*Conference report*

# A workshop on Marfan syndrome, 10 June 1989, Farmington, CT, USA

Marfan syndrome is a serious dominantly inherited connective tissue disorder with skeletal, cardiovascular, and ocular manifestations. Typically, diagnosis is made during childhood, but not infrequently the disorder is diagnosed during adolescence or even early adulthood. The fundamental defect has eluded definition despite 30 years of research efforts. Successful mapping of the Marfan syndrome gene would facilitate the provision of accurate genetic counselling to persons at risk, help to resolve questions of genetic heterogeneity, enable prenatal diagnosis to be performed, and, in characterisation of the genetic defect, promote future research into rational therapies.

This workshop was convened in order to pool linkage data for the delineation of a current exclusion map, to organise future collaboration which will reduce unnecessary duplication, and to examine genetic heterogeneity and variability of clinical expression, answers to which are required for meaningful interpretation of linkage data. The 15 participants included the three groups who contributed linkage data: Tsipouras/Sarfarazi/Blanton/Schwartz (Farmington), Farndon/Child/Pope/de Groote (Birmingham and London), and Eiberg (Copenhagen). Data were also contributed by Peltonen (Helsinki), Boileau/Junien (Paris), and Francomano (Baltimore).

## Clinical aspects

In its classical form, Marfan syndrome is associated with abnormalities of the eye (ectopia lentis), aorta (dilatation and aneurysm of the ascending aorta and aortic regurgitation), and skeleton (dolichostenomelia, upper segment/lower segment ratio 2 SD below mean for age, pectus deformity, and kyphoscoliosis). These manifestations represent major diagnostic criteria. In addition, other diagnostic signs are frequently observed in affected subjects, which can be defined as minor or auxillary criteria: myopia, mitral valve prolapse, arachnodactyly, mild joint laxity, tall stature, pes planus, striae distensae, pneumothorax, and dural ectasia. It was generally agreed that a person suspected of being affected with Marfan syndrome should exhibit at least one manifestation from the major diagnostic criteria in two of the three systems involved, skeletal, cardiovascular, and ocular, in addition to an assortment of auxillary signs. Clinical manifestations when coupled with a positive family history should permit the diagnosis to be made or rejected in over 90% of cases. There is still a significant fraction, 10% of cases, in which no definitive diagnosis can be made. The previous figures have been reported by Pyeritz and McKusick,[1] but the workshop felt they represented actual figures encountered in their practice.

## Gene mapping

Genetic linkage studies in families with Marfan syndrome should take into consideration the variability of clinical expression between various members of a family and also the clinical heterogeneity as expressed by phenotypic differences between various families. The workshop felt that the first problem can be adequately addressed by a careful clinical examination, including slit lamp ophthalmoscopy and echocardiography of as many persons suspected of being affected in a family as possible. This cross sectional clinical data collection contributes to the delineation of a composite phenotype for an individual family and could therefore be used as the measure to define the extent of the phenotypic expression of a Marfan syndrome mutation. This approach also provides information regarding the age of onset of the various manifestations, primarily of the aortic root dilatation, and addresses the still unresolved question of reduced penetrance in Marfan syndrome. Another valuable approach is the nosological documentation in a longitudinal fashion, which facilitates knowledge of the natural history of the condition and defines its clinical heterogeneity. Reports of families with Marfan syndrome lacking manifestations from either the cardiovascular or the ocular systems abound. Indeed two of the families studied by two different groups (Tsipouras, Farmington, and Child, London) lacked aortic manifestations in all affected subjects studied, yet they presented with typical skeletal and cardiovascular manifestations. The workshop felt that evaluation of affected subjects by the same experienced

observer is critical for accurate diagnosis and delineation of the natural history.

Marfan syndrome has, over the years, been considered as the prototypic heritable disorder of connective tissue and a prime example of gene pleiotropy. Partly because of historical reasons, research interest from the very beginning concentrated on collagens as the cause of this syndrome. With one notable exception, various types of fibrillar and non-fibrillar collagens have been excluded as candidate molecules. The list includes COL1A1, COL1A2, COL2A1, COL3A1, COL5A2, and COL6A3. Fibrillin, a glycoprotein of the elastin associated microfibrillar system, has also been suggested as a candidate molecule. The evidence consists of decreased indirect immunofluorescence in the skin and cultured fibroblasts in the majority of patients after the use of monoclonal antifibrillin antibodies. Cutis laxa, homocystinuria, and Ehlers-Danlos syndrome also give similar results. It appears that reduced fluorescence is a non-specific phenomenon.

The workshop felt that, in addition to the accurate designation of a person as affected or not, all subjects in the screening panel of families must be tested for identity with DNA hypervariable probes. Combination of all linkage results compiled on 25 families did not identify a locus for which the pooled data or a lod score from a single family reached 3.0, accepted as the minimum score required for the recognition of linkage. The EXCLUDE program showed that a substantial proportion of the genome had been excluded as a probable location for Marfan syndrome (Blanton, Sarfarazi, Farmington). Regions lacking data included 5p, 6q, 8, 9p, 10p, 12p, 13, 15, 17p, 18, 20p, 21, and 22. Maximum efficiency in the use of further DNA probes will be achieved by continued collaboration. The workshop agreed to relay all new linkage results to one centre (Sarfarazi, Farmington) for compilation of an updated exclusion map for distribution to participants every three months.

As possible clues to gene location, reports were invited of cases of Marfan syndrome associated with chromosomal anomalies or other genetic conditions. Child (London) reported on a patient with a 6q;15q reciprocal translocation that needs to be pursued further with prometaphase karyotype banding. Reports of two, possibly three, known cases of subjects with Marfan syndrome and neurofibromatosis were also mentioned. These subjects need to be carefully examined and karyotyped. An attempt will be made for any new families ascertained to be typed for serum/plasma proteins and cell surface antigens in the laboratory of Hans Eiberg (Copenhagen).

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1 Pyeritz RE, McKusick VA. The Marfan syndrome: diagnosis and management. *N Engl J Med* 1979;**300**:772–7.