Clinical Characteristics of a Familial Inherited Myxomatous Valvular Dystrophy Mapped to Xq28
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OBJECTIVES
The purpose of this study was to describe the phenotypic characteristics of an inherited myxomatous valvular dystrophy mapped to Xq28.

BACKGROUND
Myxomatous valve dystrophies are a frequent cause of valvular diseases, the most common being idiopathic mitral valve prolapse. They form a group of heterogeneous diseases difficult to subclassify. The first mapping of the gene for a myxoid valvular dystrophy to Xq28 allowed investigation of the phenotype of affected members in a large family and characterization of the disease.

METHODS
Among the 318 members in the pedigree, 89 agreed to participate in this study. Phenotypic characteristics were investigated using clinical examination, transthoracic echocardiography and biological analysis (F.VIII activity). Genetic status was based on haplotype analysis.

RESULTS
Among 46 males, 9 were hemizygous to the mutant allele and had an obvious mitral and/or aortic myxomatous valve defect, and 4 had undergone valvular surgery. All had typical mitral valve prolapse associated in six cases with moderate to severe aortic regurgitation. The valve defect cosegregated with mild hemophilia A (F.VIII activity = 0.32 ± 0.05). The 37 remaining males had normal valves and normal F.VIII activity. Heterozygous women were identified on the basis of their haplotypes. Among the 17 women heterozygous to the mutant allele, moderate mitral regurgitation was present in 8, associated with mild mitral valve prolapse in 1 and aortic regurgitation in 3, whereas 2 women had isolated mild aortic regurgitant murmur. In heterozygotes, the penetrance value was 0.60 but increased with age.

CONCLUSION
X-linked myxomatous valvular disease is characterized by mitral valve dystrophy frequently associated with degeneration of the aortic valves affecting males and, to a lower severity, females. The first localization of a gene for myxomatous valvular diseases is the first step for the subclassification of these diseases. (J Am Coll Cardiol 2000;35:1890–7) © 2000 by the American College of Cardiology
mentation of collagenous bundles within the valve fibrosa and accumulation of proteoglycan.

Because of the presence of valvular anomalies in type IV Ehlers-Danlos syndrome, it has been suggested that genes coding for collagen isoforms could be implicated in non-syndromic valvular diseases. However, genetic studies have failed to find a link between collagen genes and familial mitral valve prolapse (11,12). We recently identified a large French family with myxoid valvular dystrophy. Its cosegregation with mild hemophilia A enabled us to map the disease gene on Xq28 and characterize the genetic status of each patient (13).

The purpose of this study is to describe the clinical characteristics of inherited X-linked valvular dystrophy. It shows that heterozygous women, in addition to obviously affected hemizygous men, can be mildly affected by the disease. The fact that penetrance is complete in men and incomplete in heterozygous women (for whom it increases with age) provides new insight into the clinical characteristics of myxomatous valvular diseases and should improve genetic analysis of inherited valvular diseases in general.

METHODS

In our familial study, the proband was a 16-year-old boy with severe aortic regurgitation as a result of valvular dystrophy. During his hospitalization for clinical evaluation before valvular surgery, mild asymptomatic hemophilia A was detected. Subsequent inquiry revealed that a cousin had mitral valve regurgitation due to valvular dystrophy and led to the identification of a very large five-generation family.

The study was conducted according to French guidelines for genetic research. Informed written consent was obtained from each family member. Baseline measurement included a review of medical history, a physical examination with particular attention to the cardiovascular system and any connective tissues diseases, a 12-lead electrocardiogram, a two-dimensional echocardiography with color-coded Doppler analysis, blood samples for genetic studies and quantification of antihemophilic factor VIII. Ophthalmologic examination, blood samples for genetic studies and quantification of antihemophilic factor VIII. Ophthalmologic examination was performed in two affected members and was normal.

Echocardiography. The phenotypic assignment of family members was based on echocardiographic examination.

Transthoracic M-mode and two-dimensional echocardiograms were recorded according to the criteria of the American Society of Echocardiography (14) using a Sonos 2000 (Hewlett-Packard Inc., Andover, Massachusetts) with a 3.5-MHz probe, or a Sequoia C256 (Acuson Inc., Mountain View, California) equipped with a multifrequency probe (3.5 to 2.0 MHz). Examinations were recorded on SVHS videotapes for further analysis. All recordings were analyzed in a blinded manner by two experienced physicians. Measurements of mitral valves were performed on parasternal long-axis two-dimensional images (15). The length of each leaflet was determined just before valve closure. The thickness of the free edge of the mitral leaflets was measured on a selected diastolic frame that clearly separated the mitral leaflets and chordae. Valves were considered dystrophic when the thickness was superior to 4 mm. Mitral annular diameter was calculated by measuring the length of the line between the anterior and the posterior leaflet hinge points at end-diastole, just before the onset of the QRS complex, and at end-systole, before valve opening. Mitral valve prolapse was considered to exist when two-dimensional recordings in the parasternal long-axis view showed protrusion of mitral leaflets into the left atrium, crossing the line between the annular hinge points, and when the coaptation point of the leaflets remained at or above the mitral annular plane during systole (16). Mitral regurgitation was estimated quantitatively by transthoracic color Doppler flow mapping in three spatial planes. Doppler color gain was optimized by first turning down the setting completely and then increasing the scale gradually until static background noise appeared (17). The severity of mitral regurgitation was assessed by calculating the maximum regurgitating jet area (RJA) expressed as a percentage of left atrial area (RJA/LAA). Regurgitant flow signals localized in the vicinity of valve closure were considered as physiological regurgitation, and these patients were classified as unaffected (18). Mitral regurgitation was rated as mild when RJA/LAA was <20%, moderate when ≥20% to <40%, and severe when ≥40% (19).

Measurements of left ventricular outflow tract diameter (LVOTD) were obtained from parasternal long-axis two-dimensional images at the level of aortic cusp insertion, and aortic root dimensions were calculated from M-mode tracings. Aortic regurgitation was considered to exist if an abnormal diastolic flow originating from aortic cusps was identified in the left ventricular outflow tract. The diameter of the regurgitated jet (AJD) was measured at its origin in the left outflow tract. The AJD/LVOTD ratio was calculated for quantification of aortic regurgitation (20), which was rated as mild when <25%, moderate when ≥25% and <40% and severe when ≥40%. Tricuspid valve images were recorded in four-chamber apical views, and the pulmonary valve was analyzed in high left parasternal short-axis view.

Patients were defined as affected when echocardiographic examination showed mitral valve dystrophy associated or
not with mitral valve prolapse, aortic valve dystrophy or mild to severe aortic regurgitation.

**Biological analysis.** Anthemophilic factor VIII (F.VIII) activity was estimated by a one-stage clotting assay based on activated partial thromboplastin time, using F.VIII-deficient plasma (Diagnostica Stago, Gennnevilliers, France) on an STA analyzer (Diagnostica Stago). The Second International Reference Preparation for Factor VIII-related activity (National Institute for Biological Standards and Control, London, United Kingdom) was used as a standard.

**Genetic study.** A detailed linkage study of this family has been reported elsewhere (13).

Only male phenotypes were used to calculate the lod score because the number of affected males was sufficient to produce a highly significant score. Moreover, penetrance in obligate female carriers (Fig. 1), unlike that in males, was not complete and could have been misleading. Two-point linkage analysis found a maximal lod score of 5.91 at $\theta = 0$ for markers INT-13 and DXS1108. Based on the results of the linkage study, patients who had valvular defect and who inherited the complete haplotype were affected. Females heterozygous to this haplotype were defined as carriers.

**Statistical methods.** Statistical analysis was performed using Student’s $t$ test and the Mann-Whitney $U$ test. A $p$ value of less than 0.05 was considered significant. Results are expressed as the mean ± SD.

**RESULTS**

The proband, a 16-year-old boy (Patient V-11), had class II dyspnea according to the New York Heart Association classification. He was of normal size and morphology, and a physical examination found no connective tissue or joint abnormalities. Cardiac auscultation revealed aortic regurgitant murmur, and echocardiography showed severe aortic regurgitation. Aortic root dimensions were normal as confirmed by a nuclear magnetic resonance study of the thoracic aorta. The left ventricle was enlarged (end-diastolic diameter 34 mm/m²), with normal systolic function. Mild hemophilia A was diagnosed at the time of aortic valve replacement.

Histological examination of the excised valve showed typical features of myxomatous valvular disease, with
marked thickening of the free edge of the valve. Light microscopy using blue-alcyan, hemalun-eosin-safran and Weigert stains was performed, showing extensive accumulation of proteoglycan and fragmentation of the collagenous bundle. Aortic root analysis was strictly normal.

The same hematologic disease was identified in his cousin (Patient V-9) when he underwent valvuloplasty for severe mitral regurgitation due to mitral valve dystrophy. This second case led to the identification of a very large family. Among the 318 members of the pedigree, 302 are still alive and 89 accepted to participate in the study (Fig. 1): 43 females (36±17 years) and 46 males (22±15 years). A valve defect was found in 22 (9 males and 13 females) of these subjects. None of the subjects was the result of a consanguineous mating. No family member showed clinical evidence of syndromic disorders such as Marfan or Ehlers-Danlos disease.

### Clinical characteristics of males

Among the 46 males (Table 1), 9 had obvious aortic and/or mitral valve defect and were classified as affected, including 4 who underwent valvuloplasty. Subsequent to surgery, one patient was asymptomatic and three had dyspnea (two class II, one class I). Seven of the nine affected males had mitral regurgitant murmur. No differences were found between affected and unaffected patients concerning age and body surface area.

### MITRAL VALVE DEFECT

All affected men had mitral valvular dystrophy (Fig. 2), and one had undergone mitral valvuloplasty when he was 18 years old (Patient V-9). Mitral valves were characterized by thicker anterior (AML) and posterior (PML) leaflets, longer AML and PML, and larger mitral annular diameters at end-diastole and end-systole. Mitral valve dystrophy was associated with moderate biowpering in all but one (Patient V-10) of the affected males (mean anterior leaflet prolapse: 3.1±1.5 mm). Mitral regurgitation was moderate in four patients (IV-48, V-10, V-11, V-13; RJA/LAA = 0.37±0.02) and severe in five (III-12, III-6, III-16, IV-50, V-9; RJA/LAA = 0.46±0.07).

### AORTIC VALVE DEFECT

As aortic valve dystrophy is difficult to assess by transthoracic echocardiography, we chose to quantify aortic regurgitation, which was associated with mitral valve dystrophy in six affected men. In each of these patients (III-6, III-16 and V-11), the severity of aortic regurgitation led to valve replacement at 42, 24 and 16 years of age, respectively. Histological examination of the aortic valves found abnormalities similar to those described in the proband. In the other three men (III-12, IV-50, and V-10), aortic regurgitation was quantified as mild or moderate, with an AJD/LVOTD of 0.1, 0.24 and 0.26, respectively. Aortic root diameters and the left ventricular outflows tract were normal and did not differ significantly in affected and unaffected men. The three remaining affected men had no detectable aortic valve defect.

### Table 1. Echocardiographic Characteristics of Men

<table>
<thead>
<tr>
<th></th>
<th>Affected Males (n = 9)</th>
<th>p Value</th>
<th>Unaffected Males (n = 37)</th>
</tr>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>31 ± 17</td>
<td>NS</td>
<td>20 ± 14</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.70 ± 0.25</td>
<td>NS</td>
<td>1.43 ± 0.51</td>
</tr>
<tr>
<td>Thickness of AML (mm)</td>
<td>4.7 ± 0.7</td>
<td>&lt; 0.0001</td>
<td>2.0 ± 0.4</td>
</tr>
<tr>
<td>Thickness of PML (mm)</td>
<td>3.8 ± 0.6</td>
<td>&lt; 0.0001</td>
<td>1.8 ± 0.4</td>
</tr>
<tr>
<td>Length of AML (mm)</td>
<td>28.1 ± 2.4</td>
<td>0.0004</td>
<td>22.1 ± 4.4</td>
</tr>
<tr>
<td>Length of PML (mm)</td>
<td>13.6 ± 1.7</td>
<td>0.0002</td>
<td>10.1 ± 1.8</td>
</tr>
<tr>
<td>DMAD (mm)</td>
<td>31.3 ± 3.0</td>
<td>0.0002</td>
<td>23.8 ± 5.1</td>
</tr>
<tr>
<td>SMAD (mm)</td>
<td>35.2 ± 3.3</td>
<td>0.0004</td>
<td>27.5 ± 5.3</td>
</tr>
<tr>
<td>ARD (mm)</td>
<td>30.6 ± 2.2</td>
<td>NS</td>
<td>27.1 ± 1.1</td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>53.7 ± 6.8</td>
<td>0.0014</td>
<td>43.5 ± 7.8</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>36.7 ± 10.0</td>
<td>NS</td>
<td>29.8 ± 6.0</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>69 ± 8</td>
<td>NS</td>
<td>68 ± 7</td>
</tr>
</tbody>
</table>

AML = anterior mitral leaflet; ARD = aortic root diameter; DMAD = diastolic mitral annulus diameter; LAD = left atrial diameter; PML = posterior mitral leaflet; LVDD = left ventricular diastolic diameter; SMAD = systolic mitral annulus diameter.

### Figure 2

Parasternal long-axis two-dimensional view, at end diastole (A) and end systole (B), performed in an affected male (Patient IV-48), showing the structural abnormalities of the mitral valve with thickening of mitral valve leaflets (A) and a mild prolapse (B).
Affected males had larger left ventricular diastolic diameters, whereas left atrial diameters did not differ significantly. Ejection fractions were similar in the two groups.

Finally, the phenotypic status of men could easily be characterized because affected patients had obvious valvular dystrophy clearly differentiating them from the normal phenotype.

HEMATOLOGIC DEFECT. Because of low F.VIII biological activity in the proband and his cousin (0.31 and 0.29, respectively), hemophilia A was suspected in cosegregation with the valve defect. Von Willebrand disease was excluded, and mild hemophilia A was detected in all men affected by valvular disease, whereas all unaffected men had normal F.VIII activity (0.32 ± 0.05 vs. 0.91 ± 0.29, p < 0.0001) (Fig. 3).

Clinical characteristics of women. The linkage study was the key factor for detailed clinical analysis of X-linked valvular dystrophy, allowing identification of female carriers on the basis of their haplotypes and analysis of the expression of the diseased gene in heterozygous women (Fig. 1). Among the 43 females in the pedigree, 17 who inherited the diseased gene in heterozygous women (Fig. 1). The penetrance of the disease associated gene in heterozygous women was age dependent, but valve defects were seen in 5 out of 7 women over 40 years of age and in only 5 out of 10 under 40.

Characteristics of the 17 heterozygous women. All women were asymptomatic, but echocardiography identified 10 (mean age 40 ± 15 years) with mitral and/or aortic valve abnormalities. Eight had holosystolic murmurs (III-3, III-8, III-24, III-30, IV-18, IV-25, and IV-49) and moderate mitral regurgitation (mean RJA/LAA = 0.31 = 0.04), with mitral valve prolapse in one and mild aortic regurgitation in three. Two women had isolated mild aortic regurgitation.

None of these women had obvious valvular dystrophy, and echocardiographic parameters such as leaflet thickness and mitral annulus, aortic root, left ventricular outflow tract and the left ventricle diastolic diameters did not differ in heterozygous and unaffected women (Table 2).

In two heterozygous women, the valvular defect could have been due to another cause. Patient II-3, the 83-year-old mother of two affected males, had isolated moderate mitral regurgitation without valvular dystrophy or mitral valve prolapse and a history of systemic hypertension. Patient IV-26, the 19-year-old daughter of an affected male, had an atypical valve defect with moderate pulmonary regurgitation without left valve defect.

According to echocardiographic data for genetically affected women, the penetrance of the disease in heterozygous was estimated as between 0.59 and 0.71, depending on the phenotypic status of the last two cases. The penetrance of the disease-associated gene in heterozygous women was age dependent, but valve defects were seen in 5 out of 7 women over 40 years of age and in only 5 out of 10 under 40.

Characteristics of women with undetermined genetic status. Echocardiographic examinations were normal in the four women (III-34, IV-41, V-1 and V-12) with recombination events in the candidate area. The genetic status of Patient III-34 was considered normal, as her son, who inherited the same haplotype, was unaffected.

Characteristics of women with normal genetic status. If it is assumed that Patient III-34 did not inherit the “diseased” haplotype, 23 women can be considered to have normal genetic status, including 3 (III-20, IV-1, IV-4) with a valve defect and 20 with normal echocardiography.

Patient III-20, a 64-year-old woman with isolated mild

Table 2. Echocardiographic Characteristics of Women

<table>
<thead>
<tr>
<th></th>
<th>Heterozygous Women</th>
<th>p Value</th>
<th>Normal Women</th>
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<tbody>
<tr>
<td></td>
<td>(n = 17)</td>
<td></td>
<td>(n = 24)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>38 ± 18</td>
<td>NS</td>
<td>37 ± 17</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.59 ± 0.13</td>
<td>NS</td>
<td>1.61 ± 0.31</td>
</tr>
<tr>
<td>Thickness of AML (mm)</td>
<td>2.5 ± 0.5</td>
<td>NS</td>
<td>2.3 ± 0.5</td>
</tr>
<tr>
<td>Thickness of PML (mm)</td>
<td>2.1 ± 0.3</td>
<td>NS</td>
<td>2.0 ± 0.3</td>
</tr>
<tr>
<td>Length of AML (mm)</td>
<td>24.0 ± 2.9</td>
<td>NS</td>
<td>22.7 ± 2.9</td>
</tr>
<tr>
<td>Length of PML (mm)</td>
<td>11.2 ± 1.5</td>
<td>NS</td>
<td>10.6 ± 1.6</td>
</tr>
<tr>
<td>DMAD (mm)</td>
<td>25.5 ± 3.4</td>
<td>NS</td>
<td>26.2 ± 3.2</td>
</tr>
<tr>
<td>SMAD (mm)</td>
<td>29.8 ± 3.5</td>
<td>NS</td>
<td>28.8 ± 4.1</td>
</tr>
<tr>
<td>ARD (mm)</td>
<td>28.4 ± 4.4</td>
<td>NS</td>
<td>28.1 ± 3.8</td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>47.7 ± 2.7</td>
<td>NS</td>
<td>44.7 ± 2.7</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>31.1 ± 4.4</td>
<td>NS</td>
<td>29.7 ± 3.8</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>72 ± 6</td>
<td>NS</td>
<td>68 ± 6</td>
</tr>
</tbody>
</table>

AML = anterior mitral leaflet; ARD = aortic root diameter; DMAD = diastolic mitral annulus diameter; LAD = left atrial diameter; LVDD = left ventricular diastolic diameter; PML = posterior mitral leaflet; SMAD = systolic mitral annulus diameter.
mitral regurgitation (RJA/LAA = 0.12) without valvular dystrophy or mitral valve prolapse, had received thoracic radiotherapy for breast cancer 10 years before. Patient IV-1, with severe mitral regurgitation (RJA/LAA = 0.49), had experienced an episode of prolonged fever, treated by antibiotics, shortly after delivery 10 years before. A diagnosis of endocarditis was considered but never confirmed, despite the occurrence of mitral regurgitation. In these two cases, the valve defect could have been secondary to radiotherapy or endocarditis. Patient IV-4, a 33-year-old woman with mild mitral regurgitation (RJA/LAA = 0.20) associated with moderate aortic regurgitation (AJD/LVOTD = 0.27), had no clinical history indicative of acquired valvular disease. When these cases were taken into consideration, a risk of phenocopy of 0.12 was found for heterozygous women.

DISCUSSION

Valvular dystrophy with myxomatous degeneration is a frequent cause of valve defects. It has been well described in mitral valve prolapse (21) and also occurs in aortic regurgitation (22,23). Although most affected patients are asymptomatic, they risk complications such as endocarditis, spontaneous cordal rupture and sudden death. Moreover, progressive worsening of valvular regurgitation can lead to heart failure. Within the last decade, this disease has become an increasing cause of valvular surgery (representing almost 20% of such patients in our institution [unpublished data]).

The clinical spectrum of myxomatous valvular disorders, ranging from isolated mild defects to severe multivalvular lesions, is in favor of a heterogeneous disease that is in fact difficult to subclassify because of the absence of specific features, even at the histological level. To date, only genes for syndromic diseases have been mapped or cloned (1–3), but the identification of genetic defects would appear to be the key factor for determining subclassifications.

Isolated mitral dystrophy associated with billowing is the most common form of myxomatous valvular disease. It is easy to diagnose an obviously affected patient but the continuum from normal to severely affected valves, and from isolated to multivalvular defects, can complicate the identification of affected patients (5).

In our study, men were either clearly normal or affected; the latter all had an obvious mitral valve dystrophy with thicker and longer leaflets and a mild prolapse similar to abnormalities described in floppy mitral valve (21), associated with aortic regurgitation in two-thirds of cases. Valvular degeneration was not associated with other detectable cardiovascular or morphological defects. Clinical examinations of affected patients indicated a nonsyndromic disease because no features of a connective tissue disease such as Marfan or Ehler–Danlos syndrome were detected, nor were any signs of osteogenesis imperfecta. Moreover, the thoracic aorta, particularly the aortic root, was echocardiographically and histologically normal, and skin histology performed in one affected patient was normal.

An X-linked disease with anticipation. Several factors indicated that the inherited valvular disease was X-linked. There was no male-to-male transmission, the severity of myxomatous valvular disease was far greater in males and all affected men had mild hemophilia, whereas those with normal valves showed normal F.VIII activity. This also suggested that both valvular dysplasia and hemophilia A were cosegregated in the family and that the gene responsible for the valvular dysplasia was closely linked to the factor VIII gene.

One of the most striking features of this disease is a tendency toward earlier severity from generation to generation. Reconstruction of the haplotype of ancestors indicated that the male in generation I was probably genetically affected and responsible for the transmission of the disease. Although no clinical cardiac analysis exists for this man, it is unlikely that he had severe valvular disease because he died at 65 years of age from peritonitis without any indication of cardiovascular symptoms. In generation III, three males were affected. The disease was identified when they were in their 40s, and two of them underwent valvular surgery, at ages 51 and 49 years. In generation IV, two men were affected. The diagnosis of valvular disease was made during their 20s, and at ages 30 and 24 years, they are still asymptomatic with moderate mitral regurgitation. Finally, four males of generation V are affected by the disease. Two underwent valvular surgery at the age of 17 years because of severe mitral (V-11) or aortic (V-9) valvular regurgitation, and two others (16 and 12 years old) are severely affected. This apparent tendency toward earlier severity could actually be due to improvement of echocardiographic techniques. However, similar tendencies were noted in two previous descriptions of this disease. In the family reported by Monteleone and Fagan (10), a four-generation patient died of cardiac failure due to valvular disease when he was eight months old, whereas several men from the previous generation were still alive, although clinically affected. In the family described by Newbury-Ecob et al (24), a fourth-generation baby died from valve defect and cardiac failure 24 h after birth, whereas his grandfather in the second generation was asymptomatic until the age of 25 years and underwent valve replacement at the age of 41 years. This tendency toward earlier severity, called anticipation, needs to be confirmed in other families.

An X-linked disease with mildly affected female carriers. Our clinical observations differ from those previously described for X-linked valvular dysplasia, even though the same genetic disease is probably involved. An important result not previously described is the identification of an intermediate phenotype in heterozygous women. With the mapping of the gene in monozygous males, it has become possible to identify female carriers on the basis of their haplotypes and to analyze the expression of the disease gene.
As has been demonstrated for idiopathic mitral valve prolapse, there was no clear delineation between normal and abnormal valves, and there is a continuum from normal to abnormal valves because some heterozygous women in our study had normal echocardiography, whereas others had mitral or aortic regurgitation, giving a penetrance value of 59% to 71%, which increased with age. Furthermore, valve defects were less severe than in men, as shown by the absence of differences in mitral valve thickness, length and diameter between affected heterozygous and normal women and by a better outcome (no valvular surgery). This could have been due to the low accuracy of transthoracic echocardiography in identifying small valve defects.

Implications for genetics of myxomatous valve dystrophies. The clinical phenotype of patients with mitral valve prolapse constitutes a continuum from Marfan syndrome to isolated mitral valve prolapse. To emphasize the involvement of mitral valve prolapse, aorta, skeleton and skin, patients with connective tissue disorder have been described using the acronym MASS phenotype (25). Isolated mitral valve prolapse is by far the most frequent syndrome (4), and one study has identified at least two different phenotypes with a strong family pattern (7). Both forms appear to be inherited in an autosomal dominant manner (6). This mode of inheritance was also identified in other studies that have reported family cases (26–28). However, epidemiological studies have shown striking results that can hardly be explained by this mode of inheritance. The mitral valve prolapse is twice as frequent in females as in males (8), it is more severe in men than in women (9), as confirmed by several surgical series of mitral valve prolapse as well as myxoid aortic valve regurgitation in which the patients were largely male (22,23), and no clear delineation exists between normal and affected patients, especially women. Although these results could have been due to hormonal as well as environmental factors, they are still surprising for an autosomal dominant disease.

Contrary to idiopathic mitral valve prolapse, X-linked valvular dystrophy seems to be a rare disease, described only twice (10,24). This could have been due to the rarity of the disease or to misinterpretation in the mode of inheritance of the valvular defect. Indeed, the presence of affected heterozygous women, particularly in small pedigree, the tendency toward earlier severity (the anticipation of the disease), the risk of phenocopies and the low sensitivity of echocardiography could be clinically misleading. Owing to the presence of these confounding factors, it is possible that some patients with myxomatous valve defects may have been affected by an unidentified X-linked valvular disease. In this respect, only male-to-male transmission can rule out an X-linked disease.

Conclusions. It is quite likely that myxomatous valvular diseases are heterogeneous and that myxoid degeneration is the initial pathway for several protein defects that will not be identified with conventional clinical tools. The first localization of a gene for nonsyndromic myxomatous valvular diseases should facilitate the subclassification of this complex group of diseases. Ultimately, the cloning of the gene will give a new insight into the pathophysiology of these diseases.

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