Role of HLA genes in familial spondyloarthritis

Said-Nahal and colleagues report an intriguing finding of an association with HLA-DR4 independent of B27 in families with ankylosing spondylitis (AS), including spondyloarthropathy (SpA), independent of B27 in families with ankylosing spondylitis. The study is by the same authors, following on from their previous work. The authors state that no difference was noted in B27-DR4 haplotype frequencies in patients and ethnically matched healthy controls. Many previous studies have not reported any such association, including a similar preliminary study by the same authors. Although these studies were mainly case-control studies, population stratification is highly unlikely to cause a false negative finding if the effect size of the reported association with DR4 is as high as Said-Nahal and colleagues describe.

We are concerned that both the family and case-control results are biased by the statistical approach employed. Multicase families were used in the study, yet a form of transmission test for linkage disequilibrium (TDT) was used which is only suitable for single affected families, and is a valid test only of linkage, and not association, when applied to multicase families. As opposed to association studies, linkage and association. We would be interested to see the results of a further analysis allowing for these considerations.

References

Authors’ reply
We thank Brown and colleagues for their interest in our recent publication. In their comment, they raise a number of questions which we have tried to address. The reported effect of HLA-DR4 appears to be independent of linkage with HLA-B27, meaning that it is not accounted for by linkage disequilibrium with HLA-B27. However, this observation does not necessarily imply that it is independent of HLA-B27, considering that HLA-B27 was almost constant among patients with familial spondyloarthropathy (SpA) (in other words, the DR4 effect may combine with the B27 effect, rather than being truly independent).

In our study the presence of DR4 increased the risk of developing SpA among HLA-B27 carriers (odds ratio = 2.8, 95% confidence interval 1.4 to 5.7), which is far less than the effect of HLA-B27. This result is based on HLA-DRB1 typing of 185 patients and of 71 healthy siblings. Only one of the previous association studies cited by Brown and colleagues had comparable sample size. Even in that study, however, no more than two thirds of the patients belonged to multiplex families and their controls were from the general population. Therefore the DR4 effect may be specific for familial disease, requiring the use of healthy siblings from multiplex families as B27+ controls, to demonstrate an association. Considering previous studies cited by Brown and colleagues were presumably underpowered to detect a DR4 effect. This was obviously the case with our preliminary report which concerned only 13 of the 70 multiplex families included in the present publication.

We used Spielman’s transmission disequilibrium test (TDT) to examine whether the transmission of HLA alleles to patients differed from random. As opposed to association studies, these statistics are not exposed to population stratification bias. Yet, it was originally designed to test the transmission of biallelic markers in single families, and we agree with Brown and colleagues that its results in multiplex families need to be interpreted with caution. Hence linkage of the disease examined with a locus in a region might interfere with the results of a TDT applied to another locus in the same region, which might wrongly be noted as evidence for preferential association with that marker. In our study we illustrated by the influence of linkage disequilibrium with HLA-B27, which affected the transmission of several alleles at HLA-A, C, and DR loci, when studying all haplotypes together. However, when the analysis was confined to the non-B27 haplotypes, all of these alleles appeared to be randomly transmitted, except for HLA-DR4. Such unique disequilibrium strongly suggested that HLA-DR4 itself contributed to SpA predisposition, albeit as already discussed in our publication, we could not entirely rule out that it was secondary to a preferential association between SpA and another major histocompatibility complex gene. Additional studies will clearly be needed to confirm our results. However, according to our present data, we would have needed to type 50 more multiplex families to reach a power sufficient to demonstrate a DR4 effect, by using statistics developed for general pedigrees as suggested by Brown and colleagues.

Finally, regarding the conclusions of the study, we disagree with Brown and colleagues that our results reflected both linkage and association, because any HLA-B27 haplotype identified in a family was counted only once, even if present in several patients.

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References

BOOK REVIEWS

Disease modifying therapy in vasculitides

The target readership for this slim book on the treatment of vasculitis is identified from the outset. Only one chapter is on standard regimens based on cyclophosphamide and steroids. There is widespread recognition of the potential toxicity of standard treatment, especially with prolonged usage. Thus two more chapters deal with alternative approaches to conventional immunosuppressive drugs, discussing methotrexate—which is in widespread use—and the newer agents, mycophenolate mofetil and desoxyapurinol. Five subsequent chapters deal with more experimental treatments, ranging from tumour necrosis factor blockade through intravenous immunoglobulin to various forms of anti-T cell treatment.

This is thus mainly an update for those specialists already familiar with the standard treatment for vasculitis and all its problems. Minor but important aspects of disease control, such as control of blood pressure, renal function, and even psychological support, are not considered as the editors are dealing only with disease modifying approaches. As such, this is a timely review of knowledge in a rapidly advancing field which will also provide good reading for those who see vasculitis less frequently. It should convince them that there are alternative approaches for relapsing or resistant cases, even if they have received full courses of standard treatment. Referral of cases to specialist centres may even be encouraged, which is probably the aim of the editors, to ensure a sufficient pool of patients to conduct the necessary studies that will advance knowledge in these rare but serious disorders.

The chapters have been written by those at the forefront of their fields who have largely discussed the benefits and the risks of the treatments they describe. This will help clinicians faced with difficult treatment choices to make decisions relevant to their individual patients. The idea of a single treatment for a diverse set of diseases that can affect any organ is no longer appropriate. Different stages of disease require different approaches. In the future, treatment may be further individualized according to pathogenesis, as suggested by the chapters on the virus related systemic vasculitis and the prevention of relapse in ANCA related small vessel vasculitis. The last is particularly relevant as patients with ANCA associated vasculitides form a major part of the systemic vasculitis seen in Europe/america and because relapse is one of the major problems now that initial remission can be induced in at least 90% of patients. Movement in this field in the past 10 years has occurred and the reader is given clear indications of the current excitement in this steadily progressing area.

Vasculitis

Seventy contributors collaborated with the editors to produce this work on vasculitis and vasculopathies that may mimic inflammatory vessel diseases. The first four chapters deal with classification of vasculitides and syndromes relevant to ANCA associated small vessel vasculitis. The last is particularly relevant as patients with ANCA associated vasculitides form a major part of the systemic vasculitis seen in Europe/americand because relapse is one of the major problems now that initial remission can be induced in at least 90% of patients. Movement in this field in the past 10 years has occurred and the reader is given clear indications of the current excitement in this steadily progressing area.

The last well structured chapters and the slighty deficient illustrations and explanation of abbreviations may be because this is a first edition, but the book probably lives up to the expectations of the authors and the readership, and can fill a gap in the market.
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