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GRAND ROUND
Other

A previously undescribed pathogenic variant in FBN1 gene causing Marfan syndrome: a case report

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Background Marfan syndrome (MFS) is an autosomal dominant multisystem connective tissue disorder with increased risk of aortopathy with a high risk of subsequent life-threatening aortic dissection. Diagnosing this condition is reliant on recognizing clinical features and genetic testing for confirming diagnosis, using the revised Ghent criteria.

Case summary We identified a 49-year-old patient who presented with dyspnoea, with Marfan syndrome (MFS) and a previously unreported variant in the fibrillin-1 gene (*FBN1*), designated c.7016G>C. Prior to identifying the new gene variant, this patient did not meet the revised Ghent criteria for MFS diagnosis. We present clinical and molecular evidence supporting the likely pathogenic nature of this variant, leading to earlier therapy and intervention.

Discussion The discovery of a new pathogenic gene will expand the current aortopathy and MFS database and may lead to more informed clinical management decisions for the timing and nature of interventions.

Keywords Case report • Marfan syndrome • FBN1 • Pathogenic variant • Thoracic aortic aneurysm

ESC Curriculum 7.5 Cardiac surgery • 9.1 Aortic disease

Learning points

- To demonstrate that a high index of suspicion for the presence of Marfan syndrome (MFS) should lead to further genetic testing when the diagnosis is not met by Ghent nosology criteria.
- To show that vigorously pursuing the diagnosis of MFS leads to earlier therapy and intervention for cardiovascular complications, such as an aortic aneurysm.

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Introduction

Marfan syndrome (MFS) is an autosomal dominant multisystem connective tissue disorder with an increased risk of aortopathy with a high risk of subsequent life-threatening aortic dissection. Diagnosing this condition is reliant on recognizing clinical features, such as skeletal abnormalities that may include long thin extremities, sternal abnormalities, scoliosis, arachnodactyly, joint hypermobility, flat feet, and associated abnormalities like high arched palate. In addition, one would look for striae, lens dislocation, and cardiac abnormalities including mitral valve prolapse and mitral regurgitation.[1] Diagnosis may also be reliant on genetic testing, and the revised Ghent criteria[2] (*Table 1*).

Timeline

Month 0
First Cardiology Clinic visit
Month 1
Laboratory blood tests
Electrocardiogram
Transthoracic echocardiogram
Stress myocardial perfusion imaging
Month 3
Coronary angiogram
Computed tomography chest angiography
Cardiac magnetic resonance imaging
Month 4
Genetic medicine consultation
Genetic testing
Month 5
Cardiovascular surgery consultation
Month 7
Cardiovascular surgical intervention performed
Month 20
Follow-up assessment and imaging.

Case presentation

A 49-year-old Caucasian male was referred to Cardiology Clinic with progressive shortness of breath on exertion; New York Heart Association (NYHA) functional Class II. He denied any other symptoms suggestive of heart failure, arrhythmias, or ischaemia. He had no history of diabetes mellitus, hypertension, respiratory illnesses, renal disease, or coronary artery disease. The patient smoked since adolescence but quit 4 years prior to his visit. The patient was not on chronic medications. He was estranged from his family for a very long time, and he had no details about their medical history or care.

On physical examination, the patient was found to be tall at 198 cm, and weighed 101 kg. He had a blood pressure of 90/60 mmHg sitting, heart rate of 70 beats per minute, cardiovascular examination revealed jugular venous pulsation to be within normal limits, a normal S1 and S2, no S3 or S4, and a systolic ejection murmur, Grade 1/6 on the Levine scale, over the aortic area with no radiation. There was no evidence of heart failure, including no pedal oedema. He had a positive wrist sign, and dysmorphic features including enophthalmos, malar hypoplasia, retrognathia, and pectus carinatum. The rest of his physical examination was unremarkable.

Laboratory workup included a normal haemoglobin and creatine of 151 g/L and 84 µmol/L, respectively. Electrolytes and liver function results were within normal limits.

An electrocardiogram was performed and was normal (*Figure 1*). Heart failure biomarkers (BNP or NT-proBNP) would have been useful to diagnose heart failure but were not available within the regional health care system. He underwent stress myocardial perfusion imaging that ruled out ischaemia but demonstrated a left ventricular ejection fraction (LVEF) of 36% at rest and 43% post-stress. A transthoracic echocardiogram revealed left ventricular (LV) global hypokinesis, with LVEF of 40–45%. There was mild aortic insufficiency. The aortic root was dilated at 4.9 cm in diameter and Z-score of 4.66 (*Figure 2*).

Computed tomography angiography of the thoracic aorta revealed dilated coronary sinuses at 4.4 cm × 4.6 cm × 4.8 cm (*Figure 3*). A cardiac MRI study revealed a mildly reduced LVEF at 43%, with evidence of mild concentric LV hypertrophy (*Video 1*).

Given the patient's clinical features, and the dilated aortic root, MFS was suspected, but he did not meet the criteria for diagnosis when applying the revised Ghent Criteria for Diagnosing Marfan Syndrome (*Table 1*), with only the presence of aortic Z-score > 2 and 4 points for systemic findings. Therefore, genetic investigations were sent. The molecular genetics report for MFS and related aortopathies revealed that this patient is heterozygous for a sequence variant in the fibrillin-1 gene (*FBN1*), designated NM_000138.4: c.7016G>C (*Table 2*), which is predicted to result in the amino acid substitution p. Cys2339Ser. Cysteine residues in fibrillin-1 (FBN1) form disulfide bonds which are important for proper protein folding. The substitution of a different amino acid in FBN1 can create or destroy a cysteine residue and results in disruption of the disulfide bonds which causes protein misfolding that has been reported to cause MFS phenotypes.[1,3] This particular variant has not been reported previously and is absent in the Genome Aggregation Database (GnomAD) population database, as well as ClinVar, which are the resources that aggregate, harmonize, and archive sequencing data and the relationships among genetic variations and phenotypes.

Different substitutions affecting the same amino acid residue (p.Cys2339Tyr; p. Cys2339Arg; p. Cys2339Gly) were reported to be pathogenic for MFS.[4,5]

The patient was started on ramipril and metoprolol with titration as tolerated. According to guideline recommendations,[6,7] the patient underwent a valve-sparing root replacement, an excellent outcome, and recovery (*Figure 4*). There were no postoperative complications. At 13 months of follow-up, the patient's shortness of breath was resolved and he was pleased to return to his excellent premorbid status. The patient's echocardiogram at 13 months post-operatively revealed an intact aortic repair and graft, with only mild aortic valve insufficiency and an improved LVEF at 55%. The patient remains clinically well.

Discussion

Marfan syndrome is an autosomal dominant multisystem connective tissue disorder. It is the result of mutations in the *FBN1*, a gene made of 66 exons which is located on chromosome 15q21.1.[8] There are over 2000 mutations identified that are associated with MFS. Many reported pathogenic variants are private variants, only found in one individual or family. Clear genotype–phenotype correlations have been difficult to establish, as all of the identified *FBN1* variants to date appear to be involving almost all the gene 66 exons.[9] This has resulted in limitation in correlating specific genetic variant's association with certain severe phenotypes, like aortic aneurysms or LV dysfunction.

Fibrillins are essential components of the extracellular matrix of the connective tissue, and as a result, mutations in the genes encoding fibrillins can result in significant disruption of the structure of the connective tissue.[10]

A clinical diagnosis is made using the revised Ghent nosology, which will diagnose or exclude MFS in ~95% of cases.[2] The penetrance of some features is age dependent, so the nosology must be

Table 1 Criteria for Marfan syndrome diagnosis from revised Ghent criteria

Diagnosis of MFS in the absence of family history:
(1) Aortic root dilatation Z ≥ 2 AND ectopia lentis = MFS
(2) Aortic root dilatation Z ≥ 2 AND FBN1 = MFS
(3) Aortic root dilatation Z ≥ 2 AND systemic score ≥ 7 = MFS
(4) Ectopic lentis AND FBN1 associated with known aortic dilatation = MFS
In the presence of family history:
(5) Ectopia lentis AND family history of MFS = MFS
(6) Systemic score ≥ 7 AND family history of MFS = MFS
(7) Aortic root dilatation Z ≥ 2 above 20 years old, ≥ 3 below 20 years old +family history of MFS = MFS

FBN1, fibrillin-1 mutation; MFS, Marfan syndrome; Z, Z-score.
These criteria are applied in absence of discriminating features of Shprintzen Goldberg syndrome, Loeys-Dietz syndrome, or vascular Ehlers Danlos syndrome.

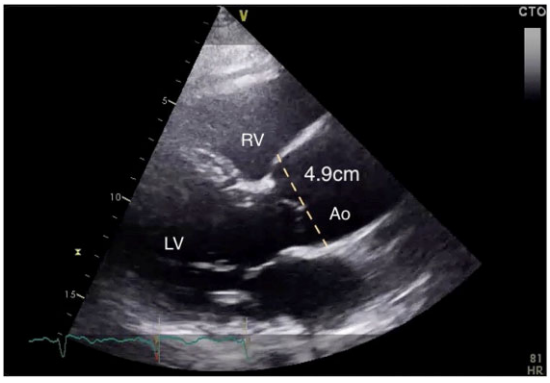


Figure 2 2D echocardiogram (parasternal long-axis view) showing the dilated aortic root. Ao, aortic root; LV, left ventricle; RV, right ventricle.

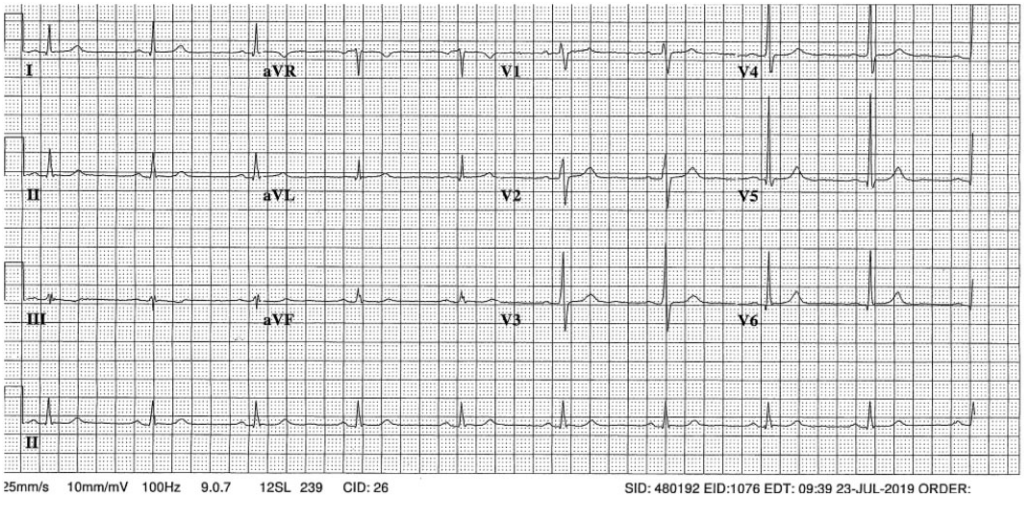


Figure 1 Twelve-lead electrocardiogram revealing sinus bradycardia, otherwise normal.

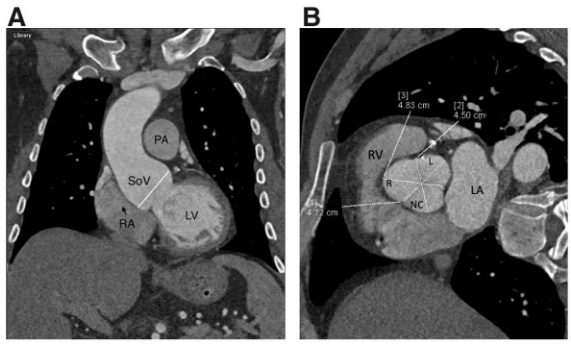
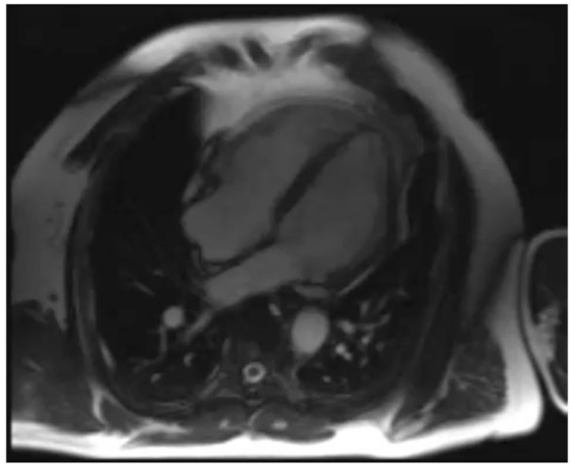


Figure 3 Coronal view (*A*) and axial view (*B*) cardiac computed tomography demonstrating dilated sinuses of valsalva. CT, computed tomography; L, left coronary sinus; LA, left atrium; LV, left ventricle; NC, non-coronary sinus; PA, main pulmonary artery; R, right coronary sinus; RA, right atrium; RV, right ventricle; SoV, sinuses of valsalva.



Video 1 Four-chamber view cardiac magnetic resonance demonstrating mildly reduced left ventricular systolic function. MRI, magnetic resonance imaging.

used with caution in young patients. Molecular testing may be helpful in this context.

A small number of clinical trials in MFS patients support the use of beta-blockers or losartan in combination with beta-blockers in lowering the rate of aortic root dilatation, though these studies do not show a difference in aortic dissection incidence. Accordingly, there is a possible benefit in initiating these medication in MFS patients, even with a mildly dilated aortic root.[6] In addition, the threshold for surgical intervention in the form of thoracic aortic repair or replacement, is an aortic root diameter equal to or greater than 5.0 cm in the case of MFS, compared to a 5.5 cm threshold for a degenerative thoracic aortic aneurysm.[6,7] This is based on results of previous studies that showed MFS patients with aortic root diameters of 5.0 cm or greater have an annual risk of death or aortic dissection of 0.17%, while MFS

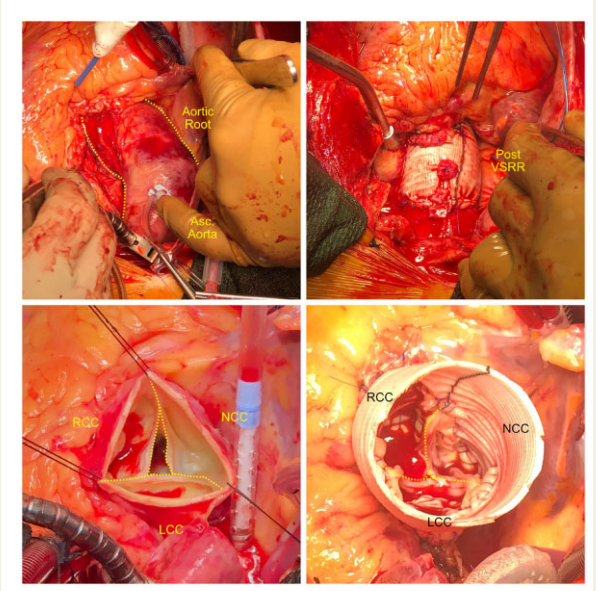


Figure 4 Valve-sparing aortic valve replacement. Asc. Aorta: ascending aorta; LCC, left coronary cusp; NCC, non-coronary cusp; RCC, right coronary cusp of the aortic valve; VSRR, valve-sparing aortic root replacement.

Table 2 Undescribed mutation in FBN-1 gene

Gene, transcript	Mode of inheritance, gene OMIM®	DNA variations, predicted effects, zygosity	dbSNP ID number	Highest allele frequency in a gnomAD population	*In silico* missense predictions	Interpretation
FBN-1, NM_000138.4	AD, 134797	c.7016G>C, p. Cys2339Ser, Heterozygous	Undocumented	Not present	Damaging	Likely pathogenic

AD, autosomal dominant; dbSNP, single nucleotide polymorphism database; gnomAD, genome aggregation database; OMIM®, Online Mendelian Inheritance in Man®.

patients with aortic root diameters of <5.0 cm have an annual risk of <0.05% for death or aortic dissection.[11]

Although MFS is a multisystem connective tissue disorder, the main causes of morbidity and mortality are due to its cardiovascular system involvement. Medical literature review demonstrates that untreated aortopathies, including aortic aneurysms and dissection, and valvular abnormalities associated with MFS lead to a shortened life expectancy.[12] This highlights the importance of a robust diagnostic workup and early referral of patients with confirmed MFS by their physicians to cardiologists for a thorough assessment of cardiovascular abnormalities, as well as to other specialists, like ophthalmologists, to address associated features like lens dislocation, spine specialists to address spinal deformities, and respirologists for issues like spontaneous pneumothorax due to bullous lung disease.

Another important point of discussion is the presence of LV dysfunction in association with MFS. A growing body of evidence in the medical literature shows that of all subjects diagnosed with MFS, it is estimated that 8% will develop secondary LV dysfunction due to significant mitral or aortic valvular regurgitation or ischaemic heart disease, while primary LV dysfunction can be found in 3% of all MFS population.[13] The exact underlying mechanism of developing primary LV dysfunction is still a matter of debate. Since the myocardium also contains fibrillin, a theorized pathological process involving structural myocardial fibrillin defects due to the *FBN1* pathological variants may provide an explanation for the development of LV dysfunction in the absence of significant valvular disease.[14] Although the exact cause of this patient's systolic dysfunction is unknown, we speculate that it may be, at least in part, due to primary cardiomyopathy seen in some patients with MFS.

Clinical and genetic screening of family members of subjects with MFS is indicated. In this case, the patient was estranged from his family and was not able to make contact with them.

Conclusion

This newly reported data will expand the current aortopathy and MFS database and may lead to more informed clinical management decisions such as earlier treatment and surgical repair for an aortic aneurysm and screening of family members where possible.

Lead author biography

Asem Suliman, MD, Finished his medical education and training at Garyounis University, Benghazi, Libya. Dr. Suliman moved to Canada and pursued post graduate training in internal medicine at Memorial University of Newfoundland and Labrador, then Cardiology at University of Manitoba. He is finishing a year in Advanced Echocardiography training at McMaster University in Hamilton, Canada. His interests include cardiac imaging, heart failure, and preventative cardiology.

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Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that consent for submission and publication of this case report including images, laboratory work and associated text has been obtained from the patient in line with COPE guidance.[15]

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