Annotation

Marfan syndrome: a mystery solved

Marfan syndrome is a serious connective tissue disorder inherited as an autosomal dominant trait. The systemic nature of the disorder is manifested with symptoms of the eye (ectopia lentis), aorta (dilatation, aneurysm, and aortic regurgitation), and skeleton (dolichostenomelia, upper segment/lower segment ratio 2 SD below mean for age, pectus deformity, and kyphoscoliosis). The condition is characterised by significant intrafamilial variability of clinical expression and also by consistent phenotypic differences between various families.¹

Marfan syndrome imparts significant morbidity to subjects affected by it and, if untreated, it reduces significantly life expectancy.² The diagnosis of Marfan syndrome is a clinical one. Approximately 15% of affected subjects have a negative family history, as they probably represent new mutations.¹

The fundamental defect in Marfan syndrome was recently elucidated with the parallel application of positional and functional mapping.³⁻⁷ Marfan syndrome is caused by mutations of the fibrillin gene on chromosome 15.⁷ Over the years different molecules of the extracellular matrix of the connective tissue, such as collagen, elastin, decorin, hyaluronic acid, and others, have been proposed as candidates in the aetiology of Marfan syndrome.⁸

Positional mapping was undertaken by several investigators. A number of three generation families were genotyped for various markers in an effort to map the Marfan syndrome locus. An exclusion map was generated by pooling the data of a consortium of investigators, which excluded approximately 75% of the genome.⁹ The Marfan syndrome locus was mapped to 15q15→q21 by Kainulainen *et al*³ and its location was subsequently confirmed.^{4,5} A 10 point map of the region flanking the Marfan syndrome/fibrillin locus has been generated by Sarfarazi *et al*.¹⁰ The map appears in this issue of the Journal.

Low¹¹ in 1961 reported the existence of two groups of microfibrils in the extracellular matrix of the connective tissue. Among the morphological characteristics noted in one of the two groups of microfibrils were an average diameter of 10 nm, a cross section that sometimes appeared to have a hollow centre, a beaded appearance, and a proximity to basement membranes frequently in association with elastic fibres. Hence, these structures were designated elastin associated microfibrils. A 350 kd glycoprotein called fibrillin and at least three smaller proteins have been identified as the structural constituents of the elastin associated microfibrils.^{12,13} A variety of antibodies, both monoclonal and polyclonal, have

been raised against several of the microfibrillar proteins.^{12,14} The tissue distribution of the elastin associated microfibrils is wide, including the ciliary zonule, aortic media, periosteum, perichondrium, mesangial region of renal glomerulus, etc.¹⁵ Two monoclonal antibodies recognising different epitopes within the fibrillin molecule proved to be extremely useful in the study of Marfan syndrome.¹⁴

Indirect immunofluorescence studies of skin and cultured skin fibroblasts from patients with Marfan syndrome showed a deficiency of the elastin associated microfibrils by using the previously mentioned fibrillin monoclonal antibodies.^{16,17} This abnormality bred true in multiplex families.^{16,17} The previous findings were in general agreement with the observations by Milewicz *et al*¹⁸ that cultured skin fibroblasts from patients with Marfan syndrome showed any one of the following abnormalities in the metabolism of fibrillin: (1) abnormal secretion, (2) decreased synthesis, (3) abnormal extracellular assembly, (4) and no observed abnormality. The results of the immunohistochemical and biochemical studies taken together strongly suggested that fibrillin is aetiologically related to Marfan syndrome.

The cloning, characterisation, and chromosome mapping of the fibrillin gene was accomplished by two groups of investigators.^{6,19} Interestingly enough, the fibrillin gene maps in the same region as Marfan syndrome, 15q15→q21.⁶ Genetic linkage studies in multiplex families with Marfan syndrome using fibrillin gene specific markers clearly showed genetic linkage to the fibrillin locus.^{6,7,20} Genetic analysis strongly indicated the absence of locus heterogeneity in Marfan syndrome.²⁰ However, Boileau *et al*²¹ reported a family in which the phenotype segregated discordantly with the fibrillin gene and eight other chromosome 15 markers. A G to C transversion at nucleotide 716 in one fibrillin allele resulting in a substitution of proline (P) for arginine (R) at codon 239 (R239P) was found in two unrelated subjects affected with the condition.⁷ This observation contributed definite evidence that Marfan syndrome is caused by mutations in the fibrillin gene.

In the process of cloning the fibrillin gene on chromosome 15, two other closely related genes located on chromosomes 5⁶ and 17 (F Ramirez, personal communication) were identified. The fibrillin gene on chromosome 5 transcribes a message of approximately 10 kb in size. A disorder phenotypically related to Marfan syndrome, congenital contractural arachnodactyly, was found to be genetically linked to the fibrillin gene located on chromosome 5.⁶

More work remains to be done. The development of a reliable diagnostic test remains high on the priority list. This will permit the establishment or exclusion of diagnosis of Marfan syndrome in clinically equivocal cases. Genetic linkage studies with fibrillin gene specific markers can at present be used for genotypic diagnosis, both prenatally and postnatally, in informative families. It remains to be seen whether a small or large number of fibrillin gene mutations will be identified in association with Marfan syndrome. An international collaborative effort is under way with the objective of establishing a clinical/genotypic correlation in Marfan syndrome if it exists. The latter will lead to the design of rational therapeutic modalities. Finally, the development of a mouse or rat recombinant animal model will be a prerequisite to effective gene therapy.

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