Variability of aortic stiffness is not associated with the fibrillin 1 genotype in patients with Marfan's syndrome

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SCIENTIFIC LETTER

Variability of aortic stiffness is not associated with the fibrillin 1 genotype in patients with Marfan's syndrome

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Marfan's syndrome (MFS) is an autosomal dominant connective tissue disorder, with clinical manifestations in the skeletal, ocular, and cardiovascular organ systems, caused by mutations in the fibrillin 1 gene (*FBN1*). MFS shows full penetrance but with considerable clinical variability both between and within families. More than 500 different mutations have been identified so far, scattered throughout the gene and usually unique to individual families.

Prognosis in MFS is mainly determined by progressive dilatation of the aorta, potentially leading to aortic dissection and death at young age. Recently, we have shown that increased aortic stiffness is an independent predictor of progressive aortic dilatation.[1]

It has been suggested that genetic variation in *FBN1* as assessed by analysis of an intragenic polymorphism (variable number tandem repeat (VNTR) polymorphism in intron 28) is an important factor contributing to risk associated with pulse pressure and aortic stiffness in healthy middle aged men and in patients with coronary artery disease.[2 3] In patients with MFS the association between aortic stiffness and the *FBN1* genotype or *FBN1* mutations has not been investigated previously.

Our purpose was to investigate the association between aortic stiffness parameters and the FBN1 genotype in patients with MFS. The genotype was characterised by the mutation on the one hand and by a specific intragenic FBN1 polymorphism on the other.

PATIENTS AND METHODS

A cohort of 67 patients with MFS (31 men, mean (SD) age 32 (10) years) representing 51 families with an identified *FBN1* mutation underwent cardiac magnetic resonance imaging in the Academic Medical Centre (Amsterdam, the Netherlands) (41 patients) and the Ghent University Hospital (Belgium) (26 patients). MFS had been diagnosed according to the Ghent criteria. Eighteen patients (27%) had previously undergone an elective aortic root replacement. Fifty eight patients (83.6%) were taking β blockers. Twelve families were represented with two patients and one family with five patients.

The *FBN1* gene was molecularly analysed by established techniques.[4] The VNTR polymorphism (TAAAA in intron 28 of *FBN1*) was analysed by previously described techniques.[2]

Magnetic resonance images were acquired with a 1.5 T system (Magnetom Vision; Siemens Medical Systems, Erlangen, Germany). Aortic distensibility and pulse wave velocity were assessed as previously described.[5]

Data are given as mean (SD). Comparisons were performed by χ^2 test for categorical variables and analysis of variance for continuous variables. Data were statistically analysed with the SPSS statistical package (SPSS Inc, Chicago, Illinois, USA). The level of significance was set at $p < 0.05$.

RESULTS

In this group of 67 patients, 51 different mutations were present. Thirty five patients (51%) had either a missense or in-frame deletion mutation (group 1). Twenty nine patients (45%) had a mutation leading to a premature termination codon (group 2). Eighteen of the 29 (64%) missense mutations were cysteine substitutions ($group1_{sub}$).

The VNTR polymorphism was identified in 59 patients. In total, three alleles were identified as 2, 3, and 4 according to the number of TAAAA repeats. These corresponded to four genotypes, with 2–2, 2–3, and 2–4 accounting for 97% of the population. The major genotypes were used for further analysis.

The 2–2 genotype was present in 54% of patients, 2–3 in 27%, and 2–4 in 15%. When compared with a control sample of 37 healthy subjects from the same locality, this distribution was very similar.

Baseline characteristics according to mutation types or to VNTR polymorphisms did not differ with regard to age, sex, previous Bentall procedure, or β blocker use. Patients with a nonsense mutation had a slightly higher body surface area.

We found no significant differences between the groups of mutations in any of the aortic stiffness parameters (table 1).

In a subanalysis comparing cysteine substitutions versus premature termination codon mutations, no significant differences were observed. Aortic stiffness within the 10 families with two affected and in one family with five affected varied greatly. No differences in aortic stiffness parameters were observed between the genotypes identified by the VNTR polymorphism.

This study found no association between the *FBN1* genotype and aortic stiffness parameters in patients with MFS.

The functional consequences of the different *FBN1* mutation types are difficult to assess, mainly because the precise function of fibrillin 1 is not completely understood. Fibrillin 1 is one of the major constituents of the 10–12 nm microfibrils composing the extracellular matrix. Microfibrils are extensible themselves and may contribute to the mechanical properties of mature elastic tissues by means of load redistribution between individual elastic fibres.

From recent observations, it is becoming clear that fibrillin 1 is not merely a structural protein. Fibrillin 1 subserves an important functional role in the complex transforming growth factor β signalling pathway. At least part of the clinical spectrum of the disease, such as mitral valve prolapse, is related to transforming growth factor β induced mechanisms. The precise link between the aortic manifestations and this signalling pathway has not been elucidated yet, but the effect of the *FBN1* mutations will at least partly be explained through these complex mechanisms.

Several attempts have been made to identify possible genotype–phenotype correlations in MFS, but none has been convincing so far.

Table 1 Aortic stiffness parameters in both mutation groups, in the subgroup of cysteine mutations (groups 1_{sub}), and in each polymorphism group

Variable	Mutation group			VNTR polymorphism		
	Group 1 (n = 35)	Group 1_{sub} (n = 18)	Group 2 (n = 29)	2–2 (n = 32)	2–3 (n = 16)	2–1 (n = 9)
Pulse wave velocity (m/s)	5.3 (1.7)	5.7 (1.9)	5.4 (1.2)	5.0 (1.0)	5.8 (2.2)	5.4 (1.1)
Distensibility (10^{-3}/mm Hg)						
Ascending aorta*	3.8 (1.8)	3.3 (2.1)	3.4 (2.3)	3.9 (2.5)	5.6 (2.6)	3.9 (2.2)
Descending thoracic aorta	3.7 (2.0)	3.3 (1.8)	3.2 (1.7)	3.6 (2.6)	3.6 (2.2)	4.5 (2.6)
Abdominal aorta	4.0 (2.2)	3.6 (2.4)	3.0 (1.6)	3.3 (1.9)	3.9 (2.2)	5.5 (5.8)

Data are mean (SD).
*Measured in patients without aortic root replacement.
VNTR, variable number tandem repeat.

Another observation reinforcing the lack of evidence for genotype–phenotype correlations is the high degree of intrafamilial variability with respect to onset of disease, organ system involvement, and severity. This intrafamilial variability is also seen for aortic stiffness in patients with MFS, as shown in the present study. It seems likely that aortic stiffness resembles the extreme clinical variability in patients with MFS.

In two recent studies an association between an *FBN1* polymorphism and different parameters of aortic stiffness in normal subjects and in patients with coronary artery disease has been suggested.[2 3]

We assessed the influence of this polymorphism in our patient group, thus also taking the effect of the normal allele into account. We found no association between any of the assessed aortic stiffness parameters and the different polymorphisms. In patients with an *FBN1* mutation further explanations for the variation in aortic stiffness should be sought outside the *FBN1* gene (such as genetic modifying gene loci or environmental factors).

We showed that, similar to other genotype–phenotype associations, correlations between *FBN1* genotype and aortic stiffness are very poor in patients with MFS. This reflects the high variability of disease severity in these patients. This variability cannot be accounted for by an effect of the normal allele, as shown by the lack of an association between aortic stiffness parameters and a VNTR polymorphism. Other modifiers of phenotypic expression must be implicated, which is the subject for further studies.

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The study was approved by the local ethics committees (University Hospital Ghent, Belgium and Academic Medical Centre Amsterdam, the Netherlands) and individual oral and written informed consent was obtained from each patient.

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