It has been known for some time that many rheumatic and autoimmune conditions are complex in nature, i.e. they have both environmental and multiple genetic aetiological components. The dissection of complex traits has previously been difficult as existing analytical approaches, designed for single-gene disorders, are largely inappropriate.

It is now possible to apply new techniques to unravel complex genetic conditions and define them at the DNA sequence level. This has largely resulted from the application of advances in molecular biology, information technology and the construction of detailed genetic linkage maps for the human genome. The rewards for success are potentially great and could include the identification of novel therapies, the ability to refine diagnosis and to target treatment more effectively, and the prediction and quantification of disease risk.

The new approach, often called Whole Genome Screening (WGS), examines the human genome for areas linked with disease susceptibility, starting at one end and finishing at the other. By using ~350 highly polymorphic markers, the genome can be divided into sections of around 10 cM. Each can be successively tested for linkage with disease, in nuclear families with at least two affected siblings. Under Mendelian inheritance, for any marker locus with multiple alleles, siblings are expected to share a given parental allele 50% of the time. A significant distortion towards greater sharing of alleles in affected siblings is indicative of genetic linkage with the disease. Large numbers of affected sibling pair (ASP) families are required to detect genes making a relatively weak contribution and this strategy has been dependent on the development of automated high-throughput genotyping [1]. It has already been highly successful in identifying regions of linkage in insulin-dependent diabetes (IDDM) [2, 3] and other conditions [4, 5]. Less enlightened critics have described such ‘exclusion mapping’ as being a ‘fishing expedition’, inferring that a level of serendipity is involved. In one respect, this is completely unfounded as the hypothesis driving this highly systematic approach is that multiple susceptibility genes exist within the genome for a given disease. However, in another respect, this is fishing for genes as, at present, no alternative strategy exists for identifying genes unless there is an a priori rationale for their implication in disease aetiology.

ASP-based approaches offer a number of advantages over traditional linkage analysis. Firstly, they are not based on fitting a genetic model; thus, not knowing the number of genes or mode of inheritance does not present a problem. Secondly, analysis is restricted to affected individuals; this means that only penetrant genes are being examined and any misassignment of unaffected family members who are carrying the disease allele can be ignored.

Rheumatology provides a rich area for those studying complex conditions and many arthritic diseases have a significant oligogenic contribution to susceptibility. Major ASP WGS analyses are under way to dissect the genetics of rheumatoid arthritis (RA), osteoarthritis, ankylosing spondylitis, juvenile chronic arthritis and systemic lupus erythematosus. Preliminary results have been reported for both the French and UK RA WGS studies [6, 7]. In both countries over 200 ASP families have been genotyped with markers at an average genomic spacing of 11 cM. Although analysis of the first 100 families in both studies gave some suggestions of linkage, with the exception of the HLA locus on chromosome 6, these were lost when data from the second 100 families were incorporated. Why should this be and what lessons can be learned?

At the 5% level of significance, approximately five false-positive linkage results would be expected for every 100 comparisons made. Thus, over 15 false positives would be predicted for the 300 or so markers used in a WGS. Analysis of a second data set of the same size will only rarely give the same false positive again and linkages can thus be critically re-evaluated. Absolute confirmation, however, requires a larger data set, the size of which depends on the number of hints of linkage detected and number of ASPs in the initial screen [8].

A further point that these studies demonstrate is the close relationship between the number of families analysed and the size of genetic effect which can be detected. Geneticists have found it useful to quantify the genetic component of disease susceptibility by calculating the coefficient of familial clustering (\(\lambda_s\)). This is calculated as a ratio of the disease risk for siblings of affected cases to the population prevalence. Estimates of \(\lambda_s\) for RA range from 5 to 10. As individual susceptibility loci are identified, their contribution can also be estimated and this can be expressed as a proportion of the total familial component. In RA, the \(\lambda\) for HLA is calculated as being 1.8 [9] and this suggests that HLA accounts for approximately one-third of the genetic susceptibility. It has been predicted that there are at least two loci in addition to HLA and it is, therefore, highly likely that the remaining RA susceptibility loci each contribute a small effect.

Added to this is the problem that complex arthritic conditions such as RA exhibit considerable clinical heterogeneity. This heterogeneity will undoubtedly
have an underlying genetic basis. Thus, a gene which contributes to a particular feature of RA will be more difficult to detect in the total set of ASP families than in siblings positive for the disease feature. The bottom line is that to detect the level of genetic effects predicted in RA, 500–1000 ASP families may be required for a WGS.

In their recent article on the future directions of complex disease genetics, Risch and Merikangas [10] considered the numbers of ASP required to detect loci with moderate effects. Based on their calculations, detection of a locus $\lambda = 1.2$ would require between 400 and 500 sib-pair families, depending on the frequency of the disease alleles. Risch and Merikangas suggest that the trend in complex genetics will begin to shift back towards candidate gene screening using the Transmission Disequilibrium Test (TDT) which detects linkage only in the presence of an association [11]. This approach has the advantage of requiring only single cases and their parents, which are considerably easier to collect than sibling pairs.

To take the analogy of fishing further, it is worth suggesting that candidate gene screening (using both linkage and association studies) represents a valid and parallel approach to trawling through the genome [12]. As our understanding of the biology of chronic inflammatory and autoimmune conditions increases, a large number of genes come to mind as being strong candidates and are perhaps worthy of targeting directly. By dangling a hook and line in the right place, the chances of success may increase considerably.

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REFERENCES

FOOT PROBLEMS IN RHEUMATOLOGY

The manifestations of rheumatic disease are frequently encountered in the foot. The magnitude and distribution of articular, periarticular and skin disturbances vary between the diseases. The destructive qualities of synovitis in rheumatoid arthritis (RA) with pain and gross deformity in the forefront are readily identifiable. Other typical related features include hallux rigidus associated with osteoarthritis, plantar calcanegal enthesopathies with seronegative arthropathies, the podagra of gout and the nail dystrophies of psoriasis, and keratoderma blennorrhagica of Reiter’s disease.

The epidemiology of rheumatic foot disease is not well addressed in the literature. Foot pain and disability in the population as a whole are not understood, although current work being undertaken by the ARC Epidemiology Research Unit (G. Macfarlane, personal communication) will address this important anomaly. Hospital-based surveys of RA admissions indicate that nearly one-third of patients recall painful feet as the presenting symptom of their disease [1]. In the same survey, between 50 and 86% of patients had clinical involvement at the time of study, 90% had complained of foot pain at some time during the course of their disease, and between 88 and 92% had radiological changes in their feet [1–3].

The weight-bearing loads of stance and gait place high physical and mechanical demands on the foot for activities of daily living. It is much more difficult to protect the foot in the same way as the hand, and joint-protection strategies such as bed rest and wheelchair usage can be counterproductive. Consequently, it is easy to understand why the foot becomes a chronic site of pain and a major source of functional limitation and disability. Yet in published
studies, the hand received greater attention by clinicians and researchers.

The goals of foot care are to relieve pain, maintain function, and improve quality of life utilizing safe and cost-effective treatments. The means by which to measure the achievement of these goals have been addressed by several workers. Budiman-Mak developed a valid and reliable Foot Function Index as a measure of the impact of foot pathology on function in terms of pain, disability and activity restriction [4]. This measure has been employed in clinical research in the USA, but this instrument is not in routine clinical use in the UK. Platto et al. [5] explored the relationship in RA patients between functional ambulation using the Sickness Impact Profile ambulation subscale; lower limb and foot pain using the Ritchie Articular Index; deformity measured using a novel observational structural index of both rearfoot and forefoot deformity and gait parameters. This work found that the presence of foot pain, particularly in the rearfoot, limits ambulation and alters normal gait variables. However, structural deformity of the foot seemed to have less impact on mobility and gait. Other potentially useful outcome measures of foot function are foot pressures measured either on a pressure platform or, more recently, inside the shoe using pressure insoles [6, 7]. The latter offers exciting potential as accurate in-shoe plantar pressures are valuable for determining foot function in the normal working environment alongside the potential to evaluate footwear and orthosis efficacy. Finally, advances in imaging techniques may also provide improved diagnostic accuracy for soft-tissue pathology.

Little is known about the relative clinical and cost-effectiveness of foot interventions in rheumatology, including cornerstone practices such as the removal of skin callusities, the use of foot orthoses and prescribed footwear, and forefoot reconstructive surgery. Indeed, previous research, mainly from uncontrolled studies, has largely reported negative findings [6, 8–10]. These are now being acted upon as more robust studies are developed and funded. The Arthritis and Rheumatism Research Council database of research identified three foot-related randomized controlled trials in progress (N. Sandford, personal communication). The projects, two of which are lead by podiatrists, encompass an investigation of the efficacy of corticosteroid injections for plantar heel pain, foot orthoses in RA and forefoot arthroplasty in RA. Clearly, more work is required in this area.

We would argue that chiropody, or podiatry as is the preferred term within the state registered profession, can offer a valuable service to rheumatology patients. In the UK population, it has been estimated that 50% of people over 65 would benefit from podiatry treatment, whereas only 10–20% currently receive such care [11]. There is no published literature determining the podiatric needs of rheumatology patients. It is our impression that many rheumatologists are poor at making referrals to podiatrists and purchasing footcare, and that podiatrists are bad at marketing themselves. Despite being a small profession, podiatry has not failed to capitalize on the development of extended roles and there is little reason why these cannot be exploited in rheumatology, as advocated by Dickson [12]. Several podiatry units have developed a comprehensive foot service following Department of Health guidelines which recognized arthrosis of the foot as a priority area [13]. A comprehensive service delivered across hospital and community settings can include basic footcare and hygiene delivered by podiatry assistants, specialist footcare including education, provision of footwear and orthoses, management of foot ulceration, etc., and foot surgery undertaken by appropriately qualified podiatrists. The latter is not yet widely available and remains the most controversial of developments. Until appropriate legislation has been agreed, expansion will very much depend on local circumstances (often influenced by local orthopaedic surgeons and their interpretation of Royal College of Surgeons guidelines). Nonetheless, early evidence has revealed that integrated podiatry/orthopaedic clinics and foot surgery undertaken by podiatrists can produce comparable outcomes to orthopaedic surgery alone, whilst reducing waiting list times and the need for further foot care [14–16].

Perhaps more importantly, the general need for podiatry in rheumatology should be determined. An appropriate model to follow may be that of the British Diabetic Association who, in collaboration with the Society of Chiropodists and Podiatrists, undertook a comprehensive review of podiatry provision in diabetes in 1987 [17]. The final report has made valuable recommendations and has been used as a catalyst to improve provision throughout the UK. Combined podiatry/appliance/rheumatology clinics to which patients with specific foot problems can be referred may eventually prevent the need for radical foot surgery which is so often the route taken for painful feet in RA.

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