

**THE MARFAN SYNDROME AND RELATED  
PHENOTYPES**



Delineation of various phenotypes and analysis of the fibrillin gene (FBN1) for putative mutations

BY .

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*A thesis submitted for the Degree of Doctor of Medicine*

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## ABSTRACT

### THE MARFAN SYNDROME AND RELATED PHENOTYPES

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Marfan syndrome is an autosomal dominant connective tissue disorder involving multiple organ systems which, if untreated, shortens life expectancy mainly because of cardiovascular complications. It has an incidence of at least 1 in 5,000 live births. The phenotype represents a continuum, one end of which merges with the normal population. The disease is caused by mutations in the FBN1 gene, which encodes the fibrillin-1 protein. Fibrillin, a component of extracellular matrix microfibrils, has a highly repetitive structure including forty-seven EGF-like motifs, seven cysteine-rich TGF- $\beta$ 1 BP motifs and two hybrid motifs.

The clinical and molecular study of patients with unequivocal Marfan syndrome, or an undiagnosed connective tissue disorder that has some features in common with Marfan syndrome, forms the basis of this thesis. The clinical features of these forty-eight patients are described. The phenotype of six Marfan patients in whom a FBN1 mutation was determined, patients with Shprintzen-Goldberg syndrome or Furlong syndrome (two Marfanoid-craniosynostosis disorders), and two children with congenital aneurysms of the great vessels, are presented.

The molecular screening of 44% of the FBN1 gene coding sequence for putative mutations is detailed. Five novel heterozygous single base pair changes in the FBN1 gene were identified in five separate Marfan syndrome families. These were G2113A, G2132A, T3163G, G3458A and A7868C. These result in the amino acid substitutions A705T, C711Y, C1055G, C1152Y and H2629P, respectively. Three of the characterised mutations, C711Y, C1152Y and C1055G result in replacement of cysteine by another amino acid; the latter two occur within EGF-like motifs in exon 27 and 25, respectively. The A705T mutation occurs at exon 16 adjacent to the GT splice site. The H2629P mutation occurs immediately adjacent to one of the conserved cysteines in the second-to-last EGF-like domain. The A705T and C711Y mutations at exon 16 and 17, respectively, are the first documented in the second TGF- $\beta$ 1 BP-like motif. Polymorphisms, believed to be normal variants, were identified in exons 15 and 28 of FBN1 in nine patients.

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