG. Although the frequency of the PI*Z allele is increased 100-fold in WG, still only 5 % of all WG patients carry the defective allele. As Borgmann and Haubitz point out, a role of PI*Z as a major pathogenetic factor for the development of WG is therefore unlikely. Finally, due to the rarity of the disease, the number of subjects studied is usually too low to generate robust data. With few exceptions (7, 8), the number of patients was less than 100 in most studies. However, large numbers of patients are required, especially if the SNP under study has a

low frequency. Polymorphisms of genes encoding cytokines, adhesion molecules, or co-stimulatory molecules have been linked with AAV or particular phenotypes such as WG. Since at least some of these SNPs are also linked to other autoimmune diseases like diabetes mellitus, Graves disease or SLE, it is likely that these SNPs may contribute to or entertain autoimmune reactions in general, rather than having a specific impact on a certain disease phenotype.

In summary, the data reviewed in this issue imply that, as in many other autoimmune diseases, the impact of genetics on the pathogenesis of AAV is multifactorial rather than being the consequence of mutations following Mendelian rules. How, in this context, might the genetic studies of AAV contribute to better understanding of the pathogenesis or better outcome in clinical practice? Probably certain phenotypes within the broad spectrum of AAV can be classified based on their genetic profile. Genetic classification might provide information on prognosis and/or might facilitate the identification of patients who are at highest risk for certain severe manifestations like diffuse alveolar haemorrhage or rapid progressive glomerulonephritis. In addition, certain genetic profiles may predict a patient's response or non-response to certain forms of treatments.

Genetics in AAV: Arole for genomic research

Since the genome of each human being contains ~ 6 million variable sites (e.g. single nucleotide polymorphisms, SNPs) of which many are in genes without an identified function (9), studies of a few SNPs will not suffice to define the multifactorial nature of AAV. New analytic approaches are needed to identify the molecular differences between certain clinical subsets within the broad spectrum of AAV. A novel approach to identify as yet unknown candidate genes is based on the principle of linkage disequilibrium. If still unidentified genetic factors are in proximity to an SNP on the same chromosome, recombination between these two genes will occur only

rarely over generations. In genetic terms, the SNP and the genetic factor are linked. But also by using other well-described markers, the highly informative microsatellites, these unknown factors can be identified in case control studies.

By the use of such an extended association screen in a cohort of 150 WG patients, recently a significantly disease-associated microsatellite was identified within and in the vicinity of apoptosis-related genes (7). This marker representing the retinoid X receptor (*RXR*B) gene is localised in the major histocompatibility complex (MHC) region between the *HLA-DBP1* and *DAXX* genes. HLA-DBP1 typing and fine mapping demonstrated a strong association of WG with *DBP1*0401* and an extended haplotype *DBP1*0401/RXR*B03 (7). Two additionally associated loci (*Casp14*, *RIPK1*) may influence the development of WG by interfering with (the regulation of) apoptosis. A logical step to extend the current efforts to catalogue SNPs is the analysis of haplotypes, i.e. series of linked polymorphisms. Analysis of haplotypes like *DBP1*0401/RXR*B03 may generate novel insights into the genetic profiles of certain phenotypes in AAV. Genes of as yet unknown function may be discovered by this approach.

Very recently, the development of microarray technology has opened up new avenues in the study of gene expression profiles and vast numbers of SNPs in human disease. The power of microarray analysis – already applicable today – lies in the possibility of studying >10,000 – 100,000 SNPs simultaneously rather than individual markers. Hence a plethora of association data can be established efficiently, as was recently evidenced for another multifactorial disorder, multiple sclerosis (Gödde R *et al.*, 2004, submitted). In the future such microarray approaches will be used in cohorts of AAV patients to explore differences in terms of outcome (disease severity and damage) and clinical manifestations between subjects with certain genetic profiles.

Description of the linkage between certain genetic variations and given phenotypes of AAV will only be the first step in the translation of genomic research into clinically relevant insights. The study of the proteins includes their functional characterisation. In this respect it needs to be stressed that >33% of the human genes and their derived protein isoforms have not yet been characterized in detail and no functional data are available to date (9, 10). Thus, analyses of the respective genes and proteins associated with AAV or certain phenotypes are likely to provide completely novel insights into the pathogenesis of AAV.

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