Haploinsufficient *FBN1* variants are associated with a higher risk of aortic complications in pregnant women with Marfan syndrome

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ABSTRACT

Background and purpose: Haploinsufficient (HI) *FBN1* variants have been shown to be associated with a higher risk of aortic events in the Marfan syndrome (MFS) population compared with dominant negative (DN) variants. We sought to determine whether *FBN1* genotype is associated with the rate of obstetric/fetal outcomes and aortic complications in prima- and multigravida women.

Methods: This retrospective study analyzed clinical data collected for 52 prima- and multigravidas with MFS who were genotype-positive for DN or HI *FBN1* variants.

Results: Overall, 62% of the women developed primary (aortic dissection or aneurysm rupture) or secondary (corrective surgery or aortic dilatation) outcomes. The HI genotype was associated with a 4-fold higher rate of aortic events compared with the DN genotype (P = 0.03). The peripartum period tended to show a higher rate of aortic events in the HI group (0 DN vs 4 HI subjects, P = 0.14), in which 2 cases were fatal. MFS diagnosis was made after pregnancy in 60% of the subjects. There was no difference in obstetric/fetal outcomes between the DN and HI groups.

Conclusions: Pregnant women with HI variants in *FBN1* had an overall higher rate of aortic events compared with those with DN variants. Our data suggest that women with suspected MFS may benefit from confirmatory molecular genetic testing prior to pregnancy.

KEYWORDS

Marfan syndrome, *FBN1*, fibrillin-1, pregnancy, aortic dissection, aortic aneurysm.

Introduction

Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder characterized by skeletal, ocular, and cardiovascular manifestations. Cardiovascular manifestations affect about 80% of MFS patients and may include aortic dilatation, aneurysm, mitral valve and tricuspid valve prolapse, and enlargement of the proximal pulmonary artery [1].

MFS is caused by pathogenic variants in the *FBN1* gene that encodes fibrillin-1, a major extracellular component of connective tissue, which contains many cysteine-rich domains crucial for forming microfibrils. Fibrillin microfibrils play a key role in maintaining physical properties of tissues, proper transduction of mechanical forces, and regulation of transforming growth factor-β (TGFβ) signaling [2]. Thus, any genetic variant that is predicted to affect the structure of elastic fibers and extracellular matrix may alter TGFβ bioavailability and signaling, which are proposed molecular pathophysiological mechanisms underlying the phenotypic presentation of MFS [3].

Haploinsufficient (HI) *FBN1* genetic variants result in a reduced amount of and/or unstable fibrillin-1 protein, while dominant-negative (DN) variants are often associated with abnormal fibrillin-1 folding. About two-thirds of *FBN1* pathogenic variants [these are typically missense, but can include in-frame insertion/deletion (indel) variants] are DN and mostly impact cysteine and calcium-binding residues that then affect extracellular matrix organization by disrupting fibrillin-1 folding and protein–protein interactions [4,5]. In contrast, HI variants (mostly nonsense, frameshift, and splice site variants) are associated with decreased TGFβ sequestration, and consequently elevated TGFβ levels [3]. Disrupted structure of the extracellular matrix and aberrant TGFβ signaling pathways resulting from pathogenic variants in *FBN1* manifest in 60-80% of adult MFS patients as progressive aortic root dilatation [6].

Aortic dilatation is a major risk factor for thoracic aortic aneurysm and dissection, which are the leading causes of morbidity and mortality in MFS patients [7]. The progression of aortic disease and aortic events such as aortic dissection have been shown to be associated with *FBN1* genotype [8,9]. This suggests that *FBN1* genotype may be an important factor to be consid-

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ered in the clinical management of MFS patients.

Pregnancy is associated with hemodynamic changes such as increases in blood volume and heart rate, and hormonal changes that affect the normal function of aortic elastic fibers, and therefore may increase the risk of aortic events [10]. While the rate of aortic dissection during pregnancy in the general population is low (0.0004%), it is 4-fold higher in patients with a documented connective tissue disorder such as MFS [11–14]. Significantly higher rates of fetal and neonatal complications are also associated with maternal MFS [15].

Data describing the association between *FBN1* genotypes, aortic events and pregnancy outcomes are currently limited. Such data could prove beneficial in guiding MFS pregnancy risk counselling and peripartum management; therefore, in this study, we retrospectively reviewed the clinical data of 52 *FBN1* genotype-positive prima- and multigravida women with MFS to investigate the rates of aortic complications, related death and pregnancy outcomes.

Patients and methods

Study design and patient population

In this descriptive study, Mayo Clinic electronic health records dated from January 1990 to March 2018 were searched to identify prima- and multigravida women aged 18 years and older with MFS-related genetic testing. Additional subjects were identified through a search of the Mayo Clinic Laboratories' genetic testing database (Rochester, MN, USA). General and obstetric history data were obtained from clinic notes spanning the following time periods: before pregnancy, pregnancy, postpartum (3 months following childbirth), and post-pregnancy. The observation time was defined as the median time between last pregnancy and the time of the primary outcome, or secondary outcome (when the primary one was absent), or the date of the last available clinical record for those who were event-free at the end of observation (as of March 2018).

Collected data included the time of genetic MFS diagnosis, maternal age at the time of pregnancy, history of miscarriage, stillbirth and neonatal death, delivery mode, and family history of MFS. Clinical records were reviewed for the indication of aortic root dilatation, aneurysm, corrective surgery, aortic dissection and aneurysm rupture. Information regarding ocular and skeletal manifestations was also collected.

Other patient population data used for comparison (i.e. data from MFS male and nulligravida women aged > 18 years old) were collected as previously described [8]. Pathogenic and likely pathogenic *FBN1* variants (according to American College of Medical Genetics/Association for Molecular Pathology 2015 guidelines) [16] were classified as HI and DN as described previously [8]. The study was approved by the Mayo Foundation Institutional Review Board and patient informed consent was not required.

Outcomes

Obstetric/fetal outcomes were defined as miscarriage, preterm birth (before 37 weeks of pregnancy), preterm loss, stillbirth and neonatal death. The following were defined as primary cardiovascular endpoints: aortic dissection, aneurysm rupture, and/or death related to aortic dissection/aneurysm rupture. Aortic dissection was defined as any dissection (type A or type B); aneurysm rupture was defined as any type (abdominal, cerebral or thoracic). Secondary endpoints were aortic corrective surgery or aortic root dilatation.

Statistical analysis

A T-test was used to perform comparisons of continuous variables, and a chi-square test (or Fisher's exact test as appropriate) was used for comparisons of nominal variables between groups. In a sensitivity analysis, we limited our sample to probands only (n = 43). Data are presented as mean ± standard deviation or count and percentage. P-values < .05 were considered statistically significant.

Results

Study population

Clinical and genetic data were collected for 52 prima- and multigravida women with pathogenic or likely pathogenic *FBN1* variants: 22 were classified as DN and 30 as HI (Supplemental Table 1). The average maternal age at the time of last pregnancy or pregnancy with a primary aortic complication was 28 years, and it ranged from 19 to 44 years. There was no significant maternal age difference between the DN group and HI group (28 ± 5 years vs 27 ± 8 years, P = 0.63). Only one woman, an HI variant carrier, experienced an aortic dissection prior to pregnancy,

The median observation time for women who experienced no primary or secondary outcome during pregnancy was 14.5 years (interquartile range: 6.8 – 24.0). In total, 69% of the women developed a cardiovascular phenotype defined as a primary outcome (aortic dissection, aneurysm rupture or related death) or secondary outcome (aortic dilatation, and corrective surgery) (50% patients with DN and 83% patients with HI variants, P = 0.01) (Table 1).

Obstetric/fetal outcomes

There were, in total, 133 live births with no difference in child birth rate between the DN and HI groups (2.7 vs. 2.5 children per woman, respectively, P = 0.96) (Table 2). Overall, 119/133 pregnancies (89%) ended in a vaginal delivery. The rate of C-section delivery was numerically 3-times higher in women with HI variants than in women with DN variants, however this difference was not statistically significant (P = 0.26). Three women (5.8%), all with HI variants, had preterm delivery, in all cases in the context of aortic dissection and emergency C-section, at gestational ages of 31, 36 and unspecified weeks. In total, there were 11 preterm losses, 1 stillbirth, and 4 neonatal deaths, with no difference between the DN and HI groups. The 4 neonatal deaths were all recorded in the same woman (with an HI variant) and were described to be due to an undefined "heart condition".

MFS diagnosis in relationship to pregnancy

Most of the subjects (60%) did not receive a diagnosis of MFS (clinical and/or molecular) until after pregnancy, even though

Table 1 Rates of primary and secondary endpoints by *FBN1* genotype.

	DOMINANT NEGATIVE (DN) N = 22	HAPLOINSUFFICIENT (HI) N = 30	TOTAL N = 52	*P-VALUE* DN vs HI
	N (%)	N (%)	N (%)	
Primary endpoints	**2 (9%)**	**11 (37%)**	**13 (25%)**	0.03
dissection/aneurysm	2 (9 %)	11 (37%)	13 (25%)	0.03
- before pregnancy	0 (0%)	1 (3%)	1 (2%)	1.00
- pregnancy/postpartum	0 (0%)	4 (13%)	4 (8%)	0.14
- after pregnancy	2 (9%)	7 (23%)	9 (17%)	0.27
dissection-/aneurysm-related death	0 (0 %)	6 (20%)	6 (12%)	0.03
- pregnancy/postpartum	0 (0%)	2 (7%)	2 (4%)	0.50
- after pregnancy	0 (0%)	4 (13%)	4 (8%)	0.13
Secondary endpoints*	**9 (41%)**	**14 (47%)**	**23 (44%)**	0.68
aortic repair surgery				
- before pregnancy	0 (0%)	0 (%)	0 (0%)	1.00
- after pregnancy	3 (14%)	6 (20%)	9 (17%)	0.72
dilated aorta#				
- before pregnancy	0 out of 6 measured	0 out of 6 measured	0 out of 14 measured	n/a
- during pregnancy	0 out of 7 measured	0 out of 6 measured	0 out of 15 measured	n/a
- after pregnancy	6 out of 15 measured	8 out of 13 measured	14 out of 28 measured	0.26
Primary + Secondary endpoints	**11 (50%)**	**25 (83%)**	**36 (69%)**	**0.01**
- before pregnancy	0	1 (3%)	1 (2%)	1.00
- pregnancy/postpartum	0	4 (13%)	4 (8%)	0.13
- after pregnancy	11 (50%)	21 (70%)	32 (62%)	0.14

*Secondary outcome if primary endpoint absent, # if no aortic surgery recorded

Table 2 Rates of obstetric/fetal outcomes, MFS diagnosis before pregnancy and positive family history of MFS.

	DOMINANT NEGATIVE (DN) N = 22	HAPLOINSUFFICIENT (HI) N = 30	TOTAL N = 52	*P-VALUE* DN vs HI
	N (%) or N [rate]	N (%)	N (%)	
Livebirths	59 [2.7/female]	74 [2.5/female]	133 [2.6/female]	0.96
C-section	3 (5%)	11 (15%)	14 (11%)	0.26
Stillbirths	1 [0.05/female]	0	1 [0.02/female]	0.43
Neonatal deaths	0	4 [0.1/female]	4 [0.03/female]	0.15
Miscarriages/preterm losses	7 [0.3/female]	4 [0.1/female]	11 [0.2/female]	0.87
MF diagnosis before pregnancy#	10 (45%)	11 (37%)	21 (40%)	0.52
aorta measured *	8 (80%)	7 (64%)	15 (71%)	0.41
BB management *	3 (30%)	6 (86%)	9 (43%)	0.39
Positive family history	15 (62%)	11 (37%)	26 (50%)	0.02

clinical and/or molecular, * during pregnancy in subjects with prior MF diagnosis

at least 34% of them had a positive family history of MFS. Only 3 out of 21 women who were clinically diagnosed with MFS prior to pregnancy had also received genetic testing and a confirmatory molecular diagnosis. The frequency of patients clinically diagnosed with MFS prior to pregnancy was similar in the DN and HI group (45% vs 37%, P = 0.52). Of the subjects who had an MFS diagnosis prior to pregnancy, 71% had their aorta monitored and 43% received beta blocker (BB) treatment during pregnancy.

The rate of patients with prior MFS diagnosis who received at least one aortic imaging investigation was similar in the two groups, however the frequency of BB treatment during pregnancy among women with HI variants was more than double the rate recorded in the DN group (86% vs 30%, P = 0.39). Of note, none of the patients receiving pharmacological treatment during pregnancy experienced an aortic event during pregnan-

cy/postpartum or during follow up. All the women who experienced aortic dissection received a molecular diagnosis of MFS during or after pregnancy (Table 3). Of the women who experienced aortic complications, only one woman (1/2) with a DN variant and one woman (1/11) with an HI variant received a clinical diagnosis prior to pregnancy. Both women with DN variants who experienced aortic dissection had ocular and skeletal features of MFS, while 9 of the 11 women with HI variants showed no skeletal or ocular manifestations.

Aortic outcomes

In total, 25% of the subjects (13/52, P = 0.03) developed a primary aortic complication in pregnancy, postpartum, or during follow up (Table 1). Aortic events recorded in this dataset include type A dissections (n = 4), type B dissections (n = 5), and dissection/aneurysm rupture of unknown type (n = 4) (Table 3). The overall rate of aortic events in prima-/multigravida women was 6.4% higher than in the MFS male group, and 6.7% higher than in nulligravida women, however these differences were not statistically significant (P = 0.36 and P = 0.35, respectively).

Overall, women with HI variants experienced a 4-fold higher rate of aortic events compared with the group with DN variants (37% vs 9%, P = 0.03). Furthermore, 55% of all aortic events recorded in the HI group were fatal, while no related death was observed in the DN group. During the peripartum period (pregnancy and 3 months post-partum) there were no aortic events in the DN group. In contrast, 4 subjects with HI variants experienced aortic dissection during the peripartum period, of whom 2 died (Table 3). Also, higher rates of aortic events (23% vs 9%, P = 0.27), aortic repair surgery (20% vs 14%, P = 0.72) and dilated aorta (62% vs 40%, P = 0.26) were observed during follow up in women with HI variants as opposed to DN variants. We obtained similar findings in a sensitivity analysis of the proband group only (Supplemental Table 2).

The association of HI genotype with a higher rate of aortic

Table 3 Detailed clinical and genetic information regarding prima- and multigravida women who experienced aortic complications (primary outcome).

AGE, (Y)	TIME OF AORTIC COMPLICATION IN RELATION TO THE PREGNANCY			DESCRIPTION CLINICAL OUTCOME	CLINICAL PRESENTATION	CLINICAL (C) OR OLECULAR (M) DIAGNOSIS IN RELATION TO PREGNANCY		*FBN1* VARIANT
	Before	During	After		O	Before	During/After	
Dominant Negative (DN) variants								
27			X	type A aortic dissection 21 years after pregnancy	O, S	C	M	c.5782T>C (p.C1928R) (LP)
26			X	type B aortic dissection 14 years after pregnancy	O, S		M	c.625T>C (p.C209R) (LP)
Haploinsufficient (HI) variants								
26	X	X		type A aortic dissection at age 25, type B dissection at 25 weeks of pregnancy, emergency C-section delivery at 31 weeks of pregnancy	–	C	M	c.4255dup (p.Gln1419Profs*12) (P)
19		X		type A aortic dissection, emergency C-section delivery at 36 weeks of pregnancy, death 48 hrs after the delivery	–		M	c.5129T>A (p.Leu1710*) (P)
24		X		type A aortic dissection, death 15 hrs after the delivery	S	Susp C	M	c.4337-2A>G (P)
44		X		aortic dissection of unknown type	–		M	c.7819+4A>G (P)
?			X	aortic dissection of unknown type, death at age ~30 years	–		M	c.6784_6787delCAAA (p.Gln2262Trpfs*28) (P)
28			X	type B aortic dissection 7 years after pregnancy	–		M	c.7621delT (p.Cys2541Alafs*141) (P)
35			X	type B aortic dissection 13 years after pregnancy	O,S		M	c.656G>T (p.Glu189*) (P)
35			X	type B aortic dissection 5 years after pregnancy	–		M	c.7999G>T (p.Glu2667*) (P)
34			X	aortic dissection of unknown type 6 years after pregnancy, death	–		M	c.4429dupG (p.Glu1477Glyfs*14) (P)
25			X	aorta rupture 3 years after pregnancy, death	–	Susp C	M	c.5067dupT (p.Met1690Tyrfs*13)(P)
?			X	type B dissection, death (age 42)	–		M	exons 1-65 deletion(P)

O – ocular presentation of MFS, S – skeletal presentation of MFS, C – clinical diagnosis of MFS, M – molecular diagnosis of MFS, Susp – suspected, P – pathogenic variant, LP – likely pathogenic variant.

events was also observed in the cohort of nulligravidas (P = 0.008) and males (P = 0.01) with MFS (Figure 1). HI genotype was associated with 5% and 4.2% higher rates of aortic events in pregnant women vs men and vs nulligravida women, respectively, however these findings showed no statistical significance (P = 0.66 and P = 0.72, respectively).

FBN1 variants

In this dataset, we identified 3 unique multi-exon deletions in 4 subjects, 3 unique variants affecting splicing in 3 subjects, 19 unique loss-of-function variants (8 nonsense and 11 frameshift) in 23 subjects, and 16 unique missense variants in 22 subjects. Fifty-nine percent of the identified variants were previously described in the literature or in ClinVar.

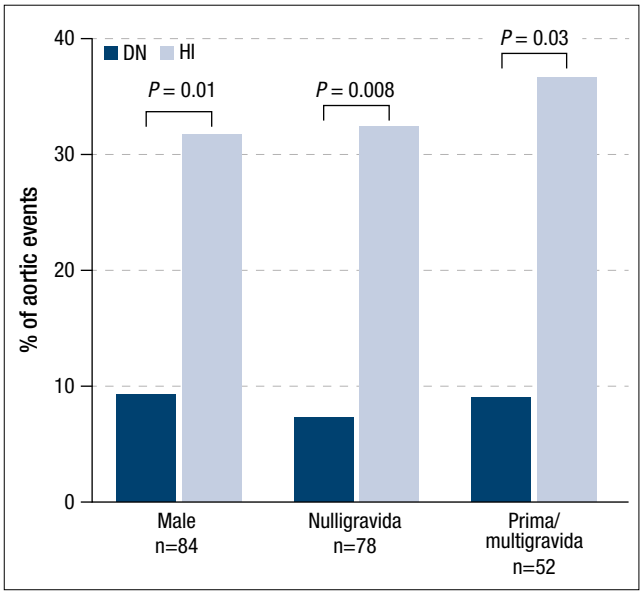
Two missense variants were located in the TGFβ-binding protein domains affecting cysteine residues. Fourteen missense variants were located in the calcium binding EGF-like domains disrupting cysteine residues and amino acids critical for calcium binding (Supplemental Table 1). Aortic events were noted in 8 individuals with loss-of-function variants, in 2 individuals with missense variants, in 2 individuals with splice-site variants, and in 1 individual with a multi-exon deletion (Table 3).

Discussion

In this study, we sought to investigate the association between *FBN1* genotype and the rate of aortic events and fetal complications in prima- and/or multigravida women with genetically-confirmed MFS. Our data suggest that HI *FBN1* variants are associated with worse pregnancy-related and long-term post-pregnancy aortic outcomes. There was no clear evidence for an association with obstetric/fetal outcomes, but our dataset was limited in this regard.

In our data series, the overall rate of aortic events and aortic dilatation is consistent with the rates reported in other studies in MFS subjects in a similar age range [17,18]. Prima- and multigravidas with HI variants had an overall higher rate of aortic complications (aortic dissection or aneurysm) and aortic root dilatation, and tended to have a higher rate of prophylactic aortic root surgery compared with those carrying DN variants. These findings agree with the growing body of evidence demonstrating that individuals with HI *FBN1* variants are at greater risk of aortic events and cardiovascular death compared with carriers of DN variants [8,9,19,20].

Figure 1 Rates of aortic events (primary endpoints) in a male, nulligravida and prima/multigravida MFS populations according to *FBN1* genotype.



We also observed that the overall rate of aortic events tended to be higher (albeit with no statistical significance) in women who had been pregnant than in never-pregnant women and males. The fact that males are reported to have significantly more aortic events than females in some studies [17,18], but not in our study, suggests that pregnancy may increase the overall risk of aortic complications [21]. Indeed, several studies have previously demonstrated that the prevalence of aortic complications and aortic dilatation is higher in women with a prior pregnancy; whether the prevalence of HI genotype was higher in this group is unknown [22,23]. However, it should be noted that our populations were small, and larger populations should be studied to confirm these findings.

Strikingly, in our dataset there were 4 women (13%), all HI variant carriers, who experienced aortic dissection (and in 2 cases, subsequent death) during the peripartum period, while no aortic events during the peripartum period were recorded in woman with DN variants. Although this difference is not statistically significant, it may suggest a potential meaningful association pointing towards a higher pregnancy-associated risk of aortic complications in patients with an HI genotype. Whether this numerically elevated risk was associated with prior aortic dilatation, its progression, and/or lack of BB therapy remains unclear since these data were unavailable for 3 out of the 4 subjects.

MFS often remains undiagnosed prior to pregnancy and may be recognized only after life-threatening complications arise in pregnancy or at the time of MFS diagnosis of newborns and children [21,24]. Our data also indicate that many of the women in the study were not diagnosed until later in life. In this dataset, 40% of women received clinical and/or molecular MFS diagnosis prior to pregnancy; 71% of these had aortic imaging and 43% received a prophylactic BB prescription, which could have accounted for the better outcomes observed in this group.

Our data showed that 3 out of 4 patients who experienced aortic events during pregnancy had no aortic imaging and received no BB prophylactic treatment. Of the 10 subjects who received BB treatment during pregnancy, none experienced aortic complications during a follow-up period (regardless of *FBN1* genotype), and only 2/10 patients required a prophylactic aortic surgery. Although there is still active debate regarding the efficacy and therapeutic benefit of prophylactic prescription of BBs and other antihypertensive drugs, strict blood pressure control is recommended in MFS patients during pregnancy to reduce the risk of aortic dilatation [25].

The phenotypic manifestations of MFS vary widely, with most occurring in ocular, skeletal and cardiovascular systems. Some patients may appear asymptomatic or without prominent manifestations, making clinical diagnosis challenging, espe-

cially in the setting of a negative/unknown family history [26]. Sometimes aortic complications experienced during pregnancy and/or a clinical diagnosis of MFS in a newborn or child leads to genetic testing and MFS diagnosis of apparently asymptomatic mothers. In our study, 69% of women had no clinical (ocular and/or skeletal) presentation prior to an aortic event. This finding highlights the need for more careful screening of patients with subtle clinical signs of MFS, especially women planning pregnancies [27]. MFS diagnosis before pregnancy would allow for proper pregnancy counseling and clinical management during and after pregnancy, as is currently recommended. It is conceivable that this improved management could possibly allow cases of aortic complications and related death to be avoided. Current guidelines recommend prophylactic aortic root surgery before pregnancy when aortic root dilatation is greater than 40-45 mm [28,29]. As an alternative to surgery, the 2010 American guidelines recommend avoiding pregnancy if the aortic root is greater than 40 mm [28]. However, a more informed approach to surgery or pregnancy avoidance may be possible during pre-pregnancy counseling if genetic testing is performed and positive.

Pregnancy in women with MFS is reported to be associated with an increased incidence of obstetric, fetal, and neonatal complications [21]; whether the incidence of these events is elevated in carriers of HI variants is currently unknown. In this dataset, the *FBN1* genotype appeared not to have a significant effect on the rates of stillbirth, neonatal death, preterm loss, and spontaneous abortion. The overall rate of cesarean delivery was 11%, and was higher in women with the HI genotype. A 32% caesarean delivery rate is reported in the general pregnant population in Northern America [30], whereas in pregnant women with heart disease it is 47% [31], and in the MFS population ~ 40% [15]. The reason for the comparatively lower rate of caesarean deliveries in our data series is unclear. All preterm deliveries were observed in the setting of emergency intervention related to aortic dissections in HI variant carriers.

The strength of our study lies in the fact that both the HI and DN groups were equally represented. A major limitation is the relatively small sample size which prevented us from performing survival analysis. Additionally, detailed information describing aortic root size and dilatation progression during pregnancy was unavailable for most of the cases. Although our results should be interpreted with caution and no clinical decision should be made based on genotype alone, we anticipate that the findings observed in this dataset may represent a real trend in MFS female populations, and may therefore have implications for the design of more extensive studies incorporating subanalyses according to *FBN1* genotype. The effectiveness of pharmacological interventions and of types of surveillance in the context of *FBN1* genotype also warrants further investigation.

In conclusion, prima- and multigravida women with an HI genotype were found to have a higher rate of aortic events compared with those with DN variants both during the peripartum period and during a follow-up period. Further exploration is warranted, which may provide evidence that pregnant women with the HI genotype might benefit from more strict clinical surveillance and treatment, particularly before and during pregnancy. Our preliminary data suggest that women planning pregnancy may benefit from genetic testing if MFS is suspected, both to substantiate diagnosis and potentially inform management decisions.

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