Autoantibodies in twins discordant for rheumatoid arthritis

Rheumatoid arthritis (RA) is characterised by frequent occurrence of autoantibodies. The anti-cyclic citrullinated peptide antibodies (anti-CCP) are now used routinely as they may antedate the development of seropositive RA, because their diagnostic sensitivity and specificity is better than rheumatoid factors (RFs), and because they may predict a more severe outcome.[1–3] Previous studies have observed an increased prevalence of RF and anti-CCP in first-degree relatives of patients with RA.[4] One study on RA discordant twin pairs provided evidence for genetic effects on IgM-RF and IgG-RF independent of HLA-DR.[5] Anti-CCPs have been reported to be independently associated with the HLA-DRB1 shared epitope, PTPN22 and smoking,[6] and there is strong evidence for a link between anti-CCP and smoking.[7 8]

We wished to examine if the occurrence of selected autoantibodies in RA is attributable to shared genetic and/or environmental factors. For this purpose we performed a co-twin control study including both monozygotic (MZ) and dizygotic (DZ) RA discordant twin pairs. This design corresponds to a matched case–control study, where the RA affected twin in each pair is the case while the unaffected co-twin serves as control. The presence of an autoantibody is the exposure and RA the outcome. Only pairs discordant for exposure contribute to the conditional logistic regression analysis performed separately for the MZ and the DZ pairs.

This design enabled us to stratify for the effect of age and sex in DZ pairs and for genes as well in MZ pairs.

Thus, if RA and autoantibody production have a shared environmental background, the odds ratio (OR) for the autoantibody in MZ twins would significantly exceed that of DZ twins since genetic variability is eliminated in MZ pairs. Conversely, if shared genetic factors are involved a significantly higher OR in DZ twins than in MZ twins would be expected.

Twelve monozygotic and 32 dizygotic RA discordant twin pairs from a previously published twin study[9] were tested for the presence of IgM-RF and IgA-RF, antikeratin antibodies and anti-CCP antibodies. The results are presented in table 1.

The OR was >1 for all four autoantibodies in either zygosity group in accordance with the well-established relationship between these autoantibodies and RA, but in the MZ group statistical significance was only reached for anti-CCP antibodies. Since there is no genetic variation within MZ twin pairs it

Table 1 Number of RA discordant pairs by antibodies and zygosity

Antibody	Zygosity group	Antibody-positive RA twins with a non-RA antibody-negative co-twin	Antibody-positive non-RA twin with an RA antibody-negative co-twin	OR for RA (95% CI) according to presence or absence of antibody		Ratio DZ/MZ ORs
AKA	DZ	14	0	179.4	(3.6 to 591.9)	46
	MZ	3	1	3.9	(0.5 to 17.8)	
CCP	DZ	15	0	290.0	(3.9 to 622.0)	2
	MZ	6	0	146.1	(1.4 to 281.6)	
IgA-RF	DZ	16	0	204.5	(4.1 to 660.8)	29
	MZ	6	1	7.0	(0.9 to 30.4)	
IgM-RF	DZ	18	2	9.5	(2.3 to 32.1)	3
	MZ	7	2	3.0	(0.8 to 13.0)	

Owing to cells with zero observations, OR and 95% plausibility intervals are estimated from standard Bayesian techniques (assuming a Dirichlet-multinomial distribution of probabilities of counts).[10]
AKA, antikeratin antibody; CCP, cyclic citrullinated peptide; DZ, dizygotic; MZ, monozygotic; RA, rheumatoid arthritis; RF, rheumatoid factor.

follows that there must be an underlying environmental covariation between the occurrence of these autoantibodies and RA. Furthermore, for all four antibodies OR was higher in DZ than in MZ twins, suggesting an additional underlying genetic covariation between these antibodies and RA, particularly for antikeratin antibody and IgA-RF. The already established association between the shared epitope and anti-CCP-positive RA suggests that variation of the shared epitope within DZ discordant pairs may explain the higher OR for anti-CCP in DZ twins.

In conclusion, this first study on anti-CCP and antikeratin in twins suggests that both environmental and genetic effects may influence the expression of these autoantibodies.

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