In 1985, Strom et al described two families in which rheumatoid arthritis (RA) appeared in several members over three consecutive generations.1 Although these pedigrees taken alone could implicate dominant inheritance, the overall picture with RA pedigrees indicates a complex mode of inheritance, with incomplete penetrance of predisposing genes and probably several genes being involved in the diseases process. In addition, an interesting observation in both pedigrees described by Strom’s group and one which is difficult to understand in terms of classical Mendelian genetics is that the disease tended to start progressively earlier over the generations (60 to 81 years in the grandparents, 36 to 47 in the parents, and 12 to 28 in the probands). For both families, the clinical details of the individuals suggested that not only was the disease starting earlier, but it was also becoming more severe over the generations.1 Is there any possible explanation for this observation, and does this anecdote have any potential repercussions for our understanding of the genetics of the rheumatic diseases?

There are a number of monogenic diseases in which various aspects of increasing severity and earlier age of onset from generation to generation (an epidemiological observation known as ‘genetic anticipation’) are now well established. Examples of such disorders, for which unstable trinucleotide repeats close to or within the disease predisposing gene have been demonstrated include: fragile X syndrome,2 myotonic dystrophy,3 Huntington’s disease,4 spinobulbar muscular atrophy,5 and spinocerebellar atrophy type 16 (for general reviews see references 7–10). For one of these diseases, myotonic dystrophy (MD), there was considerable debate from the beginning of the 20th century whether genetic anticipation was a true phenomenon, or a bias of ascertainment (principally because families in which parents started with the disease early in life and offspring late in life are intuitively more difficult to find than those families in which the opposite applies).11 What managed to convince the anticipation sceptics of their misplaced cynicism was the description in 1992 of a molecular correlate for the epidemiological observation. It was found that at the 3’ non-coding region of the MD-predisposing gene (found by linkage studies to be a protein kinase gene on chromosome 19) there is a CTG trinucleotide repeat. This is present in all individuals, but the number of repeating CTG copies in normal populations is distributed in a Gaussian fashion between six and 30 copy numbers.7 This is transmitted stably from generation to generation. However, if an increase beyond 30 copy numbers takes place, this appears to produce an allele which acts in an unstable fashion in its transmission. If premutant marginally expanded alleles (not associated with disease phenotype) are transmitted in germline cells, they seem capable of undergoing large expansions in early zygotic cell divisions.12–14

Similarly, unstable trinucleotide repeats have been described in the other diseases listed above. There are many unanswered questions, both as to what defect in DNA replication leads to these expansions, and as to how the increases in copy numbers lead to disease phenotypes. However, in the diseases listed there is variable evidence of a direct correlation between the size of the expansion and the severity of the disease, and an inverse correlation with the age of onset.15 Molecular biology has provided an objective marker of the epidemiological observation of anticipation in these monogenic diseases.

The majority of common rheumatological diseases, such as RA, are not monogenic in their aetiology, with multigene families such as the two pedigrees described by Strom et al being the exception rather than the rule. Is there any evidence that genetic anticipation operates in genetically more complex diseases? Disorders in which the aetiology is multifactorial, and yet in familial cases there is good evidence for increasing severity and decreasing age of onset over the generations include bipolar affective disorder,16 schizophrenia,17 testicular germ cell tumours,18 and hypertrophic cardiomyopathy.19 In these diseases, the epidemiological evidence for genetic anticipation is already leading to searches for unstable genetic elements, such as expanded trinucleotide repeats, which might account for at least part of their genetic aetiology.

The table lists the features of RA (as well as many of the other complex musculoskeletal diseases) which are difficult to understand in terms of Mendelian genetics. These features could have a number of genetic and epidemiological explanations, but could also lend themselves to a model in which unstable genetic elements play a part.20–24 In diseases in which unstable trinucleotide repeats have been demonstrated, such as myotonic dystrophy and Huntington’s disease, the paternal age at which the affected individual is conceived has been shown to predict age of onset in the patient, with older fathers tending to have children with a younger age of onset of disease.25 This may reflect ongoing mitoses throughout the lifetime of the paternal germ cells, with increasing chances of unstable premutant alleles expanding over time. Ova do not undergo further mitoses after the birth of the female, so that it can be predicted that increased mitoses in male germ cells should give an increase in the mutation rate for fathers versus mothers. There are, however, examples of unstable alleles being maternally transmitted. The unstable trinucleotide repeat in fragile X syndrome appears to be restricted to maternal transmissions,26 and congenital myotonic dystrophy occurs only in the offspring of affected mothers, not of fathers.11 The mechanisms for maternal transmissions are currently elusive.

What are the repercussions of this developing area for the common, multifactorial musculoskeletal diseases? The epidemiological phenomenon of genetic anticipation can be better understood now that important breakthroughs have occurred in the molecular basis of this observation. Consequently, any evidence for anticipation in diseases such as RA may lead to a similar search for unstable genetic elements. In this issue of the Annals we present preliminary evidence in RA to suggest that anticipation may not be

Features of rheumatoid arthritis and other complex musculoskeletal diseases that are consistent with unstable genetic elements (references are for rheumatoid arthritis)

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restricted to the two families described by Strom et al., but may occur in most families in which consecutive generations are affected.24 We also suggest that within pedigrees in which mothers and offspring are affected by RA, the parental ages of conception may have predictive value in the proband age of RA onset. As has been argued exhaustively over this century with respect to myotonic dystrophy, these observations are prone to ascertainment bias and need to be confirmed in larger and more detailed studies. However, we feel that our first step in this direction has been sufficiently encouraging to warrant further epidemiological studies, as well as searches for unstable genetic elements in the DNA of families with evidence of vertical disease transmission. The epidemiology is equally applicable to other multifactorial musculoskeletal diseases, such as familial forms of osteoarthritis and the seronegative spondarthropathies.

Our understanding of the complexities of molecular biology is proceeding rapidly. A recent review drew the attention of rheumatologists to two newly recognised genetic mechanisms that may be relevant in musculoskeletal disease:27 genetic imprinting, in which the parental origin of an allele is critical in its expression, and X chromosome inactivation, with which differences in the proportion of parental X chromosomes inactivated in females may be influential in disease states. We would like to suggest that genetic anticipation also merits the attention of rheumatologists. Epidemiological phenomena in monogenic diseases eventually led to molecular correlates. A similar line of enquiry in musculoskeletal diseases may produce further understanding of their complex clinical and genetic features.

Department of Rheumatology
City Hospital,
Nottingham NG5 1PB,
United Kingdom

Department of Integrative Biology,
University of California at Berkeley,
Berkeley, CA 94720, USA

Correspondence to: Dr C M Deighton.

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C M Deighton and G Thomson

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