GENETIC MAPPING IN THE CONNECTIVE TISSUE DISORDERS

The use of modern methods of molecular genetic analysis has greatly facilitated the investigation of disorders with a genetic component. The past few years have witnessed a deluge of publications detailing the fine chromosomal mapping and characterization of the mutant loci in many common monogenic diseases. The unravelling of the genes and mutations responsible for Duchenne/Becker muscular dystrophy [1] and cystic fibrosis [2] provide particularly dramatic examples of the ultimate power of these techniques. However, the insights that have also been gained into many of the heritable connective tissue disorders are also noteworthy. Mutations at the type I collagen loci (COL1A1 and COL1A2) are invariably responsible for the dominantly inherited variants of osteogenesis imperfecta (OI) and mutations in type III collagen (encoded at the COL3A1 locus) cause type IV Ehlers-Danlos syndrome, characterized by a tendency to rupture of the blood vessels and other hollow internal viscera [3, 4]. In a proportion of cases of hereditary progressive arthro-ophthalmopathy (Stickler's syndrome) and some forms of chondrodysplasia but not others the disease co-segregates with alleles at the type II (cartilage) collagen locus, COL2A1 [5–8].

In applying genetic mapping techniques to any condition a critical assessment of the phenotype is absolutely essential. This applies equally whether one is testing candidate loci, such as collagens, or conducting a systematic search through the genome for linkage markers in conditions where there are no prior clues to the identity or chromosomal localization of the mutant locus. The difficulties which may arise from variable expression of the phenotype are well exemplified by type I OI. Within one family there may be individuals crippled by multiple fractures whose growth is severely stunted as well as others suffering only accelerated postmenopausal osteoporosis. Failure to assign the correct phenotype to even one individual within such a family could generate the appearance of discordant segregation of the disease and the mutant locus. The risk of such spurious results can be minimized by excluding any individuals in whom there is the slightest doubt about the phenotype from further analysis. In OI the presence of extra-articular features or the use of radiographs to detect subclinical osteoporosis may be of considerable help. However, in other conditions the full range of the phenotype may be incompletely characterized and there may be a lack of supplementary investigations available to clarify the situation in borderline cases. In addition, some individuals might possess the mutant gene without expressing any demonstrable phenotypic effects.

In this edition of the journal, Dr Henney [9] and his co-workers have faced up to just such a problem in investigating the joint hypermobility syndrome (JHS). Joint hypermobility not infrequently accompanies a wide range of heritable disorders, including the Marfan syndrome and numerous osteochondrodysplasias as well as the Ehlers–Danlos syndromes (EDS). The underlying causes probably differ between these conditions, reflecting the contribution to joint mobility from such disparate factors as the shape and size of the articular surfaces and the strength of the para-articular structures. The protean manifestations of JHS, as outlined by Henney et al., suggest that a deficiency of the extracellular connective tissue matrix may be involved. They also suggest that the condition may be diagnosed in the absence of joint features if the subject has sufficient extra-articular features and an unequivocally involved first-degree relative. However, the lack of rigorously tested diagnostic criteria represents a real obstacle to the accurate application of genetic segregation analysis. In consequence, only relatively guarded conclusions can be drawn from these studies. Even in disorders such as type II EDS that are relatively well defined clinically there is clearly a difference in the pathology at a molecular level since some cases are caused by mutations in type I collagen genes and others are not [reviewed in 10]. For further progress to be made in this rather ill-defined syndrome it will be necessary to develop more stringent diagnostic criteria to enable the study of less heterogeneous disease populations. This is one of the aims of the ‘special interest’ group which convened recently [11].

In the analysis of conditions such as JHS there are two major approaches to mapping the responsible genes. It is possible to use a series of polymorphic DNA markers to produce a saturation map of the genome but this is relatively time consuming and expensive. Where there are clues to the identity of potential candidate genes it is likely to be more productive to concentrate on these. Both these approaches have been recently applied to the search for the gene responsible for the Marfan syndrome, now known to be the fibrillin gene on chromosome 15 [12]. Important lessons can be learnt from these studies which may have implications for the study of other connective tissue disorders, including JHS. The discovery that the Marfan syndrome was caused by mutations in the fibrillin gene ultimately depended on three separate lines of research. First, the mutant locus was mapped to the short arm of chromosome 15 using classical genetic linkage analysis [13]; second, fibrillin defects were observed in the vast majority of patients with the Marfan syndrome using immunohistological techniques [14]; third, one of the major fibrillin genes was localized to the same region of chromosome 15 as the Marfan locus and causal mutations within this gene were demonstrable in the Marfan syndrome [15]. During the process of localizing the Marfan locus to chromosome 15, one approach was to test candidate loci, such as the collagen genes, as the mutant loci [16]. This approach has the advantage of providing a relatively quick answer to a specific question although there may be some difficulties. For instance, type I collagen is a heterotrimer of two α1 [1] chains and one α1 [1] chain, muta-
tions in any of which could produce disease. Consequently, it is essential to exclude both type I collagen loci in a given family before one can with confidence exclude mutations in type I collagen from causing the disease, a lesson clearly demonstrated from the study of osteogenesis imperfecta [3]. This type of argument could equally well apply to other complex macromolecular components of the extracellular matrix. The so-called exclusion maps of the genome used to help locate the mutant locus on chromosome 15 in the Marfan syndrome did not take account of this possibility [17]. It was fortunate therefore that there was no significant heterogeneity in the condition at the molecular level [18] although the closely related syndrome of congenital contractual arachnodactyly is actually linked to another fibrillin gene on chromosome 5 [19]. It seems quite unlikely that a similar lack of heterogeneity will exist in conditions like JHS, so that the possibilities for exclusion mapping must be rather limited.

With the current state of knowledge the most likely means of progress in JHS would appear to lie with the demonstration of specific defects in individual affected patients, analogous to the demonstration of fibrillin defects in the Marfan syndrome. With this in mind the previous demonstration of alterations in the ratios of type III collagen: types I + III collagen remains probably the most interesting biochemical observation to date in this condition. Further segregation analysis of the fibrillar collagen gene loci in this disorder might therefore be rewarding but only after the application of the strictest diagnostic criteria in a much larger number of families than those characterized to date.

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REFERENCES