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Evidence for a genetic component to disease severity in RA

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Abstract

Rheumatoid arthritis (Ra) is partly heritable; genetic and serological markers are known to confer risk of developing pathology. But given clinical heterogeneity in Ra, can we predict who will develop severe disease? Substantial heritability of erosive progression rates has now been identified, but better prognostic biomarkers remain wanting.

Uncontrolled chronic intra-articular inflammation from rheumatoid arthritis (RA) culminates in debilitating and irreversible erosive damage to joints. the rate of progression to structural joint damage has been dramatically altered in the past 20 years by treatment with conventional DMARDs, such as methotrexate, and more recently with the use of second-line biologic therapies (for example, TNF antagonists). Nonetheless, RA severity varies markedly among affected patients, ranging from self-limited disease in the absence of treatment to severe disease resulting in profound structural damage despite state-of-the art therapy. to what extent this clinical heterogeneity is genetically determined has been unclear. Now, Knevel *et al.*[1] have calculated that 58% of the variation in radiographic bone erosion progression rates among patients with RA is due to genetics ($P = 0.003$). If more severe disease is genetically distinct from a milder course, it might be possible to identify those patients at greatest risk of damage. Clinical realization of this genetic potential, however, will be a challenge.

Serological markers, including rheumatoid factor (RF) and anti citrullinated protein antibodies (ACPA), and inflammatory markers including ethrythrocyte sedimentation rate and C-reactive protein level, correlate with disease severity and joint destruction.[2,3] Despite being the most common RA biomarkers in clinical use, however, none are highly predictive of disease severity and their utility for prognosis in clinical practice is limited.[4]

The genetic component of susceptibility to RA has long been appreciated;[5] familial studies implied high heritability of disease risk, which has been borne out in subsequent studies. Overall heritability of RA is thought to be roughly 65% (Box 1). Therefore, a family history of RA is an important part of the clinical evaluation of patients with the disease. Genetic association studies for RA susceptibility have been remarkably successful, identifying risk alleles within the MHC and throughout the genome. These discoveries have added to our understanding of the aetiology and pathogenesis of disease, and promise to facilitate the development of new targeted therapies.

In contrast to RA risk, however, relatively little research into the genetics of disease severity has been done to date. Assessing factors that predispose to a more (or less) severe disease course is difficult—challenges include a lack of large cohorts of patients with RA who have

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been clinically characterized in a consistent manner, the difficulty in recruiting large samples of their affected relatives with clinical data, and difficulty in measuring and adjusting for challenging confounders such as healthcare access and treatment course. Several studies have tested whether candidate locus alleles, including RA risk alleles, correlate with disease severity, but the results have been mixed.[6] If genetic predictors of joint damage severity could be discovered, then they might serve as extremely useful biomarkers. Genetic markers offer key advantages over inflammatory markers; they are amenable to high-throughput assay and are stable over time and treatment course. Moreover, identifying genes that are associated with disease severity would shed further light on the pathophysiology of RA, particularly of severe disease.

If disease progression or severity were influenced strongly by genetic factors, then it should be a familial trait—that is, on average, closely related individuals should present more similar disease courses than unrelated individuals. A twin study in 2006 found suggestive evidence of familiality of radiographic joint destruction in patients with RA. Van der Helm-van Mil and colleagues[7] found that ten monozygotic twin pairs had more similar Sharp–van der Heijde scores (which quantify the severity of joint destruction in RA on the basis of hand and foot radiographs) than eight dizygotic twins, although the study was small and the difference was not significant.

The study by Knevel *et al.*[1] used icelandic databases that offer uniquely comprehensive insights into population genetics. Relatedness was found to be a significant predictor of differences in the rate of joint destruction (measured by changes in the sharp-van der Heijde score over the years since diagnosis) in a sample of >250 patients with RA, leading to an estimated 58% heritability for the rate of bone erosion progression in RA.

Knevel and colleagues utilized the research cohort of the Landspitali National University Hospital of Iceland, in which 325 patients with RA had radiographs available, the unique resource of the Icelandic genealogy records, as well as genome-wide single-nucleotide polymorphism genotype data (collected by deCODE Genetics)[8] available for 267 of the patients.[1] Investigators have leveraged the unique advantages of the deCODE genetics cohort—which include a fairly isolated population with a nationalized healthcare system and excellent genealogical records—to make rapid progress in answering many challenging questions in complex trait genetics.[8] Knevel *et al.*[1] demonstrated a correlation between pair-wise differences in joint destruction rates and pair-wise genetic relatedness assessed using both genealogy-derived kinship coefficients and identity-by-descent estimates based on the genotype data. These estimates assess realized relatedness, which can vary substantially among (for example) non-identical siblings due to random Mendelian segregation.[9] Consistent with a bona fide genetic contribution to the rate of joint destruction, the identity-by-descent analysis yielded a greater and more statistically significant estimate of heritability (58%, $P = 0.003$) than that arrived at using genealogy-derived kinship coefficients (45%, $P = 0.018$). Providing additional supporting evidence that RA severity is heritable, the results will motivate investigators to pursue further studies to identify the underlying genetic factors.

We note certain limitations to the study. The patients whose data were available to Knevel *et al.*[1] included both ACPA positive and ACPA negative individuals, and analyses within ACPA status strata were equivocal. This area is important for future investigation, because positive ACPA status correlates with increased disease severity and is associated with different genetic susceptibility factors. In addition, possible confounding by environmental factors, including healthcare access (through individual family habits as well as socioeconomic status) and treatment strategy could not be adjusted for. The authors noted

that most of the sampled data came from before the era of aggressive treatment, and that variation in treatment probably does not have a major role in their cohort.[1]

In summary, this population-based study by Knevel *et al.*[1] adds to the mounting evidence for the genetic basis of the severity of joint erosion in RA. A genetic component for disease severity would suggest that relatives of patients with severe RA, in addition to being more likely to develop disease, are also more likely to develop severe erosive RA. Currently, little can be done to prospectively predict disease severity. These results imply that better biomarkers (including genetic markers) might be found for RA severity and prognosis, and that the formidable arsenal of genomic medicine can be brought to bear specifically on severe, erosive disease.

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References

1. Knevel R, et al. Genetic predisposition of the severity of joint destruction in rheumatoid arthritis: a population-based study. Ann. Rheum. Dis. 2012; 71:707–709. [PubMed: 22219137]
2. van Gaalen FA, et al. Association between HLA class II genes and autoantibodies to cyclic citrullinated peptides (CCPs) influences the severity of rheumatoid arthritis. Arthritis Rheum. 2004; 50:2113–2121. [PubMed: 15248208]
3. Lindqvist E, Eberhardt K, Bendtzen K, Heinegard D, Saxne T. Prognostic laboratory markers of joint damage in rheumatoid arthritis. Ann. Rheum. Dis. 2005; 64:196–201. [PubMed: 15458956]
4. Smolen JS, et al. The need for prognosticators in rheumatoid arthritis. Biological and clinical markers: where are we now? Arthritis Res. Ther. 2008; 10:208. [PubMed: 18557991]
5. Lawrence JS, Ball J. Genetic studies on rheumatoid arthritis. Ann. Rheum. Dis. 1958; 17:160–168. [PubMed: 13559935]
6. Marinou I, Maxwell JR, Wilson AG. Genetic influences modulating the radiological severity of rheumatoid arthritis. Ann. Rheum. Dis. 2010; 69:476–482. [PubMed: 20124360]
7. van der Helm-van Mil AH, Kern M, Gregersen PK, Huizinga TW. Variation in radiologic joint destruction in rheumatoid arthritis differs between monozygotic and dizygotic twins and pairs of unrelated patients. Arthritis Rheum. 2006; 54:2028–2030. [PubMed: 16732568]
8. 2010. deCODe genetics [online] http://www.decode.com/company/
9. Visscher PM, et al. Assumption-free estimation of heritability from genome-wide identity-by-descent sharing between full siblings. PLoS Genet. 2006; 2:e41. [PubMed: 16565746]
10. MacGregor AJ, et al. Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. Arthritis Rheum. 2000; 43:30–37. [PubMed: 10643697]

Box 1 Modelling heritability and familiality of complex traits

Physical traits that are influenced by many independent factors are often normally distributed, including most quantitative traits, such as height. For a disease trait (in which the phenotype is binary, being either affected or unaffected), quantitative geneticists assume that a normally distributed underlying phenotype, termed liability, manifests as disease when it exceeds a threshold determined by the prevalence of disease. An individual's phenotype is essentially the sum of environmental and genetic variables, and so the population distribution of phenotypes can be viewed as the sum of two distributions—genetic and environmental components.

If the quantitative trait is normalized to have a mean of zero and variance of one, then the distributions of the genetic and environmental components of the trait will have variances equal to the heritability, and to one minus the heritability, respectively.

Related individuals have correlated genetic values for a quantitative trait. For example, monozygotic twins have the exact same genetic values, and siblings' genetic values have a correlation of 0.5. Relatives' phenotypic correlations, then, are their genetic correlations, reduced by the contribution of environment (that is, their relatedness multiplied by the heritability of the trait, which is between zero and one). Concordance for a binary disease trait can be mathematically transformed to phenotypic correlation on the underlying liability scale, and used to derive the relationship between concordance rate ratio (the proportion of first-degree relatives of patients who are also affected by the disease, over the population prevalence) and heritability. As these analyses do not account for the possibility that close relatives might also have correlated environmental values, twin studies often compare monozygotic and dizygotic twins in order to control for this confounding. MacGregor *et al.*[10] estimated heritability from monozygotic and dizygotic twins jointly, accounting for shared environment, and estimated heritability for rheumatoid arthritis to be ~65%.