

VIEWPOINT

Should patients with recent onset rheumatoid arthritis be offered genetic screening?

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Advances in molecular based technology and their application to the study of disease aetiology and pathology are having a significant and increasing impact on the practice of clinical medicine. This methodology can be applied not only to single gene disorders such as cystic fibrosis, but also to complex polygenic disorders such as ischaemic heart disease, certain cancers, and rheumatoid arthritis (RA). Some of the genetic factors identified may prove useful in screening for disease risk or indicating prognosis.

A recent Government document¹ summarised how the application of genetics may be increasingly useful in medicine, and suggested that it may soon be appropriate to screen patients with early rheumatoid arthritis (RA) for HLA genotypes associated with a poor prognosis in order to guide treatment decisions. A similar recommendation was made in a recent paper by Emery and Salmon.² Here, we review the evidence that has led to this suggestion and discuss the factors that need to be considered before genetic screening of patients with recent onset RA could be recommended as a routine procedure.

Background

To date, the strongest genetic association identified for RA is with the HLA complex. Since Statsny's original observation in 1978 that RA is associated with HLA-DR4,³ many confirmatory studies have been published. It gradually became clear that different HLA-DR specificities were associated with RA in different ethnic groups.⁴ The application of DNA sequencing and molecular based typing to detect HLA-DRB1 alleles showed that those associated with RA (HLA-DRB1*0101, *0102, *0401, *0404, *0405, *0408, *1001, and *1402) shared a consensus amino acid sequence (QKRAA or QRRAA) at positions 70–74 of the third hypervariable region of the HLA-DRB1 chain—a position that influences its interaction with the T cell receptor. These studies led to the so called 'shared epitope' hypothesis, which unifies the various genetic associations in different populations.⁵ Using molecular techniques, it is now possible confidently to infer HLA-DRB1 genotypes (including whether individuals are homozygous) and to detect alleles carrying the shared epitope in a relatively simple, rapid, and inexpensive way.

Susceptibility versus severity

Considerable debate has centred around whether genes bearing the shared epitope are associated with susceptibility to the development of RA, or with a worse prognosis amongst RA sufferers. This distinction was initially suggested by a cross-sectional population based study of prevalent RA cases in the Netherlands, which found no association between HLA-DR4 and RA, but did find an association with radiological erosions.⁶ Similarly, a recent study of incident cases of RA seen in general practice in Norfolk (the Norfolk Arthritis Register)⁷ found only a weak association with HLA-DR4. In contrast, most hospital clinic series of RA patients demonstrate a strong association with HLA-DR4⁸ or the shared epitope, and this is more pronounced in patients with one of the most severe variants of RA, Felty's syndrome.⁹ Other studies have suggested that having a 'double dose' of the shared epitope, in particular HLA-DRB1*0401 and HLA-DRB1*0404 combinations may also confer a worse prognosis. Weyand *et al*¹⁰ found that HLA-DRB1*0401/*0401 homozygotes had the greatest risk of major organ involvement and 'compound heterozygotes' (HLA-DRB1*0401/*0404) the greatest risk for nodular RA. Two studies in the United Kingdom have also suggested that the greatest risk for severe RA is associated with the HLA-DRB1*0401/*0404 genotype.^{11 12} Both these genotypes (HLA-DRB1*0401/*0401 and HLA-DRB1*0401/*0404) are, however, relatively rare in the UK population. Tables 1 and 2, respectively, summarise published data on the prevalence of RA associated genotypes in various populations, and on the frequency of erosions in RA patients with particular genotypes. In summary, these tables show that almost all patients with established RA possess the shared epitope. However, in early disease the frequency of the shared epitope is not increased significantly. Patients who are homozygous for the shared epitope, in particular if they have the HLA-DRB1*0401/*0401 or HLA-DRB1*0401/*0404 genotype, are at the greatest risk of developing radiological erosions. However, collectively these patients account for a very small proportion of those whose disease is erosive. Thus most patients (74%) who have erosive disease are not homozygous for the shared epitope.

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Table 1 Prevalence (as reported by various sources) of certain genotypes in control subjects and groups of patients with rheumatoid arthritis (RA)

	Normal white population (%)	Community based		Hospital based		Erosive RA (%)
		Early RA (%)	Early RA (%)	Early RA (%)	Established RA (%)	
SE-	48 ¹¹ 55 ¹³	36 ¹⁵ 52*	36 ¹³	13 ¹¹	26 ¹³ 44*	
SE+	45 ¹³ 52 ¹¹	48* 64 ¹⁵	64 ¹³	87 ¹¹	56* 74 ¹³	
HLA-DR4	31† 38 ⁸	42 ⁷	55 ¹⁶	66 ⁴ 74 ⁸	44* 58 ¹⁶	
SE+/SE-	35†	28*	—	—	32* 96 ¹⁰	
SE+/SE+	9†	19* 23 ¹⁵	23 ¹³	21 ¹⁴	24* 26 ¹³ 46 ¹⁰	
HLA-DRB1 *0401/*0401	1.3 ¹¹ 1.4 ¹³	3*	6 ¹³	5 ¹¹	3* 11 ¹⁰	
HLA-DRB1 *0401/*0404	1.1 ¹¹ 1.3	5*	9 ¹³	14 ¹¹	9* 12 ¹³ 14 ¹⁰	

*Unpublished data from the Norfolk Arthritis Register.¹⁷ patients with disease duration less than two years.

†Unpublished data from the Arthritis Research Council Epidemiology Research Unit.

¹⁰All patients in this study were seropositive, with disease duration more than three years.

SE = Shared epitope.

Targeting treatment in RA

There is an increasing body of evidence that early treatment of RA, particularly if it reduces the erythrocyte sedimentation rate or C reactive protein concentration to normal, results in a better outcome, at least in the short term.^{19 20} However, it is important to emphasise that the natural history of early RA is highly variable. Some patients will go into remission with no treatment, while in others it is impossible to maintain a normal acute phase response even with aggressive treatment including cytotoxic and steroid drugs. Rheumatologists would welcome a test that would correctly categorise, at onset, an RA patient's future course. Such a test, depending on its predictive qualities, might be used to identify those patients destined to have a good outcome who could be treated symptomatically, or alternatively those with the worst prognosis who might be candidates for aggressive treatment. However, the latter approach presupposes that those with the worst outlook have disease which is amenable to current treatment. No studies have yet been performed that demonstrate, for example, that those RA patients with the HLA-DRB1*0401/*0404 genotype respond to medication. Similarly, there are no studies that demonstrate that early

Table 2 Prevalence of erosions at two years in patients with rheumatoid arthritis (RA) with particular genotypes

Genotype	With erosions (%)
SE-	19 ¹⁸ 30*
SE+	23 ¹⁸ 42*
HLA-DR4	50*
SE+/SE-	39*
SE+/SE+	29 ¹⁸
HLA-DRB1*0401/*0401	50*
HLA-DRB1*0401/*0404	60* 91 ¹³
All RA patients	36* 69 ¹³

¹³ At one year.

¹⁸Only HLA-DRB1*0401, *0404, *0405.

*Unpublished data from the Norfolk Arthritis Register.¹⁷

SE = Shared epitope.

treatment of RA will prevent the subsequent development of extra-articular disease.

The two principal outcome measures in RA are the development of radiological erosions and the development of functional disability. Whilst there is a degree of overlap between these two measures, it is by no means complete. The genetic associations of 'disabling' RA are much weaker than those for 'erosive' RA.²¹⁻²³ Thus, while patients who are shared epitope positive have about double the risk of developing erosions compared with those who are shared epitope negative, the risk of being functionally disabled at one year is the same in the two groups (Norfolk Arthritis Register data). It is therefore important that treatment decisions in RA should not centre solely on the aim of preventing erosions. Patients with no erosions may experience significant pain and disability, and they too require appropriate treatment.

Screening issues

Before a screening test is introduced, certain criteria require consideration.²⁴ These criteria were developed for use when the introduction of population screening for disease (for example screening for hypertension) may be considered, but they can be applied equally well to the introduction of a screening test in early disease to predict future outcome. They are examined here in the context of genetic screening of patients with early RA in order to predict the development of erosions:

(1) The population being screened should be at relatively high risk of developing the disease.

Patients with early RA are at high risk (1 in 3) of developing erosions, so this criterion is satisfied.

(2) The undiagnosed disease should be of concern to the community being screened.

Whilst RA patients are often not aware of the significance of erosions, their physicians are aware. Patient education can ensure that this criterion is met.

(3) The undiagnosed disease (erosions) should be more amenable to treatment at an early stage than it would be later.

As outlined above, this point has not been proven in the patients who screen positive.

(4) Individuals for whom the screening test is positive should be assured follow up evaluation.

Genetic screening in RA patients should only be offered and interpreted by physicians in a position to provide expert long term management.

(5) The test should be highly sensitive and specific.

Table 3 shows the sensitivity and specificity of the different genotypes. None satisfies the requirement to be both sensitive and specific (as shown in the receiver operator characteristic curves (figure)). The most appropriate test would be for the shared epitope.

(6) The test should be applicable and acceptable to a large number of individuals.

Genetic screening would be performed using blood or mouth wash samples, which is generally acceptable.

Table 3 Sensitivity and specificity of HLA genotype in predicting erosions in community and hospital based populations of patients with rheumatoid arthritis (RA)

	Community based RA (Norfolk)		Hospital based RA (Birmingham)	
	Sensitivity	Specificity	Sensitivity	Specificity
SE+	56	60	74 ¹³	61 ¹³
HLA-DR4	44	76	72 ²⁵	58 ²⁵
SE+/SE+	21	87	26 ¹³	88 ¹³
HLA-DRB1				
*0401/*0401	3	97	—	—
HLA-DRB1				
*0401/*0404	9	99	12 ¹³	97 ¹³

SE = Shared epitope.

(7) The test should be simple; it should be accomplished easily and quickly.

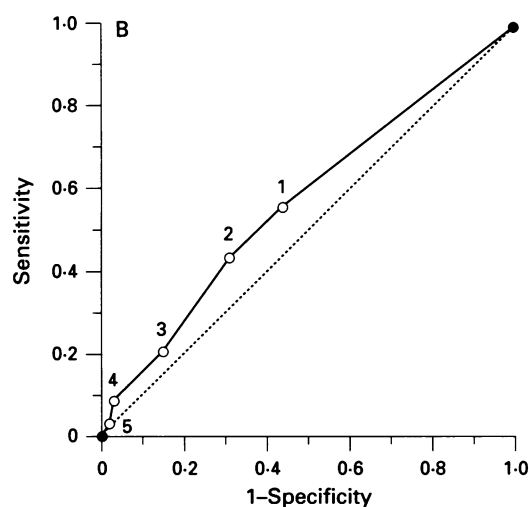
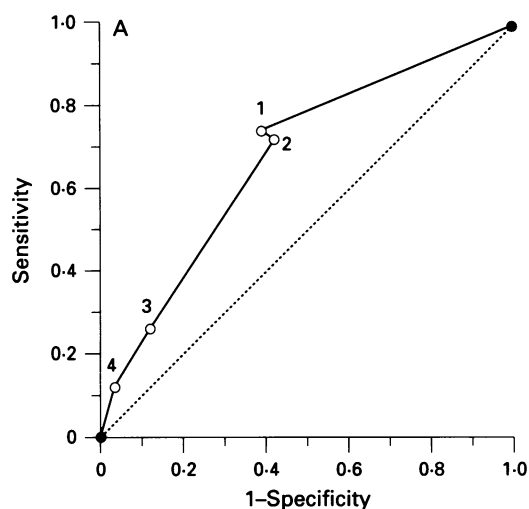
DNA based molecular tests could be tailored to meet these requirements.

(8) The test should be harmless to the individual being tested.

Blood tests carry minimal risk to the individual. However, incorrect interpretation of the result may be harmful.

(9) The test should be cost effective.

This is an achievable target, though the cost and



Receiver operator characteristic (ROC) curves for predicting erosions—A: using 120 hospital based patients with RA from Birmingham; B: using 95 community based patients with RA from Norfolk. ROC curves plot sensitivity over (1 - specificity). Tests with a high sensitivity and high specificity deviate maximally from the diagonal line and have a large area under the curve. Poorly discriminating tests lie on or near the diagonal line, which represents what one would expect by chance. 1 = Shared epitope positive; 2 = HLA-DR4; 3 = shared epitope homozygous; 4 = HLA-DRB1*0401/*0404; 5 = HLA-DRB1*0401/*0401

therapeutic benefit of early intervention require evaluation.

Discussion

When considering introducing a screening test, it is important to consider the implications both of a positive and of a negative test. Most patients with RA are shared epitope positive. However, given that a person has developed RA, the finding of a negative shared epitope test is not reassuring: 19–30% of RA patients who are shared epitope negative develop erosions. There is some evidence from Sweden that in patients who are shared epitope negative their disease may become erosive later (after two years).²³ Thus one could not recommend withholding antirheumatic treatment in this group. Those at greatest risk of eroding have the HLA-DRB1*0401/*0404 genotype. It could be argued that if these patients were identified early they could be targeted for the most aggressive treatment. However, it is possible that this small group of patients are just the ones who do not respond to treatment. What of a negative test for HLA-DRB1*0401/*0404? The great majority of patients whose disease becomes erosive do not possess this genotype. They may be the ones who do respond to treatment and whose disease course can be altered. So, for the time being, genetic screening in RA should remain a research tool. We need to set up well designed clinical outcome studies of RA patients stratified by HLA-DRB1 genotypes and given a range of treatments.

We still have much to learn about the significance of the presence and absence of RA associated genotypes in the prognosis and response to treatment of RA patients.

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