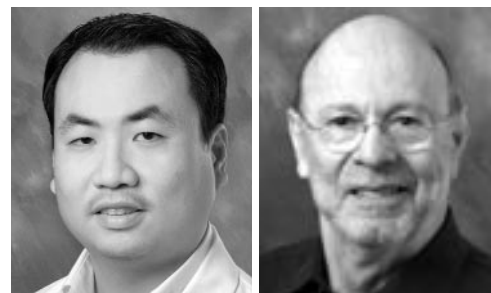


# The Predictive Power of Anti-Cyclic Citrullinated Peptide Antibodies: Window into Understanding Gene/Environment/Immunity Interactions



Palindromic rheumatism (PR) appears to be an ideal substrate upon which to examine the role of anti-cyclic citrullinated peptide antibodies (anti-CCP) as predictors of susceptibility or severity of rheumatoid arthritis (RA). In this issue of *The Journal*<sup>1</sup> data presented from a unique and unusual set of patients give us a chance to examine this question in more detail than previously possible. PR is characterized by brief, acute, and recurrent episodes of mono- or oligoarthritis that can be associated with extensive inflammation in surrounding soft tissue, which resolves spontaneously with no residual clinical or radiographic changes. Studies have observed that about one-third to one-half of patients with PR will develop RA, with the interval between presenting with PR and converting to RA varying from a few months to more than 20 years<sup>2</sup>. In the past, attempts had been made to find clinical characteristics that might predict the development of RA in patients with PR, but no significantly reliable parameter could be defined<sup>2</sup>. Russell, *et al*, in their current study, report that almost half of their patients with PR had progressed to RA after a mean followup of 5.4 years, and 83% of these patients who progressed to RA had anti-CCP antibodies in sera collected at baseline. They conclude that the presence of anti-CCP antibodies in patients with PR may predict their future development of RA. Their study not only highlights the relationship of PR to RA but also provides us with some speculation about the potential predictive power of the anti-CCP antibody in a more general sense.

## **CAN ANTI-CCP ANTIBODIES PREDICT DEVELOPMENT OF RA IN PATIENTS WITH EARLY ARTHRITIS?**

Several studies have shown that anti-CCP positivity in the setting of early arthritis is strongly related to developing RA in these patients. For instance, Visser, *et al* found that among patients seen at an early arthritis clinic with less than 2 years of signs and symptoms, the strongest associations for per-

sistent versus self-limiting arthritis were symptom duration of  $\geq 6$  months, with an odds ratio (OR) of 5.49, and anti-CCP positivity, with an OR of 4.58<sup>3</sup>. These investigators also discovered that the strongest association for erosive versus non-erosive arthritis was for anti-CCP positivity, with an OR of 4.58. In another early arthritis study, also conducted in The Netherlands, Jansen, *et al* noted that having values of IgM rheumatoid factor  $> 40$  or anti-CCP  $> 50$  predicts which patients with early arthritis will receive a clinical diagnosis of RA with a sensitivity of 55.4% and a specificity of 96.7%<sup>4</sup>. Finally, Van Gaalen, *et al* described a cohort of 346 patients who presented to an early arthritis clinic and were diagnosed with undifferentiated arthritis at their baseline evaluation; 28 were lost to followup and excluded from further analysis<sup>5</sup>. In the 318 remaining patients from this cohort, 69 were anti-CCP-positive and 249 were anti-CCP-negative at baseline. Of the 69 anti-CCP-positive patients, 83%, 90%, and 93% of them fulfilled American College of Rheumatology RA criteria after 1, 2, and 3 years, respectively. In contrast, among the 249 anti-CCP-negative patients, 18%, 24%, and 25% fulfilled ACR RA criteria after 1, 2, and 3 years, respectively. The presence of anti-CCP antibodies was a significant risk factor for RA, with an OR of 37.8 (95% confidence interval 13.8–111.9). The data among these studies are remarkably similar: The presence of anti-CCP antibodies can help predict which patients with early arthritis may develop RA. However, it must be noted that the above mentioned patient populations are potentially very similar in terms of demographics and other features, and the studies come from the same geographic area.

## **CAN ANTI-CCP ANTIBODIES PREDICT SEVERITY OF DISEASE IN RA?**

Among those already with an established diagnosis of RA, anti-CCP positivity has been able to predict, in numerous

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studies, the severity of disease. RA patients with anti-CCP have more radiographic joint damage as compared to those without these antibodies<sup>6-13</sup>. These patients also are more likely to have a greater degree of radiographic progression<sup>7,10,13-15</sup>. Other studies have revealed that RA patients with anti-CCP antibodies are more likely to have a higher erythrocyte sedimentation rate, C-reactive protein, and Disease Activity Score 28<sup>7,15,16</sup>. Along with its predictive power in developing RA, emerging data demonstrate that anti-CCP positivity can also provide prognostic information on the severity of the disease.

#### **CAN ANTI-CCP ANTIBODIES PREDICT DEVELOPMENT OF RA PRIOR TO SYMPTOM ONSET?**

Analyses performed on stored blood samples of patients with RA who donated blood prior to developing symptoms of RA have shown that anti-CCP antibodies can be present years before developing any symptoms, and in certain settings, may be able to predict who will develop RA. Nielen, *et al* studied 79 patients with RA who donated blood prior to symptom onset<sup>17</sup>. They observed that 40.5% of patients became anti-CCP-positive prior to symptom onset, and the median time from first anti-CCP positivity to symptom onset was 4.8 years, with a range from 0.1 to 13.8 years. These investigators analyzed the diagnostic characteristics of anti-CCP antibodies for the 5 years prior to symptom onset, and found that the 5 year positive predictive value (PPV) for anti-CCP in the RA blood donor patient population was 96.6%. They also calculated the risk of developing RA within 5 years for the general population as well as for those at “high risk,” which they defined as having 2 or more first-degree relatives with RA. They discovered that the 5 year PPV for anti-CCP in the “high risk” population was 69.4%, and in the general population it was 5.3%. In another similarly conducted blood donor study, Rantapaa-Dahlqvist, *et al* noted that anti-CCP antibodies could be detected up to 9 years prior to symptom onset<sup>18</sup>. Once individuals began being anti-CCP-positive, the titers increased significantly until the disease manifested; the same trend was seen on an individual patient basis as well. Berglin, *et al* performed another study on pre-RA blood donor samples and found that anti-CCP positivity gave an OR of 25.1, and the combination of anti-CCP antibodies and shared epitope (SE) gene carriage gave an OR of 66.8 for the risk of developing RA compared with not having any of these factors<sup>19</sup>.

A recently published study by Klareskog, *et al* also highlights the connection between anti-CCP antibodies with SE to the development of RA, and demonstrates the important association between the environmental trigger of cigarette smoking and this connection<sup>20</sup>. In their case-control study of recent-onset RA subjects, these researchers found that the relative risk (RR) of developing RA rises dramatically for smokers with 2 copies of SE. This risk applied to only anti-CCP-positive RA and not anti-CCP-negative RA. Ever-

smokers with no SE copies had a RR of 1.5 for developing anti-CCP-positive RA; with one copy, the RR rose to 6.5, and with 2 copies, the RR rose to 21. In comparison, never-smokers with one copy of SE had a RR of 3.3, and with 2 copies they had a RR of 5.4. RR was not increased for anti-CCP-negative RA, even with smoking, 2 copies of SE, or both. The demonstrated gene-environment-immunity interaction from this set of patients provides a hypothetical model for the etiology for RA. Taken together, these prediction studies demonstrate the importance of a biomarker (anti-CCP antibodies) as an intermediate step in the development of RA from genetic predisposition through environmental risk, autoimmune mechanisms of disease perpetuation, and finally full-blown disease.

#### **CONCLUSION**

Emerging data strongly suggest that anti-CCP antibodies have the power to predict the development of RA in patients with early arthritis, the severity of disease in patients with established RA, and the possibility of future onset of RA in certain high-risk populations. The report in this issue by Russell, *et al* noting that anti-CCP positivity in the setting of PR predicts development of RA further supports this concept. As well, it adds data to the continuing issue of how to define PR — as part of the spectrum of RA or as a separate, unconnected process. However, this whole issue raised by their contribution is most certainly greater in scope and impact. We should ask ourselves what additional biomarkers can predict established (or perpetuated) RA or its remission? What are the key autoimmune mechanisms for disease perpetuation? And, among these undiscovered factors, what are the relationships to the as-yet-unknown environmental risks (other than what has been demonstrated for cigarette smoking)? Finally, much of the above referred data comes from fairly homogeneous patient populations in limited geographic areas. We need to continue these experimental observations in larger and more heterogeneous cohorts. There appears to be much more work to do.

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