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The Genetics of Rheumatoid Arthritis:

New Insights and Implications

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Rheumatoid arthritis (RA) is a common disabling systemic inflammatory disorder that causes chronic joint destruction. However, by most assessments, the consequences of treated disease have become less severe during the past 20 years. An armamentarium of second-line drugs, including methotrexate and biologic agents such as tumor necrosis factor (TNF) inhibitors, in combination with widely accepted treatment strategies, which include early treatment and treatment that targets low disease activity,[1] has led to a reduction in disease activity for patients with RA throughout much of the developed world.[2] Despite highly effective treatments, approximately 20% of patients continue to experience pain, disability, and joint destruction. In addition, even with effective treatment, RA has been linked to increased cardiovascular mortality,[3] perhaps because of long-standing high levels of systemic inflammation. The residual disease activity among patients whose disease is difficult to manage and the associated cardiovascular mortality remain important management challenges.

Improved identification of patients who are likely to experience severe disease is needed. Effective patient stratification could improve overall RA outcomes by facilitating individualized treatment approaches that maximize benefit while reducing iatrogenic harm. Proposed approaches include characterizing genetic predilections to severe disease and poor outcomes. Genetic studies also have been pivotal in generating new insights into disease pathogenesis which, in turn, may provide a basis for novel therapies with favorable therapeutic profiles.

Understanding of the genetic basis for RA has recently progressed with the description of specific variations within genes encoding the peptide-binding regions of HLA molecules because these regions had not been well characterized. Specific genetic variations give rise to distinct differences in amino acid composition in these regions that are then presented to T lymphocytes. The genetically driven differences in the peptide-binding region may provide a biological basis for the continued immune activation in RA.[2,4]

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It is with this background that the report by Viatte and colleagues[5] in this issue of *JAMA* provides new insights about recently described genetic factors that increase the risk of developing RA. The study by Viatte et al suggests that these same factors are significantly associated with disease severity and increased risk of mortality in persons with RA.

The authors used data from several cohorts of English patients, including 2 cohorts to evaluate radiologic severity (1691 patients from a primary care inception cohort and 421 patients from a secondary care cohort; 1 cohort to assess mortality (2432 patients from a primary care inception cohort); and 1 cohort to examine treatment response (1846 patients enrolled at initiation of TNF inhibitor therapy), and evaluated the associations between various HLA-DRB1 haplotypes, defined by amino acids at positions 11, 71, and 74, and these clinical outcomes.

The authors found that valine at position 11 had the strongest association with radiological severity (erosions in 74% of homozygote carriers (43/58), 61% of heterozygotes (130/213), and 48% of noncarriers (150/314); and with all-cause mortality among patients with inflammatory polyarthritis (2.5% per year among carriers [324 deaths in 1116 patients over 13 208 person-years] vs 1.9% per year among noncarriers [319 deaths among 1398 patients over 17 196 person-years]) (hazard ratio, 1.16; 95% CI, 1.03–1.31).

The results of the study by Viatte et al are important for 3 reasons. First, these findings may add to the ability to predict outcomes of RA, thus helping to optimize therapeutic strategies for different patients. Second, the findings may add to the understanding of the molecular mechanisms that determine disease course and mortality. In both aspects, however, the present findings have to be put into context. Even though this genetic predilection to disease confers an increased risk of disease severity, it only explains a minor part of the inter-individual differences between patient outcomes, in a disease process for which environmental and lifestyle factors, as well as biomarkers, have a larger explanatory value.[6–8] The way forward in this area will be to use the current genetic findings as one component in the construction of updated prediction algorithms that consider additional genetic differences, environmental and life style factors, biomarkers, and clinical characteristics.

Third, the findings by Viatte et al also help to inform understanding of disease pathogenesis by strongly implicating HLA-dependent immune events not only for the onset of RA, but also for disease course and mortality. This is an important message because it implies that therapies directed against HLA-dependent events, such as specific T-cell responses, are likely to be efficient for various aspects of the disease course.

Interpretation of treatment response data requires consideration of several methodological issues. Determining factors that influence treatment response is challenging and adjustment for baseline variables has been shown to produce biased results. Glymour et al[9] and Yanez et al[10] have suggested that baseline adjustment may yield paradoxical findings (ie, a factor that actually increases progression can appear to decrease progression). There are at least 2 reasons for this: first, regression to the mean often affects the outcome measure, in this case the Disease Activity Score (DAS). To be included in the cohort used to assess TNF response

in the study by Viatte et al, patients were required to have high DAS levels. However, because measurement of this parameter is associated with noise,[11] a spuriously high baseline DAS can regress to its mean (often lower) value at follow-up measurement and some of that apparent decrease in DAS may not reflect actual improvement in underlying disease activity, but rather variation in measurement. Any factors associated with high levels of disease activity at baseline (in this case the VKA haplotype that encodes the peptide-binding region of HLA) would be spuriously found to be associated with DAS response. In addition, conditioning on baseline disease activity can create associations of a one factor (eg, VKA haplotype) with other factors affecting response (a phenomenon labeled collider bias or index event bias[12]), making it difficult to identify whether the first factor is actually related to treatment response. Although Viatte et al did adjust for the baseline value of the DAS in analyzing DAS response, unadjusted results are less likely to be biased.[9]

For example, the unadjusted findings (presented in Table 5 in the article) suggest a very minor association between VKA haplotype and DAS response (ie, no alleles, mean decline in DAS of 2.43; 2 alleles, a mean decline in DAS of 2.58, a difference of 6%). The European League Against Rheumatism response differences between allele groups are similar. There is further evidence that the association between VKA haplotype and TNF response may be weak. In adjusted analyses, the odds ratio is approximately 1.2 for each level of response (there are 2 levels of response). However, improvement in the DAS score per allele of this haplotype is 0.12 on a scale that ranges from 0 to 10 and for which the minimal clinically important difference in the DAS score is 1.2.[13] Thus, even if corroborative analyses suggest an association of this haplotype with response, the effect on treatment response is small and less than other major factors affecting response.

Although the findings reported by Viatte and colleagues may not have immediate clinical implications, identification of the precise HLA variants that influence disease course is of great interest. These observations open the door to further research, including replication for this haplotype and discovery related to its combination with other determinants of disease development and progression. Such discoveries will prove helpful both to understand and predict the variable disease course and response to therapy that occurs in patients with rheumatoid arthritis.

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References

1. Smolen JS, Aletaha D. Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges. Nat Rev Rheumatol. [published online February 17, 2015].
2. Kievit W, Fransen J, de Waal Malefijt MC, den Broeder AA, van Riel PL. Treatment changes and improved outcomes in RA: an overview of a large inception cohort from 1989 to 2009. Rheumatology (Oxford). 2013; 52(8):1500–1508. [PubMed: 23657913]
3. Snow MH, Mikuls TR. Rheumatoid arthritis and cardiovascular disease: the role of systemic inflammation and evolving strategies of prevention. Curr Opin Rheumatol. 2005; 17(3):234–241. [PubMed: 15838230]

4. Raychaudhuri S, Sandor C, Stahl EA, et al. Five amino acids in three HLA proteins explain most of the association between MHC and seropositive rheumatoid arthritis. Nat Genet. 2012; 44(3):291–296. [PubMed: 22286218]
5. Viatte S, Plant D, Han B, et al. Association of HLA-DRB1 haplotypes with rheumatoid arthritis severity, mortality, and treatment response. JAMA.
6. Saevarsdottir S, Wedrén S, Seddighzadeh M, et al. Patients with early rheumatoid arthritis who smoke are less likely to respond to treatment with methotrexate and tumor necrosis factor inhibitors: observations from the Epidemiological Investigation of Rheumatoid Arthritis and the Swedish Rheumatology Register cohorts. Arthritis Rheum. 2011; 63(1):26–36. [PubMed: 20862678]
7. Sandberg ME, Bengtsson C, Källberg H, et al. Overweight decreases the chance of achieving good response and low disease activity in early rheumatoid arthritis. Ann Rheum Dis. 2014; 73(11):2029–2033. [PubMed: 24818635]
8. Hambardzumyan K, Bolce R, Saevarsdottir S, et al. Pretreatment multi-biomarker disease activity score and radiographic progression in early RA: results from the SWEFOT trial. Ann Rheum Dis. 2014; 0:1–8.
9. Glymour MM, Weuve J, Berkman LF, Kawachi I, Robins JM. When is baseline adjustment useful in analyses of change? an example with education and cognitive change. Am J Epidemiol. 2005; 162(3):267–278. [PubMed: 15987729]
10. Yanez ND III, Kronmal RA, Shemanski LR. The effects of measurement error in response variables and tests of association of explanatory variables in change models. Stat Med. 1998; 17(22):2597–2606. [PubMed: 9839350]
11. Heegaard C, Dreyer L, Egsmose C, Madsen OR. Test-retest reliability of the Disease Activity Score 28 CRP (DAS28-CRP), the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) in rheumatoid arthritis when based on patient self-assessment of tender and swollen joints. Clin Rheumatol. 2013; 32(10):1493–1500. [PubMed: 23754243]
12. Dahabreh IJ, Kent DM. Index event bias as an explanation for the paradoxes of recurrence risk research. JAMA. 2011; 305(8):822–823. [PubMed: 21343582]
13. van Riel PL. The development of the Disease Activity Score (DAS) and the Disease Activity Score using 28 joint counts (DAS28). Clin Exp Rheumatol. 2014; 32(5 suppl 85):S-65–S-74.