SAS Journal of Medicine
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

Genetics

Clinical Spectrum of Marfan syndrome and Related Phenotypes: A Case Series of Eight Moroccan Patients

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DOI: https://doi.org/10.36347/sasjm.2026.v12i11.015 | **Received:** 22.09.2026 | **Accepted:** 18.11.2026 | **Published:** 20.11.2026

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Abstract **Case Series**

Background: Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder caused by pathogenic variants in *FBN1*. The revised Ghent nosology (2010) allows a diagnosis on clinical grounds alone, but molecular confirmation strengthens it and helps exclude overlapping disorders. In Morocco, *FBN1* testing is rarely available in public hospitals and remains largely out of pocket. ***Case Series*:** We report eight patients (six males, two females; median age 21.5 years, range 18–54) referred for a marfanoid phenotype and assessed without molecular testing. Each patient was classified into one of three categories: MFS fulfilling the revised Ghent criteria, clinically suspected MFS, or Marfan-like phenotype. Four patients fulfilled the Ghent criteria (aortic root dilatation with ectopia lentis, aortic root dilatation with a systemic score ≥ 7, or a first-degree family history with ectopia lentis). The other four had clinically suspected MFS: all had a systemic score ≥ 7 (range 10–15) and one had ectopia lentis, but none had aortic root dilatation or a first-degree relative with MFS. Systemic scores ranged from 9 to 15. Ectopia lentis was found in four patients and aortic root dilatation in two, one of whom also had a type B aortic dissection. Parents were consanguineous in three families. Plasma homocysteine was normal in all patients. ***Conclusion*:** Careful application of the Ghent criteria, systematic echocardiography, slit-lamp examination and pedigree analysis allow a reliable classification of patients when genetic testing is unaffordable. Because the features of MFS appear with age, patients with clinically suspected MFS may later fulfil the criteria and require long-term follow-up. Better access to *FBN1* testing would confirm the diagnosis in these strongly suspected cases and enable family screening.

Keywords: Marfan Syndrome, Ghent Nosology, *FBN1*, Clinical Diagnosis, Systemic Score, Consanguinity, Genetic Testing, Morocco.

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INTRODUCTION

Marfan syndrome is a systemic, autosomal dominant disorder of connective tissue caused by mutations in *FBN1*, the gene encoding the extracellular matrix protein fibrillin-1 [1]. It mainly affects the cardiovascular, ocular and skeletal systems; aortic root aneurysm and dissection are the leading causes of premature death [1]. Reported prevalence varies with the method used: 6.5 per 100,000 in a Danish registry using the revised criteria, 10.2 per 100,000 in Taiwan, against the frequently quoted figure of 20 per 100,000 [2, 3].

The diagnosis rests on clinical criteria. The revised Ghent nosology, published in 2010, gives more weight to the two cardinal features, aortic root aneurysm/dissection and ectopia lentis [4]. Other cardiovascular, ocular, skeletal, dural, cutaneous and pulmonary findings contribute to a systemic score, and a score of 7 or more counts towards the diagnosis [4]. *FBN1* testing is not mandatory but carries more weight than in the earlier nosology [4]. In patients who fulfil the revised Ghent criteria, a pathogenic or likely pathogenic *FBN1* variant is found in about 80% to 90% of cases [5, 6].

In Morocco, as in many low- and middle-income countries, molecular testing is not part of routine care. Moroccan reports of MFS are mostly single case reports centred on a complication: aortic dissection revealed by lens dislocation, mitral valve prolapse or ectopia lentis [7–9]. Case series describing the full

clinical spectrum, pedigrees and the practical limits of diagnosis without genetic confirmation remain scarce.

We report eight Moroccan patients with a marfanoid phenotype assessed without molecular testing. We classify them into three diagnostic categories according to the revised Ghent nosology, describe their phenotype and family structure, and discuss the reliability and pitfalls of a purely clinical diagnosis in a context of high consanguinity and limited access to genetic testing.

PATIENTS AND METHODS

This is a descriptive case series of eight patients followed at the Department of Genetics, Avicenne Military Hospital, Marrakech, Morocco, between December 2021 and August 2026. The report follows the CARE guidelines for case reports.

Inclusion: patients referred with a suspected or established clinical diagnosis of MFS, whatever the reason for referral.

Assessment: each patient had:

- A medical history, including pregnancy, delivery and psychomotor development;
- A three-generation pedigree drawn according to standard nomenclature, recording parental consanguinity and similar cases in relatives;
- A full clinical examination with height, weight, arm span and upper-to-lower segment ratio, and a systematic search for the items of the Ghent systemic score, with photographs;
- Transthoracic echocardiography, with the aortic root diameter at the sinuses of Valsalva and the Z-score, and assessment of the mitral valve;
- An ophthalmological examination with refraction and slit-lamp examination after pupil dilation;
- Imaging when indicated: spinal radiographs, chest computed tomography (CT) with the Haller index, CT angiography;
- Routine laboratory tests and plasma total homocysteine.

Systemic score:

The systemic score was calculated according to the revised Ghent nosology (maximum 20 points) [4]. The point for a reduced upper-to-lower segment ratio (< 0.85) with an increased arm span-to-height ratio (> 1.05) was counted only in the absence of severe scoliosis. Features secondary to another cause, such as a pneumothorax due to tuberculosis, were not counted.

Diagnostic Categories: each patient was classified into one of three categories:

- **Category 1 – MFS Diagnosed according To the Revised Ghent Criteria:** patients fulfilling the clinical diagnostic criteria [4]. Without a family history: aortic root dilatation ($Z \geq 2$) or dissection combined with ectopia lentis or a systemic score ≥ 7. With a family history of MFS in a first-degree relative independently diagnosed: ectopia lentis, a systemic score ≥ 7 or aortic root dilatation ($Z \geq 2$ after age 20 years, $Z \geq 3$ before). When aortic involvement was combined with a systemic score ≥ 7, clinical features of Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome and Shprintzen-Goldberg syndrome were sought, as required by the nosology [4].
- **Category 2 – Clinically Suspected MFS:** patients with a phenotype suggestive of MFS but not fulfilling all the criteria, for example a systemic score ≥ 7 or ectopia lentis without aortic root dilatation and without a first-degree family history.
- **Category 3 – Marfan-Like Phenotype:** patients with some morphological features of MFS but without sufficient criteria for the diagnosis (systemic score < 7, no cardinal feature and no family history).

Genetic Testing: *FBN1* testing is not performed in our department and must be outsourced to laboratories abroad; no patient could afford it (see Discussion).

Follow-up: all patients remain under clinical, echocardiographic and ophthalmological follow-up, with a visit every 6 months.

Ethics:

Written informed consent for publication, including photographs, was obtained from each patient, or from a parent or legal guardian for minors. Faces were cropped from all photographs, and names were removed from pedigrees.

CASE PRESENTATIONS

Case 1:

A 19-year-old man, second of two children of non-consanguineous parents (the maternal grandparents are related). Pregnancy, delivery and development were normal. He has bronchiectasis. His father died with diabetes and pulmonary tuberculosis; his sister and five paternal half-siblings were unaffected. He was 1.83 m tall with an arm span of 1.89 m (ratio 1.03) and an upper-to-lower segment ratio of 0.70. Examination showed positive wrist and thumb signs, pectus carinatum, scoliosis, hindfoot deformity, skin striae and facial features. Echocardiography showed mitral valve prolapse with mitral regurgitation and a normal aortic root. The ophthalmological examination showed myopia > 3 dioptres without ectopia lentis. The point for body proportions was not counted, because the arm span-to-height ratio was below 1.05. Systemic score: 12/20. Ghent criteria not fulfilled: no aortic root dilatation, no ectopia lentis, no family history. Close follow-up is

necessary: with time, a major sign, in particular aortic root dilatation, may appear; combined with his systemic score ≥ 7, it would fulfil the Ghent criteria and move him to category 1.

Category 2: Clinically Suspected MFS.
Case 2

A 22-year-old man, eldest of three children of consanguineous parents, referred for scoliosis. Development was normal. A paternal cousin has MFS; the parents have no features of the disease. He was 1.90 m tall, weighed 68 kg and had an arm span of 2.02 m (ratio 1.06) with an upper-to-lower segment ratio of 0.82. Examination showed positive wrist and thumb signs with arachnodactyly, pectus carinatum, severe thoracolumbar scoliosis, hindfoot deformity, reduced elbow extension, joint hypermobility, skin striae and three facial features (dolichocephaly, enophthalmos, down-slanting palpebral fissures). He had a history of spontaneous pneumothorax. Echocardiography showed mitral valve prolapse and a normal aortic root. The ophthalmological examination showed ectopia lentis and myopia > 3 dioptres. Plasma homocysteine was normal. Because of the severe scoliosis, the point for body proportions was not counted. Systemic score: 15/20. Ghent criteria not fulfilled: ectopia lentis and a high systemic score, but a normal aortic root and no first-degree family history (the affected relative is a cousin). Close follow-up is necessary: with time, a major sign may appear; aortic root dilatation, combined with his ectopia lentis, would fulfil the Ghent criteria and move him to category 1.

Category 2: Clinically Suspected MFS
Case 3

A woman diagnosed at 54 years of age, fifth of nine children of non-consanguineous parents, with no similar case in the family. She presented with progressive visual loss from 2016, leading to bilateral blindness in 2018, caused by ectopia lentis complicated by retinal detachment. She had fractures of both forearms after minor trauma in 2017, and asthma since 2006. She was 1.70 m tall, with a disproportionately long arm span. Examination showed positive wrist and thumb signs with arachnodactyly, pectus excavatum, hindfoot valgus, thoracolumbar scoliosis, reduced elbow extension, unexplained skin striae and facial features (dolichocephaly, enophthalmos and retrognathia). Imaging showed aortic root dilatation ($Z \geq 2$). CT angiography showed an aneurysm of the descending thoracic aorta extending to both common iliac arteries, with a false lumen and intramural haematoma, consistent with a Stanford type B dissection. Echocardiography also showed hypertensive heart disease, without mitral valve prolapse. Plasma homocysteine was normal. Systemic score: 10/20. Ghent criteria fulfilled: aortic root dilatation and ectopia lentis.

Category 1: MFS diagnosed according to the revised Ghent criteria.
Case 4

An 18-year-old man, eldest of five children of non-consanguineous parents, with no similar case in the family. He had umbilical hernia repair at 2 months and presented with low back pain and joint pain. He was 1.88 m tall, weighed 67 kg and had an arm span of 1.98 m (ratio 1.053) with an upper-to-lower segment ratio of 0.82. Examination showed positive wrist and thumb signs with arachnodactyly, pectus excavatum (Haller index 3.8), thoracic scoliosis of 18°, hindfoot valgus, reduced elbow extension, joint hypermobility, skin striae and three facial features (dolichocephaly, enophthalmos, down-slanting palpebral fissures). Echocardiography showed a normal aortic root without mitral valve prolapse. The ophthalmological examination showed myopia > 3 dioptres without ectopia lentis. Systemic score: 12/20. Ghent criteria not fulfilled: no aortic root dilatation, no ectopia lentis, no family history. Close follow-up is necessary: with time, a major sign, in particular aortic root dilatation, may appear; combined with his systemic score ≥ 7, it would fulfil the Ghent criteria and move him to category 1.

Category 2: Clinically Suspected MFS
Case 5

A 21-year-old man, third of four children of consanguineous parents. His 17-year-old sister has a similar phenotype but has not yet had cardiac or ophthalmological assessment. He had surgery for a femoral fracture and for a hernia. He was 1.90 m tall, weighed 70 kg and had an arm span of 2.02 m (ratio 1.06) with an upper-to-lower segment ratio of 0.82. Examination showed positive wrist and thumb signs with arachnodactyly, pectus excavatum (Haller index 4.5), hindfoot valgus, reduced elbow extension, joint hypermobility, skin striae and three facial features (dolichocephaly, enophthalmos, down-slanting palpebral fissures). Echocardiography showed a normal aortic root without mitral valve prolapse, and the ophthalmological examination was normal. Systemic score: 10/20. Ghent criteria not fulfilled: no aortic root dilatation, no ectopia lentis; the sister cannot yet be counted as a family history. Close follow-up is necessary: with time, a major sign, in particular aortic root dilatation, may appear and, combined with his systemic score ≥ 7, would move him to category 1; the same would apply if his sister were found to fulfil the Ghent criteria.

Category 2: Clinically Suspected MFS.
Case 6

A 24-year-old man, youngest of four brothers of non-consanguineous parents. His mother has MFS. He has had asthma since the age of 1 year and had pulmonary tuberculosis complicated by a pneumothorax; chest CT showed lesions suggestive of tuberculosis. He was 1.90 m tall, weighed 68 kg and had an arm span of 2.03 m (arm span-to-height ratio 1.07) with an upper-to-lower segment ratio of 0.82. Examination showed

positive wrist and thumb signs with arachnodactyly, pectus carinatum with chest asymmetry, hindfoot valgus, reduced elbow extension, joint hypermobility, skin striae and three facial features (dolichocephaly, enophthalmos, down-slanting palpebral fissures). Echocardiography showed a normal aortic root without mitral valve prolapse. The ophthalmological examination showed ectopia lentis and myopia > 3 dioptres. Because it was secondary to tuberculosis, the pneumothorax was not counted. Systemic score: 12/20. Ghent criteria fulfilled: first-degree family history with ectopia lentis, and with a systemic score ≥ 7.

Category 1: MFS Diagnosed According to The Revised Ghent Criteria.

Case 7

A 21-year-old man, second of five children of consanguineous parents, with no family history of MFS. He had five operations for valgus clubfeet. He was 1.90 m tall, weighed 68 kg and had an arm span of 2.05 m (ratio 1.08) with an upper-to-lower segment ratio of 0.82. Examination showed positive wrist and thumb signs with arachnodactyly, pectus excavatum, severe scoliosis, hindfoot valgus and skin striae. Echocardiography showed aortic root dilatation; the chest radiograph was normal. The ophthalmological examination showed myopia > 3 dioptres without ectopia lentis. There was no hypertelorism, bifid uvula or cleft palate, and no arterial tortuosity, so Loeys-Dietz syndrome was not suspected clinically. Because of the severe scoliosis, the point for body proportions was not counted. Systemic score: 9/20. Ghent criteria fulfilled: aortic root dilatation and a systemic score ≥ 7.

Category 1: MFS Diagnosed According to the Revised Ghent Criteria

Case 8

A 36-year-old woman, sixth of eight children of non-consanguineous parents. Her daughter has a similar phenotype, and a brother has MFS with ectopia lentis; a nephew also has a suggestive phenotype. Two siblings died on day 1 (rhesus incompatibility) and one at 18 months (hydrocephalus). She had a tonsillectomy at 12 years. She was 1.78 m tall, weighed 58 kg and had an arm span of 1.90 m (ratio 1.07) with an upper-to-lower segment ratio of 0.82. Examination showed positive wrist and thumb signs with arachnodactyly, pectus excavatum, severe thoracolumbar scoliosis, hindfoot valgus, joint hypermobility and skin striae; only two facial features were present. Echocardiography was normal, with no aortic root dilatation and no mitral valve prolapse. The ophthalmological examination showed ectopia lentis and myopia > 3 dioptres. Systemic score: 9/20. Ghent criteria fulfilled: first-degree family history with ectopia lentis, and with a systemic score ≥ 7.

Category 1: MFS Diagnosed According to the Revised Ghent Criteria

No patient was classified in category 3 (Marfan-like phenotype): all had a systemic score of 9 or more.

RESULTS

The series includes six men and two women, with a median age of 21.5 years (range 18–54). Parents were consanguineous in three families (cases 2, 5 and 7). Four families had more than one affected member: a first-degree relative with MFS in two (the mother in case 6; a brother and the daughter in case 8), an affected sister not yet assessed in case 5, and an affected cousin in case 2. Routine laboratory tests, including plasma total homocysteine, were normal in all patients.

Four patients fulfilled the revised Ghent criteria and four had clinically suspected MFS; none was classified as Marfan-like phenotype (Table 1). The systemic score ranged from 9 to 15 (median 11) and reached 7 or more in all patients. Wrist and thumb signs, pectus deformity, hindfoot deformity and skin striae were present in all patients (Table 2). Ectopia lentis was found in four patients (cases 2, 3, 6 and 8) and myopia > 3 dioptres in six. Aortic root dilatation was found in two patients (cases 3 and 7); case 3 also had a type B dissection of the descending thoracic aorta. Mitral valve prolapse was found in two patients (cases 1 and 2).

Table 1: Ghent 2010 assessment and diagnostic category of the eight patients

Case	Age (y)/ sex	Consang.	Family history	Aortic root	EL	Syst. score	Ghent criteria met	Category
1	19 / M	No	None	Normal	No	12	Syst ≥ 7 only	2 – Suspected
2	22 / M	Yes	Cousin with MFS	Normal	Yes	15	EL + Syst ≥ 7, no Ao, no first-degree FH	2 – Suspected
3	54 / F	No	None	Dilated (Z ≥ 2); type B dissection	Yes	10	Ao + EL	1 – MFS (Ghent)
4	18 / M	No	None	Normal	No	12	Syst ≥ 7 only	2 – Suspected

5	21 / M	Yes	Sister with similar phenotype (not assessed)	Normal	No	10	Syst ≥ 7 only	2 – Suspected
6	24 / M	No	Mother with MFS	Normal	Yes	12	FH + EL; FH + Syst ≥ 7	1 – MFS (Ghent)
7	21 / M	Yes	None	Dilated	No	9	Ao + Syst ≥ 7	1 – MFS (Ghent)
8	36 / F	No	Brother with MFS, affected daughter	Normal	Yes	9	FH + EL; FH + Syst ≥ 7	1 – MFS (Ghent)

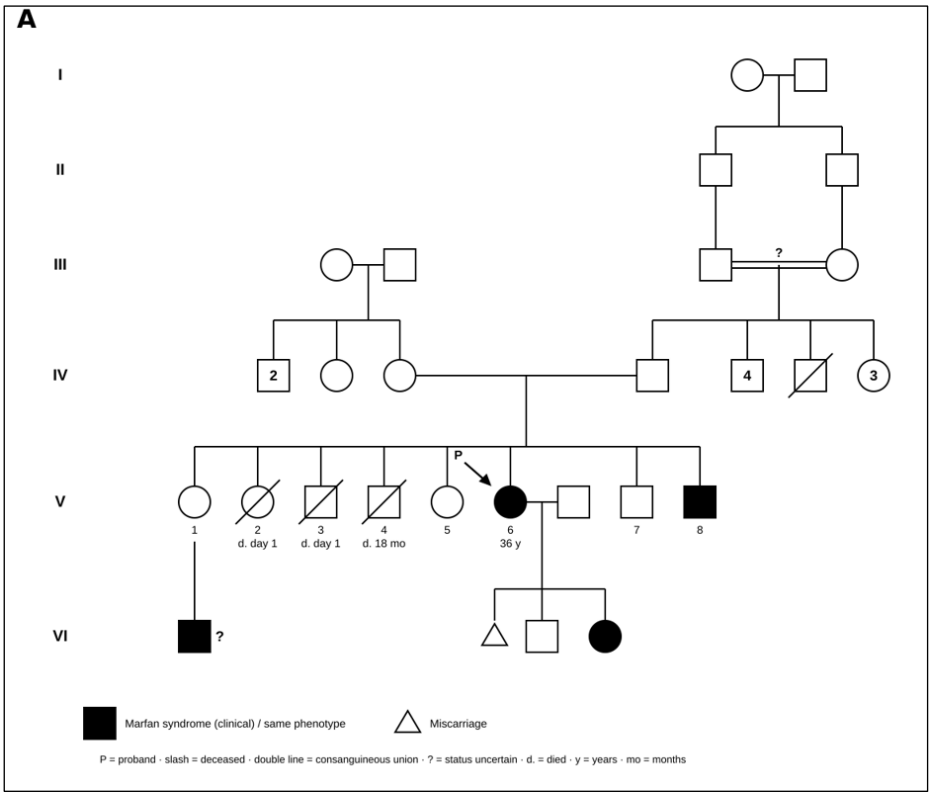
Consang., parental consanguinity; M, male; F, female; Ao, aortic root dilatation; EL, ectopia lentis; FH, family history in a first-degree relative; Syst, systemic score; MFS, Marfan syndrome; Suspected, clinically suspected MFS.

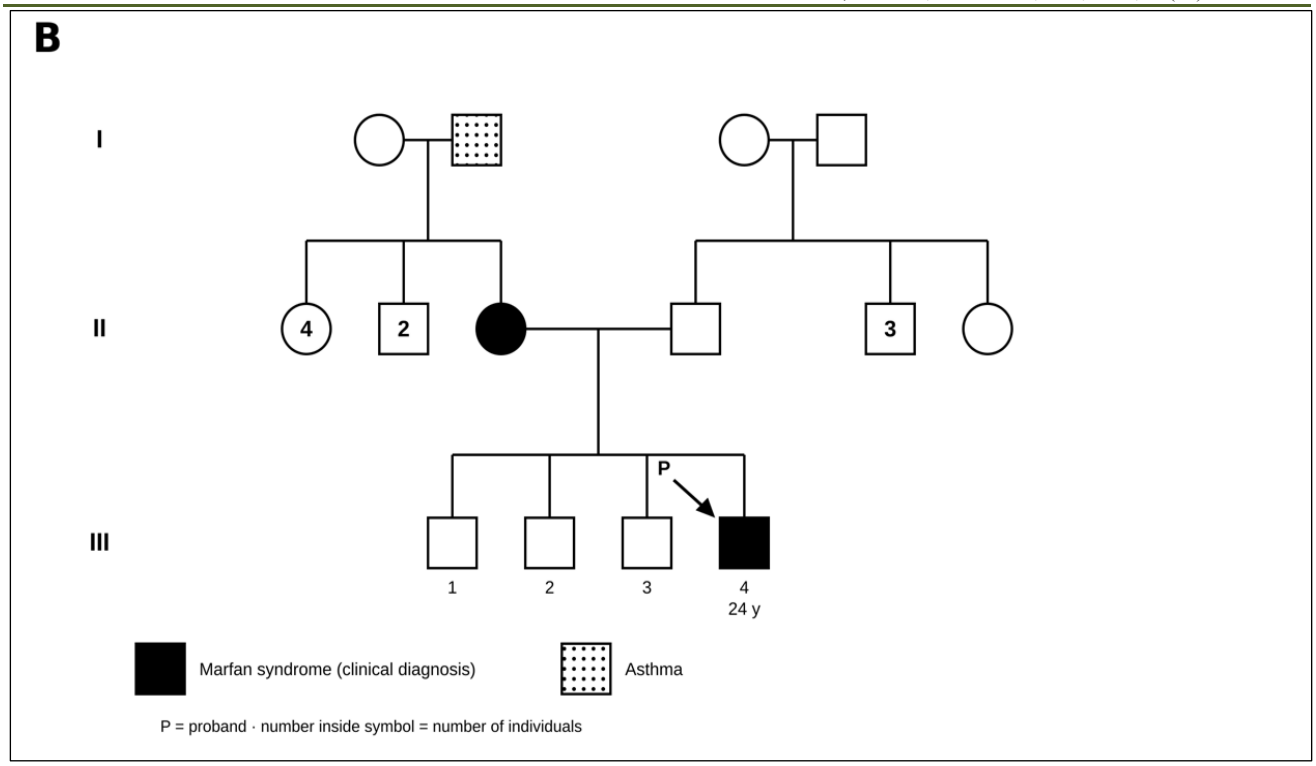
Table 2: Items of the Ghent systemic score in each patient

Item (points)	1	2	3	4	5	6	7	8
Wrist and thumb sign (3)	+	+	+	+	+	+	+	+
Pectus carinatum (2) / excavatum or asymmetry (1)	C	C	E	E	E	C	E	E
Hindfoot deformity (2)	+	+	+	+	+	+	+	+
Pneumothorax (2)	–	+	–	–	–	–[a]	–	–
Reduced US/LS and increased arm span/height, no severe scoliosis (1)	–[b]	–[c]	NM	+	+	+	–[c]	–[c]
Scoliosis or thoracolumbar kyphosis (1)	+	+	+	+	–	–	+	+
Reduced elbow extension (1)	NR	+	+	+	+	+	NR	–
Facial features, ≥ 3 of 5 (1)	+	+	+	+	+	+	NR	–
Skin striae (1)	+	+	+	+	+	+	+	+
Myopia > 3 dioptres (1)	+	+	NR	+	–	+	+	+
Mitral valve prolapse (1)	+	+	–	–	–	–	NR	–
Total (maximum 20)	**12**	**15**	**10**	**12**	**10**	**12**	**9**	**9**

Symbols: +, present; –, absent; C, pectus carinatum; E, pectus excavatum; NM, not measured; NR, not reported; US/LS, upper-to-lower segment ratio. Dural ectasia and protrusio acetabuli were not assessed. [a] Pneumothorax secondary to tuberculosis, not counted. [b] Arm span-to-height ratio 1.03. [c] Severe scoliosis.

Figure 1 shows the pedigrees of three families: two with vertical transmission and one sporadic case. Figure 2 shows representative clinical signs observed in the series.





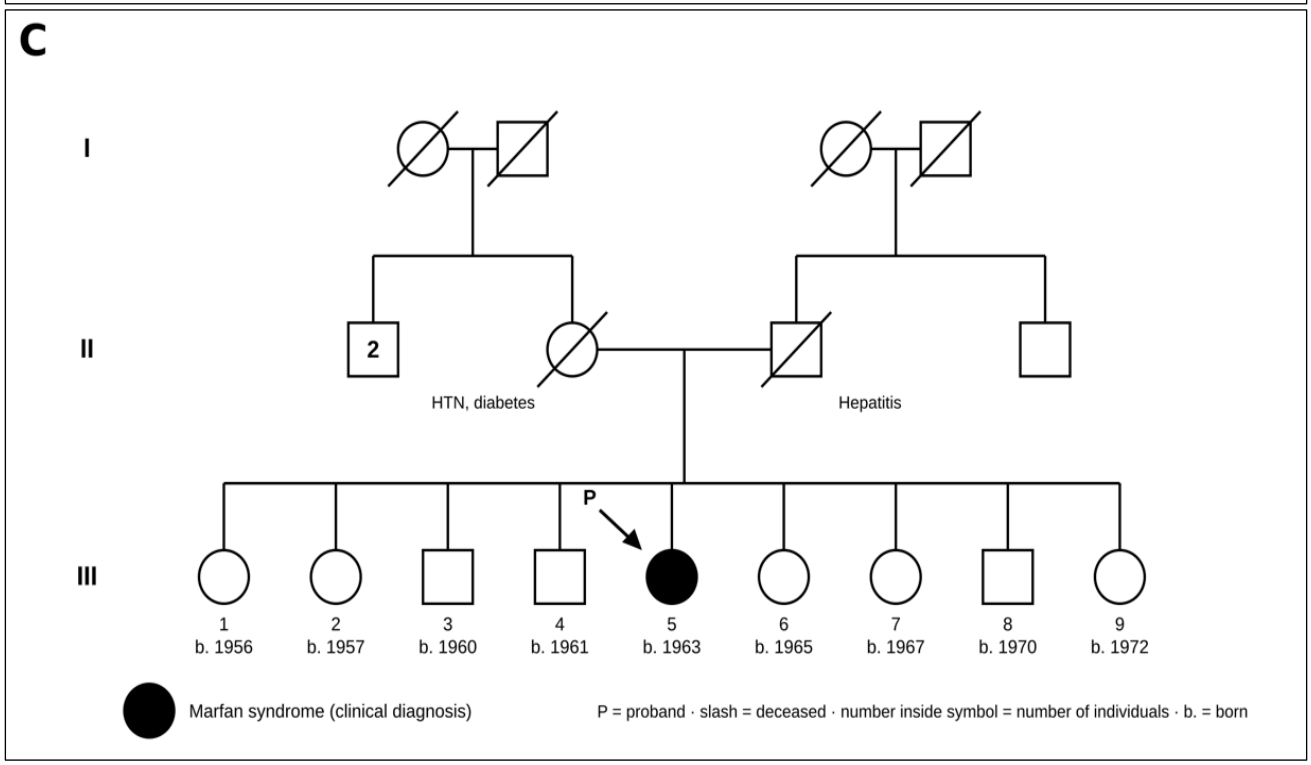


Figure 1: Pedigrees of three families. (A) Case 8: the proband (V-6), her brother (V-8) and her daughter are affected, consistent with autosomal dominant transmission; a nephew has a suggestive phenotype (?). (B) Case 6: mother-to-son transmission. (C) Case 3: sporadic case with non-consanguineous parents. Squares, males; circles, females; filled symbols, affected; slash, deceased; double line, consanguineous union; arrow (P), proband. The pedigrees of the other families are available from the authors.

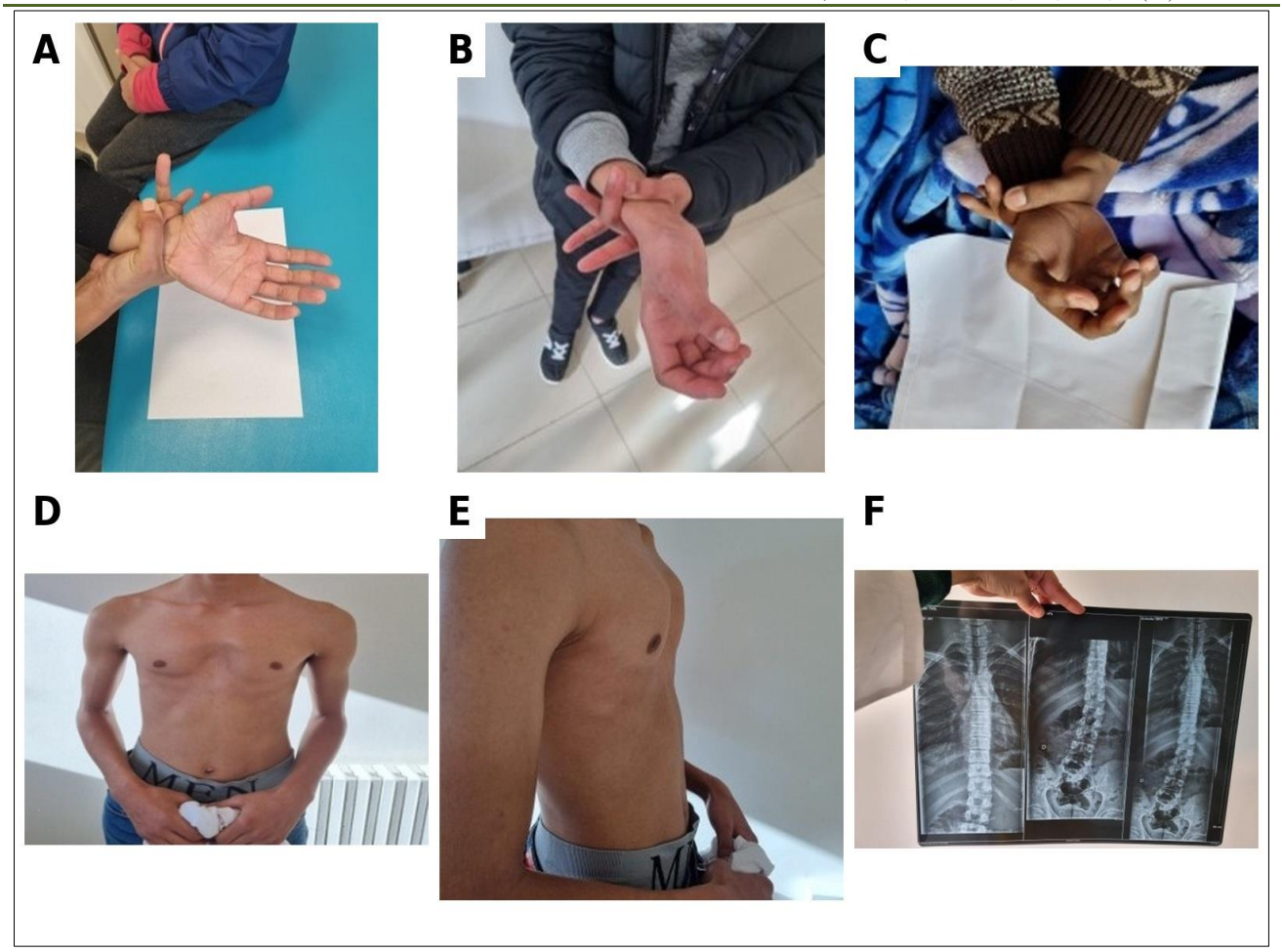


Figure 2: Representative clinical signs observed in the series. (A) Positive thumb sign (Steinberg). (B, C) Positive wrist sign (Walker-Murdoch). (D, E) Pectus carinatum, frontal and lateral views. (F) Spinal radiographs showing scoliosis

DISCUSSION

This series shows that, even without molecular testing, a structured application of the revised Ghent nosology makes it possible to classify patients with a marfanoid phenotype into clear diagnostic categories. Half of our patients fulfilled the criteria; the other half had a highly suggestive phenotype that could not be confirmed.

Three Diagnostic Categories

Classifying patients into three categories avoids two opposite errors: labelling all marfanoid patients as having MFS, and dismissing patients who do not yet fulfil the criteria. The categories also reflect how the nosology works [4]. Cardinal features carry most of the weight: case 3, with a systemic score of only 10, fulfilled the criteria through aortic root dilatation and ectopia lentis, whereas case 2, with the highest score of the series (15) and ectopia lentis, did not, because his aortic root was normal and his only affected relative was a cousin.

Without a family history, a systemic score ≥ 7 counts only when combined with aortic involvement [4]. This explains why three of our patients with scores of 10 to 12 (cases 1, 4 and 5) remain in the suspected category. Strictly applied, the nosology would classify case 2, who has ectopia lentis without aortic involvement or an *FBN1* variant, as ectopia lentis syndrome, pending further evaluation [4]. Given his very high systemic score, we considered MFS clinically suspected rather than excluded.

Family history changed the classification in two patients. In case 6, the mother's diagnosis and the patient's ectopia lentis together fulfil the criteria. In case 8, a brother with ectopia lentis and an affected daughter confirm the familial nature of the disease. In case 5, the sister will count as a family history only if she fulfils the criteria herself, which underlines the importance of assessing relatives [4].

The category of a patient is not fixed. Aortic dilatation and ectopia lentis may appear with age, so that patients with clinically suspected MFS may later fulfil the criteria. Conversely, the absence of cardinal features over many years would argue for another diagnosis.

Comparison with the Literature

Table 3 compares our patients with three published series: a large Indian cohort with molecular

confirmation [10], a French cohort of children carrying an *FBN1* mutation [11], and a small Turkish paediatric series [12].

Table 3: Comparison of our series with published series

Feature	Our series (n = 8)	Nayak *et al*., India (n = 63, *FBN1*-positive)	Stheneur *et al*., France (n = 259 children, *FBN1*-positive)	Ozdemir *et al*., Turkey (n = 11 children)
Aortic root dilatation or dissection	2/8 (25%)[a]	77%	75–80%	6/11 (55%)
Ectopia lentis	4/8 (50%)	49%	66–72%	1/11 (9%)
Mitral valve prolapse	2/8 (25%)	67%	—	11/11 (100%)
Pectus deformity	8/8 (100%)	47%	43% (0–6 y) to 62% (15–17 y)	8/11 (73%)
Scoliosis	6/8 (75%)	30%	16% (0–6 y) to 59% (15–17 y)	7/11 (64%)
Thumb and wrist sign	8/8 (100%)	Thumb 70%, wrist 68%	Wrist 28% (0–6 y) to 67% (15–17 y)	Arachnodactyly 10/11 (91%)
Hindfoot deformity / pes planus	8/8 (100%)	Pes planus 50%, talipes 24%	—	—
Hernia	2/8 (25%)	13%	—	—
Pneumothorax	1/8 (12.5%)[b]	11%	—	0/11
Skin striae	8/8 (100%)	20%	—	0/11
Familial cases	4/8 (50%)[c]	52% of families	—	—

[a] Cases 3 and 7; case 3 also had a type B dissection of the descending aorta. [b] Spontaneous pneumothorax in case 2; the pneumothorax of case 6, secondary to tuberculosis, is excluded. [c] Cases 6 and 8 (first-degree relatives with MFS), case 5 (sister not yet assessed) and case 2 (cousin). —, not reported; y, years.

Age and Sex

Our patients were diagnosed at a median age of 21.5 years, close to the median age at diagnosis of 19.0 years in the Danish national registry [2]. The male predominance (6/8) probably reflects the small sample, since the Danish registry found no sex difference [2].

Cardinal Features

Ectopia lentis, reported in 30% to 87% of patients with MFS depending on the series [14], was found in half of our patients, a frequency close to that of the Indian cohort (49%) and slightly below that of the French cohort (66% to 72%) [10, 11]. Aortic root dilatation, however, was less frequent (25%, compared with 55% to 80% in published series) [10–12]. Several factors may explain this difference: the young age of most of our patients, since aortic dilatation progresses with age [24], the absence of *FBN1* confirmation, which may include patients with other marfanoid disorders; and the referral of our patients for skeletal rather than cardiac features. In the Indian cohort, none of the index patients without a disease-causing variant met the Ghent criteria [10], and in the Turkish series an *FBN1* mutation was found in only 7 of the 11 children [12].

Skeletal and Cutaneous Features

Skeletal and cutaneous features were more frequent in our series than in published series: all patients had wrist and thumb signs, pectus deformity, hindfoot deformity and skin striae, and six had scoliosis [10–12]. This probably reflects a selection bias, because our patients were referred to a genetics clinic for their morphology. It also means that all our patients reached a systemic score of at least 9, which was decisive for the classification of patients without a family history. Pectus deformity, scoliosis and the wrist sign become more frequent with age in children [11], so young siblings in our families may still be affected without showing signs.

Family History

Four of our eight families had more than one affected member, a proportion close to the 52% of familial cases among the *FBN1*-positive families of the Indian cohort [10]. In MFS, about 25% of probands have a de novo pathogenic variant [13]; four of our patients (cases 1, 3, 4 and 7) were sporadic cases, which may reflect de novo mutations or incomplete examination of relatives.

Moroccan Reports

Previous Moroccan publications describe isolated patients revealed by a cardiovascular or ocular complication: aortic dissection with lens dislocation, mitral valve prolapse or ectopia lentis [7–9]. Case 3, with bilateral blindness due to ectopia lentis and retinal detachment and an extensive aortic dissection, illustrates the severity of a late diagnosis. Our series also shows another presentation of the disease in Morocco: young patients referred for skeletal features, in whom the cardinal features must be actively sought.

DIFFERENTIAL DIAGNOSIS

Marfanoid habitus is not specific. The Ghent nosology lists several conditions to exclude, each with its own risk profile and management: Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, Shprintzen-Goldberg syndrome, MASS phenotype and familial thoracic aortic aneurysm [4]. Clubfeet are a feature of Loeys-Dietz syndrome; in case 7, the absence of hypertelorism, bifid uvula, cleft palate and arterial tortuosity made this diagnosis clinically unlikely, but only molecular testing including *TGFBR1* and *TGFBR2* could exclude it. In case 3, hypertension may have contributed to the aortic disease, but it does not explain the ectopia lentis or the skeletal features.

Homocystinuria shares the marfanoid habitus and ectopia lentis with MFS, but differs by intellectual disability, osteoporosis and thrombosis; some patients respond to pyridoxine (vitamin B6) [15]. Its diagnosis is often delayed: in a Dutch series of 34 patients, the mean delay between ectopia lentis and the diagnosis of homocystinuria was 8 years [15]. It had to be considered in our series, which includes three consanguineous families, patients with ectopia lentis and fractures after minor trauma (cases 3 and 5). Plasma homocysteine was normal in all patients, which makes classical homocystinuria unlikely.

Consanguinity in Morocco

Consanguinity is common in Morocco: 15.25% nationally in a 2009 study, and 26.7% in a 2025 survey in the province of Settat [16, 17]. Among families with autosomal recessive disorders, the rate reaches 59% [16]. MFS itself is dominant and is not favoured by consanguinity. But in this context, recessive marfanoid disorders are more likely to be encountered, which increases the risk of misclassification when no molecular test is available. Case 5, with an affected sister and unaffected consanguineous parents, illustrates this situation.

Genetic Testing: A Financial Barrier

FBN1 testing is not available in our department and must be sent to laboratories abroad; none of our patients could afford it. In Morocco, genetic analyses can cost 1,000 to 5,000 dirhams or more for specialised panels, and molecular genetic tests outside the national nomenclature are generally not reimbursed [18]. By comparison, the 2026 minimum wage in the non-agricultural sector is about 3,423 dirhams gross per month [19]. A single test can therefore represent one or more months of income for many families.

For tests within the nomenclature, mandatory health insurance (AMO) reimburses 70% of the national reference tariff, not of the actual price, so the out-of-pocket share remains high [18]. Many genetic analyses have also long been sent to laboratories abroad, with longer delays and higher costs [20]. These barriers reflect wider challenges: a recent scoping review identified several obstacles to the implementation of genetic services in African healthcare systems [21]. In South Africa, for example, molecular testing for MFS has not yet been incorporated into routine clinical care [22].

The situation is improving. Regional initiatives such as the PerMediNA consortium aim to make genetic testing affordable in North Africa [23], and local genetic testing capacity has recently expanded in Morocco [20]. Until these services reach patients routinely, the consequences of missing molecular confirmation are concrete:

- Four of our patients remain in the suspected category; an *FBN1* variant would confirm the diagnosis in cases 1, 2, 4 and 5 [4];
- No reliable cascade screening of relatives, who must all undergo clinical and echocardiographic follow-up;
- No prenatal or preimplantation diagnosis for affected couples;
- Possible misdiagnosis of conditions with different risks and treatments, such as Loeys-Dietz syndrome.

In this context, we suggest prioritising molecular testing for patients with clinically suspected MFS, in particular those with ectopia lentis but a normal aorta (case 2), for patients with atypical features such as clubfeet (case 7), and for families with several affected members, in order to allow cascade screening. Including *FBN1* sequencing among the analyses covered by AMO would make this possible.

Long-Term Follow-Up

All eight patients remain under regular follow-up, because the phenotype of MFS evolves with age. In children, pectus deformity, scoliosis and the wrist sign become more frequent with age [11]. In adults, new manifestations continue to appear: in a Norwegian cohort re-examined after 10 years, new aortic root dilatation was detected in patients up to 70 years of age and ascending aortic disease rose from 72% to 93% of patients [24]. For young patients whose aorta is still normal, the revised Ghent nosology recommends serial echocardiography before a definite diagnosis is made [4].

This follow-up is particularly important for the four patients with clinically suspected MFS, whose aortic root is normal so far: aortic dilatation appearing later would confirm the diagnosis. Follow-up includes a clinical, echocardiographic and ophthalmological assessment every 6 months, as well as screening of first-degree relatives, in particular the sister of case 5, the daughter and nephew of case 8, and the young siblings of case 4.

Limitations

This study has several limitations. The diagnosis was not confirmed by molecular testing in any

patient. Dural ectasia and protrusio acetabuli were not assessed, so the systemic score may be underestimated. Relatives were not all examined. Finally, the small size of the series does not allow estimation of frequencies. Follow-up, which covers the study period from December 2021 to August 2026, is still short compared with the natural history of the disease, and some features may not yet have appeared.

CONCLUSION

In settings where genetic testing remains unaffordable, the diagnosis of MFS rests on rigorous application of the revised Ghent criteria: systematic measurement of the aortic root Z-score, slit-lamp examination after dilation, a detailed systemic score and a three-generation pedigree. Classifying patients into confirmed MFS, clinically suspected MFS and Marfan-like phenotype makes the uncertainty explicit and guides follow-up. Skeletal features alone are not sufficient: in our series, a high systemic score without aortic involvement or a first-degree family history did not allow a definite diagnosis. Because the features of MFS appear and progress with age, these patients must remain under long-term clinical, cardiological and ophthalmological follow-up. Wider coverage of *FBN1* testing by health insurance in Morocco would confirm the diagnosis in suspected cases, enable cascade screening of relatives and support genetic counselling.

DECLARATIONS

Consent: written informed consent for publication of clinical data and photographs was obtained from all patients or their legal guardians.

Conflicts of Interest: the authors declare no conflict of interest.

Funding: None

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