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Determinants of disease course in rheumatoid arthritis

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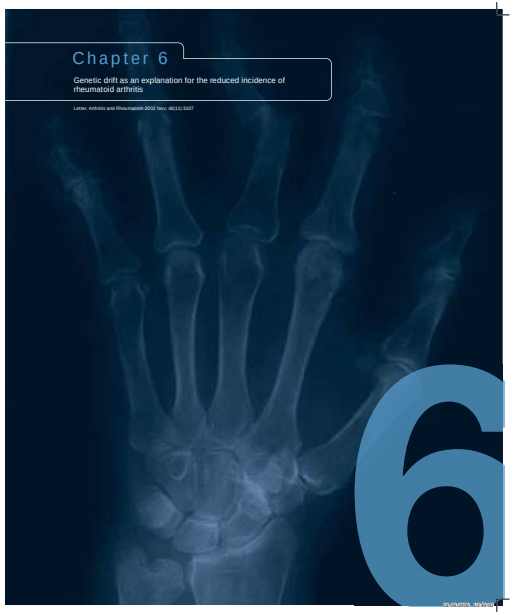
Chapter 6

Genetic drift as an explanation for the reduced incidence of rheumatoid arthritis

Letter, Arthritis and Rheumatism 2002 Nov; 46(11):3107



Genetic drift as an explanation for the reduced incidence of rheumatoid arthritisa

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To the Editor:

With great interest we read the unique report by Doran et al on the decreasing incidence of rheumatoid arthritis (RA)[1]. In the thoughtful accompanying editorial, Silman indicated that the most likely explanation for the world-wide trend of decline in incidence is a birth cohort effect [2]. Since this effect is apparent in various populations such as American whites, Pima Indians, Finnish, and Japanese patients, the explanation should be a factor that had an identical effect in all populations throughout the world in birth cohorts from 1880 to 1950. Such an effect could be either an environmental effect or an effect caused by a change in the population genome. We propose that this last explanation may be (partly) responsible for the decrease in incidence of RA.

In previous times, human reproductive success was very unevenly distributed, with a minority of fertile women who gave birth to the majority of newborns. For example, in the Australian census, 50% of the children were the offspring of 1 in 7 of the women[3]. However, in recent times this predominance steadily decreased since both fertile and less fertile women have contributed to the next generation.

Genetic factors partly control fertility. Recently, we identified one of those factors: a high innate interleukin 10 (IL-10) production is associated with high fertility[4]. Thus, before 1880, strong pressure within the genetic composition of the population was present that favours high IL-10 production. We previously demonstrated that IL-10 production is related to the composition of the IL-10 locus as defined by microsatellites; more specifically, the IL-10 R3 haplotype is associated with reduced IL-10 production[5]. Moreover, we demonstrated that IL-10 R3 protects against RA in different ethnic populations (Scottish [Glasgow, UK]: odds ratio [OR] 0.6, 95% confidence interval [95% CI] 0.39-0.92; British [Oxford, UK]: OR 0.58, 95% CI 0.38-0.87; African American [Atlanta, GA]: OR 0.38, 95% CI 0.18-0.84)[6]. The fact that the number of children per women has reduced in the birth cohorts from 1880-1940 must have had the consequence that more women with a genetic makeup for impaired fertility contributed to the offspring.

With respect to the IL-10 locus, this must have led to an increase of IL-10 R3 (which protects against RA) in the general population. This genetic drift may explain the lower incidence of RA in those born in the birth cohorts after 1880.

References

1 **Doran MF,** Pond GR, Crowson CS, O'Fallon WM, Gabriel SE. Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period. Arthritis Rheum 2002; 46:625-31.

2 **Silman AJ.** The changing face of rheumatoid arthritis: why the decline in incidence? Arthritis Rheum 2002; 46: 579-81.

3 **Cummins J.** Evolutionary forces behind human infertility [letter]. Nature 1999;397:557-8.

4 **Westendorp RG,** van Dunne FM, Kirkwood TB, Helmerhorst FM, Huizinga TW. Optimizing human fertility and survival [letter]. Nat Med 2001;7:873.

5 **Eskdale J,** Gallagher G, Verweij CL, Keijsers V, Westendorp RG, Huizinga TW. Interleukin 10 secretion in relation to human IL-10 locus haplotypes. Proc Natl Acad Sci USA 1998;95:9465-70.

6 **Eskedale J,** Mc Nicholl J, Wordsworth P, Jonas B, Huizinga T, Field M, et al. Interleukin-10 microsatellite polymorphisms and IL-10 locus alleles in rheumatoid arthritis susceptibility [letter]. Lancet 1998;352:1282-3.