Published in final edited form as:
Am J Med Genet A. 2010 February ; 152A(2): 413–416. doi:10.1002/ajmg.a.32856.

FBN1 Mutations in Patients With Descending Thoracic Aortic Dissections

Ariel Brautbar[1], **Scott A. LeMaire**[2,3], **Luis M. Franco**[1], **Joseph S. Coselli**[2,3], **Dianna M. Milewicz**[3,4], and **John W. Belmont**[1,*]

[1]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas

[2]Division of Cardiothoracic Surgery, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, Texas

[3]The Texas Heart Institute at St. Luke's Episcopal Hospital, Houston, Texas

[4]Department of Internal Medicine, University of Texas Health Science Center at Houston, Houston, Texas

Abstract

Aortic aneurysm and dissection cause significant morbidity and mortality. There are several known single gene disorders that predispose to isolated aortic disease and eventually aneurysm and dissection. *FBN1* mutations are associated with multiple clinical phenotypes, including Marfan syndrome (MFS), MASS phenotype, and familial ectopia lentis, but rarely with isolated aortic aneurysm and dissection. In this report, we describe three patients who presented with primary descending thoracic aortic dissection and who were found to have an *FBN1* mutation. None of the patients fulfilled clinical criteria for the diagnosis of MFS, and all had few or none of the skeletal features typical of the condition. Two patients had a history of long-term hypertension, and such a history was suspected in the third patient. These observations suggest that some individuals with *FBN1* mutations have significant aortic disease involvement of other systems that is typical of *FBN1* mutation-related syndromes. Superimposed risk factors, such as hypertension, may weaken the aortic wall and eventually lead to aortic dissection. Given that the cost continues to decrease, we suggest that diagnostic DNA sequencing for *FBN1* mutations in patients with thoracic aortic aneurysms and dissection may be a practical clinical step in evaluating such patients and at-risk family members.

Keywords

FBN1; aortic dissection; hypertension

INTRODUCTION

In recent years, major progress has been made in unraveling the molecular basis for predisposition to thoracic aortic aneurysms and dissections. A number of single-gene disorders,such as those caused by mutations in *TGFBR2*, *MYH11*, and *ACTA2*, have been associated with non-syndromic thoracic aortic aneurysms and dissection in adults [Pannu et al., 2005; Zhu et al., 2006; Guo et al., 2007]. Specific disorders, such as Marfan syndrome

*Correspondence to: John W. Belmont, M.D., Ph.D., Professor, Co-Director Cardiovascular Genetics Clinic, Department of Molecular and Human Genetics and Pediatrics, Baylor College of Medicine, One Baylor Plaza, R715, Houston, TX 77030. jbelmont@bcm.tmc.edu.

(MFS) and Ehlers Danlos syndrome (EDS), involve other organ systems, such as the skeleton, ocular structures, lungs, and skin, and are therefore called inherited connective tissue diseases [De Paepe et al., 1996; Beighton et al., 1998]. MFS is the most common inherited connective tissue disorder associated with aorticaneurysm and dissection. It is caused by mutations in the *FBN1* gene and is dominantly inherited. The diagnosis of MFS is based on the Ghent criteria and requires major involvement of two organ systems and minor involvement of a third. If a first-degree relative is known to have the condition, involvement of one major and one minor system is sufficient for diagnosis [De Paepe et al., 1996]. *FBN1* mutations can cause various phenotypes, including MFS, MASS phenotype, familial ectopia lentis, marfanoid habitus, and neonatal MFS [Glesby and Pyeritz, 1989; Kainulainen et al., 1994; Comeglio et al., 2002]. Only a few cases have been reported in which *FBN1* mutations led to isolated ascending aortic aneurysm or dissection [Francke et al., 1995; Milewicz et al., 1996].

In this report, we describe three patients who presented with descending thoracic aortic dissections and were subsequently found to have novel *FBN1* mutations, but who did not meet the clinical criteria for MFS. These patients presented with descending aortic dissection with or without significant aortic root dilation. The cases described here emphasize the fact that a condition caused by an underlying *FBN1* mutation may be difficult to diagnose in the absence of overt skeletal features. These data suggest that *FBN1* mutation may have a significant causal role in descending aortic dissections in a subset of patients who do not have typical features of MFS. Without molecular investigation, these cases are most likely to be attributed to a “sporadic” dissection event associated with the usual risk factors, such as hypertension. We recommend that all patients who present with thoracic aortic dissection and, in particular, descending aortic dissection be assessed carefully for connective tissue disease. As *FBN1* mutation analysis becomes more available and less costly, it may become a valuable screening tool for identification of this important subset of patients.

CLINICAL REPORTS

Patient 1

A 56-year-old Caucasian woman presented with acute descending aortic dissection (DeBakey type III) originating distal to the left subclavian artery and extending to the iliac arteries. Her medical history was significant for hypertension for 10 years treated with medication, including lisinopril, amlodipine, and metoprolol. She had ischemic heart disease, including history of myocardial infarction at age 47. She had stopped smoking 3 years before admission, and she consumed alcohol socially. Her surgical history included cholecystectomy and hysterectomy, with no postoperative complications. A computerized tomography (CT) scan at presentation showed dissection of the descending aorta and 5.6-cm dilation of the aortic root. Dural ectasia, was suspected on CT but was not observed on a subsequent MRI. Other stigmata of MFS were not documented. An aortic stent graft was placed to treat the descending dissection. The patient was lost to follow-up until 2 years later, when at age 58, she presented with an acute ascending aortic dissection that was emergently repaired.

The family history was significant for the patient's mother dying of unknown cause at age 62. The patient was the youngest of 12 siblings, all of whom died before the age of 65. Two brothers died suddenly at unknown ages. The circumstances and age of death were unknown for the other members of the family. There was no history of MFS diagnosis in this family. On physical examination, the patient's height was 177.5 cm, arm span was 178.5 cm, and upper to lower segment ratio was less than 0.85. There were no other skeletal features of MFS, and an eye exam was normal (Table I). The remainder of the Ghent criteria were

negative. *TGFBR1* and *TGFBR2* sequencing were normal. *FBN1* DNA sequencing identified a missense mutation, c4467T > A, which is predicted to lead to N1489L substitution in exon 36.

Patient 2

A 16-year-old Hispanic male presented with descending aortic dissection originating immediately distal to the origin of the left subclavian artery, extending into the abdominal aorta, and terminating at the level of the right common iliac artery. The patient's medical history included several syncopal episodes that were never evaluated. Family history was positive for sudden death of his father from a brain aneurysm at age 41 after a long history of diabetes and hypertension. None of the patient's family members were available for clinical or genetic evaluation. On physical examination, height was 193 cm, and there was mild pectus excavatum, striae atrophica, and myopia (Table I). A CT scan showed moderate aortic root dilatation of 3.8 cm at the level of the sinuses of Valsalva. Although there was no documentation of hypertension before his admission, his postoperative period was complicated by persistent hypertension with maximum systolic pressures of 145 mm Hg. *FBN1* DNA sequencing showed a heterozygous 7 base pair deletion c4253_4259delGCCAGTG in exon 34. The deletion leads to a frameshift and predicts a premature stop codon within 55 codons downstream of the deletion boundary.

Patient 3

A 24-year-old Caucasian man presented with descending aortic dissection originating distal to the subclavian artery and extending to the level of the renal arteries. Although echocardiography did not show aortic root dilation, the aortic root diameter on CT scan measured 4.5 cm. His medical history included resolved immune thrombocytopenic purpura and hypertension that was diagnosed during his early teens; however, at that time, no evaluation was performed to identify the cause of the hypertension, and no medication was prescribed. On physical examination, height was 193 cm, arm span was 208 cm, and lower segment was 100 cm (Table I). He had positive wrist and thumb sign and striae. His eye exam was normal. There was no family history of sudden death events or MFS. *FBN1* sequencing revealed heterozygous c1109insG in exon 9 leading to a predicted frameshift. Evaluation of the patient's 20-year-old sister and 26-year-old brother revealed that both had multiple striae atrophica on the trunk. The sister also had positive wrist and thumb sign, pes planus, and high arched palate. However, both siblings tested negative for the specific *FBN1* mutation found in the proband, and they both had normal aortic root measurements on echocardiography.

DISCUSSION

FBN1 mutations have been associated with variable clinical phenotypes, ranging from the MASS phenotype to classic MFS, isolated ectopia lentis, and isolated ascending aortic aneurysm and dissection [Glesby and Pyeritz, 1989; Kainulainen et al., 1994; Francke et al., 1995; Milewicz et al., 1996; Comeglio et al., 2002]. Francke et al. [1995] reported a kindred with Gly1127Ser mutation in an EGF-like domain of fibrillin-1 that was associated with ascending aortic dissection and dilation. A few family members had minor skeletal features of MFS. All family members had tall stature, regardless of the presence or absence of *FBN1* mutation, and aneurysmal surgical correction was usually performed for the positive patients in their 60s or later. Milewicz et al. [1996] described two patients who presented with aortic root dilation in their early 30s and 40s. Both patients had few Marfan skeletal features but had confirmed *FBN1* missense mutations.

Here we describe three patients who presented with dissection of the descending aorta and who, while exhibiting some features suggestive of MFS, did not fulfill Ghent criteria. All three patients had *FBN1* alterations that were causative of their aortic disease (Table II). Interestingly, Patient 3 had some of the skeletal criteria for MFS, including skin striae and wrist and thumb sign. However, both of his siblings had multiple striae, and one sibling met two of the same skeletal criteria as the proband. Because both siblings were negative for their brother's mutation, these findings may be mostly familial and unrelated to his *FBN1* mutation. In contrast to past reports [Francke et al., 1995; Milewicz et al., 1996] of patients with isolated aortic aneurysm relatively late in life, two of our patients—Patients 2 and 3—presented with dissection under the age of 30 years. Patient 2 was of Hispanic origin and had only minor involvement of the skeletal system. A recent report describes three large Hispanic families with cardiac and/or ocular features of MFS but little to no involvement of the skeletal system [Villamizar et al., 2009]. Patient 2 may be similar to these patients. Both Patients 1 and 2 had mutations that are expected to result in a truncated protein. However, Patient 1 presented with dissection of her descending aorta at 56 years of age and had an *FBN1* missense mutation.

Our findings suggest that certain missense mutations may result in aortic disease in the absence of ocular and skeletal features of MFS. Such a conclusion was also proposed by both Milewicz et al. [1996] and Francke et al. [1995]. Faivre et al. [2008] evaluated retrospectively a population of 1,009 patients from a large MFS registry. They examined the utility of *FBN1* mutation analysis when clinical criteria for diagnosis of MFS were not met. Interestingly, 7% of their study population had involvement of the descending or abdominal aorta. However, it is unclear how many of these individuals belonged to the group of patients that did not fulfill clinical criteria for diagnosis. One of Faivre et al.'s important findings was that 55% of adult patients with unfulfilled clinical criteria were correctly diagnosed after addition of FBN1 testing. In many of these patients, involvement of the cardiovascular system was lacking initially; there was only partial skeletal and ocular system involvement at the time of evaluation.

Indeed, in our Patients 2 and 3, FBN1 testing was triggered by the partial skeletal phenotype. However, these individuals had already major involvement of the cardiovascular system at time of presentation and still did not meet the Ghent criteria. In contrast to physical findings suggestive of connective tissue disease, family history of sudden death was the trigger for FBN1 testing in Patient 1. In all cases, other possible genetic causes were considered, and in some, genetic testing was performed as detailed in Table I.

We would like to suggest that for particular *FBN1* mutations, perhaps in the presence of a permissive genetic background, clinical expression of the disease is mostly vascular. Interestingly, in at least two of our patients and probably in the third, there was a clear history of hypertension. Hypertension may have been an important risk factor for aneurysm or dissection of a descending aorta already weakened by an *FBN1* mutation.

These observations raise the possibility that there are individuals with *FBN1* mutations who have mild non-vascular involvement but who have significant aortic disease, including descending aortic dissections. Superimposed factors that may weaken the aortic wall, such as long-term hypertension, may be additional risk factors that lead to the overt clinical phenotype. It would appear clinically relevant to have all patients with descending thoracic aortic dissection carefully screened for connective tissue disease. In some of these cases, FBN1 sequencing may contribute to understanding the patient's underlying predisposition.

As the cost of sequencing decreases, it would seem reasonable to obtain DNA diagnostic sequence analyses for *FBN1* mutations in most patients presenting with descending thoracic

aortic aneurysms and dissection. An important practical motivation for such investigation include the potential role of angiotensin receptor blockers (ARB) as a preventive measure for treatment of both the proband and their at-risk family members, in whom medical and surgical therapy could prevent aortic aneurysm formation or dissection. Further study is needed to understand the subset of patients who have underlying *FBN1* mutations and present with descending TAA and dissection.

Acknowledgments

This work was conducted within the Specialized Center of Clinically Oriented Research (SCCOR) in Thoracic Aortic Aneurysms and Dissections (P50 HL083794; DMM, JSC, JWB, SAL) and was supported in part by a Thoracic Surgery Foundation for Research and Education/National Heart, Lung, and Blood Institute Co-sponsored Mentored Clinical Scientist Development Award (K08 HL080085; SAL). Stephen N. Palmer, PhD, ELS, contributed to the editing of this manuscript.

REFERENCES

Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. Ehlers-Danlos syndromes: Revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). Am J Med Genet. 1998; 77:31–37. [PubMed: 9557891]

Comeglio P, Evans AL, Brice G, Cooling RJ, Child AH. Identification of FBN1 gene mutations in patients with ectopia lentis and marfanoid habitus. Br J Ophthalmol. 2002; 86:1359–1362. [PubMed: 12446365]

De Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. Am J Med Genet. 1996; 62:417–426. [PubMed: 8723076]

Faivre L, Collod-Beroud G, Child A, Callewaert B, Loeys BL, Binquet C, Gautier E, Arbustini E, Mayer K, Arslan-Kirchner M, Stheneur C, Kiotsekoglou A, Comeglio P, Marziliano N, Halliday D, Beroud C, Bonithon-Kopp C, Claustres M, Plauchu H, Robinson PN, Adès L, De Backer J, Coucke P, Francke U, De Paepe A, Boileau C, Jondeau G. Contribution of molecular analyses in diagnosing Marfan syndrome and type I fibrillinopathies: An international study of 1009 probands. J Med Genet. 2008; 45:384–390. [PubMed: 18310266]

Francke U, Berg MA, Tynan K, Brenn T, Liu W, Aoyama T, Gasner C, Miller DC, Furthmayr H. A Gly1127Ser mutation in an EGF-like domain of the fibrillin-1 gene is a risk factor for ascending aortic aneurysm and dissection. Am J Hum Genet. 1995; 56:1287–1296. [PubMed: 7762551]

Glesby MJ, Pyeritz RE. Association of mitral valve prolapse and systemic abnormalities of connective tissue: A phenotypic continuum. JAMA. 1989; 262:523–528. [PubMed: 2739055]

Guo DC, Pannu H, Tran-Fadulu V, Papke CL, Yu RK, Avidan N, Bourgeois S, Estrera AL, Safi HJ, Sparks E, Amor D, Ades L, McConnell V, Willoughby CE, Abuelo D, Willing M, Lewis RA, Kim DH, Scherer S, Tung PP, Ahn C, Buja LM, Raman CS, Shete SS, Milewicz DM. Mutations in smooth muscle alpha-actin (ACTA2) lead to thoracic aortic aneurysms and dissections. Nat Genet. 2007; 39:1488–1493. [PubMed: 17994018]

Kainulainen K, Karttunen L, Puhakka L, Sakai L, Peltonen L. Mutations in the fibrillin gene responsible for dominant ectopia lentis and neonatal Marfan syndrome. Nat Genet. 1994; 6:64–69. [PubMed: 8136837]

Milewicz DM, Michael K, Fisher N, Coselli JS, Markello T, Biddinger A. Fibrillin-1 (FBN1) mutations in patients with thoracic aortic aneurysms. Circulation. 1996; 94:2708–2711. [PubMed: 8941093]

Pannu H, Fadulu VT, Chang J, Lafont A, Hasham SN, Sparks E, Giampietro PF, Zaleski C, Estrera AL, Safi HJ, Shete S, Willing MC, Raman CS, Milewicz DM. Mutations in transforming growth factor-beta receptor type II cause familial thoracic aortic aneurysms and dissections. Circulation. 2005; 112:513–520. [PubMed: 16027248]

Villamizar C, Regalado ES, Fadulu VT, Hasham SN, Gupta P, Willing MC, Kuang SQ, Guo D, Muilenburg A, Yee RW, Fan Y, Towbin J, Coselli JS, Lemaire SA, Milewicz DM. Paucity of skeletal manifestations in hispanic families with FBN1 mutations. Eur J Med Genet. 2009 Epub ahead of print.

Zhu L, Vranckx R, Khau Van Kien P, Lalande A, Boisset N, Mathieu F, Wegman M, Glancy L, Gasc JM, Brunotte F, Bruneval P, Wolf JE, Michel JB, Jeunemaitre X. Mutations in myosin heavy chain 11 cause a syndrome associating thoracic aortic aneurysm/aortic dissection and patent ductus arteriosus. Nat Genet. 2006; 38:343–349. [PubMed: 16444274]

TABLE I. Clinical Features of the Patients According to the Ghent Nosology

Patient	**1**	**2**	**3**
Skeletal			
Age (yr)	58	16	24
Height (cm)	177.5	193	193
Weight (kg)	86.18	77	78
BSA (m^2)	2.06	2.03	2.04
Major			
Upper/lower segment ratio	1.005	NR	0.93
Arm span/height ratio	0.848	+[b]	1.077
Scoliosis of >20°	−	−	−
Thumb and wrist sign	−	−	+
Reduced extension of elbows	−	−	−
Pectus excavatum requiring surgery	−	−	−
Minor			
High arched palate	+	+	−
Facial appearance	−	−	−
Medial displacement of the medial malleolus	−	−	−
Joint hypermobility	−	−	−
Crowding of teeth	−	−	−
Ocular			
Ectopia lentis	−	−	−
Cardiovascular			
Major			
Aortic root dimension (cm)	5.6[a]	3.8[a]	4.5[a]
Aortic regurgitation	+	−	−
Minor			
Mitral valve prolapse	−	−	−
Mitral annular calcification	−	−	−
Skin and integument			
Striae atrophicae	−	+	+
Gene testing other than FBN1			
TGFBR1	nl	ND	nl
TGFBR2	nl	ND	nl
COL3A1	ND	ND	nl

+, Present; −, absent.

ND, not done; nl, normal; NR, not recorded.

[a]Greater than stated range of dimensions (1.7–3.4) cm.

[b]By report more than 1.05.

TABLE II. *FBN1* Mutations and Expected Protein Abnormalities of the Patients

	Mutation	**Protein**	**Comment**
Patient 1	c.4467T>A	N1489K	Evolutionary conserved amino acid
Patient 2	c.4253_4259delGCCAGTG	Premature stop codon 55 codons downstream of the deletion	Truncating mutation
Patient 3	c.1109_1110insG	Premature stop codon 5 codons downstream of the insertion	Truncating mutation