به نام

خداوند

جان و خرد

مرکز تحقیقات بیماریهای قلب و عروق بیرجند
C.V.D.R.C
Birjand CardioVascular Disease Research Center

دانشگاه علوم پزشکی و خدمات بهداشتی درمانی بیرجند

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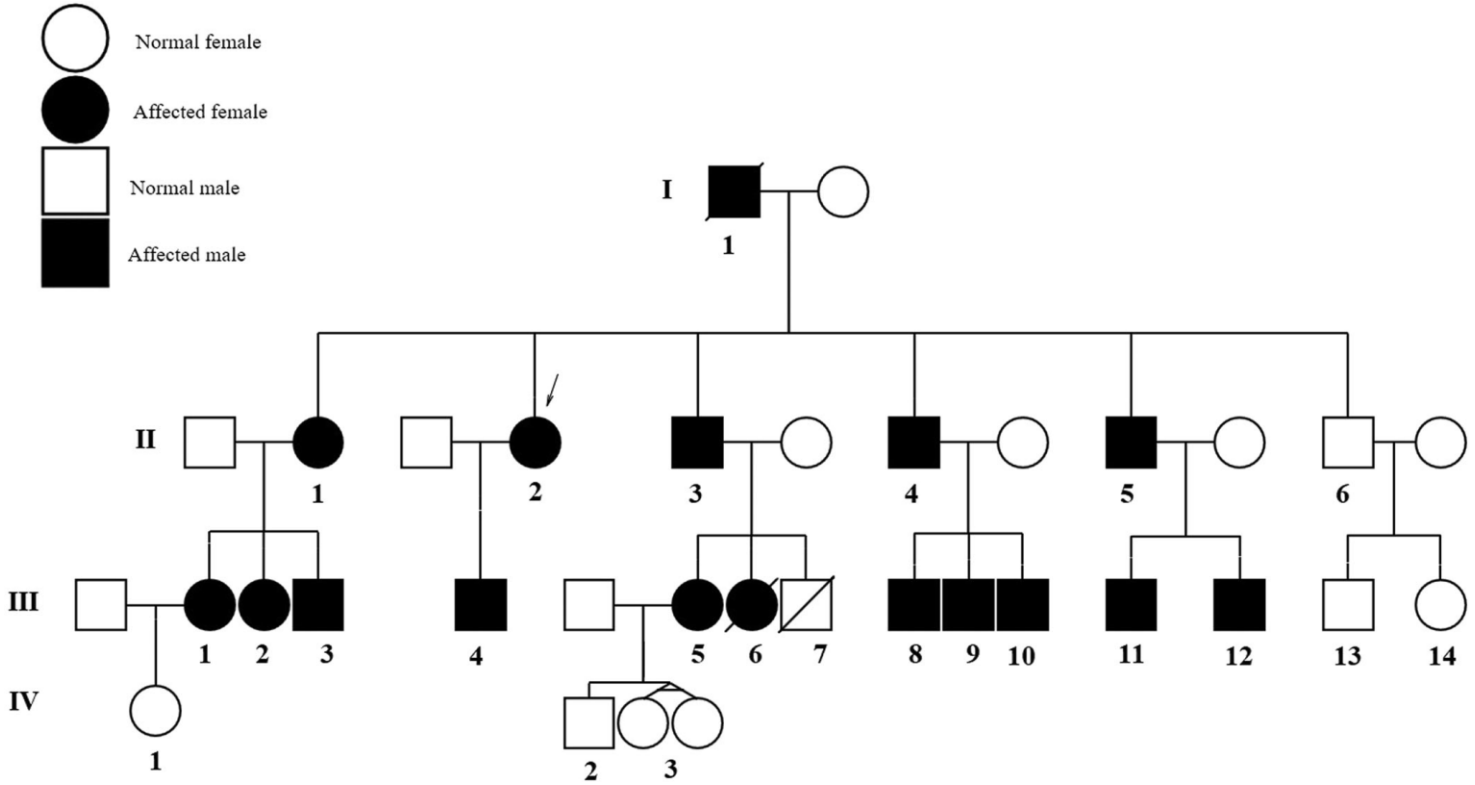


Patient characteristics

Case	Age	Cardiovascular involvement	Ocular involvement	Complication	Treatment
Father	63	MVP, MR, AI, ARD=31 mm	Iridodonesis, Ectopia lentis, VA=1 m CF	Cataract Deceased	Lens extraction OS follow up annually
First daughter	45	MVP, MR, AI, ARD=34.9 mm	Iridodonesis, Ectopia lentis, VA=0.1	Three pregnancies without complication	Lensectomy + vitrectomy + buckling + silicone oil, follow up annually
Second daughter	42	MVP, MR, ARD=22.1 mm	Iridodonesis, Ectopia lentis, VA=5 m CF, blindness OS	One pregnancy without complication, Bentall procedure, stroke	Glasses, Follow up annually, propranolol warfarin
First son	39	MVP, MR, ARD=29 mm	Iridodonesis, Ectopia lentis, VA=3 m CF	Surgery for cataract and Bentall procedure for RD	Glasses, follow up annually, propranolol warfarin

Second son	37	MVP, MR, ARD=26	Iridodonesis, Ectopia lentis, VA=4 m CF	Bentall procedure for aortic dissection	Lensectomy + vitrectomy + bukeling + silicon oil, glasses, follow up annually, propranolol warfarin
Third son	31	MVP, MR, AVR, ARD=26.8 mm	Iridodonesis, Ectopia lentis, VA=4 m CF	Bentall procedure for RD	Follow up annually, propranolol warfarin
4th son	29	Normal	Normal	-	Follow up annually
First grandchild	24	MVP MR	Iridodonesis, Ectopia lentis, VA=1 m CF	One pregnancy without complication	Glasses, follow-up annually
Second grandchild	20	MVP, MR, ARD=29.1	Iridodonesis, Ectopia lentis, VA=1 m CF	-	Follow-up annually
Third grandchild	18	MVP, MR, AI, ARD=21.8	Iridodonesis, Ectopia lentis, VA=1 m CF	-	Follow up annually
4th	16	MVP, MR,	Iridodonesis,	-	Follow up annually

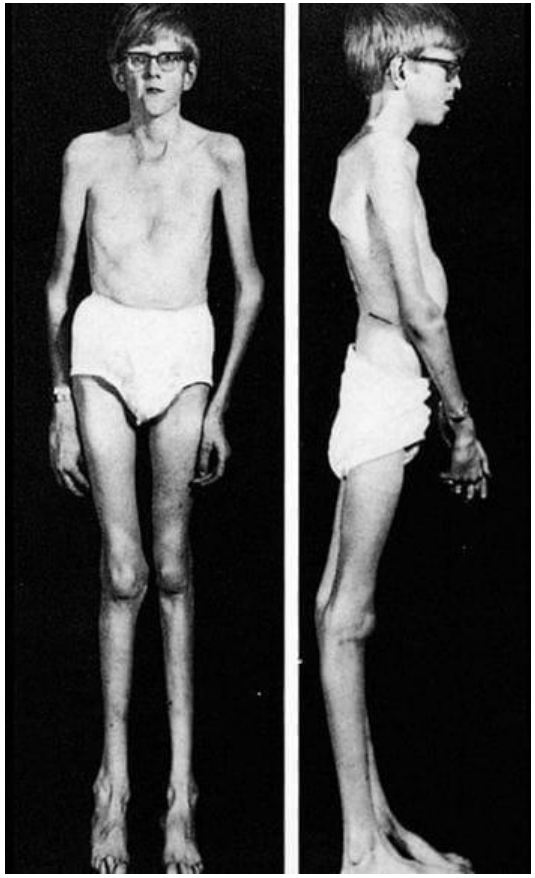
4th grandchild	16	MVP, MR, ARD=37.7	Iridodonesis, Ectopia lentis, VA=1 m CF	-	Follow up annually
5th grandchild	13	ARD=22	Iridodonesis, Ectopia lentis, VA=1 m CF	Deceased	Follow up annually
6th grandchild	12	MVP, AVP, ARD=12.3	Iridodonesis, Ectopia lentis, VA=1 m CF	-	Follow up annually
7th grandchild	11	MVP, MR, ARD=23.7	Iridodonesis, Ectopia lentis, VA=1 m CF	-	Follow up annually
8th grandchild	10	MVP, MR, ARD=31.1	Iridodonesis, Ectopia lentis	-	Follow-up annually
9th	9	MVP, TR, ARD=13.7	Iridodonesis, Ectopia lentis	-	Follow-up annually
10th	5	MVP, ARD=24.4	Iridodonesis, Ectopia lentis	-	Follow-up annually
11th	7	Normal	Normal	Deceased	Follow-up annually

12th	4	MVP, ARD=23.1	Iridodonesis, Ectopia lentis	-	Follow-up annually
13th	1	Normal	Normal	-	Follow-up annually
First great-grand child	2 months	Normal	Normal	-	Follow-up annually

TABLE 2 Clinical findings of the 17 affected members in the family.

Case ID	Age (year)	Gender	Cardiac disease	Skeletal abnormalities	Ocular abnormalities
I1	67 (deceased)	Male	+	+	+
II1	49	Female	+	+	+
II2	46	Female	+	+	+
II3	43	Male	+	+	+
II4	41	Male	+	+	+
II5	35	Male	+	+	+
II6	33	Male	–	–	–
III1	27	Female	+	+	+
III2	22	Female	+	+	+
III3	14	Male	+	+	+
III4	16	Male	+	+	+
III5	24	Female	+	+	+
III6	13 (deceased)	Female	–	+	+
III7	7 (deceased)	Male	–	–	–
III8	18	Male	+	+	+
III9	15	Male	+	+	+
III10	14	Male	+	+	+
III11	10	Male	+	+	+
III12	8	Male	+	+	+
III13	5	Male	–	–	–
III14	1	Female	–	–	–
IV1	4	Female	–	–	–
IV2	3	Male	–	–	–
IV3	1	Female (identical twins)	–	–	–

- Marfan syndrome is a rare inherited disorder that affects connective tissue . There are many different signs such as: a narrow, long body, hyperextensible joints, tearing or displacement of the eye lens, dilations and tears in blood vessels. These can vary in severity.



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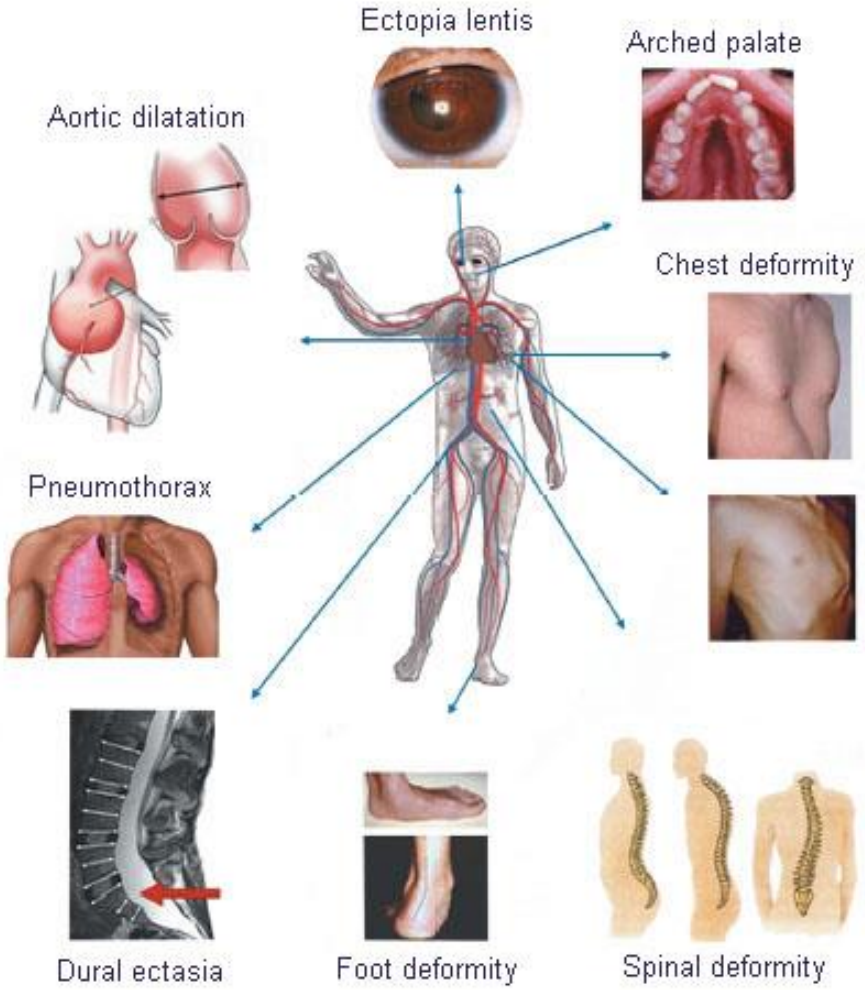
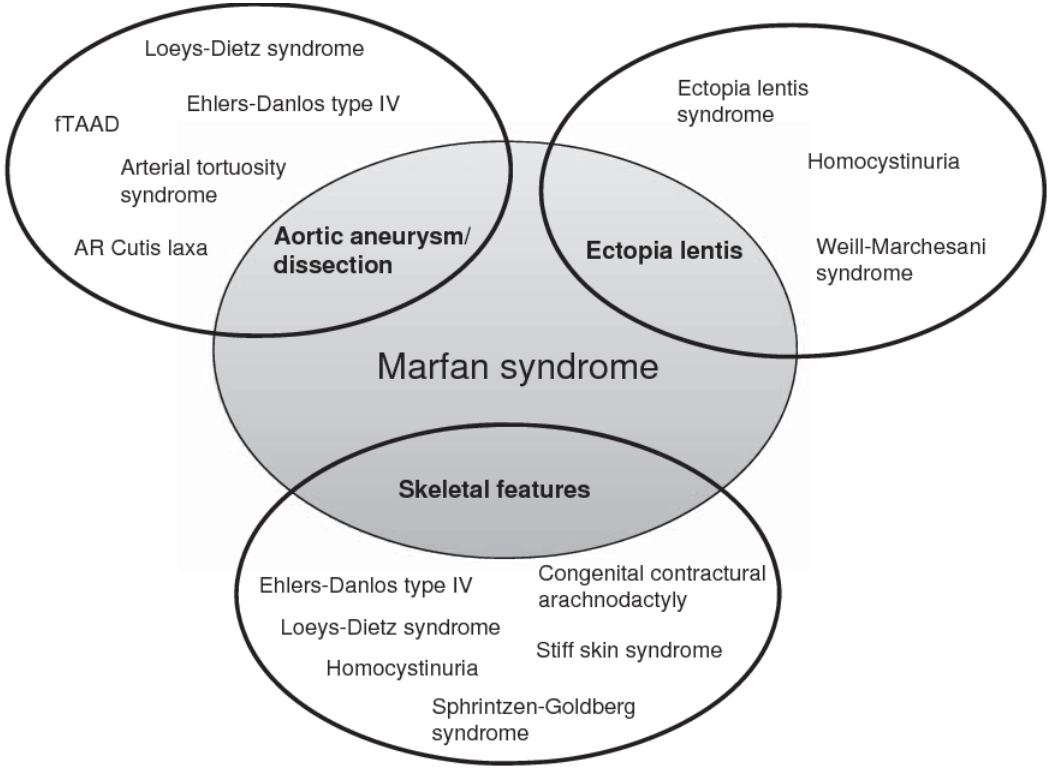
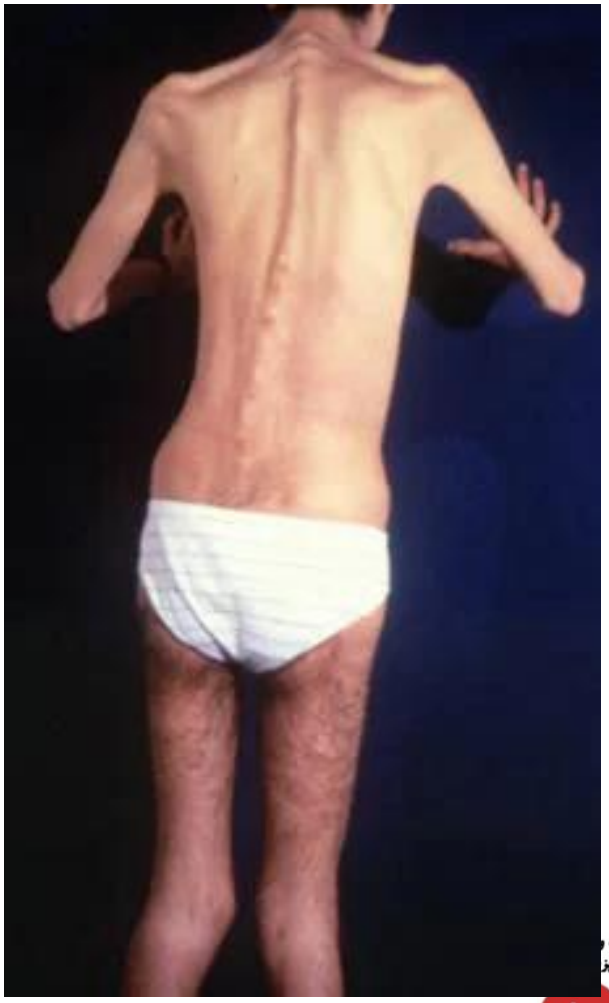


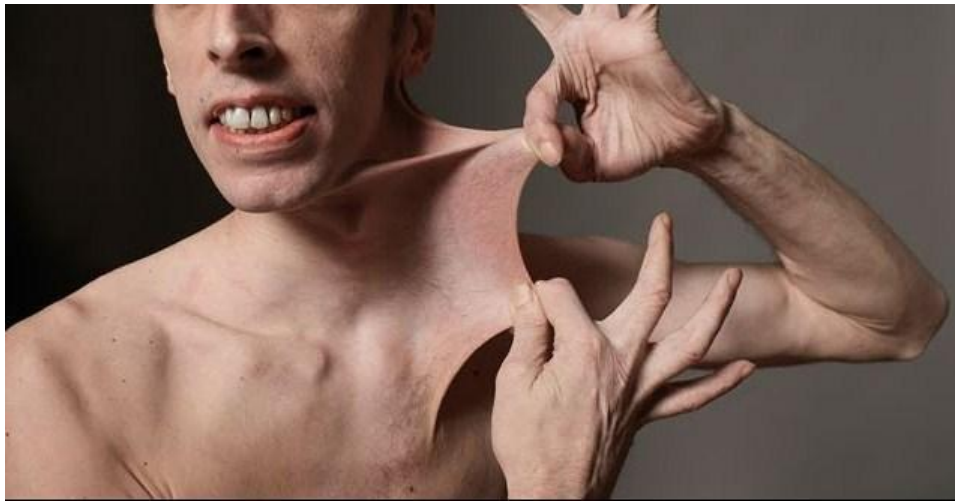
Many different heritable connective tissue disorders (HCTD) have been described

- Marfan syndrome (MFS) FBN1
- Ehlers-Danlos syndrome (EDS) COL5A/COL5A2 (collagen protein)
- Loeys-Dietz syndrome (LDS) TGBR1/2, SMAD2/3, or TGFB2/3

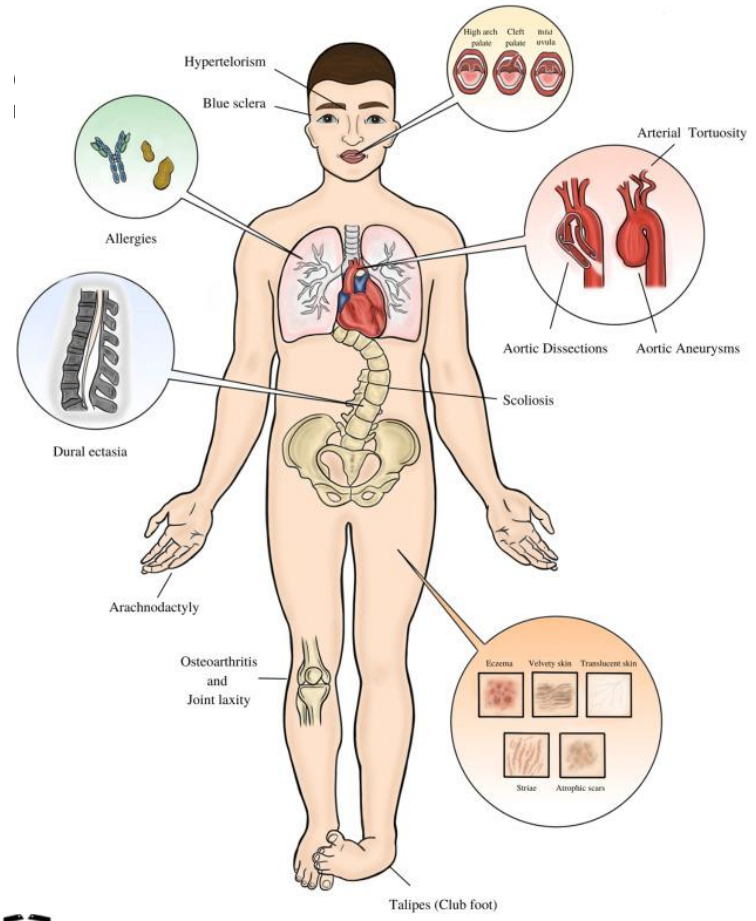


Ehlers-Danlos syndrome

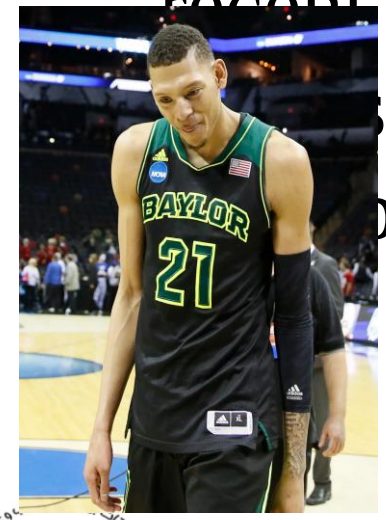


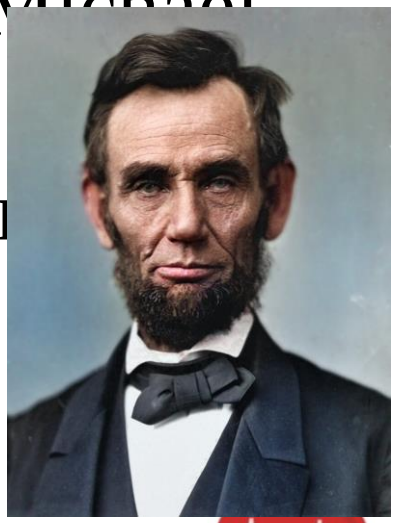


Loeys-Dietz


High arch palate
Cleft palate
Bifid uvula
Hypertelorism
Blue sclera
Arterial Tortuosity
Allergies
Aortic Dissections
Aortic Aneurysms
Scoliosis
Dural ectasia
Arachnodactyly
Osteoarthritis and Joint laxity
Eczema
Velvety skin
Translucent skin
Striae
Atrophic scars
Talipes (Club foot)

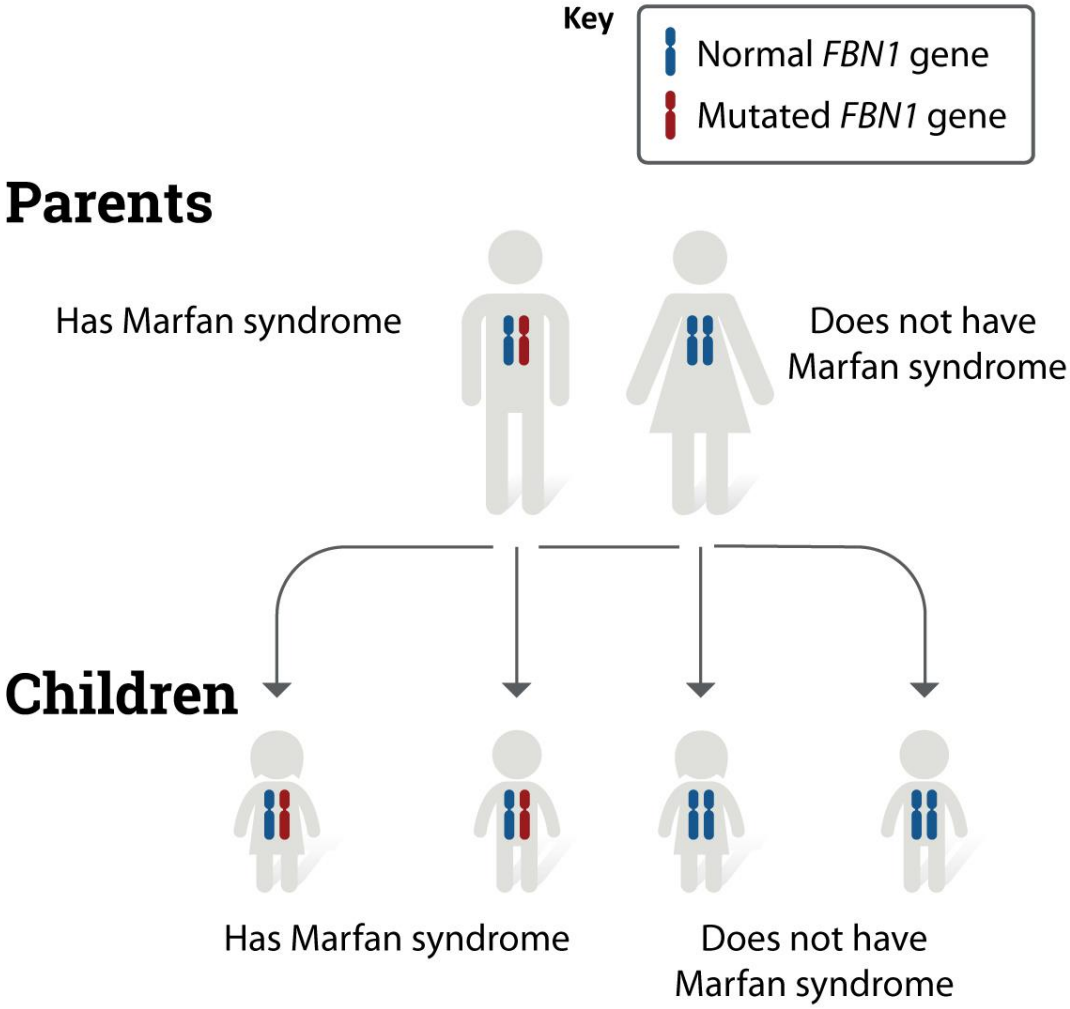
- Abraham Lincoln is the most famous American who had Marfan syndrome. So did Julius Caesar and Tutankhamen. In more recent times, Olympic swimmer M

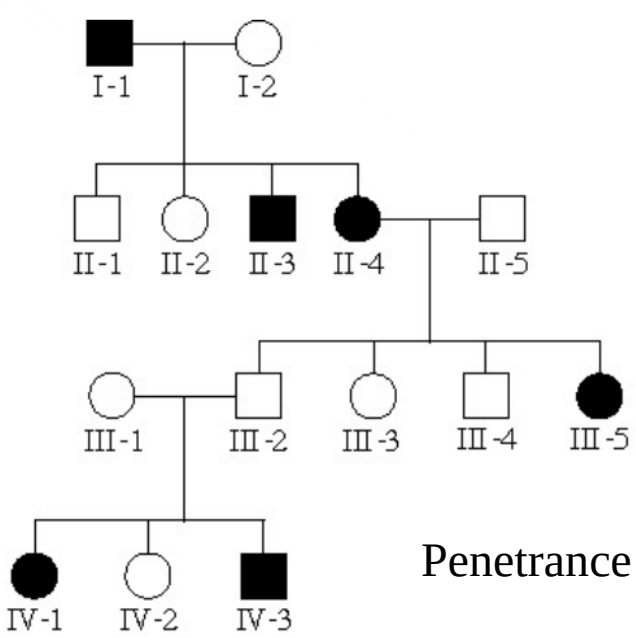




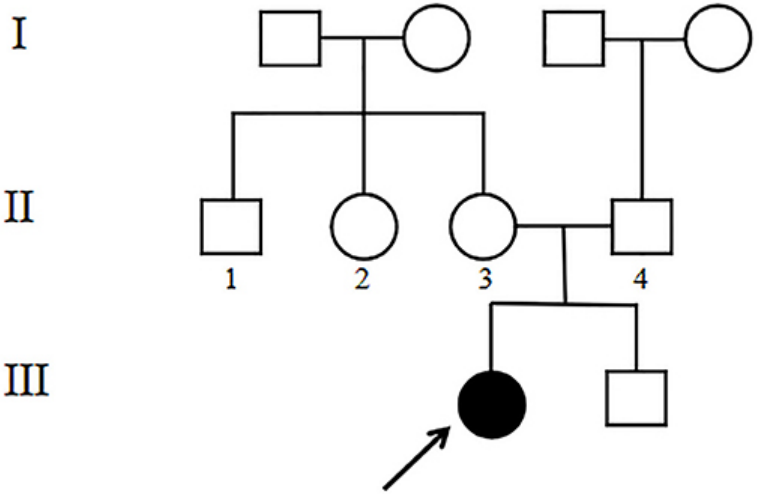
Epidemiology

- Marfan syndrome (MFS) is one of the most common inherited disorders affecting connective tissue, with a reported incidence of 1 in 3000 to 500 individuals.
- prevalence thought t be similar regardless of sex and ethnicity


Key
Normal *FBN1* gene
Mutated *FBN1* gene
Parents
Has Marfan syndrome
Does not have Marfan syndrome
Children
Has Marfan syndrome
Does not have Marfan syndrome



Penetrance



De novo mutations

Diagram presenting reasons for Marfan syndrome suspicion

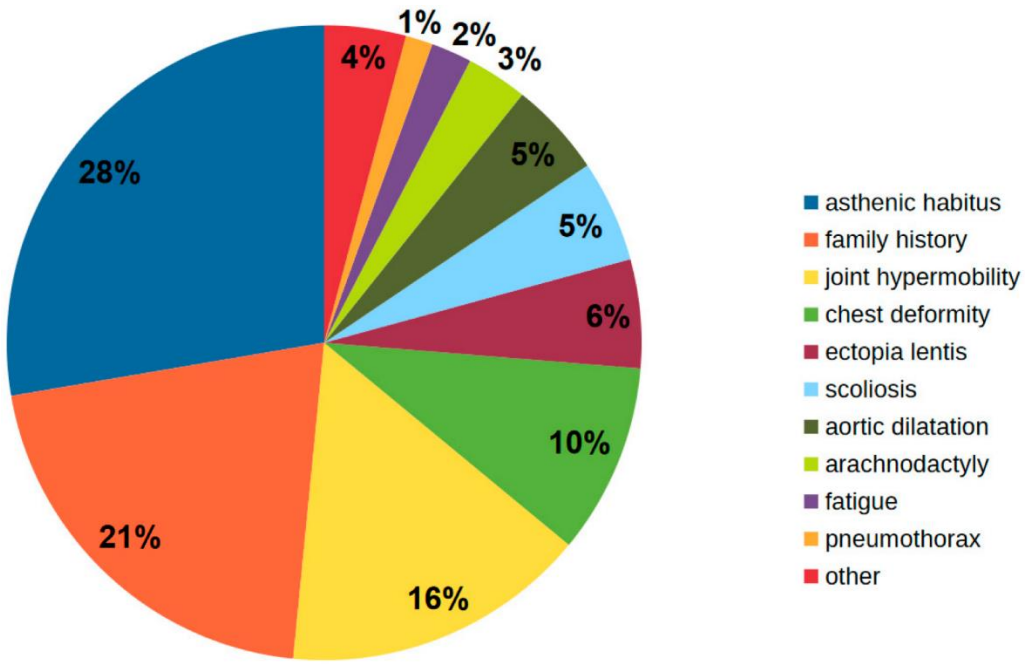
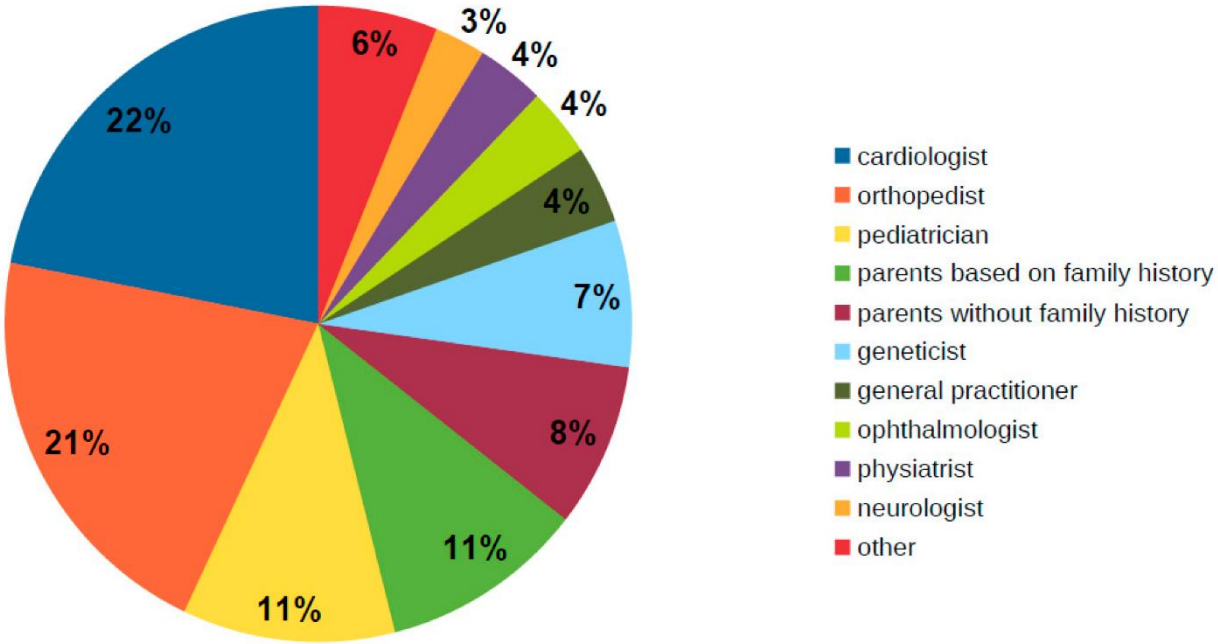
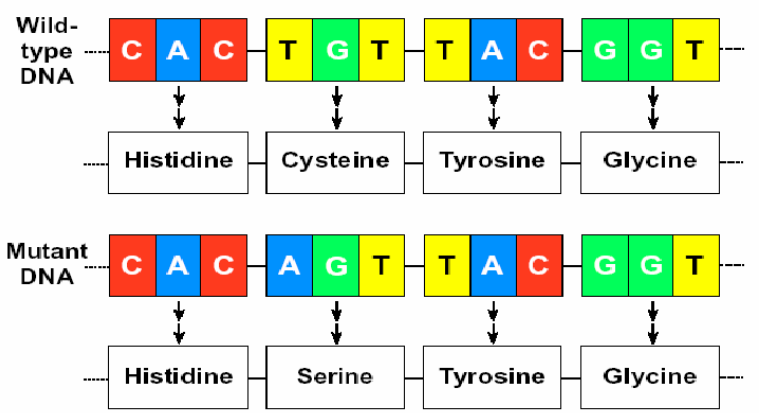


Diagram presenting specialists who were first to suspect Marfan syndrome (including parents that suspected this syndrome)

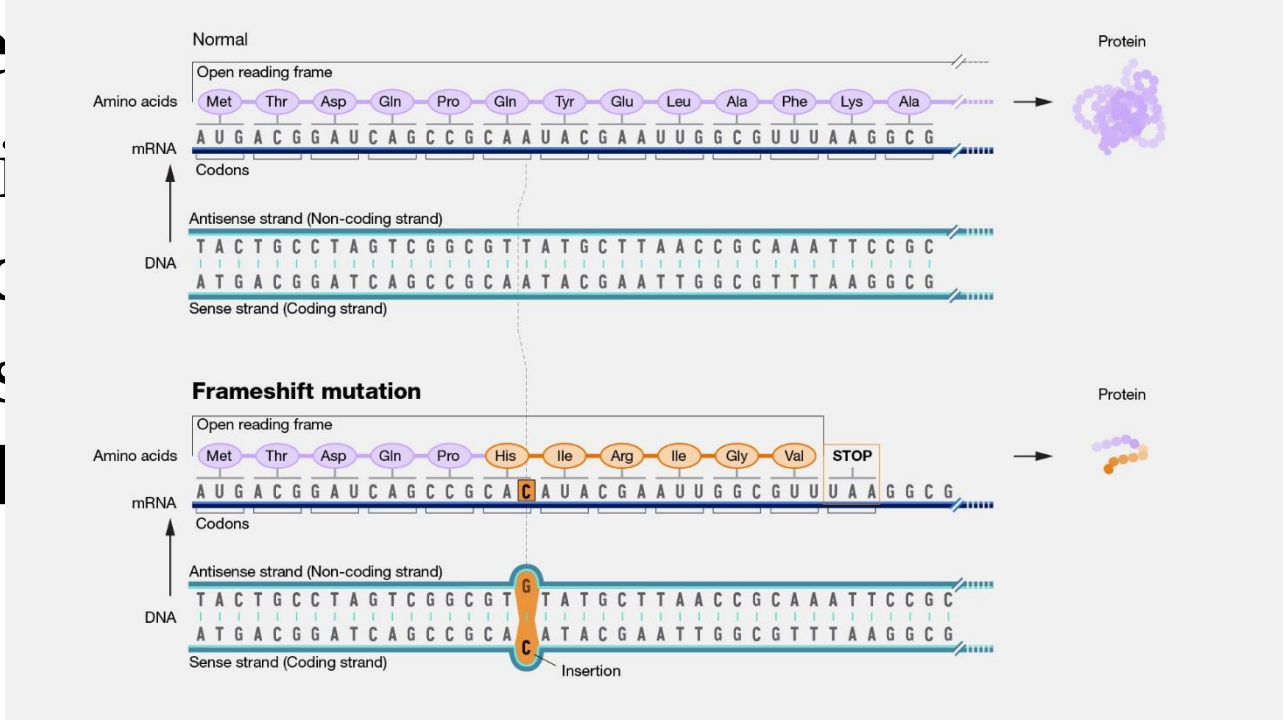


Etiology

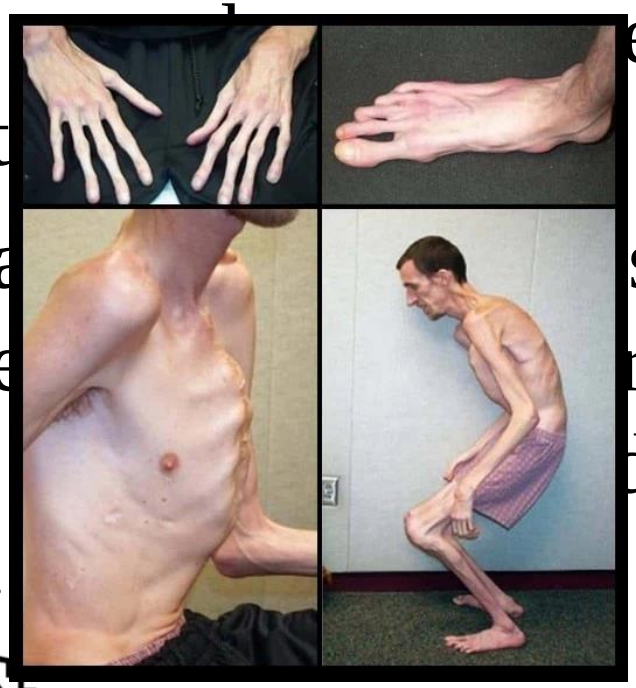
- Marfan syndrome is a genetic disorder caused by mutations in the FBN1 gene, which provides instructions for making a protein called fibrillin-1.
- Currently, over 2,900 distinct FBN1 mutations have been identified in patients with MFS.
- Missense mutations are the major type found in patients with MFS, and these mutations mainly affect cysteine residues.
- in about 25% of cases, the condition occurs due to a spontaneous mutation in the FBN1 gene, without any family history of the disorder.



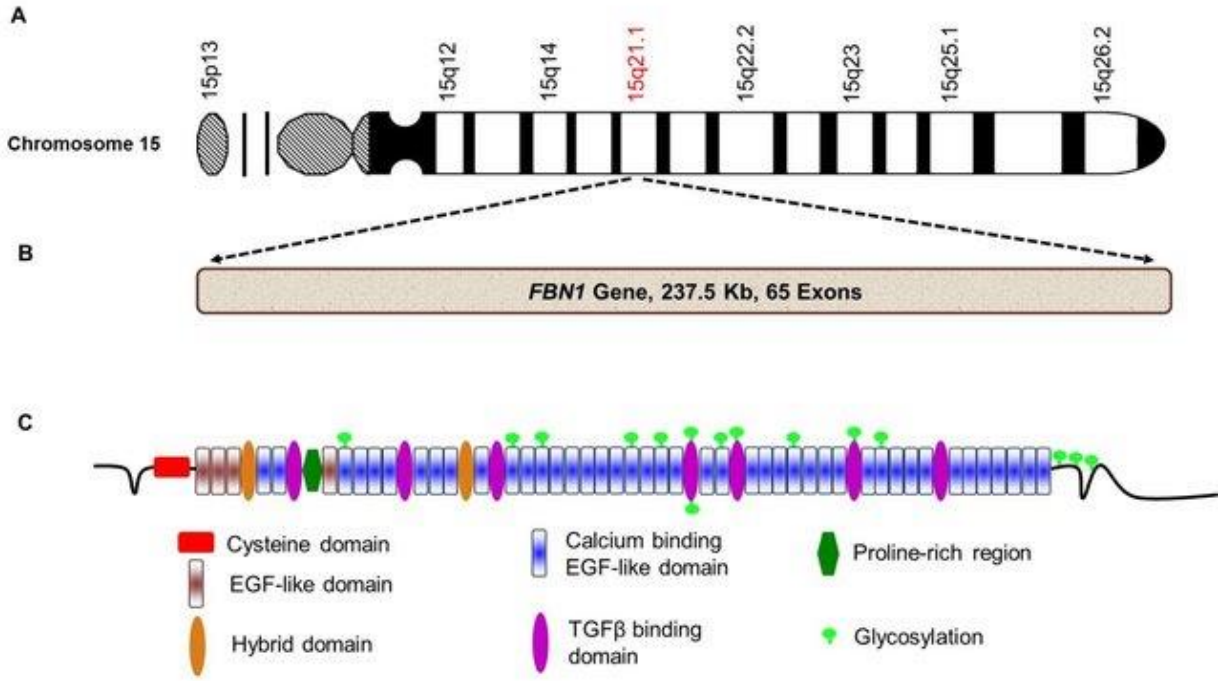
- There was a significantly higher frequency of frameshift and nonsense mutations observed in aortic dissection than in aortic ane
- whi gher
  frec ortic
  diss lens
  disl

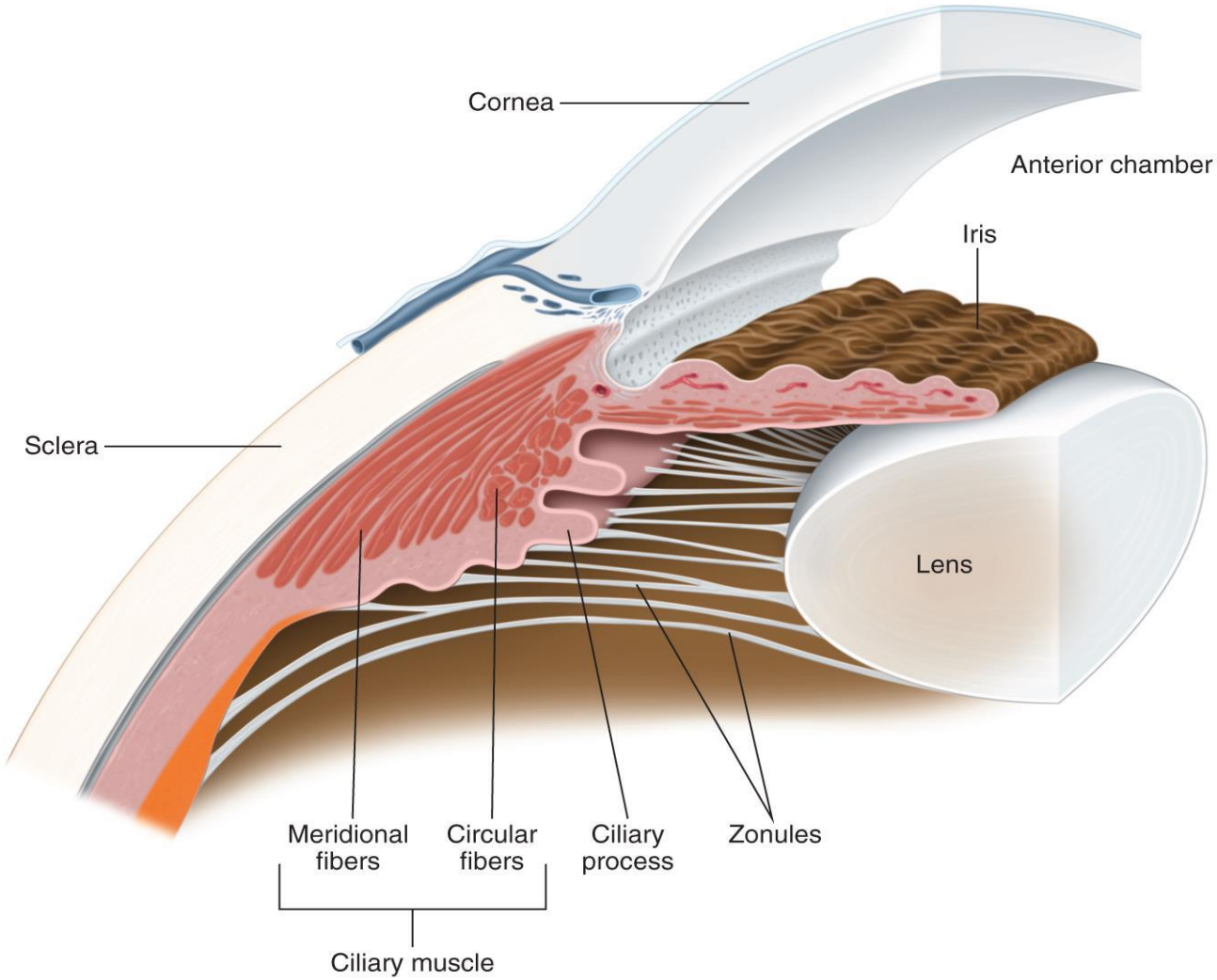


- It is important to note that Marfan syndrome can vary widely in its severity and presentation, as different mutations in the FBN1 gene can have diff ects e and functio ve t
- Thus, tha strong candid gene role in modul se d be investi nts.



Gene structure




Cornea
Anterior chamber
Iris
Sclera
Lens
Meridional fibers
Circular fibers
Ciliary process
Zonules
Ciliary muscle

Ghent criteria

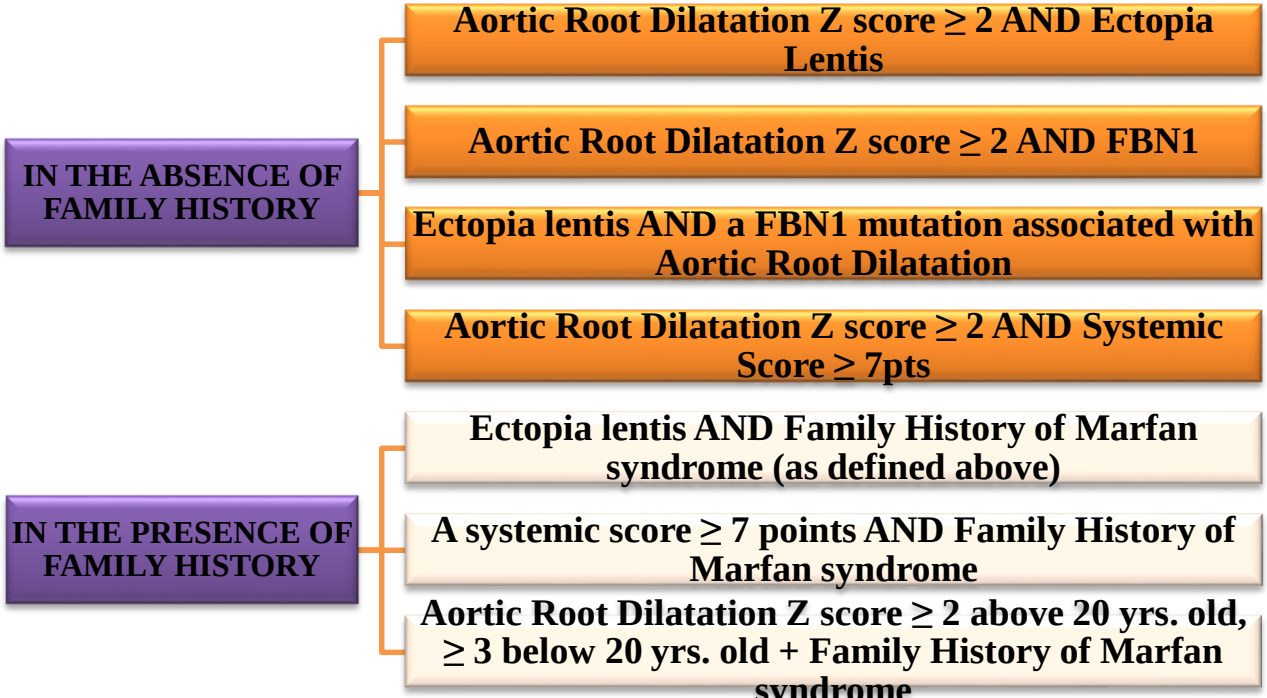
System	Major criteria	Minor criteria
Family history	Independent diagnosis in parent, child or sibling	None
Genetics	Mutation FBN1	None
Cardiovascular	Aortic root dilatation, dissection of ascending aorta	Mitral valve prolapse, calcification of the mitral valve (<40 years), dilatation of the pulmonary artery, dilatation/dissection of descending aorta
Ocular	Ectopia lentis	2 needed of the following: flat cornea elongated globe myopia
Skeletal	At least 4 of the following: pectus excavatum needing surgery, pectus carinatum, pes planus, positive wrist or thumb sign, scoliosis >20° or spondylolisthesis, armspan-height ratio >1.05, protrusio acetabulae, diminished extension elbows (<170°)	For the skeletal system to be involved 2–3 major, or 1 major and 2 minor signs should be present: moderate pectus excavatum, high arched palate, typical facial features, joint hypermobility
Pulmonary		Spontaneous pneumothorax, apical bulla
Skin		Striae, recurrent or incisional herniae
Central nervous system	Lumbosacral dural ectasia	

Table 2. Systemic score for Marfan syndrome.

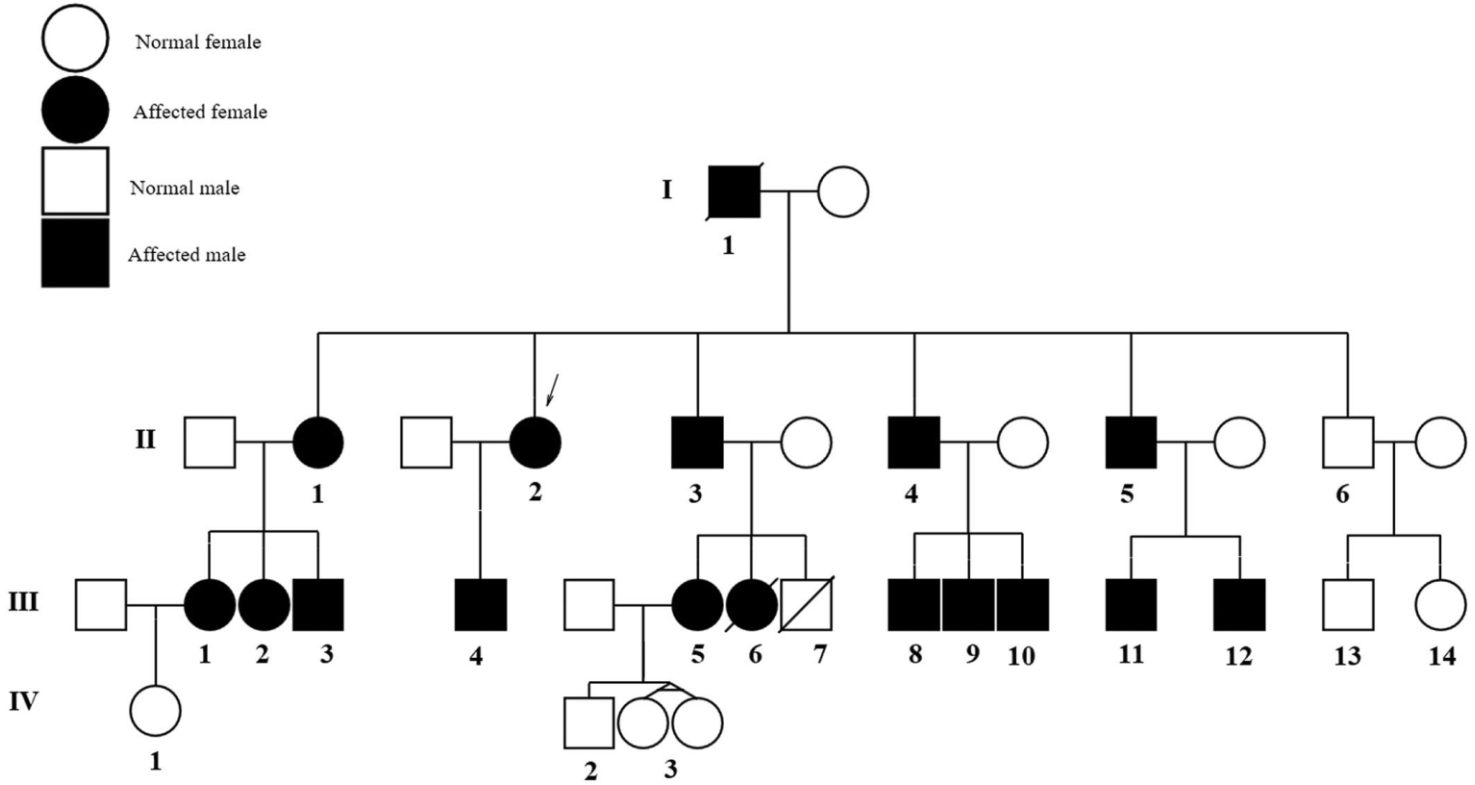
POINTS	FEATURES
3	Wrist AND thumb sign (1 point for wrist OR thumb sign)
2	Pectus carinatum deformity (1 point for pectus excavatum or chest asymmetry)
2	Hindfoot deformity (1 point for plain pes planus)
2	Pneumothorax
2	Dural ectasia
2	Protrusio acetabuli
1	Reduced upper segment/lower segment ratio AND increased arm/height AND no severe scoliosis
1	Scoliosis or thoracolumbar kyphosis
1	Reduced elbow extension
1	3/5 facial features: dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia
1	Skin striae
1	Myopia > 3 diopters
1	Mitral valve prolapse (all types)

Maximum of 20 points. A score of ≥7 indicates systemic involvement. Adapted from Loeys et al.[35]

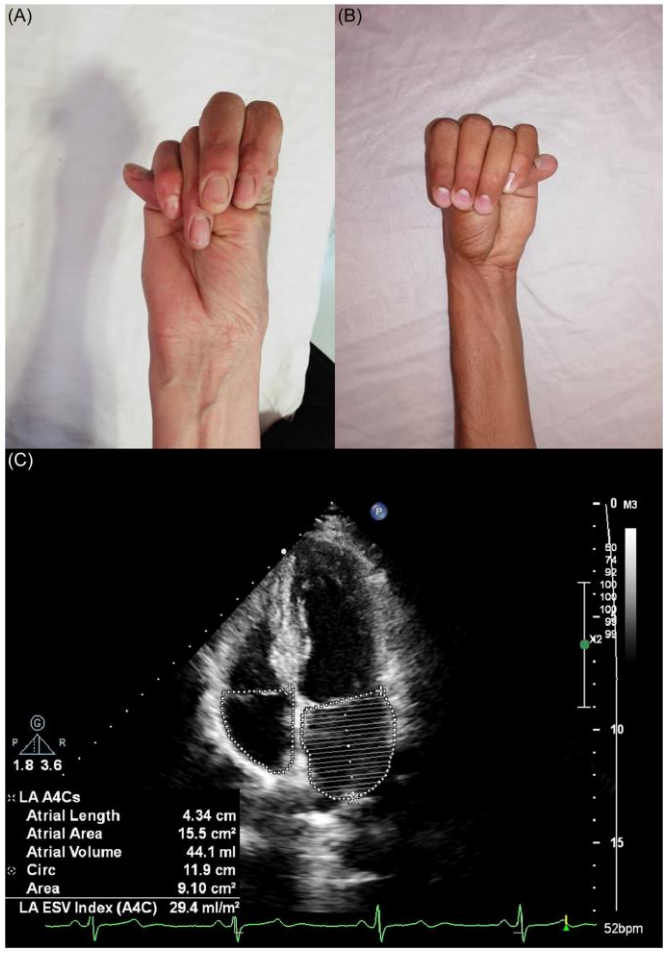
The Revised Ghent Nosology for Marfan syndrome relies on seven rules as indicated below

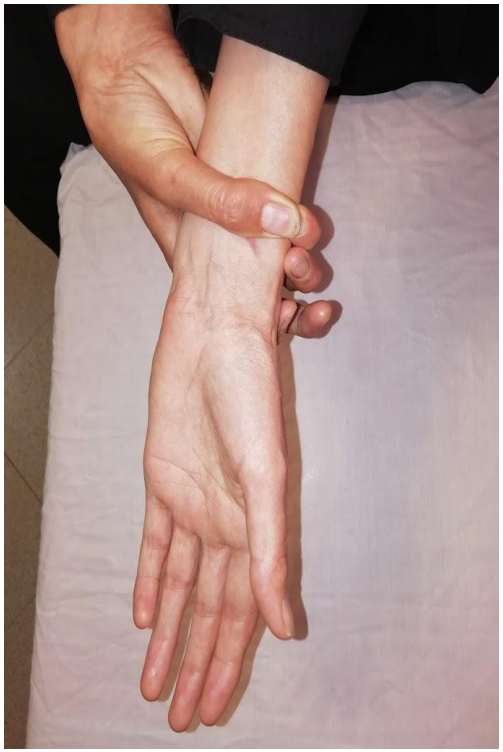


Family presentation



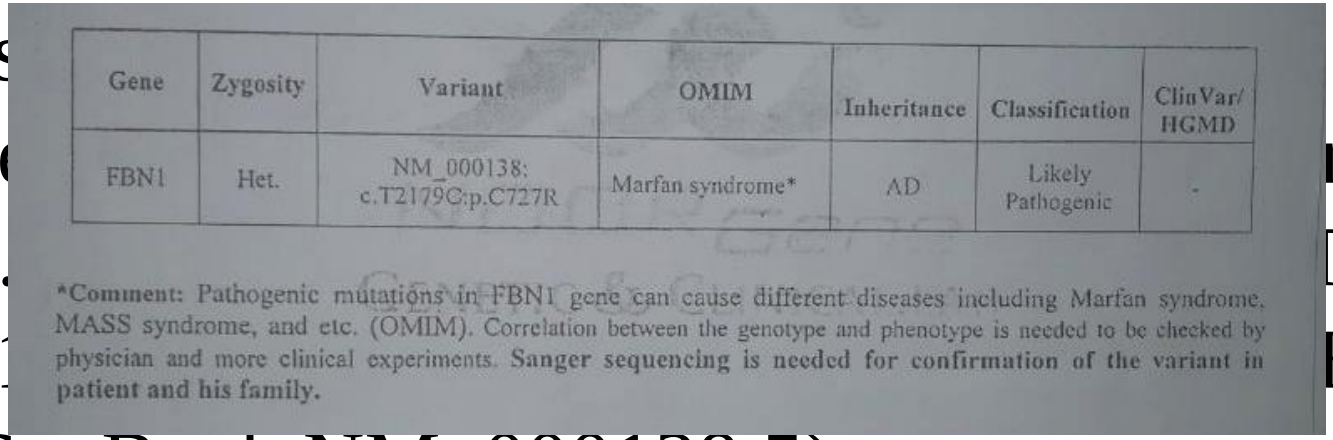
- Our proband was a **46-year-old** female patient with general **skeletal, visual, and cardiovascular problems**. She was the second sibling of non-consanguineous parents, originally from eastern Iran.
- The onset of ocular problems occurred when she was 20 years old with low visual acuity and slow progressive vision loss. The proband had a height of 169 cm and body mass index of **17 kg/m2**. She had a history of heart and brain strokes and was regularly taking warfarin.
- The son of the proband (III:4), 16 years old, had a Marfan phenotype. He had a height of **197 cm** and body mass index of **17 kg/m2.** had various clinical features including, **ocular problems**, **orthodontic problems**, **thumb and wrist signs**, striae distensae, and **pectus deformity**.





Finding

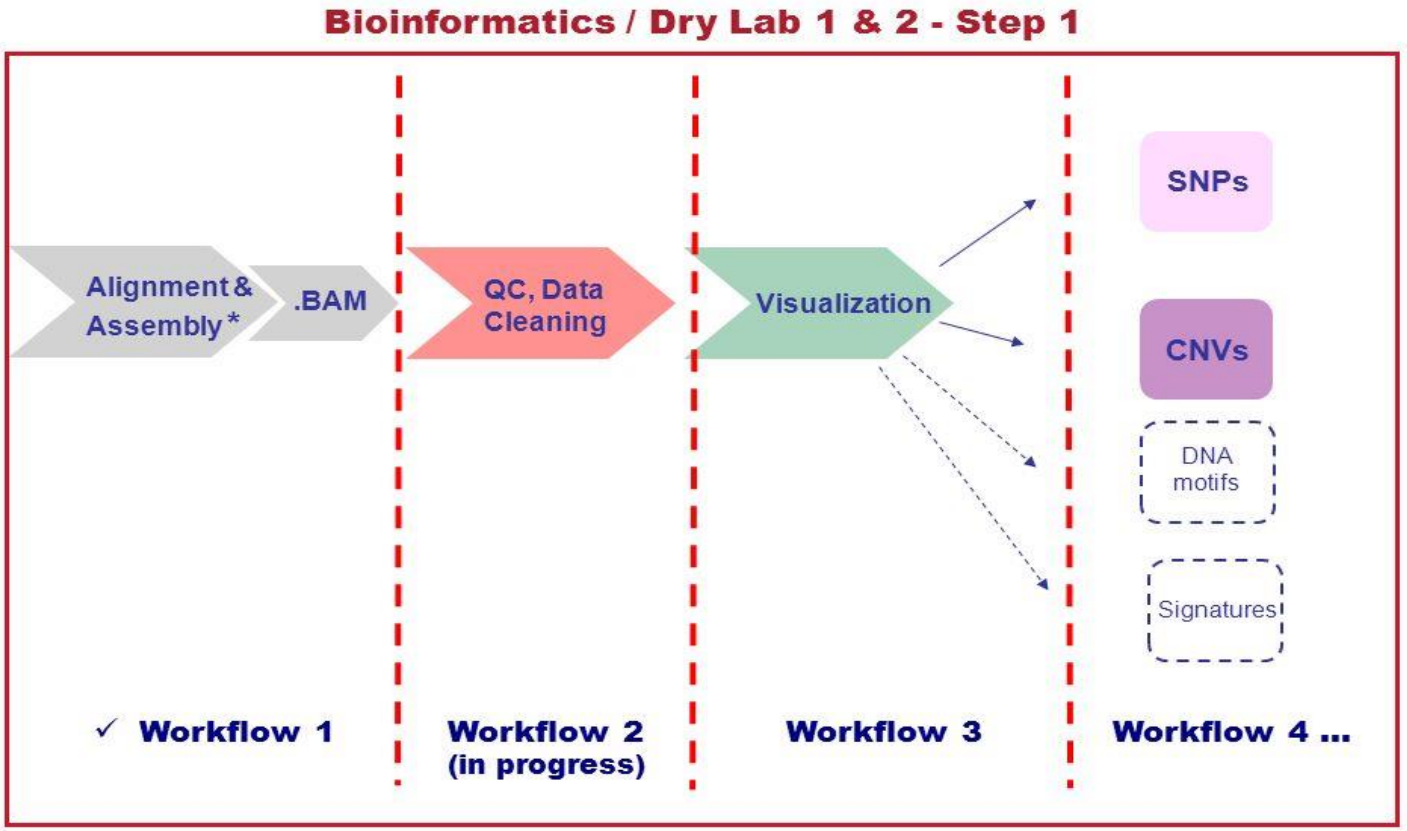
- To identify the genetic alterations causing this phenotype, we performed WES on the patient's (II:2) DNA sample.
- Us we
  id riant
  (c. T>C,
  g. BN1
  (GenBank NM_000138.5).



Gene	Zygosity	Variant	OMIM	Inheritance	Classification	ClinVar/ HGMD
FBN1	Het.	NM_000138: c.T2179C:p.C727R	Marfan syndrome*	AD	Likely Pathogenic	-

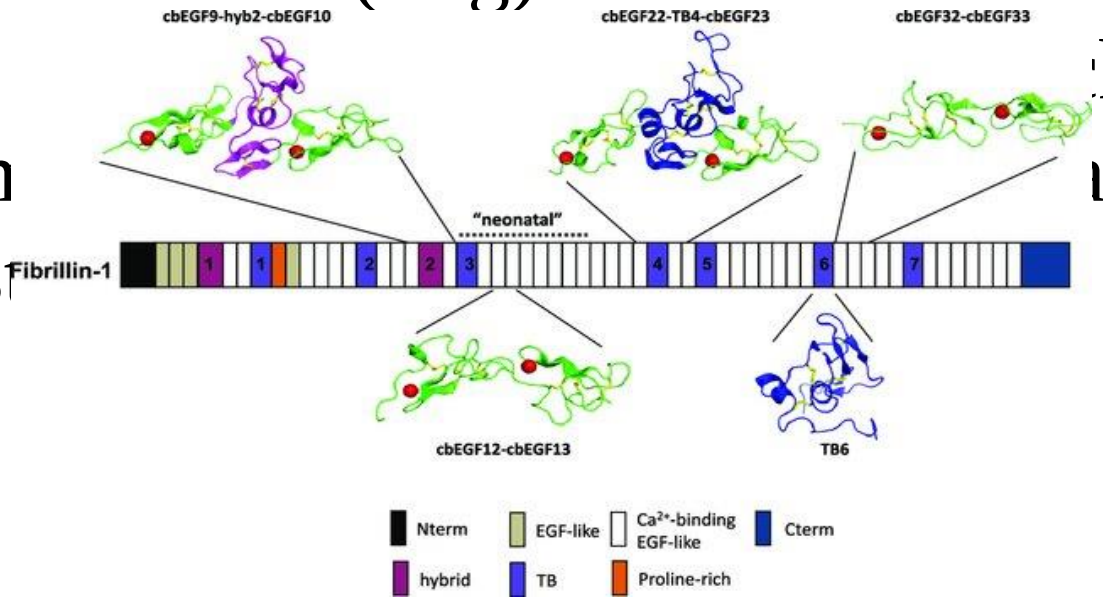
*Comment: Pathogenic mutations in FBN1 gene can cause different diseases including Marfan syndrome, MASS syndrome, and etc. (OMIM). Correlation between the genotype and phenotype is needed to be checked by physician and more clinical experiments. Sanger sequencing is needed for confirmation of the variant in patient and his family.

NGS Pipeline: general plan

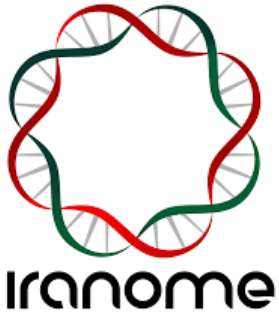


Finding

- This substitution indicates that TGT (Cys) changes to CGT (Arg) at codon. 727 located on exon [illegible]h is a calciun [illegible]s been sugges



- The variant has not been previously reported in the GME, ExAC, 1K Genome Project Phase 3, dbSNP, and Iranome databases. No [illegible] ious description [illegible] ical [illegible] if [illegible] ; v [illegible] b[illegible] clinical/ genetic databases such as the Marfan database, ClinVar, HGMD, and



Bioinformatics eval

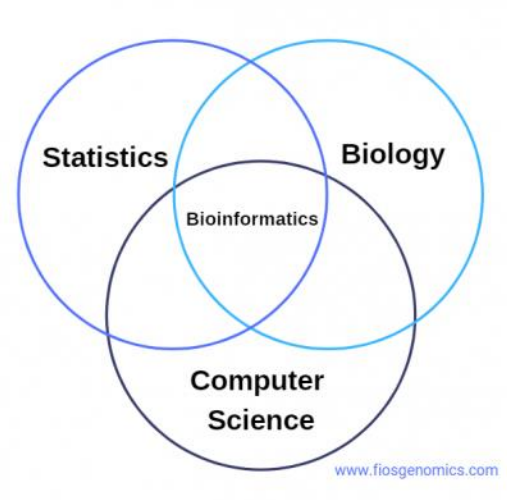
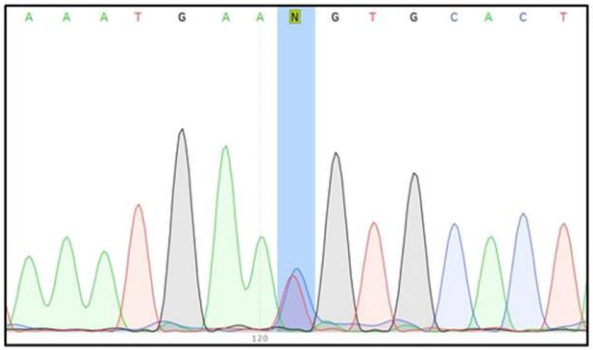


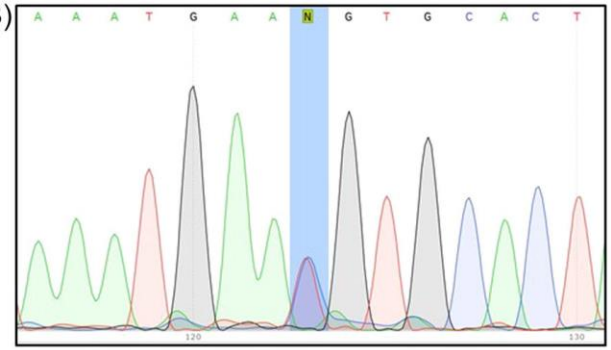
TABLE 3 In silico prediction analyses of the *FBN1* c.2179T>C variant.

Algorithm	Prediction	Score
PhyloP100	Highly conserved	8.94
PhastCons100	Highly conserved	1.0
SIFT	Damaging	0.001
Polyphen-2	Probably damaging	0.997
LRT	Deleterious	0
PROVEAN	Damaging	−10.93
PrimateAI	Pathogenic	0.917
Mutation Taster	Disease causing	1.0
MutPred	Pathogenic	0.996
FATHMM	Damaging	−5.91
EIGEN	Pathogenic	1.082
M-CAP	Damaging	0.969
CADD	Deleterious	27
BayesDel addAF	Damaging	0.577
MetaIR	Damaging	0.990
MetaSVM	Damaging	0.967

(A)



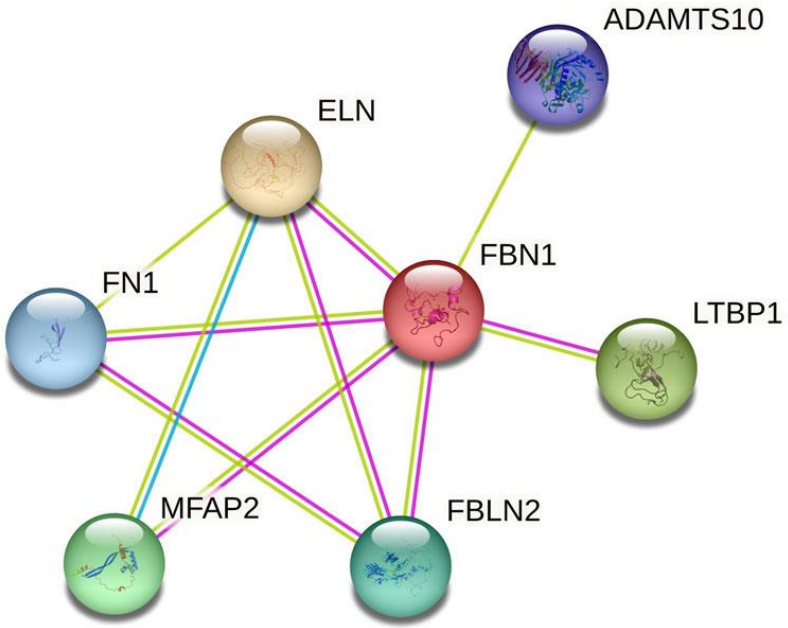
(B)

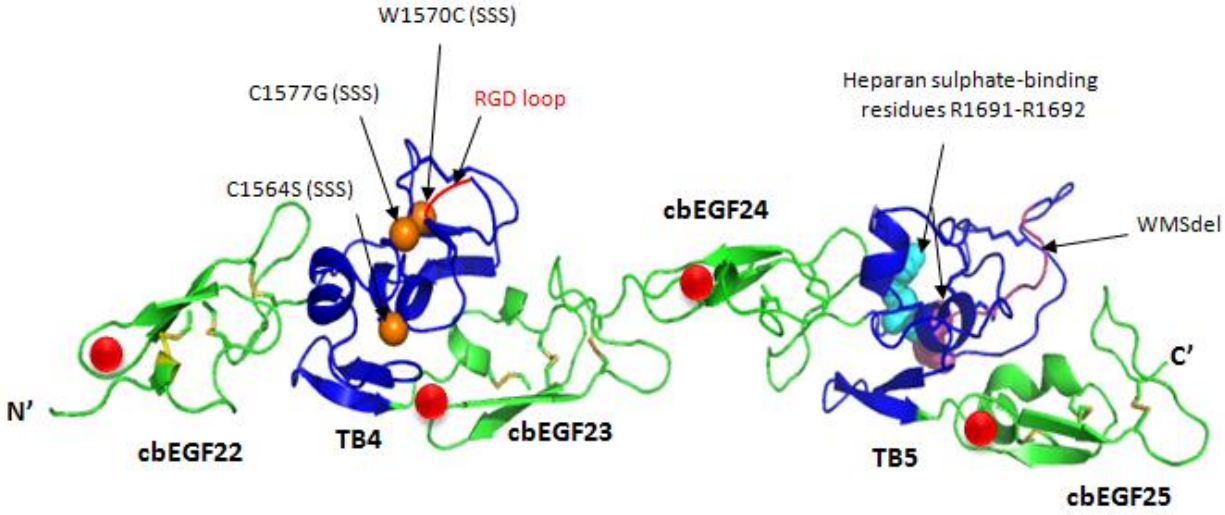


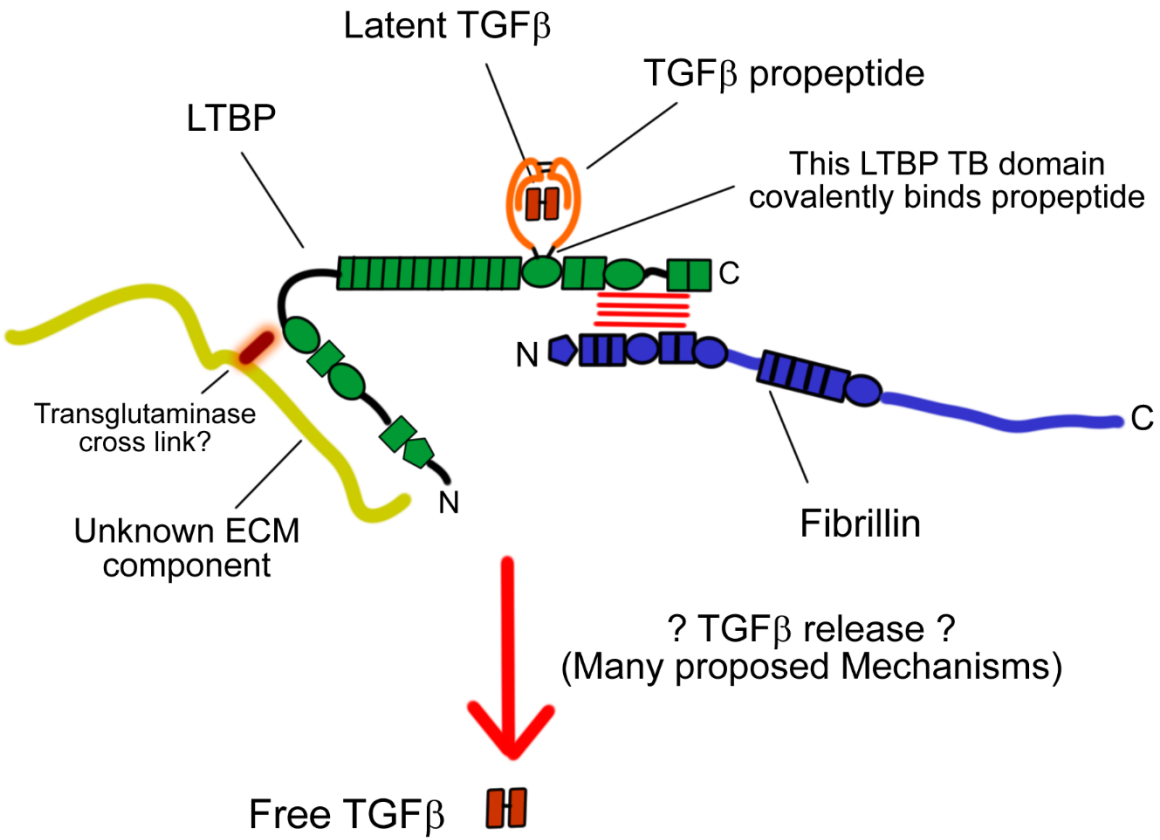
(C)

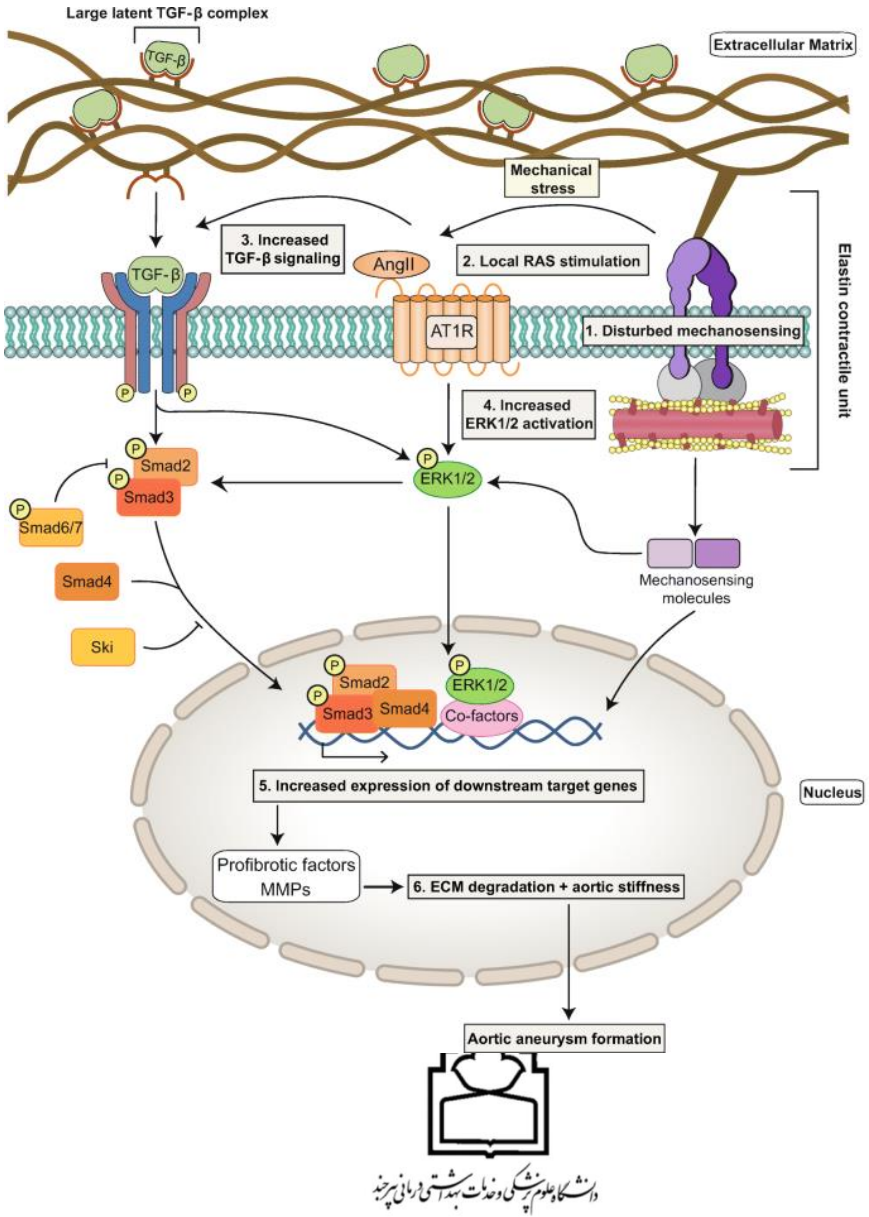
Human	SSGPGMTSAGSDINECALDPDICPNGICENLRGTYKCICNSGYEVDSTGKNCVDINECVL
Mouse	SSGPGMTSAGTDINECALDPDICPNGICENLRGTYKCICNSGYEVDITGKNCVDINECVL
Norway rat	SSGPGMTSAGSDINECALDPDICPNGICENLRGTYKCICNSGYEVDITGKNCVDINECVL
Cattle	SSGPGITSAGSDINECALDPDICPNGICENLRGTYKCICNSGYEVDSTGKNCVDINECVL
Chicken	SSGSGMTAGGNDINECLLDPDLCPNGRCENLHGTYKCICNPGYEVDSTGKNCIDIDECVL
Rhesus monkey	SSGPGMTSAGSDINECALDPDICPNGICENLRGTYKCICNSGYEVDSTGKNCVDINECVL
Chimpanzee	SSGPGMTSAGSDINECALDPDICPNGICENLRGTYKCICNSGYEVDSTGKNCVDINECVL
Horse	SSGPGMTSAGSDINECALDPDICPNGICENLRGTYKCICNSGYEVDSTGKNCVDINECVL
Domestic cat	SSGPGMTSAGSDINECALDPDICPNGICENLRGTYKCICNSGYEVDSTGKNCVDINECVL
Chinese hamster	SSGPGMTSAGTDINECALDPDICPNGICENLRGTYKCICNSGYEVDITGKNCVDINECVL
Pig	SSGPGMTSAGSDINECALDPDICPNGICENLRGTYKCICNSGYEVDSTGKNCVDINECVL
Zebra fish	SSGPGMTSAGSDINECALDPDICPNGICENLRGTYKCICNSGYEVDSSGKNCVDINECVL

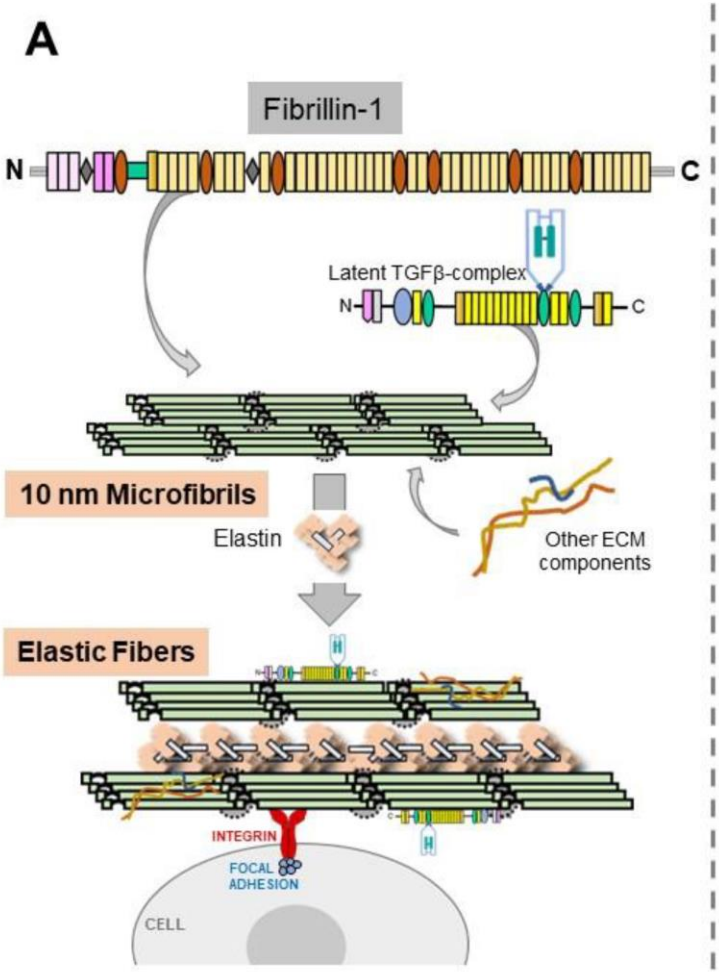
STRING




W1570C (SSS)
C1577G (SSS)
RGD loop
C1564S (SSS)
Heparan sulphate-binding
residues R1691-R1692
cbEGF24
WMSdel
C'
N'
cbEGF22
TB4
cbEGF23
TB5
cbEGF25


Latent TGFβ
TGFβ propeptide
LTBP
This LTBP TB domain
covalently binds propeptide
C
N
C
Transglutaminase
cross link?
N
Unknown ECM
component
Fibrillin
? TGFβ release ?
(Many proposed Mechanisms)
Free TGFβ





B

Cardiovascular system

TAAD
- Impaired tissue integrity
- EC dysfunction
- TGFβ dysregulation

DCM
- Defective mechanotransduction

Skeleton

OP
- TGFβ hyperactivity

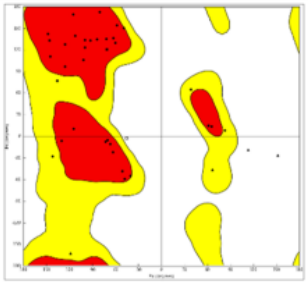
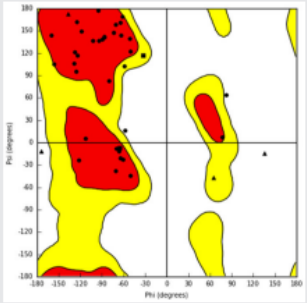
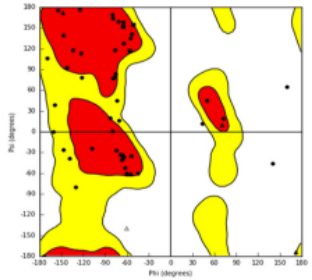
Bone overgrowth
- Loss of TGFβ signaling

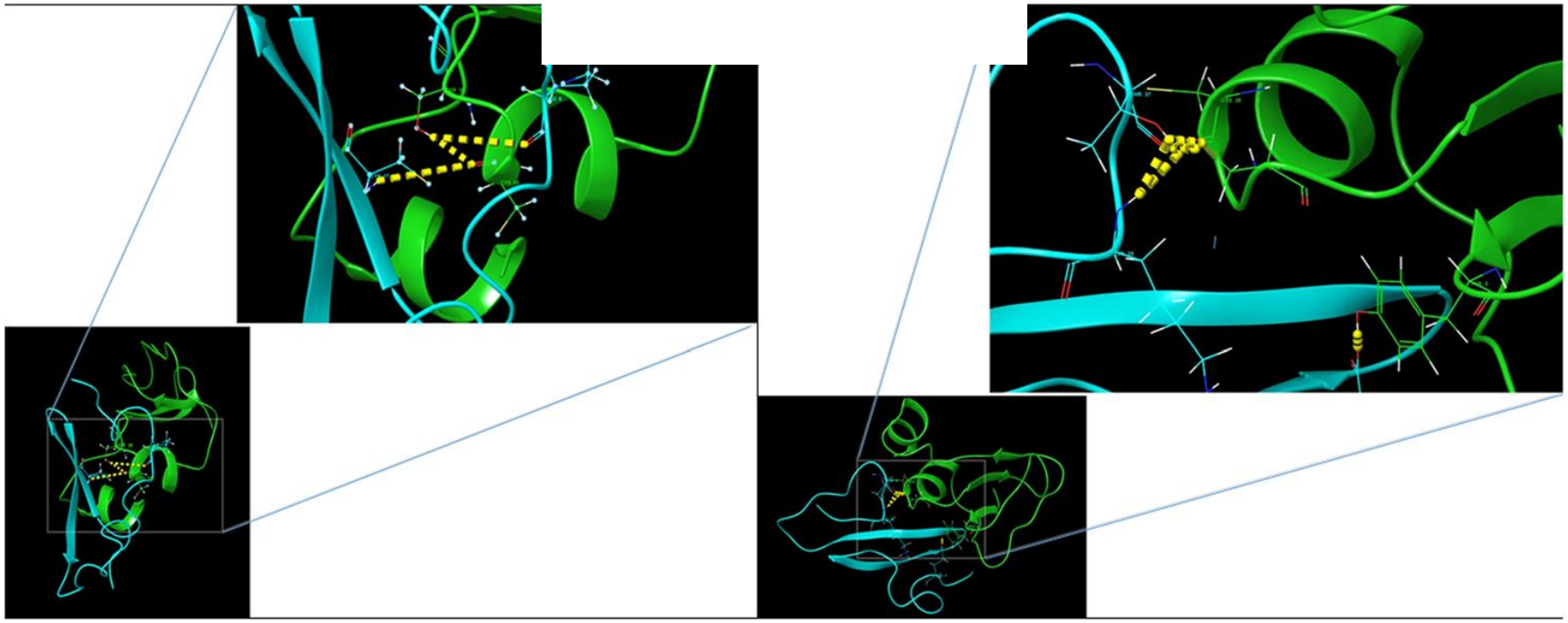
Eyes

EL
- Defective mechanointegrity

- To better understand the molecular mechanics and structural consequences of the p.C727R mutation in FBN1, the online ITASSER server was used to generate models of the EGF-like 11 domain, calcium-binding domain of Fibrillin, and C-terminal LTBP1 fragment for the mutant and wild-type.
- To better understand the molecular mechanics and structural consequences of the p.C727R mutation in FBN1, the online ITASSER server was used to generate models of the EGF-like 11 domain, calcium-binding domain of Fibrillin, and C-terminal LTBP1 fragment for the mutant and wild-type.

TABLE 4 Estimated accuracy of FBN1 (wild and mutant) as well as LTBP1 models and Ramachandran plots.

				Ramachandran analysis			
Protein name	**C-score**	**TM-score (mean ± SD)**	**RMSD (Å)**	**Plots**	**Favored**	**Allowed**	**Outlier**
FBN1-(wild)	0.37	0.76 ± 0.10	1.7 ± 1.5		33 (78.5%)	6 (14.4%)	3 (7.1%)
FBN1-(mutant)	0.30	0.75 ± 0.10	1.8 ± 1.5		35 (83.3%)	3 (7.2%)	4 (9.5%)
LTBP1	0.91	0.84 ± 0.08	1.2 ± 1.2		42 (76.4%)	9 (16.3%)	4 (7.3%)



Molecular docking of wild-type and mutant EGF-like 11; calcium-binding domain of FBN1 with C-terminal of LTBP1.

Management

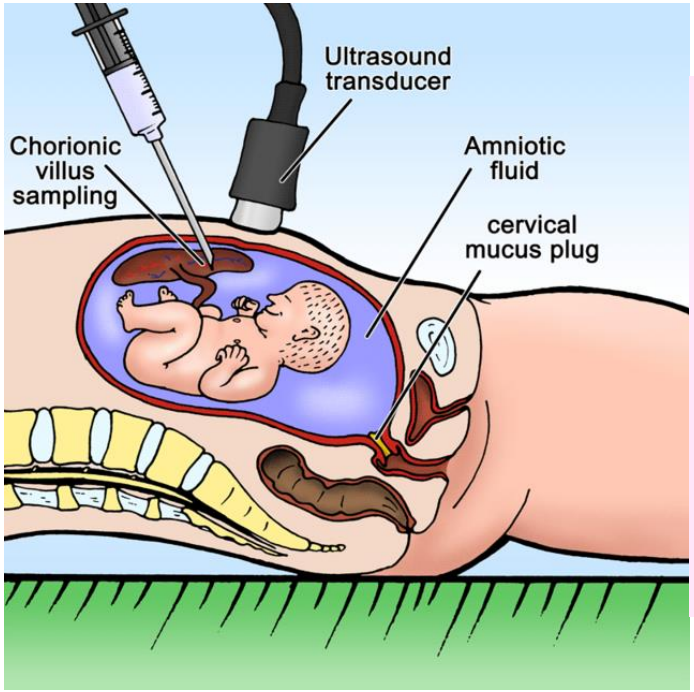
Management of Marfan syndrome involves a multidisciplinary approach, including medical, surgical, and lifestyle interventions.

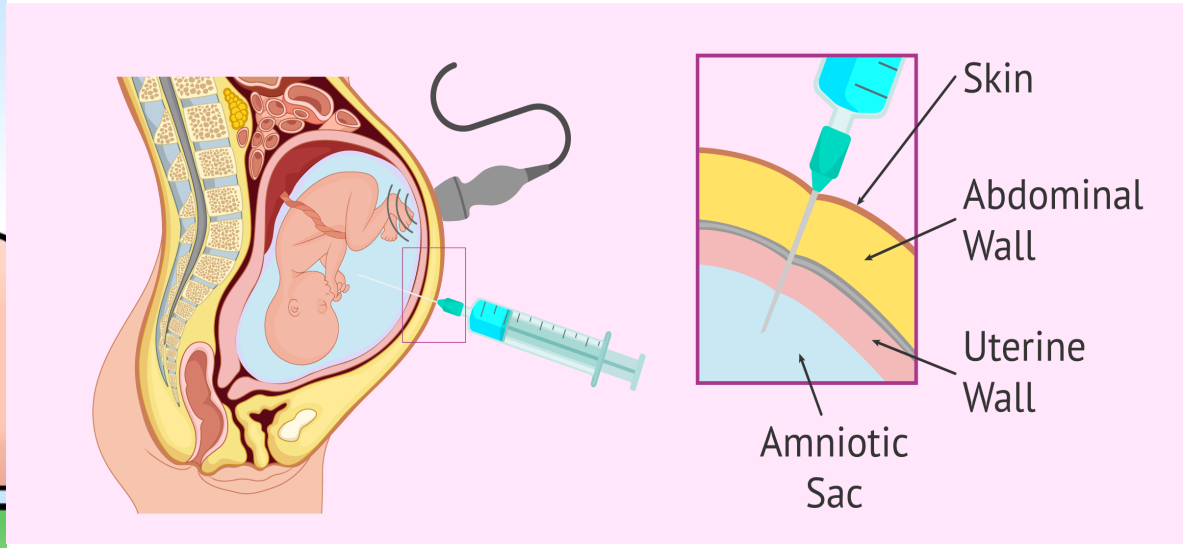
- **Medical**: Beta blockers or angiotensin receptor blockers
- **Surgery:** aortic root replacement or repair to prevent aortic dissection, mitral valve repair or replacement, or surgery to correct skeletal abnormalities such as scoliosis
- **Lifestyle**: avoiding strenuous physical activities

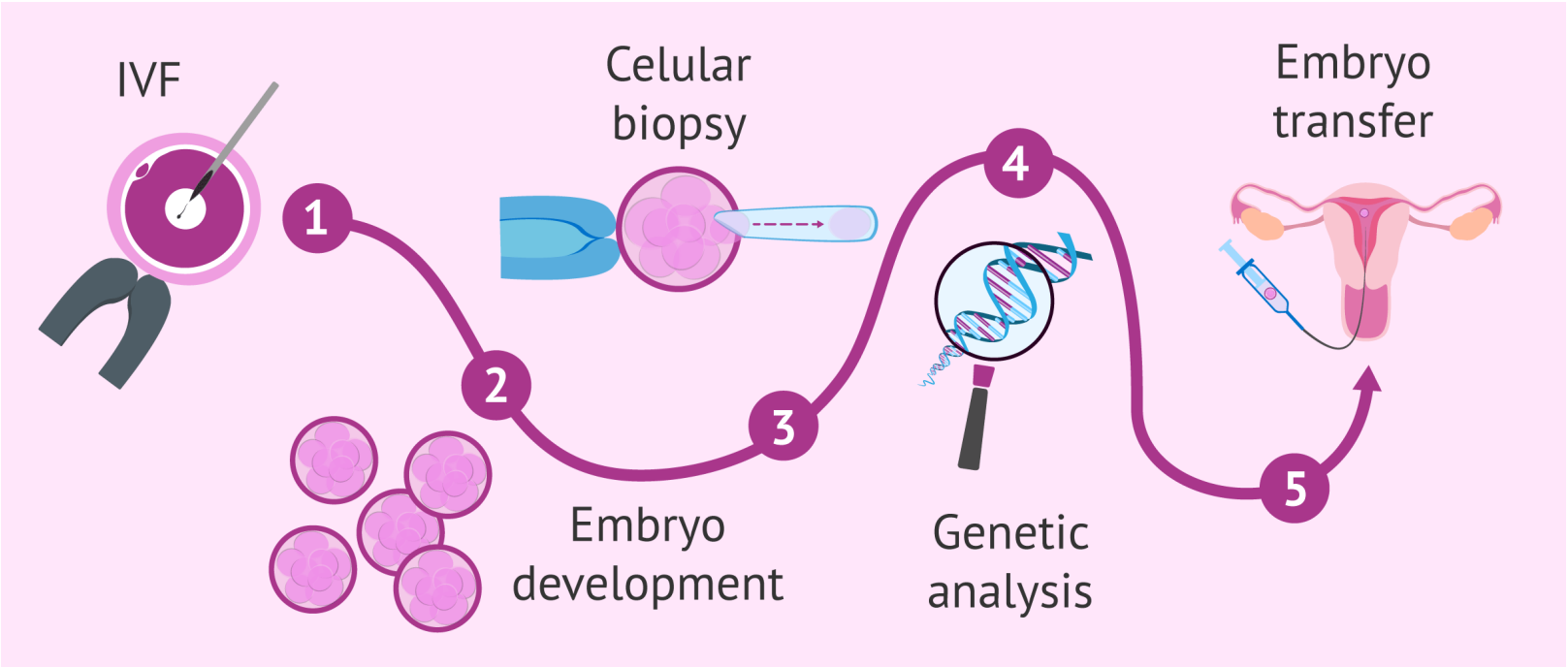
- added stress on the aorta
- worsening lens dislocation or a retinal detachment
- Bruising and internal hemorrhaging

Genetic counseling

- prenatal testing can be conducted for Marfan syndrome. Two common methods of prenatal testing for genetic disorders like Marfan syndrome are chorionic villus sampling (CVS) between 10 and 13 weeks of pregnancy and amniocentesis between 15 and 20 weeks of pregnancy.
- Additionally, in-vitro fertilization (IVF) with pre-implantation genetic diagnosis (PGD) can be used for couples who are at risk of


Ultrasound transducer
Chorionic villus sampling
Amniotic fluid
cervical mucus plug


Skin
Abdominal Wall
Uterine Wall
Amniotic Sac


IVF
Celular biopsy
Embryo transfer
1
2
3
4
5
Embryo development
Genetic analysis

Received: 25 July 2023 | Revised: 13 September 2023 | Accepted: 12 October 2023

DOI: 10.1002/hsr2.1647

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Clinical and genetic screening in a large Iranian family with Marfan syndrome: A case study

Farzane Vafaeie[1] | Zahra Miri Karam[2,3] | Abolfazl Yari[1,3] | Hossein Safarpour[1] | Tooba Kazemi[4] | Shokoofeh Etesam[5] | Mojtaba Mohammadpour[6] | Ebrahim Miri-Moghaddam[4]


مرکز تحقیقات بیماریهای قلب و عروق بیرجند
C.V.D.R.C
Birjand CardioVascular Diseases Research Center


دانشگاه علوم پزشکی و خدمات بهداشتی درمانی بیرجند


گروه قلب و عروق
دانشگاه علوم پزشکی بیرجند

بسم الله الرحمن الرحیم

MARFAN SYNDROME

KAZEMI T

28 Oct 2023

Figure 1: Family members with Marfan's syndrome. From left to right: father, first son and his daughter, second son and his two sons, third son, second daughter and her son, first daughter and her daughter.

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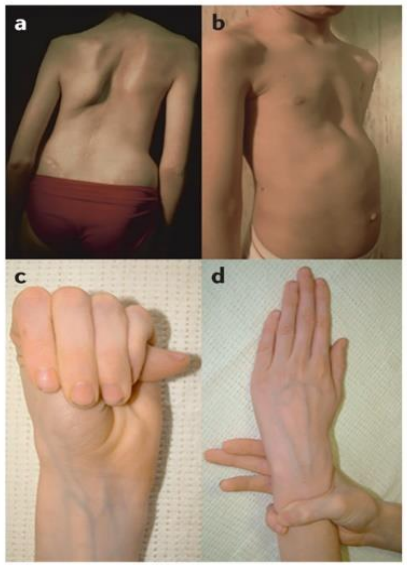
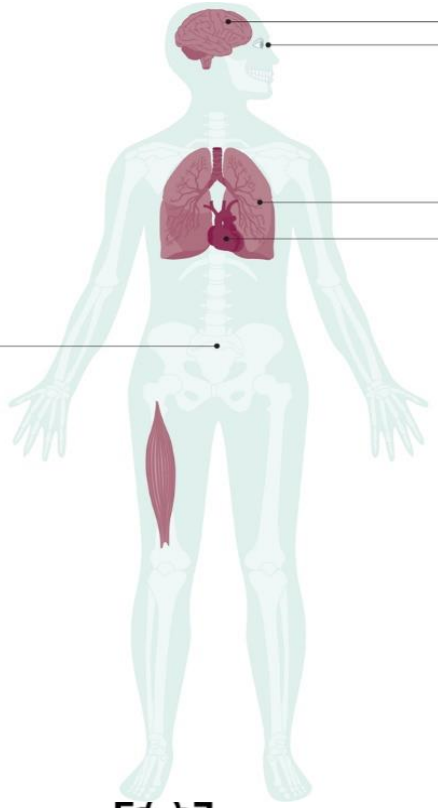
- ✓ Milewicz DM, Braverman AC, De Backer J, Morris SA, Boileau C, Maumenee IH, Jondeau G, Evangelista A, Pyeritz RE. Marfan syndrome. ***Nature Review Dis Primers. 2021*** Sep 2;7(1):64. doi: 10.1038/s41572-021-00298-7.

Marfan syndrome

Musculoskeletal and integumentary systems
- Elongated digits (arachnodactyly)
- Disproportionately long legs and arms
- Scoliosis
- Dural ectasia
- Sternal deformity (pectus deformities)
- Joint hypermobility
- Stretch marks



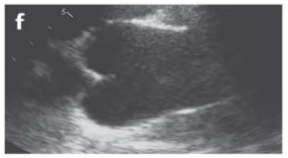


Psychosocial impact

Ophthalmic system
- Ectopia lentis
- Early cataracts

Respiratory system
- Pneumothorax
- Obstructive sleep apnoea

Cardiovascular system
- Aortic root aneurysm and dissection
- Mitral valve prolapse



MFS: Diagnosis

Ghent II criteria

Systemic features excluding aortic disease, ectopia lentis and family history for the diagnosis of MFS.

- Wrist and thumb signs (3 points)
- Wrist or thumb sign (1 point)
- Anterior chest deformity (2 points)
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- Reduced elbow extension (1 point)
- Facial features: dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, and retrognathia (1 point if 3 out 5 features are present)
- Skin striae other than due to pregnancy or obesity (1 point)
- Myopia >3 diopters (1 point)
- Mitral valve prolapse (1 point)

The total score of the systemic features is used in the diagnostic criteria.

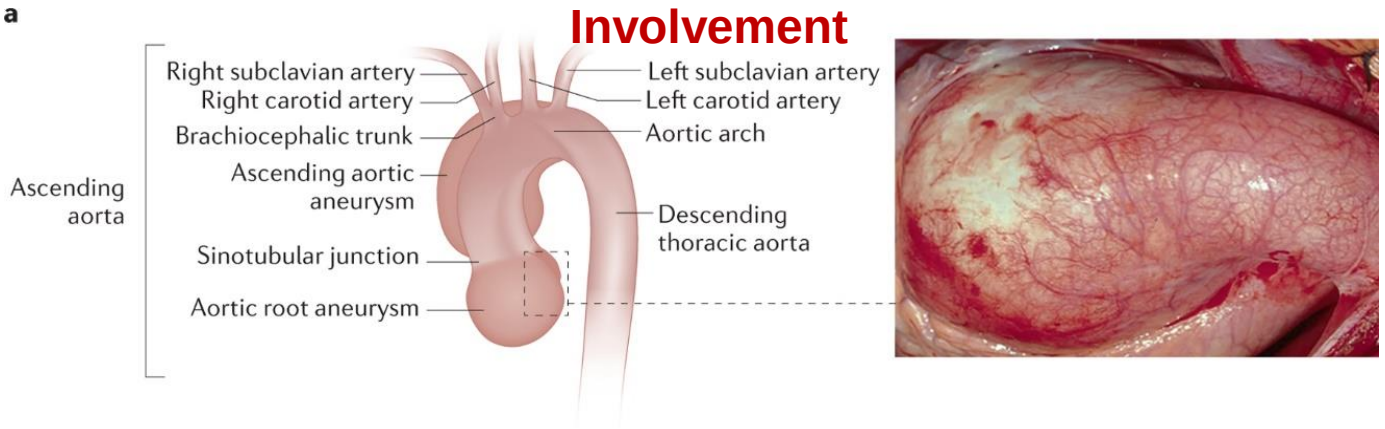
Requirement for the diagnosis of Marfan syndrome

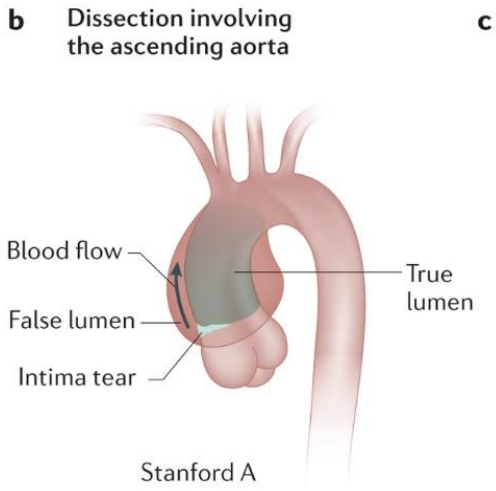
- Aortic root dilatation & ectopia lentis
- Aortic root dilatation & a *FBN1* mutation
- Aortic root dilatation & ≥7 systematic points (see above)
- Ectopia lentis with a *FBN1* mutation known to cause ascending aorta dilation
- Family history of MFS & ectopia lentis
- Family history of MFS & ≥7 systematic points (see above)
- Family history of MFS & aortic root dilatation

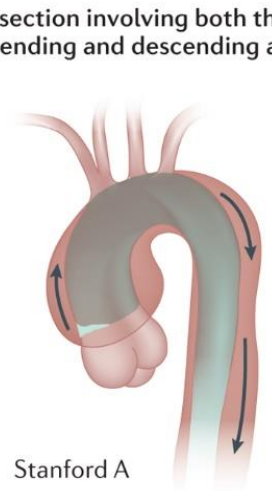
MFS: Cardiovasular

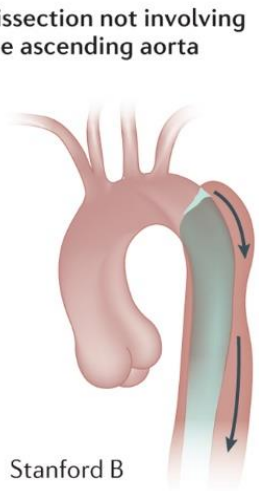
- ✓ The most severe of these clinical problems include aortic root dilatation and dissection
- ✓ Skeletal deformities such as thoracolumbar scoliosis, thoracic lordosis, and pectus excavatum, may lead to pulmonary difficulties that include restrictive airway disease and cor pulmonale if the deformities are progressive and untreated.
- ✓ Mitral valve prolapse that requires valve replacement can occur as well.

MFS: Aortic Involvement









Key issues in the assessment of Marfan syndrome

- ✓ The initial assessment should include a personal history, detailed **family history** and clinical examination including **ophthalmology** examination and transthoracic **echocardiogram**.
- ✓ The Ghent nosology **cannot exclude** Marfan syndrome in **children**, because of the age-dependent penetrance of many features.
- ✓ Younger patients with a positive family history but no fulfill the diagnostic criteria, should be offered further clinical evaluations at least until **age 18**, or until a diagnosis can be made.

Key issues in cardiovascular management in MFS

- ✓ **β-Blocker** therapy should be considered **at any age** if the aorta is dilated, but **prophylactic** treatment may be more effective in those with an aortic diameter of less than 4 cm.

- ✓ **Risk factors for aortic dissection** include:
  - aortic diameter greater than 5 cm,
  - aortic dilatation extending beyond the sinus of Valsalva
  - rapid rate of dilatation (>5% per year, or 1.5 mm/year in adults)
  - and family history of aortic dissection.

Key issues in cardiovascular management in MFS

- ✓ At least **annual** evaluation should be offered including:
  - comprising clinical history
  - examination
  - echocardiography.

- ✓ In **children**, serial **echocardiography** at **6–12 month** intervals is recommended, the frequency depending on the aortic diameter (in relation to body surface area) and the rate of increase.

Key issues in cardiovascular management in MFS

- ✓ **Prophylactic** aortic root **surgery** should be considered when the aortic diameter at the Sinus of Valsalva **exceeds 5 cm.**

- ✓ In **pregnancy**, there is an increased risk of aortic dissection if the aortic diameter **exceeds 4 cm.**
  - ○ Frequent cardiovascular monitoring throughout **pregnancy** and into the **puerperium** is advised.

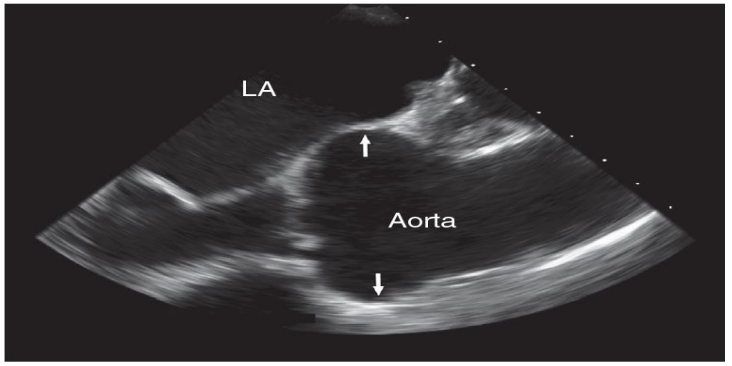


FIGURE 42.5 Transesophageal echocardiogram demonstrating an aortic roo aneurysm of 53 mm *(arrows)* in an individual with Marfan syndrome. *LA,* Left atrium

MFS : Pregnancy

Table 3 Management strategies in pregnant women with Marfan syndrome based on the size of the aorta

Aortic size (mm)	Follow-up	Delivery
<40	Follow-up monthly	Vaginal
40–45	Follow-up monthly	Cesarean section
≥45	Prophylactic surgery pre-pregnancy/or during pregnancy in women with rapid growth of the aorta	Cesarean section

Table 2 Pregnancy management in women with Marfan syndrome

Time	Recommendations	Special consideration
Preconception	To assess maternal and fetal risks: Past medical and family history Information on the aortic size before conception	Multidisciplinary care involving cardiologists, obstetricians, genetic specialists
	To provide proper information on possible prenatal diagnosis	
	Evaluation of the entire aorta: TTE, CT/MRI	TEE when needed, to assess valvular pathology
	Initiation of β-blockers	Stop ARB when contraception is stopped
	Consider elective surgery when ascending aorta ≥45 mm	Significant AR or MR with LV depression, according to the guidelines for valvular disease
During pregnancy	Serial TTE 4–12 weeks depends on the size of ascending aorta (timing see *Table 3*)	Use TEE and MRI without gadolinium when needed for optimal visualization
	Continue β-blockers	Preferable Metoprolol with target HR—reduction of 20% of rest HR
		Fetal monitoring with attention for fetal growth
		Strict control of BP
	Type A aortic dissection: Unurgent surgery is required Viable fetus: c/s followed by aortic surgery Non-viable fetus: aortic surgery with fetus-in-uterus Type B dissection: Conservative treatment with attention to fetal monitoring	Multidisciplinary care management including obstetricians, fetal care, cardiothoracic/vascular surgeon and anesthetists. Optimal perioperative management including full maternal and fetal monitoring, attention to cardiopulmonary bypass, pulsatile perfusion, etc. Serial assessment of the aorta with MRI without gadolinium, thoracic endovascular aortic repair can be considered in selected cases by an experienced team

Delivery	C-section with the ascending aorta 40–45 and >45 mm, vaginal delivery in women with diameter <40 mm	Pain management Low threshold for assisted vaginal delivery (forceps, vacuum etc.) Attention to symptoms of possible dissection Caution with epidural anesthesia due to high prevalence of dural ectasia Timely diagnosis and management of PPH
Postpartum	Continue β-blockers Clinical aortic follow-up during at least 2 months (up to 6 moths) High risk—weekly Low risk—monthly	Women's education is essential: to seek immediate medical attention when symptoms of aortic dissection occur

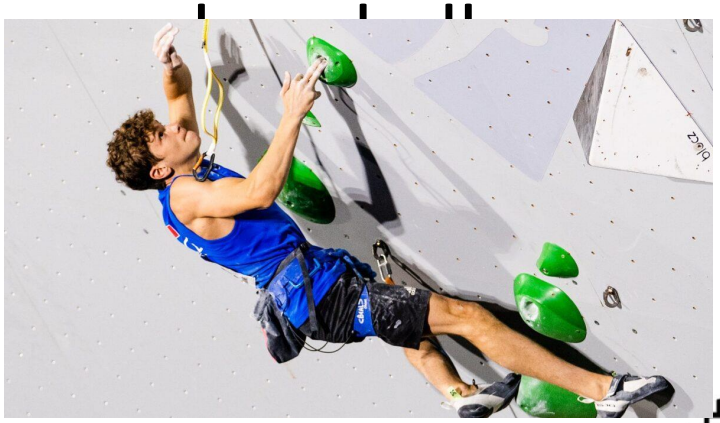
MFS : sport recommended

- ✓ Regular **aerobic activities** are recommended.

- ✓ **low-intensity activities** like golf, bowling, ….if
  - No aortic root dilation
  - No MR
  - No family history of aortic rupture or SCD.

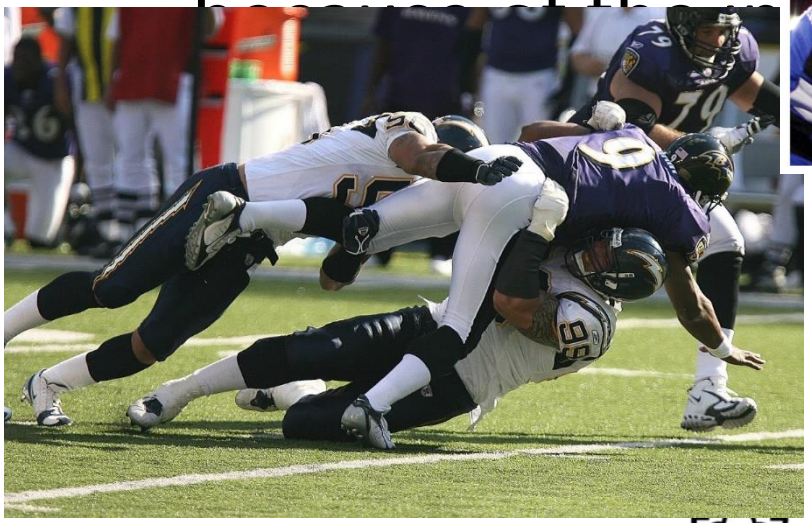
MFS : sport Not recommended

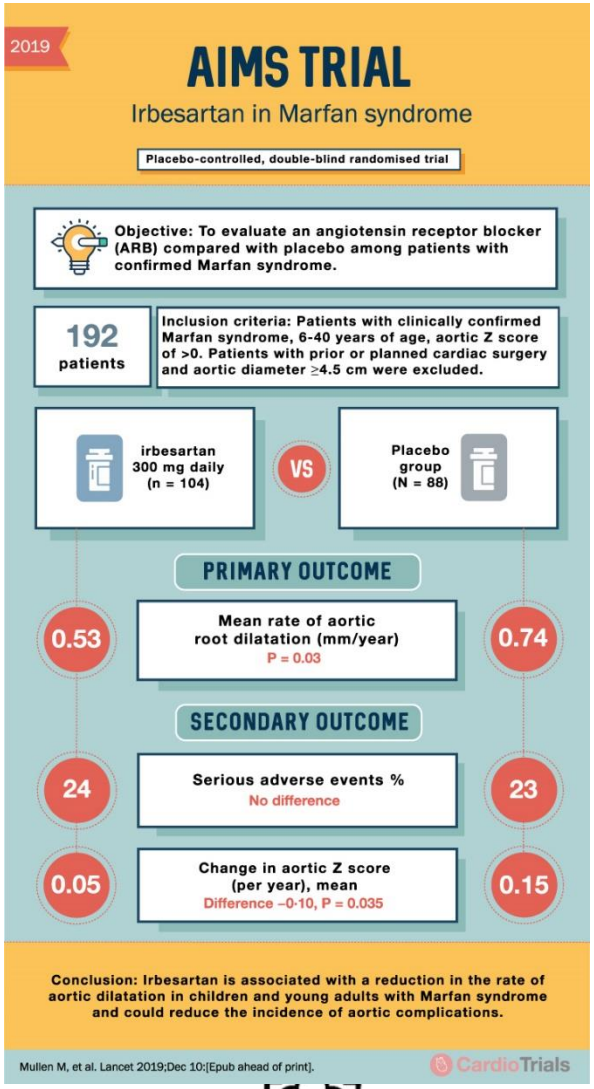
- ✓ in activities that involve **sustained muscle contraction** such as weight lifting or rock climbing.
- ✓ **High-intensity** level activities such as basketball, ice hock



MFS : sport Not recommended

- ✓ **Contact sports** are not advised to protect the aorta and the lens of the eye,
- ✓ **scuba diving** shou




2019
AIMS TRIAL
Irbesartan in Marfan syndrome
Placebo-controlled, double-blind randomised trial
Objective: To evaluate an angiotensin receptor blocker (ARB) compared with placebo among patients with confirmed Marfan syndrome.
192 patients
Inclusion criteria: Patients with clinically confirmed Marfan syndrome, 6-40 years of age, aortic Z score of >0. Patients with prior or planned cardiac surgery and aortic diameter ≥4.5 cm were excluded.
irbesartan 300 mg daily (n = 104)
VS
Placebo group (N = 88)
PRIMARY OUTCOME
0.53
Mean rate of aortic root dilatation (mm/year)
P = 0.03
0.74
SECONDARY OUTCOME
24
Serious adverse events %
No difference
23
0.05
Change in aortic Z score (per year), mean
Difference –0·10, P = 0.035
0.15
Conclusion: Irbesartan is associated with a reduction in the rate of aortic dilatation in children and young adults with Marfan syndrome and could reduce the incidence of aortic complications.
Mullen M, et al. Lancet 2019;Dec 10:[Epub ahead of print].
CardioTrials

MFS : Drug therapy for cardiovascular prevention

- ✓ In people with MFS and no previous aortic surgery:
- ○ **ARBs** reduced the rate of increase of the aortic root Z score by about one half, including among those taking a β blocker.
- ○ The effects of **β blockers** were similar to those of ARBs.
- ○ Assuming additivity, combination therapy **with both ARBs and β blockers** from the **time of diagnosis** would provide even greater reductions in the rate of aortic enlargement than either treatment alone, which, if maintained over a number of years, would be expected to lead to a delay in the need for aortic surgery.

بسم الله الرحمن الرحیم

MARFAN SYNDROME

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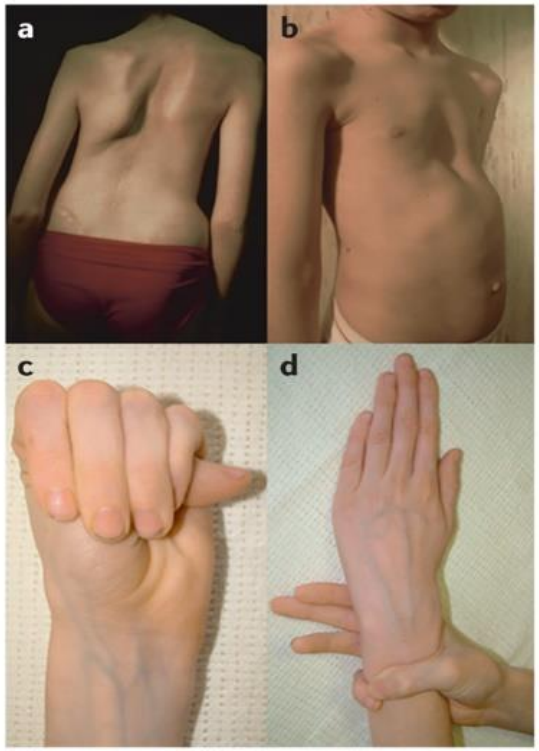

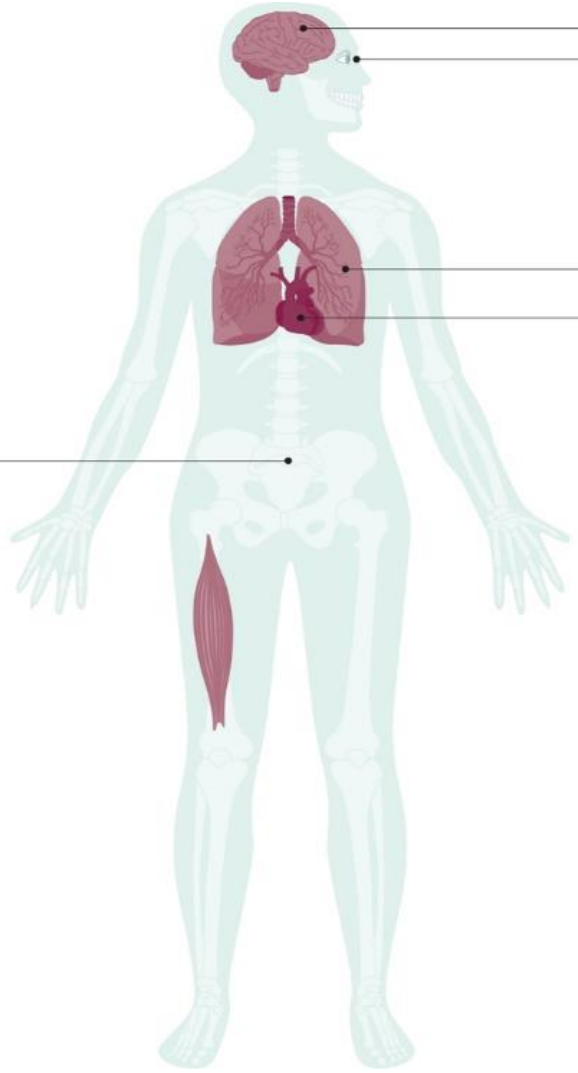

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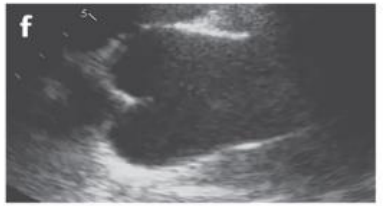

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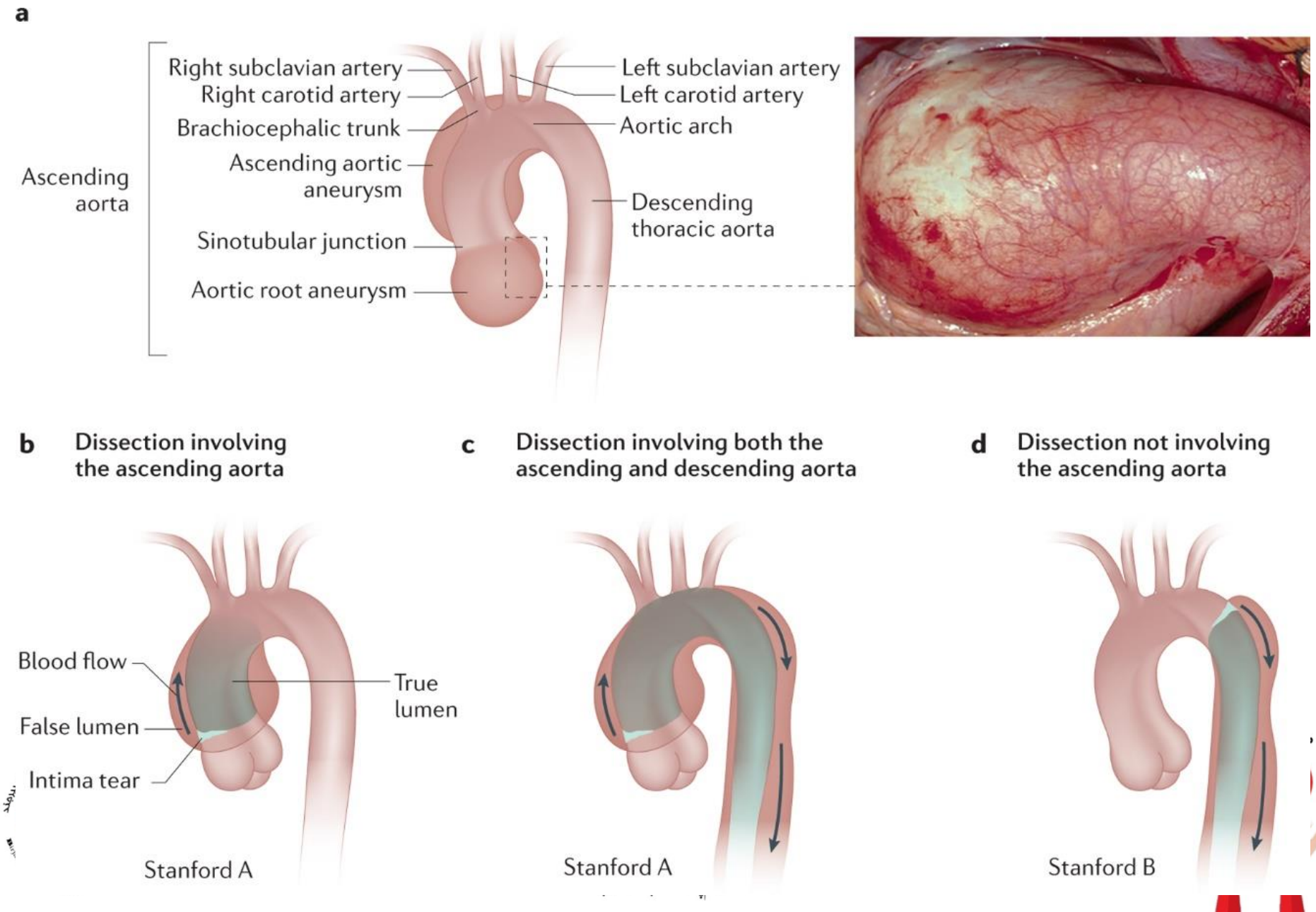
- Aortic root dilatation & a *FBN1* mutation
- Aortic root dilatation & ≥7 systematic points (see above)
- Ectopia lentis with a *FBN1* mutation known to cause ascending aorta dilation
- Family history of MFS & ectopia lentis
- Family history of MFS & ≥7 systematic points (see above)
- Family history of MFS & aortic root dilatation

MFS: Cardiovasular

- ✓ The most severe of these clinical problems include aortic root dilatation and dissection
- ✓ Skeletal deformities such as thoracolumbar scoliosis, thoracic lordosis, and pectus excavatum, may lead to pulmonary difficulties that include restrictive airway disease and cor pulmonale if the deformities are progressive and untreated.
- ✓ Mitral valve prolapse that requires valve replacement can occur as well.

MFS: Aortic Involvement



Key issues in the assessment of Marfan syndrome

- ✓ The initial assessment should include a personal history, detailed **family history** and clinical examination including **ophthalmology** examination and transthoracic **echocardiogram**.

- ✓ The Ghent nosology **cannot exclude** Marfan syndrome in **children**, because of the age-dependent penetrance of many features.

- ✓ Younger patients with a positive family history but no fulfill the diagnostic criteria, should be offered further clinical evaluations at least until **age 18**, or until a diagnosis can be made.

Key issues in cardiovascular management in MFS

- ✓ **β-Blocker** therapy should be considered **at any age** if the aorta is dilated, but **prophylactic** treatment may be more effective in those with an aortic diameter of less than 4 cm.

- ✓ **Risk factors for aortic dissection** include:
  - aortic diameter greater than 5 cm,
  - aortic dilatation extending beyond the sinus of Valsalva
  - rapid rate of dilatation (>5% per year, or 1.5 mm/year in adults)
  - and family history of aortic dissection.

Key issues in cardiovascular management in MFS

- ✓ At least **annual** evaluation should be offered including:
  - comprising clinical history
  - examination
  - echocardiography.

- ✓ In **children**, serial **echocardiography** at **6–12 month** intervals is recommended, the frequency depending on the aortic diameter (in relation to body surface area) and the rate of increase.

Key issues in cardiovascular management in MFS

- ✓ **Prophylactic** aortic root **surgery** should be considered when the aortic diameter at the Sinus of Valsalva **exceeds 5 cm.**

- ✓ In **pregnancy**, there is an increased risk of aortic dissection if the aortic diameter **exceeds 4 cm.**
  - Frequent cardiovascular monitoring throughout **pregnancy** and into the **puerperium** is advised.

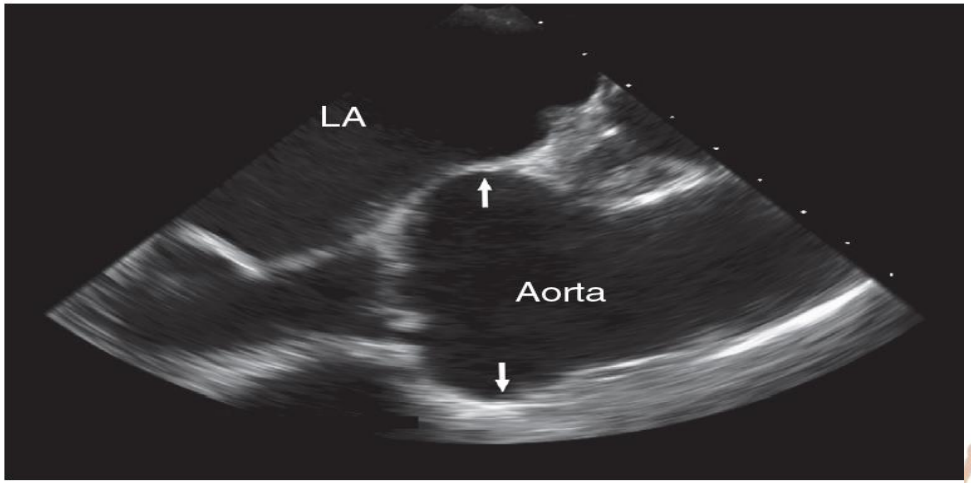


FIGURE 42.5 Transesophageal echocardiogram demonstrating an aortic roo aneurysm of 53 mm *(arrows)* in an individual with Marfan syndrome. *LA,* Left atrium

MFS : Pregnancy

Table 3 Management strategies in pregnant women with Marfan syndrome based on the size of the aorta

Aortic size (mm)	Follow-up	Delivery
<40	Follow-up monthly	Vaginal
40–45	Follow-up monthly	Cesarean section
≥45	Prophylactic surgery pre-pregnancy/or during pregnancy in women with rapid growth of the aorta	Cesarean section

Table 2 Pregnancy management in women with Marfan syndrome

Time	Recommendations	Special consideration
Preconception	To assess maternal and fetal risks:	Multidisciplinary care involving cardiologists, obstetricians, genetic specialists
	Past medical and family history	
	Information on the aortic size before conception	
	To provide proper information on possible prenatal diagnosis	
	Evaluation of the entire aorta: TTE, CT/MRI	TEE when needed, to assess valvular pathology
	Initiation of β-blockers	Stop ARB when contraception is stopped
	Consider elective surgery when ascending aorta ≥45 mm	Significant AR or MR with LV depression, according to the guidelines for valvular disease
During pregnancy	Serial TTE 4–12 weeks depends on the size of ascending aorta (timing see *Table 3*)	Use TEE and MRI without gadolinium when needed for optimal visualization
	Continue β-blockers	Preferable Metoprolol with target HR—reduction of 20% of rest HR
		Fetal monitoring with attention for fetal growth
		Strict control of BP
	Type A aortic dissection:	Multidisciplinary care management including obstetricians, fetal care, cardiothoracic/vascular surgeon and anesthetists. Optimal perioperative management including full maternal and fetal monitoring, attention to cardiopulmonary bypass, pulsatile perfusion, etc. Serial assessment of the aorta with MRI without gadolinium, thoracic endovascular aortic repair can be considered in selected cases by an experienced team
	Unurgent surgery is required	
	Viable fetus: c/s followed by aortic surgery	
	Non-viable fetus: aortic surgery with fetus-in-uterus	
	Type B dissection:	
	Conservative treatment with attention to fetal monitoring	

Delivery	C-section with the ascending aorta 40–45 and >45 mm, vaginal delivery in women with diameter <40 mm	Pain management Low threshold for assisted vaginal delivery (forceps, vacuum etc.) Attention to symptoms of possible dissection Caution with epidural anesthesia due to high prevalence of dural ectasia Timely diagnosis and management of PPH
Postpartum	Continue β-blockers Clinical aortic follow-up during at least 2 months (up to 6 moths) High risk—weekly Low risk—monthly	Women's education is essential: to seek immediate medical attention when symptoms of aortic dissection occur

MFS : sport recommended

- ✓ Regular **aerobic activities** are recommended.

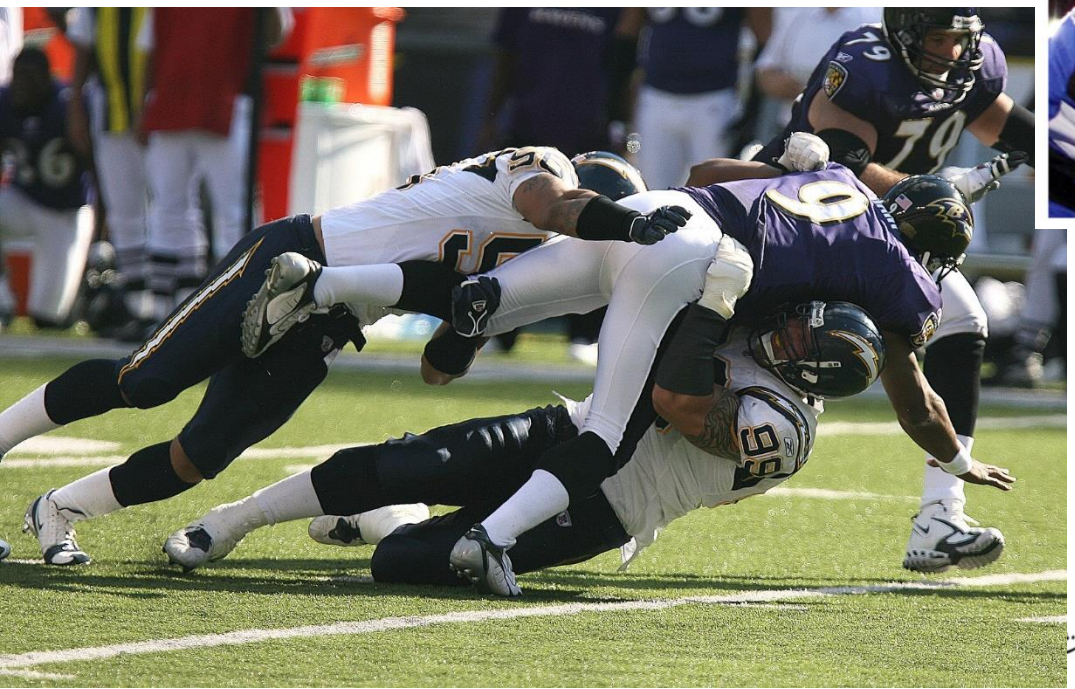
- ✓ **low-intensity activities** like golf, bowling, ….if
  - No aortic root dilation
  - No MR
  - No family history of aortic rupture or SCD.

MFS : sport Not recommended

- ✓ in activities that involve **sustained muscle contraction** such as weight lifting or rock climbing.
- ✓ **High-intensity** level activities such as basketball, ice hockey, skiing, baseball

MFS : sport Not recommended

- ✓ **Contact sports** are not advised to protect the aorta and the lens of the eye,
- ✓ **scuba diving** should be avoided because of the increased risk of pneumothorax.



2019

AIMS TRIAL

Irbesartan in Marfan syndrome

Placebo-controlled, double-blind randomised trial

Objective: To evaluate an angiotensin receptor blocker (ARB) compared with placebo among patients with confirmed Marfan syndrome.

192 patients

Inclusion criteria: Patients with clinically confirmed Marfan syndrome, 6-40 years of age, aortic Z score of >0. Patients with prior or planned cardiac surgery and aortic diameter ≥4.5 cm were excluded.

irbesartan 300 mg daily (n = 104)	VS	Placebo group (N = 88)

PRIMARY OUTCOME

irbesartan		Placebo
0.53	Mean rate of aortic root dilatation (mm/year) P = 0.03	0.74

SECONDARY OUTCOME

24	Serious adverse events % No difference	23
0.05	Change in aortic Z score (per year), mean Difference −0·10, P = 0.035	0.15

Conclusion: Irbesartan is associated with a reduction in the rate of aortic dilatation in children and young adults with Marfan syndrome and could reduce the incidence of aortic complications.

Mullen M, et al. Lancet 2019;Dec 10:[Epub ahead of print].

MFS : Drug therapy for cardiovascular prevention

- ✓ In people with MFS and no previous aortic surgery:
  - **ARBs** reduced the rate of increase of the aortic root Z score by about one half, including among those taking a β blocker.
  - The effects of **β blockers** were similar to those of ARBs.
  - Assuming additivity, combination therapy **with both ARBs and β blockers** from the **time of diagnosis** would provide even greater reductions in the rate of aortic enlargement than either treatment alone, which, if maintained over a number of years, would be expected to lead to a delay in the need for aortic surgery.