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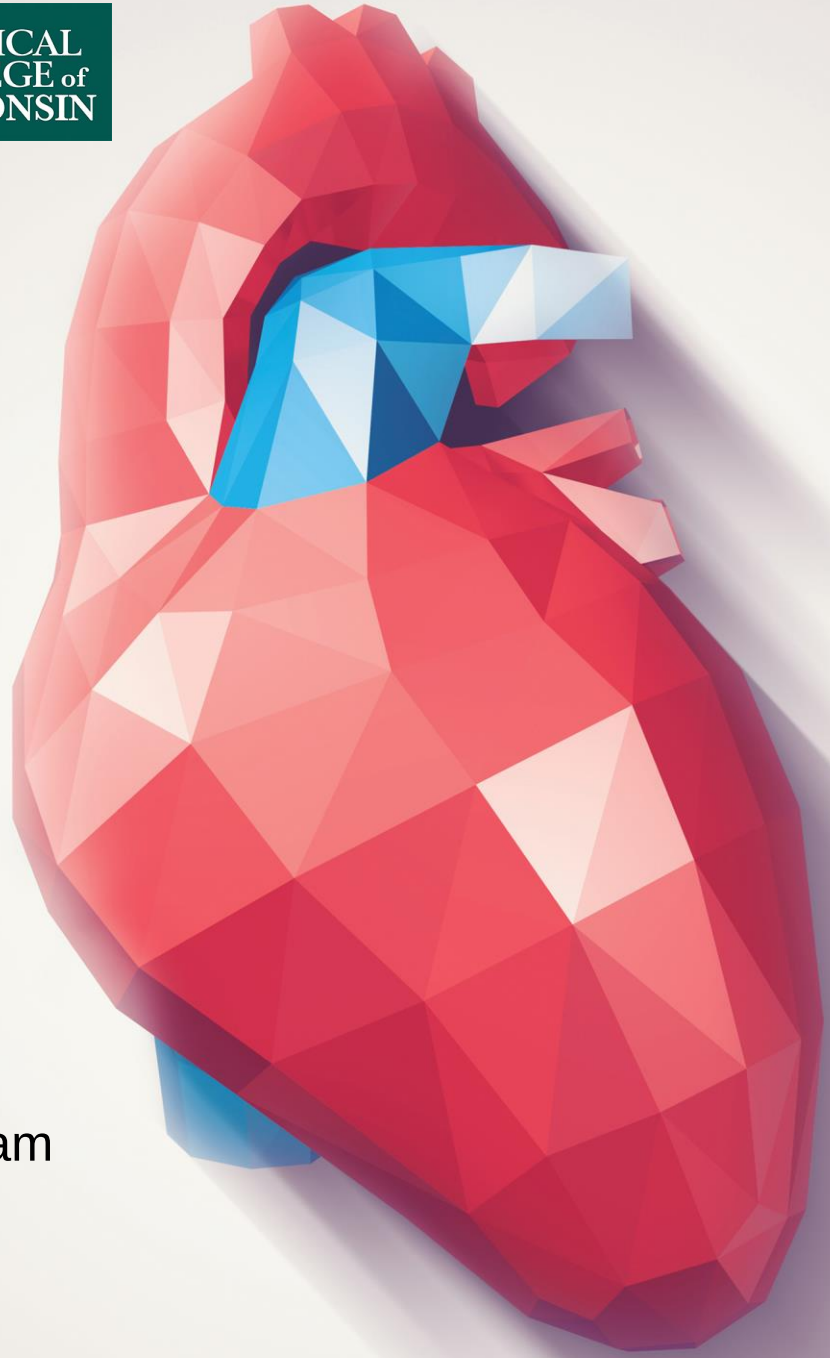

UPDATE: Risk Stratification and Management of Hereditary Thoracic Aortic Aneurysms

Salil Ginde, MD, MPH

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Children's Wisconsin and Froedtert Hospital

Medical College of Wisconsin

Objectives

- Discuss new insights into the genetic basis of hereditary thoracic aortic disease

- Utilizing both genetic testing and imaging to guide medical and surgical management

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Disclosures Dr. Salil Ginde

I have no relevant financial disclosures

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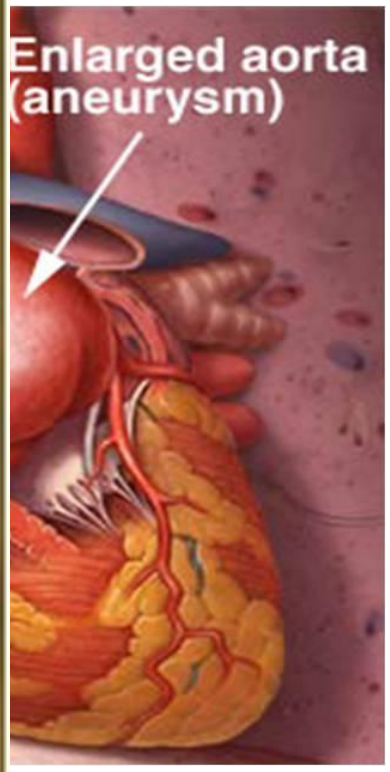
Aortic Aneurysms

Aortic dissection



Thoracic aortic aneurysm prevalence = 1%

Type A Dissection

- 50% mortality before hospital admission
- 1-2% of all deaths in Western countries

Howard DP, et al. Circulation 2013

Causes of Aortic Aneurysms

- Hypertension and/or atherosclerosis
- Inflammatory conditions
- Traumatic injury
- Genetic conditions (inherited disorder of connective tissue)

≈ 20-25% of cases

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Characterizing the Young Patient With Aortic Dissection: Results From the International Registry of Aortic Dissection (IRAD)

Table 1. Baseline Demographics of Patients in the International Registry of Aortic Dissection Based on Age Categories of <40 and ≥40 Years of Age

Variables	Age <40 n = 68 (%)	Age ≥40 n = 883 (%)	p Value
Age, yrs (mean ± SD)	30.7 ± 6.6	63.9 ± 11.5	NA
Type of dissection			NS
Type A	46 (68)	574 (65)	
Type B	22 (32)	309 (35)	
Male gender	52 (76)	596 (67)	NS
White race	55 (81)	699 (79)	NS
Diabetes	0 (0)	38 (4)	NS
Hypertension	23 (34)	635 (72)	<0.001
Atherosclerosis	1 (1)	267 (30)	<0.001
Marfan syndrome	34 (50)	19 (2)	<0.001
Prior aortic valve disease	7 (10)	74 (8)	NS
Bicuspid aortic valve (n = 516)	6 (9)	12 (1)	<0.001
Known aortic aneurysm	13 (19)	115 (13)	NS
Prior aortic dissection	5 (7)	50 (6)	NS

Januzzi et al. JACC 2004

Conditions Predisposing to Thoracic Aneurysms

- Syndromic Disorders (several non-cardiac features)
  - Marfan Syndrome
  - Loeys-Dietz Syndrome
  - Vascular Ehlers-Danlos Syndrome
  - Autosomal Dominant Polycystic Kidney Disease
  - Turner Syndrome
- Non-syndromic Disorders (near-normal phenotype)
  - Bicuspid aortic valve
  - Familial Thoracic Aortic Aneurysm/Dissection
  - Variants of Loeys-Dietz Syndrome

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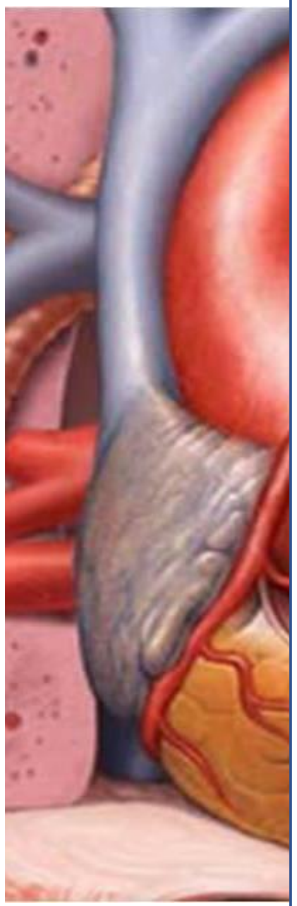


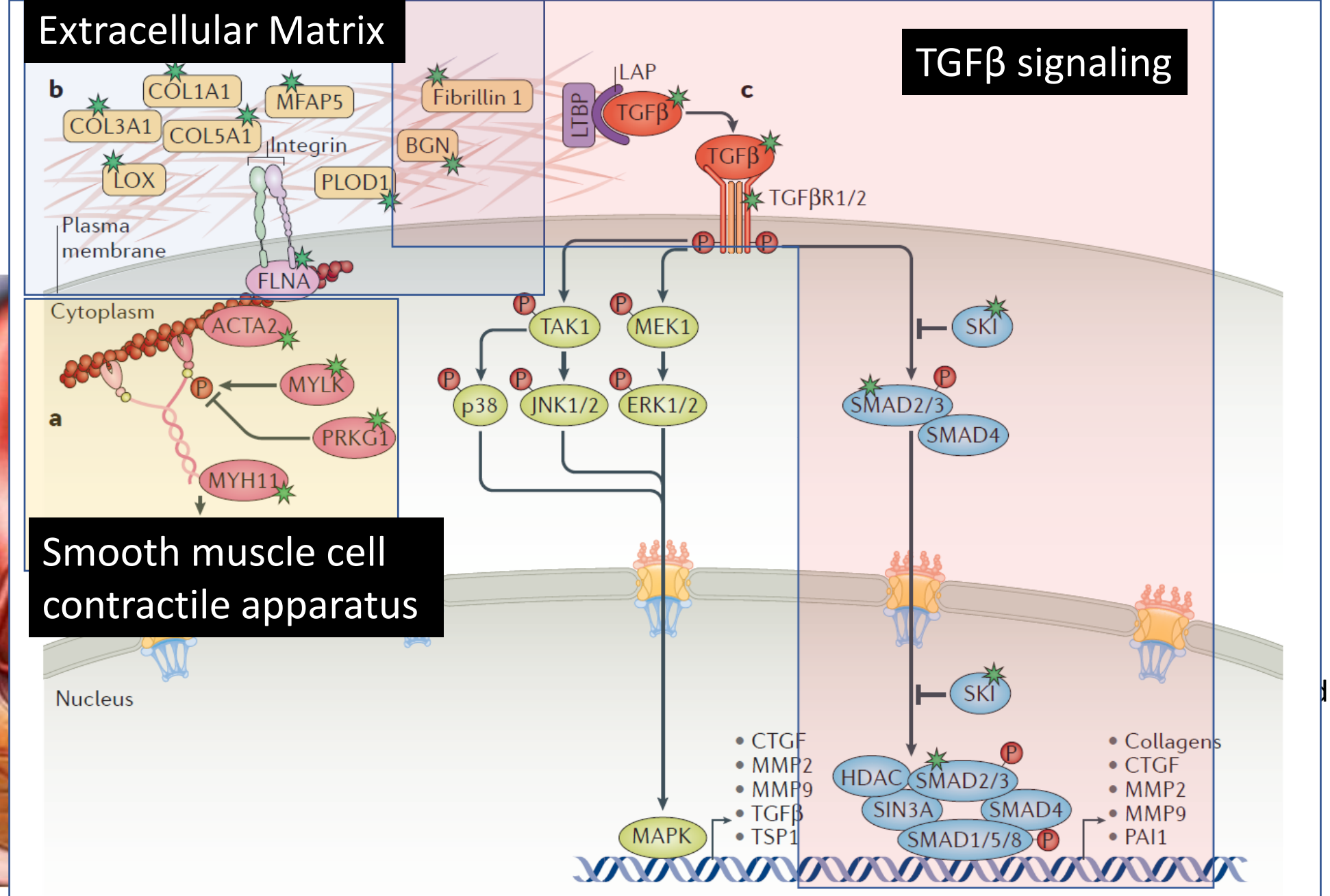


Figure 2 | **Signalling pathways involved in familial thoracic aortic aneurysms (TAA).** The proteins encoded by genes in which mutations cause familial TAA are indicated with a green asterisk. **a** | Mechanical stimuli activate

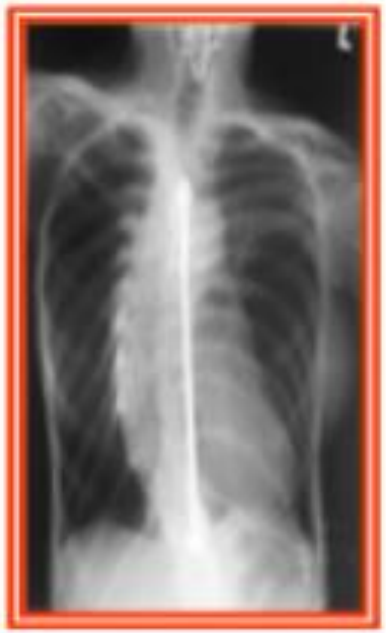
HTN)

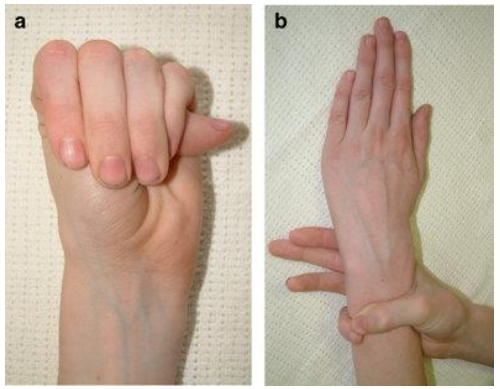
Marfan Syndrome

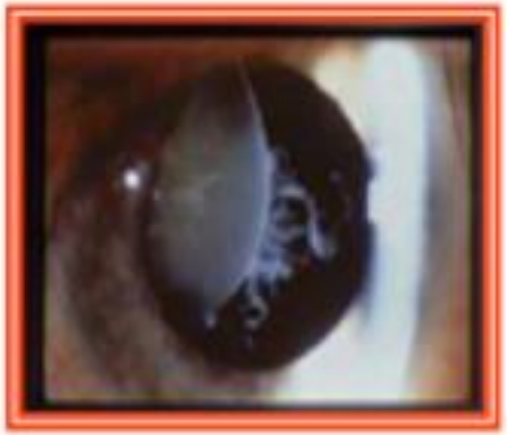
- Autosomal dominant mutation in gene coding for fibrillin -1 (FBN1)

- Three organ systems are the most affected:
  - Musculoskeletal system (pectus, scoliosis)
  - Eye (lens dislocation)
  - Aneurysms/Dissection, Mitral valve prolapse

* High degree of clinical variability

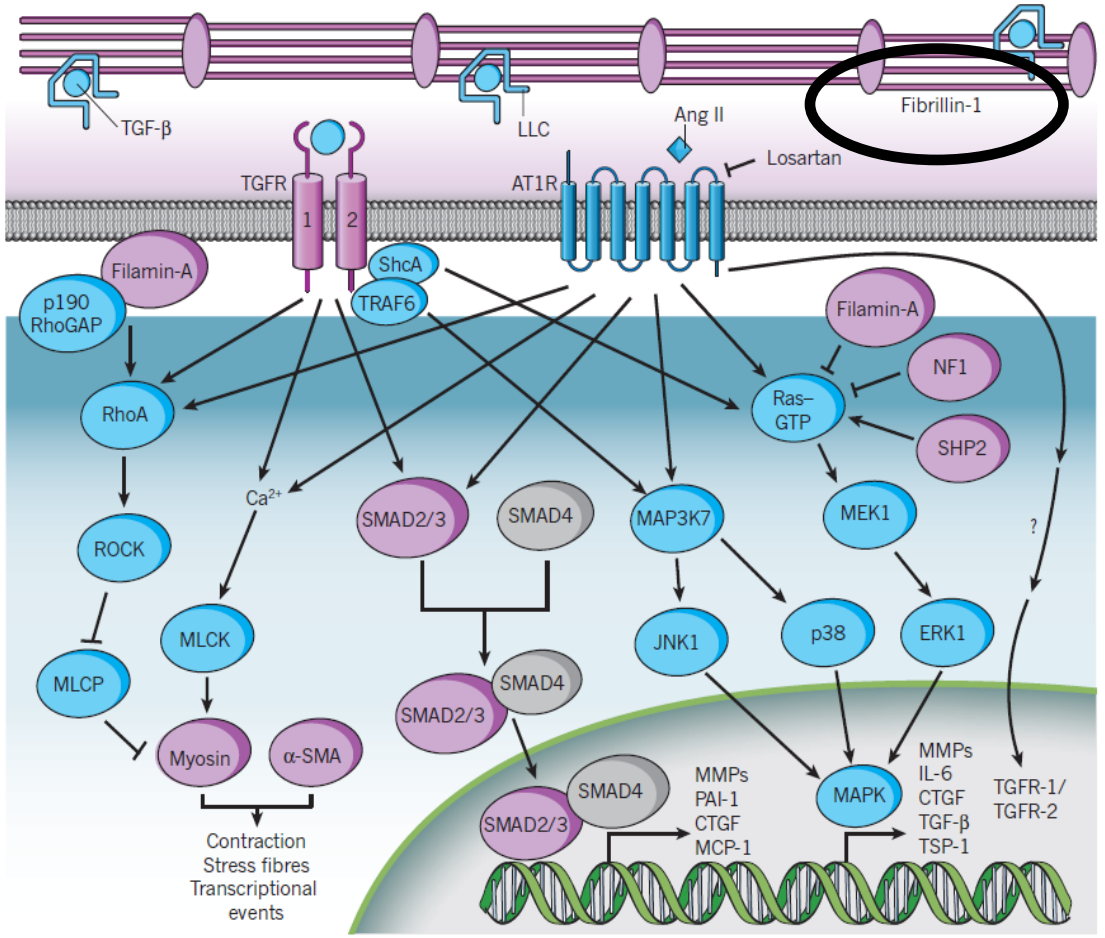






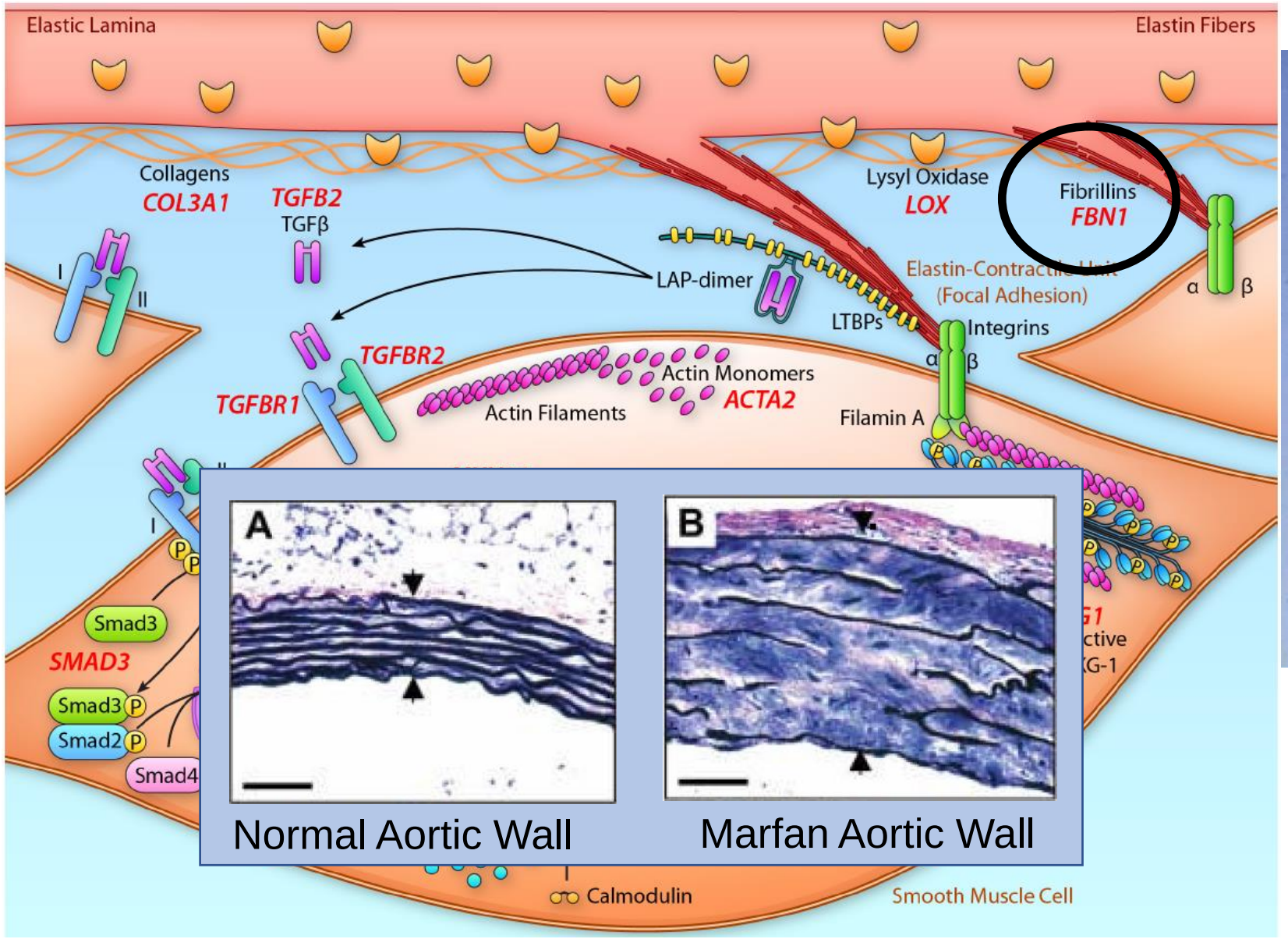
MARFAN SYNDROME

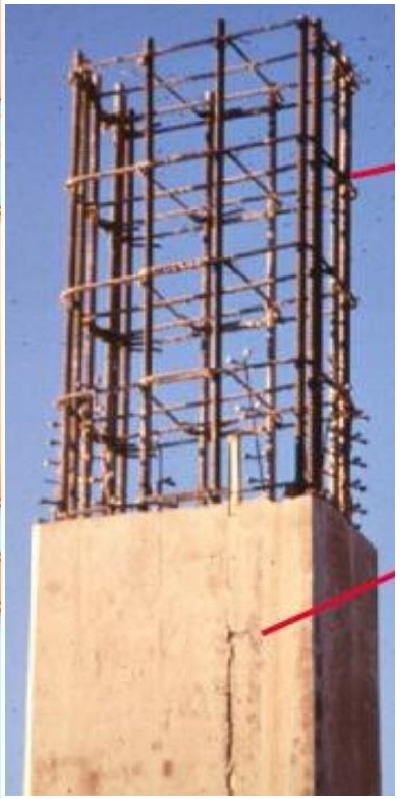
- **Autosomal dominant mutation in gene coding for fibrillin 1 (FBN-1)**
- **Extracellular matrix protein**
  - **Major component of microfibrils associated with elastin fibers**
  - **Elastin fibers**
    - **Function in mediating elastic recoil of tissues**



Dietz et al Nature 1991

Structural role of Fibrillin-1





Marfan Syndrome - Outcomes

Aortic dissection

- Aortic complications (dissection, rupture) most common causes of death
- Average life expectancy
  - In 1972 – 45 years[1]
  - In 1995 – 72 years (similar to general population)[2]

[1]Murdoch et al. N Engl J Med 1972
[2]Silverman et al. Am J Cardiol 1995

Management of Aortic Aneurysms

Goals

1. Slow the growth of the aneurysm overtime
   a) Medications
   b) Restrictions to vigorous physical activity

2. Preventative surgery before aortic dissection

PROGRESSION OF AORTIC DILATATION AND THE BENEFIT OF LONG-TERM β-ADRENERGIC BLOCKADE IN MARFAN'S SYNDROME

JENNIFER SHORES, M.D., KENNETH R. BERGER, M.D., PH.D., EDMOND A. MURPHY, M.D., SC.D., AND REED E. PYERITZ, M.D., PH.D.

- 1994
- 70 teen and adult pts with Marfan syndrome
  - 32 given propranolol
  - 38 given placebo
- Followed for up to 10 years

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Shores et al. N Engl J Med 1994

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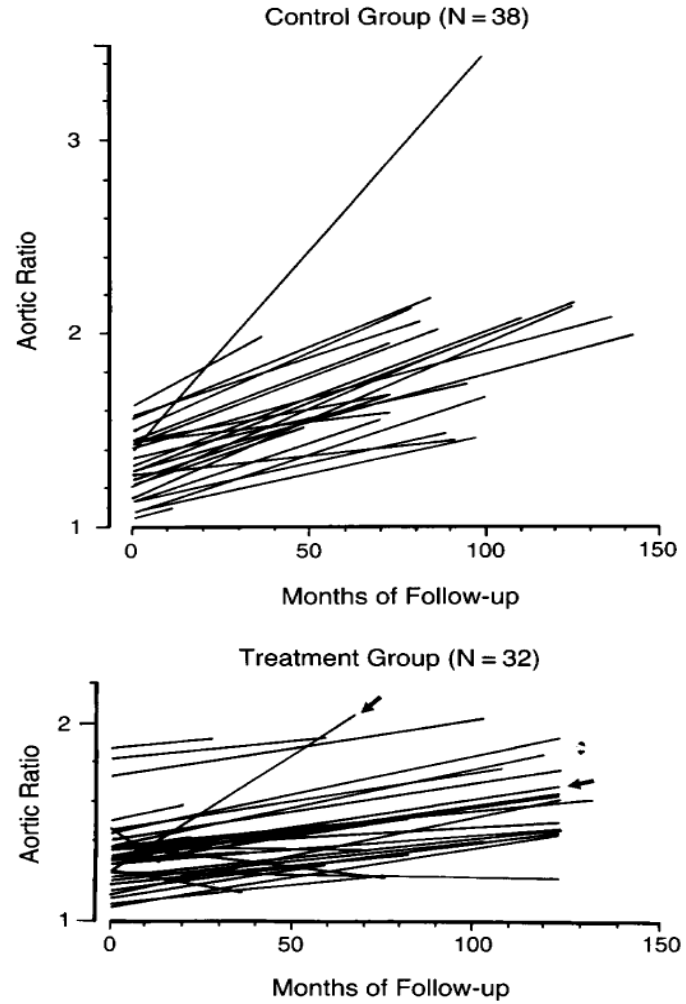
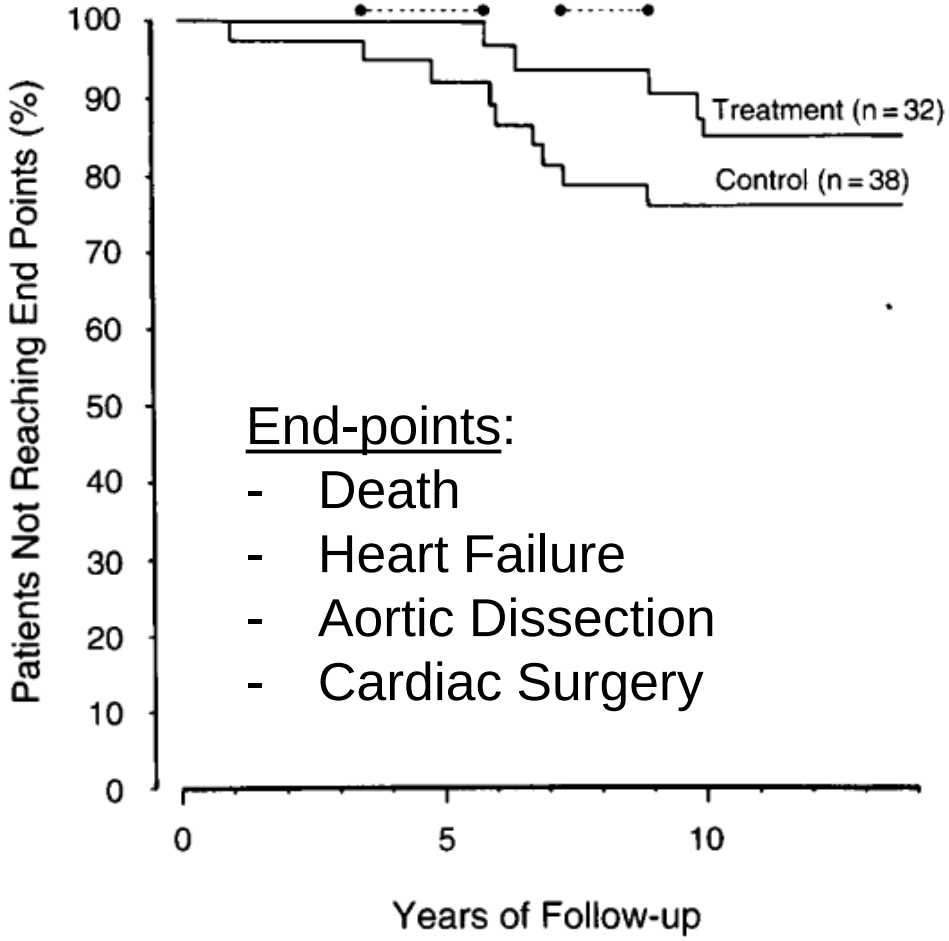
Slowed rate of aortic dilation



Lowered risk for aortic complications



End-points:
- Death
- Heart Failure
- Aortic Dissection
- Cardiac Surgery

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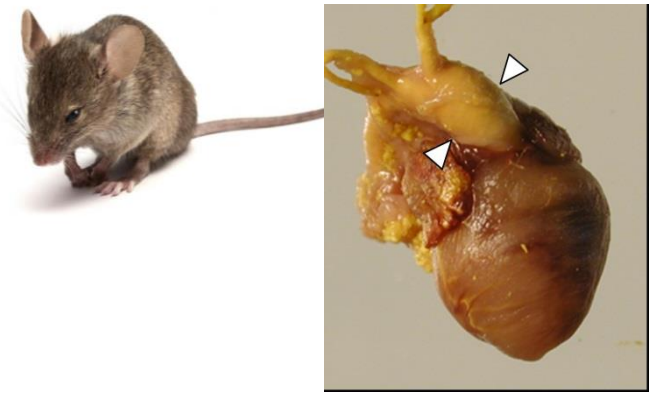
Beta-blockers and Marfan Syndrome

- Beta blockers became primary medication to slow growth of aortic aneurysms

- Subsequent studies showed that majority of patients on beta-blockers
  1. still had progression of aneurysm
  2. at risk for aortic dissection and/or needed heart surgery.

Salim, et al. Am J Cardiol 1994
Rossi-Foulkes, et al. Am J Cardiol 1999
Salamet Tierney, et al. J Pediatr 2007
Ladouceur M, et al. Am J Cardiol 2007

Marfan Mouse Model



- 2003
- Harry Dietz, MD
- Created FBN1+/- Marfan syndrome mouse mouse model (FBN1+/-)
- Fibrillin has more than a structural role

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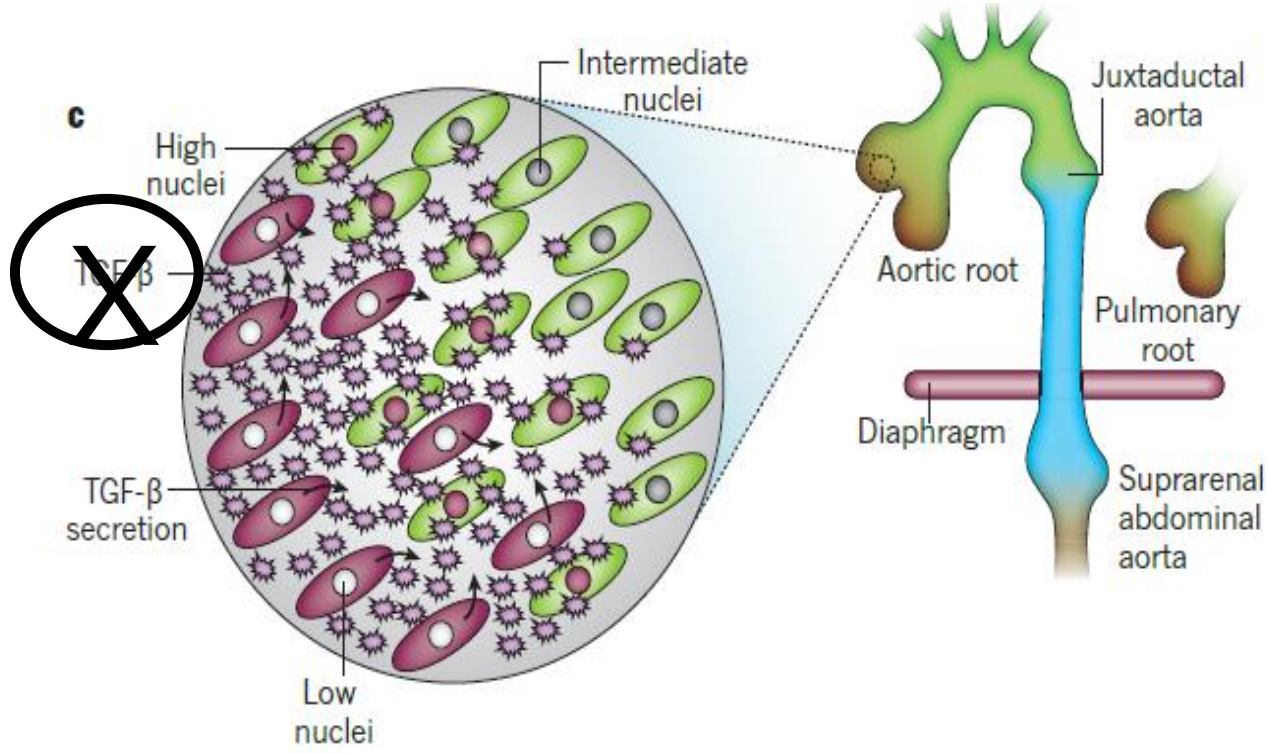
Functional role of Fibrillin-1

Mouse model showed that:

- Fibrillin-1 regulates a growth factor - TGF-B
- Mice had ↑↑ TGF-B

Regulates cellular function
- Cell proliferation
- Cell cycle arrest
- Cell apoptosis
- Cell differentation
- Extracellular formation

Losartan



Lindsay and Dietz. Nature 2011

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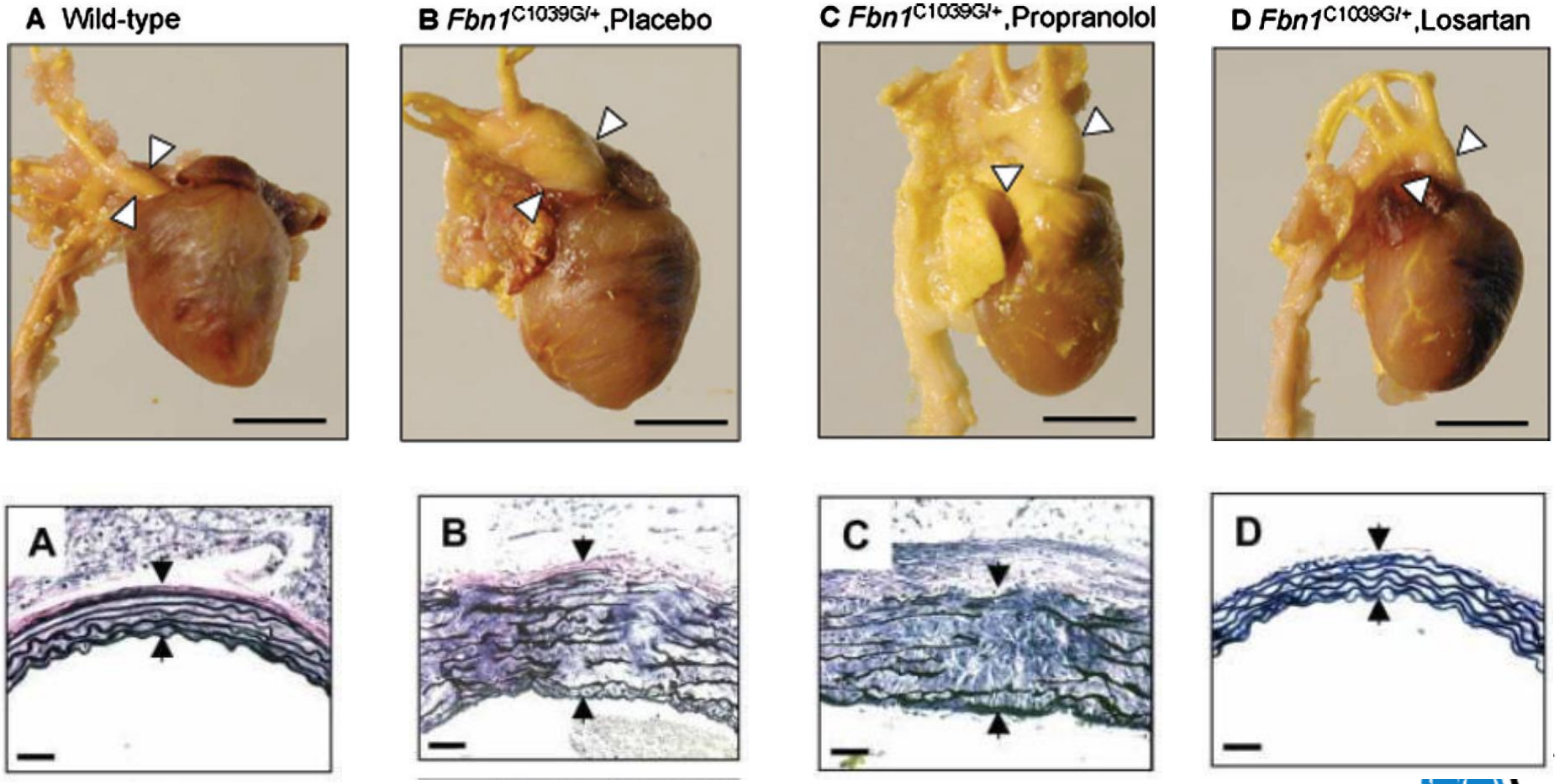
Losartan in Marfan Mouse



Habashi, et al. Science 2006

Marfan syndrome

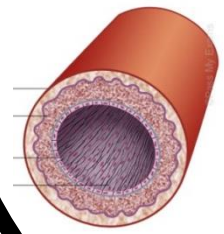
Fibrillin gene mutation

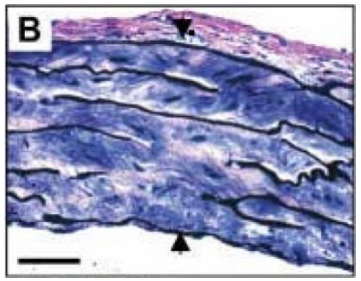
Losartan

Beta blockers

LORSARTAN vs. BETA-BLOCKERS

(fibrillin protein, connective tissue)





(blood pressure / heart rate)

Aortic Aneurysm

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 27, 2014 VOL. 371 NO. 22

Atenolol versus Losartan in Children and Young Adults with Marfan's Syndrome

- 21 centers through Pediatric Heart Network
- 608 Marfan syndrome patients (6 months to 25 years old)
  - 303 received atenolol
  - 305 received losartan
- Followed with echocardiograms for 3 years

Lacro, et al. N Engl J Med, 2014

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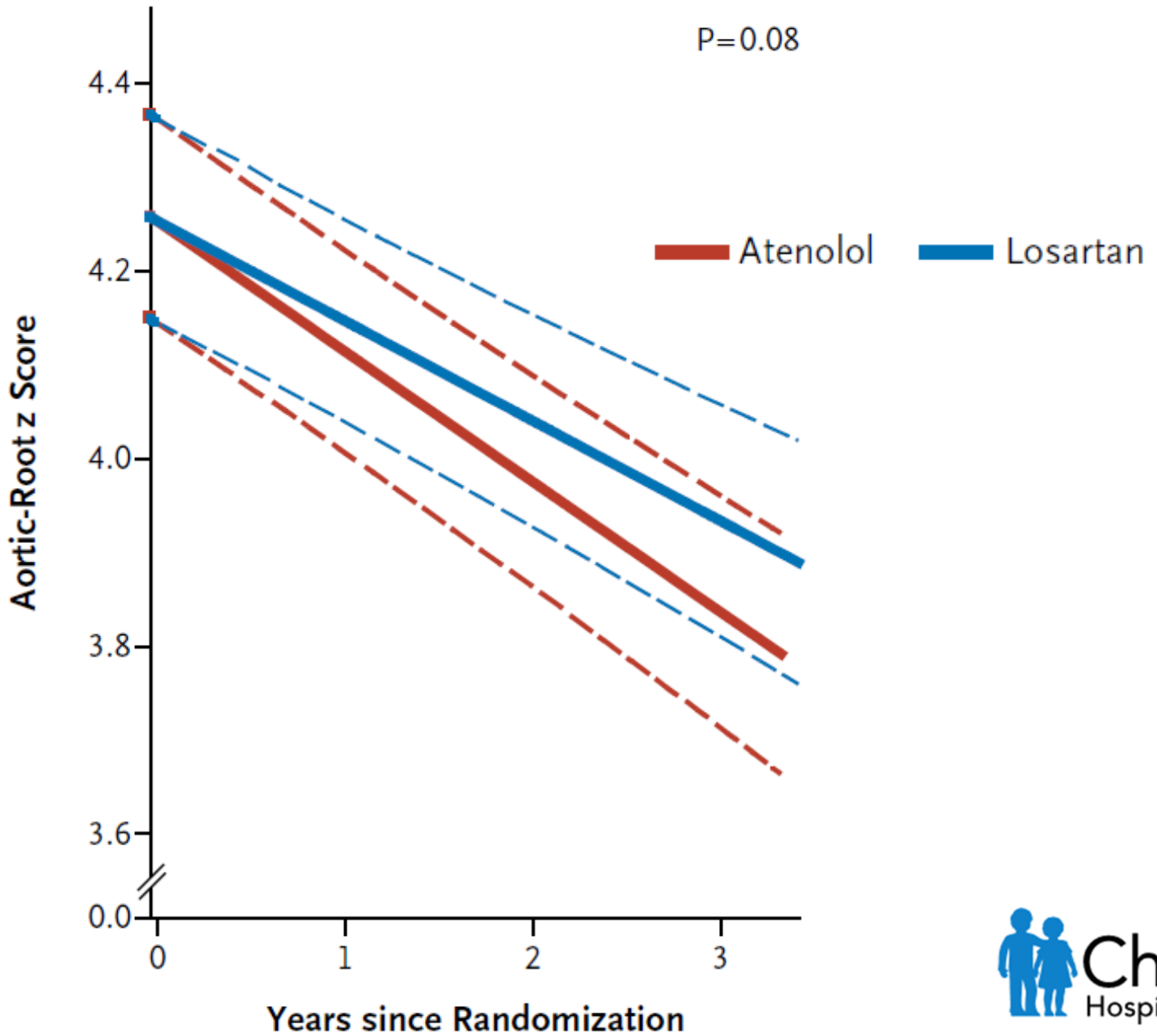

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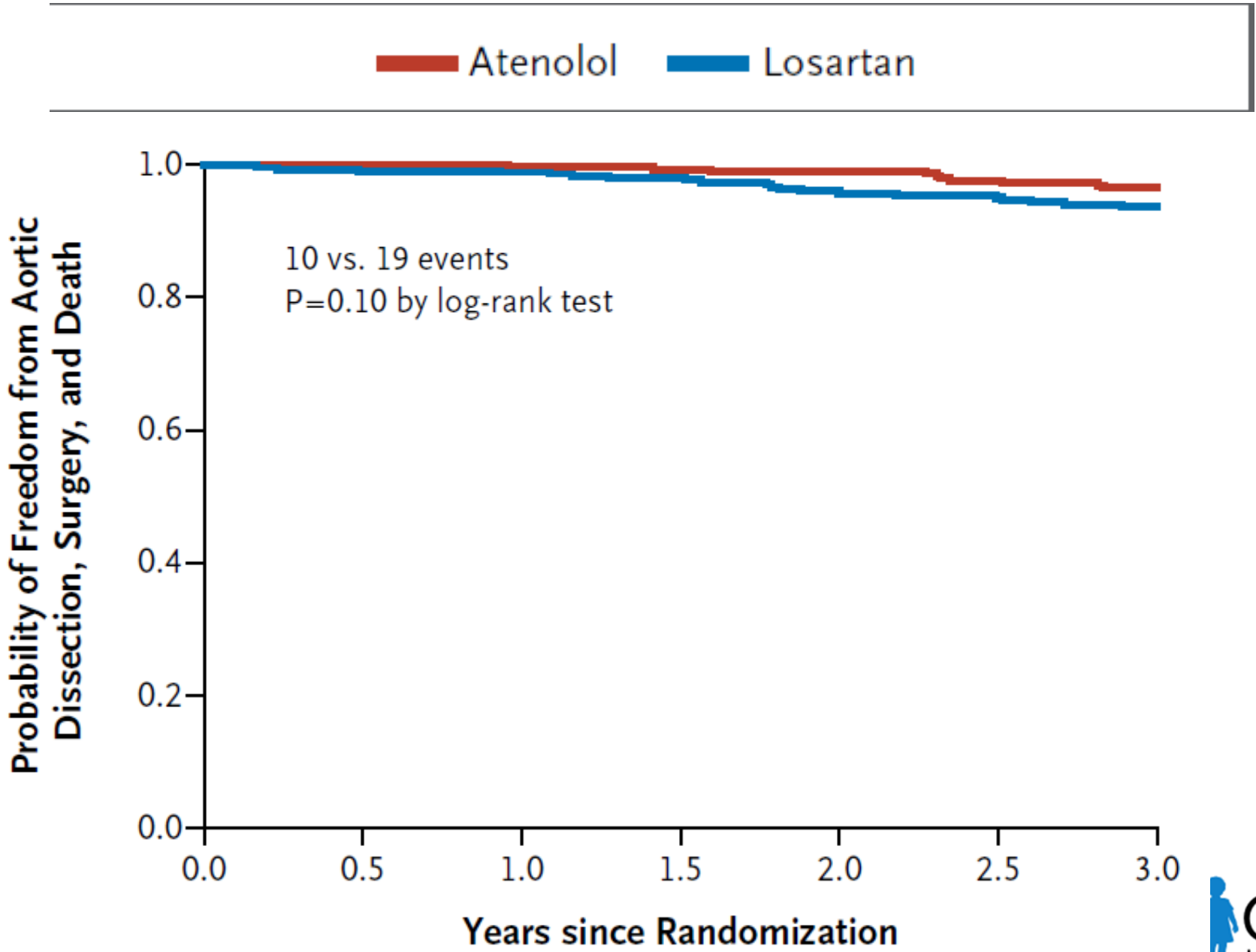

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Recommendations for Medical Management

- After Marfan syndrome diagnosed, start either beta-blocker or ARB (losartan or irbesartan)
- Monitor with echocardiogram +/- CT or MRI at least every year
- If aneurysm grows on single therapy, then add a second medication

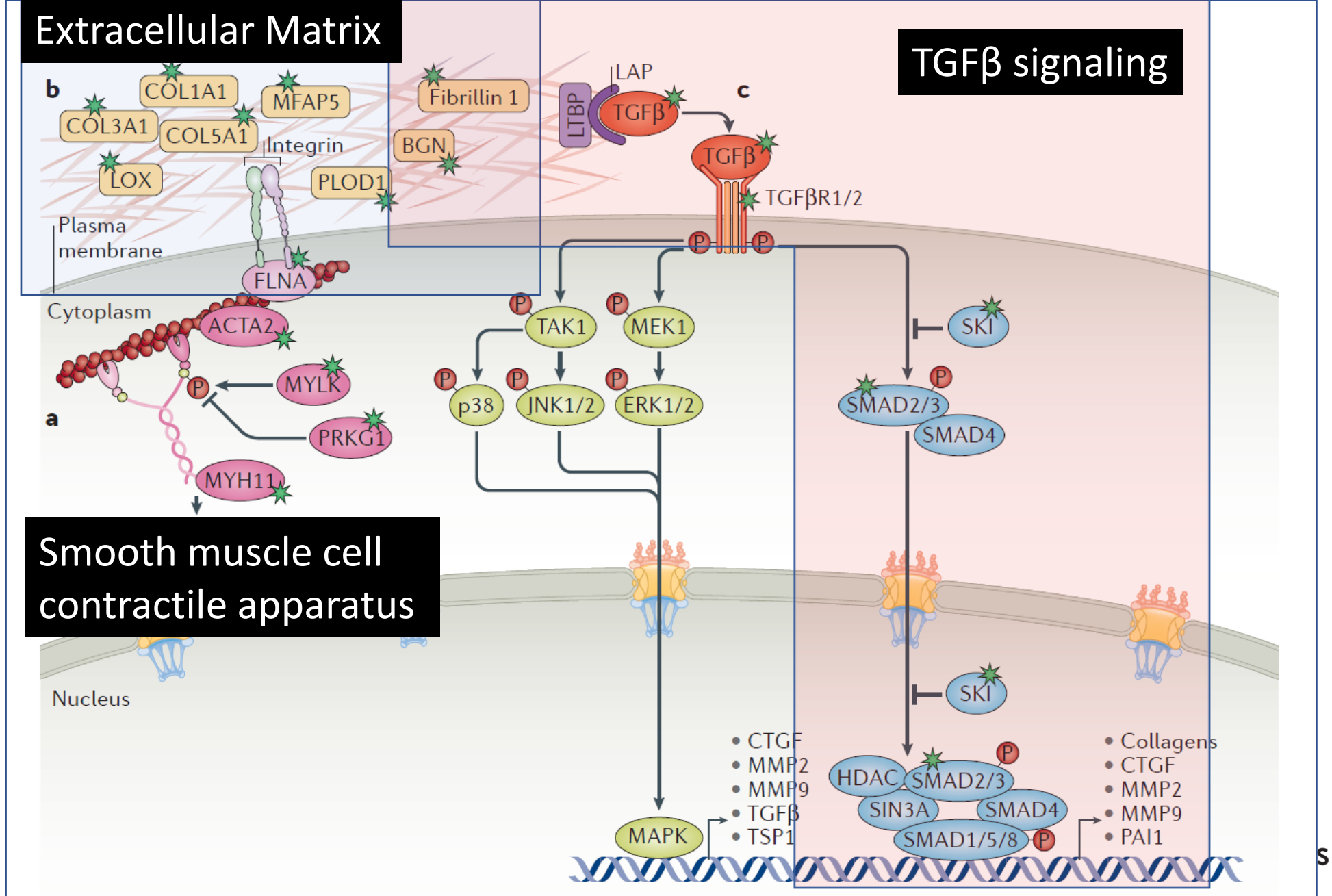

Figure 2 | **Signalling pathways involved in familial thoracic aortic aneurysms (TAA).** The proteins encoded by genes in which mutations cause familial TAA are indicated with a green asterisk. **a** | Mechanical stimuli activate

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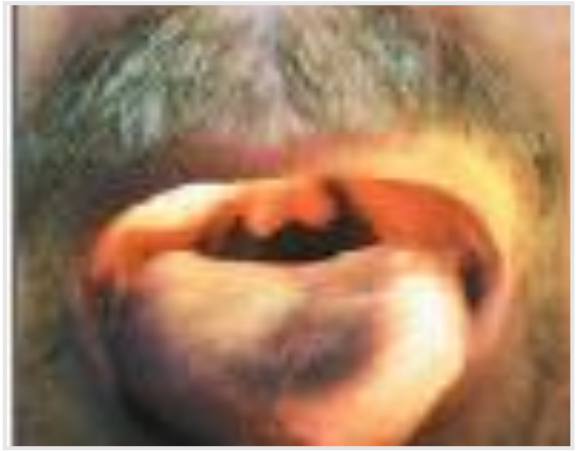
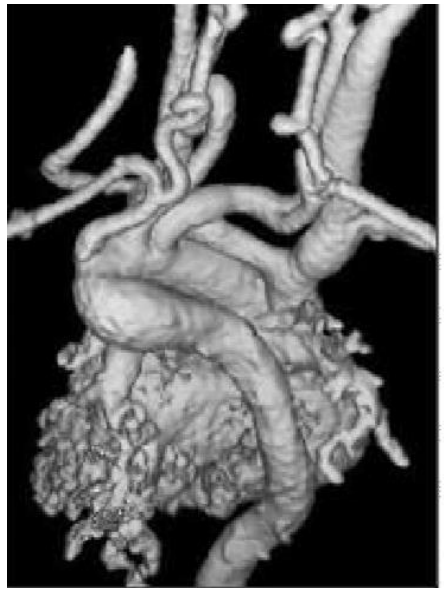
Loeys Dietz Syndrome – Discriminating Features



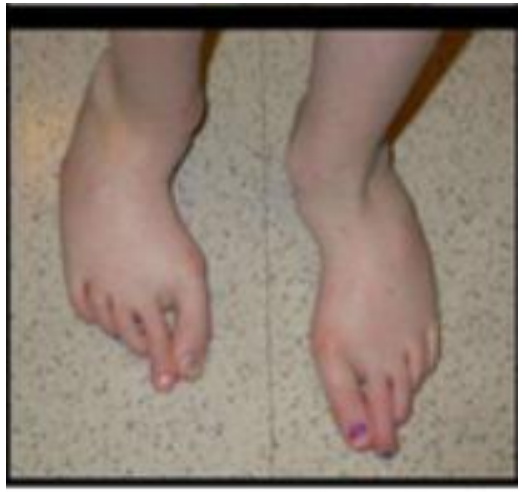
HEAD AND NECK:

Head	Craniosynostosis
Eye	**No lens dislocation**
Face	**Malar hypoplasia** / Micrognathia / Retrognathia
Eyes	**Hypertelorism** / Exotropia / Blue sclerae / Proptosis
Mouth	**Bifid uvula / Cleft palate (uncommon)**



CARDIOVASCULAR:

Aortic dissection at smaller dimensions (>4.5 cm)
Arterial tortuosity, generalized
Cerebral aneurysm



SKELETAL: **Joint laxity**

FEET **Talipes equinovarus (club foot)**

SKIN **Velvety texture** / Translucent skin

NEUROLOGIC:
- Chiari malformation
- Hydrocephalus
- DD/MR

2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the Diagnosis and Management of Patients With Thoracic Aortic Disease

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine

Criteria for Prophylactic Aortic Root Replacement:

- Marfan syndrome = 5.0 cm
- Loeys-Dietz syndrome = 4.5 cm

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Loeys-Dietz Syndrome

Genetic Variant	Aortic Event	Age at Aortic Event	Aneurysm Repair/Dissect	Type A/Type B Dissection	Aortic size at time of Dissection
TGFBR1	39%	28 yrs (12-72)	50%/50%	91%/9%	58.3 mm
TGFBR2	44%	35 yrs (8-85)	54%/46%	69%/31%	51.4 mm
SMAD3	37%	47 yrs (25-77)	30%/70%	76%/13%	54 mm
TGFB2	21%	35 yrs (31-60)	50%/50%	N/A	52 mm

Jondeau, et al. Circ Cardiovasc Genet 2016
Hostetler, et al. J Med Genet 2019
Boileau, et al. Nat Genet 2021

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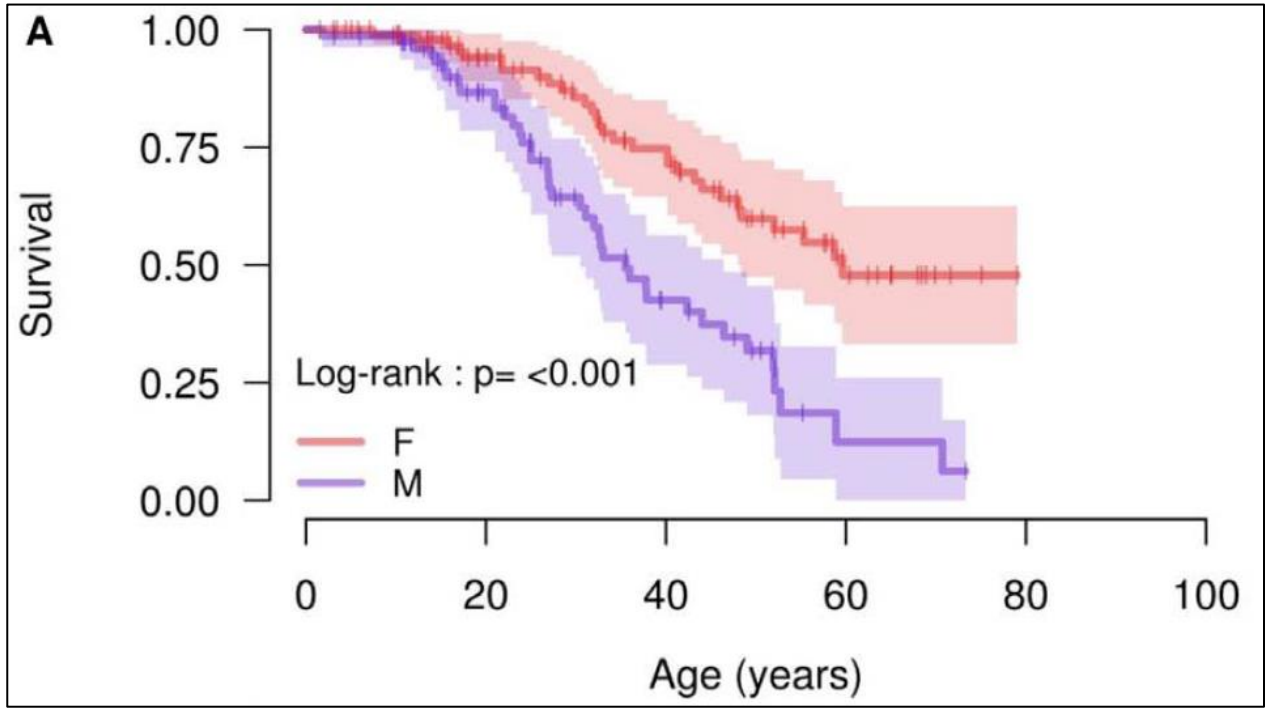
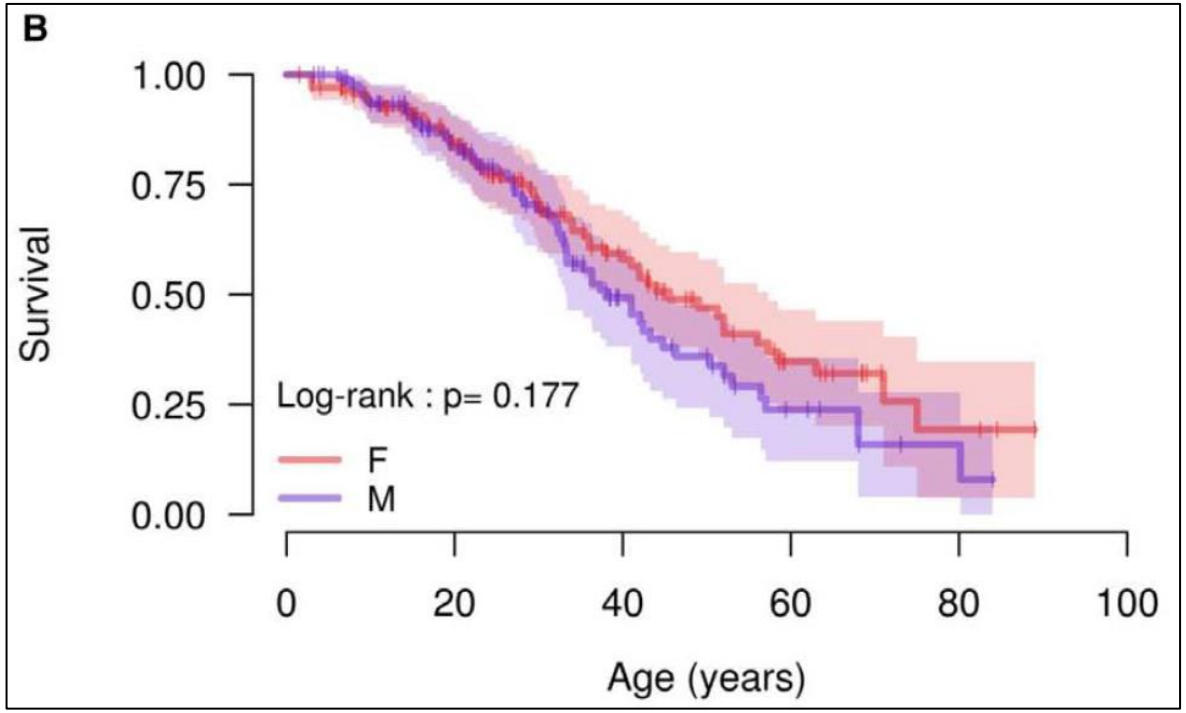
Gender Differences in Age of Aortic Events

TGFBR1 mutation



TGFBR2 mutation



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Jondeau, et al. Circ Cardiovasc Genet 2016

Loeys-Dietz Syndrome: Dissections < 4.5 cm

- TGFBR 1 and 2 (6 patients)
  - Female
  - Aortic tortuosity
  - Hypertelorism
  - Wide scars

- SMAD3 (3 patients)
  - HTN
  - History of smoking

Jondeau, et al. Circ Cardiovasc Genet 2016
Hostetler, et al. J Med Genet 2019

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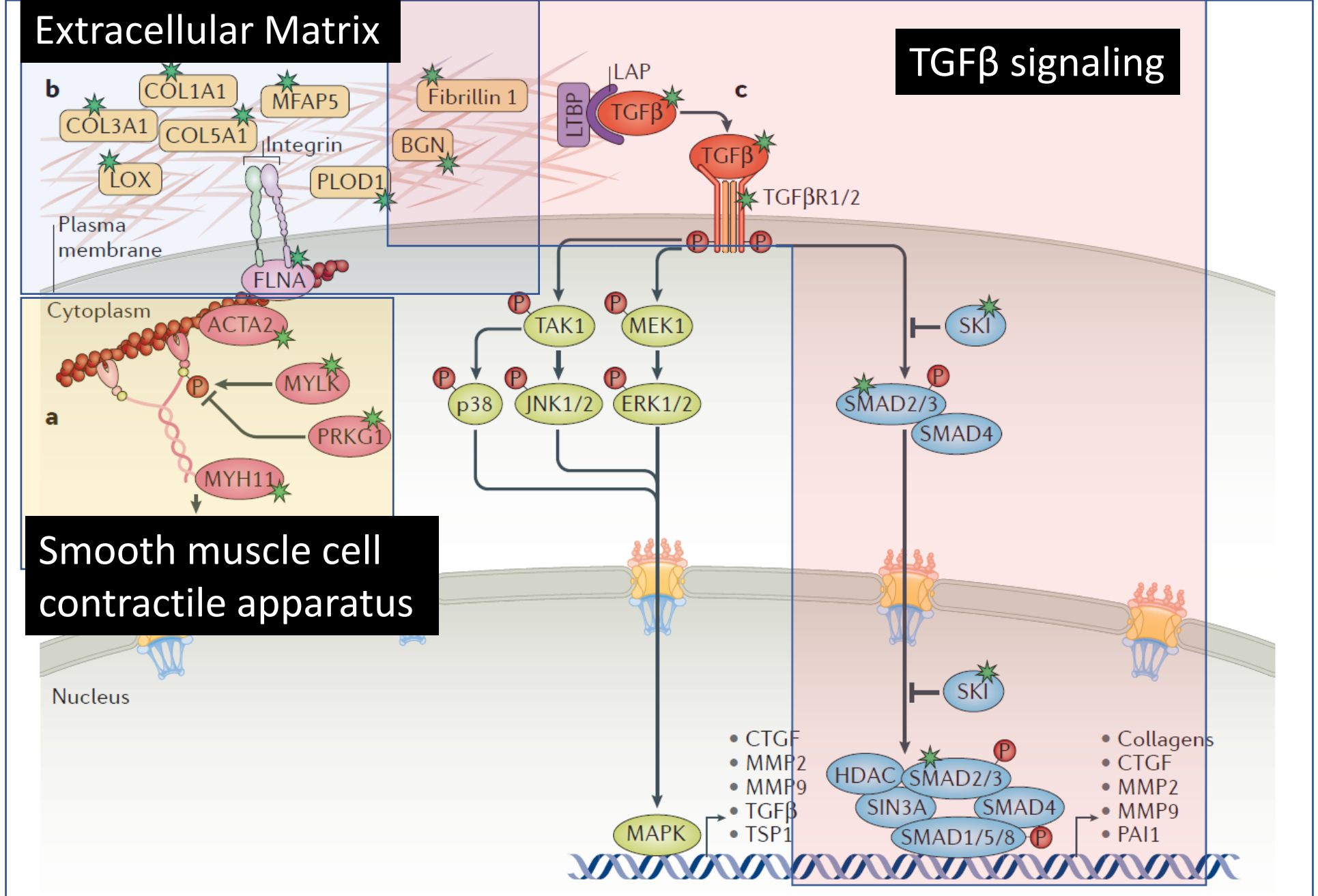
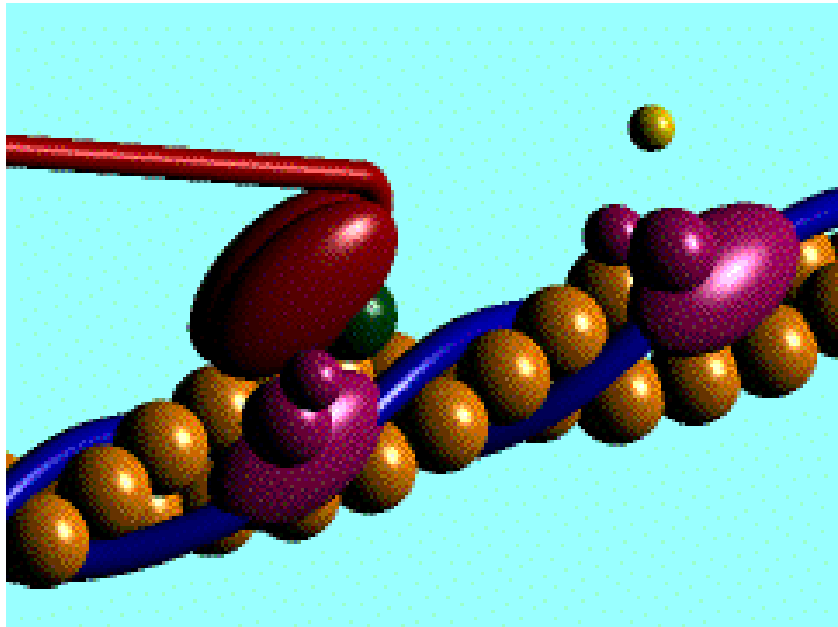


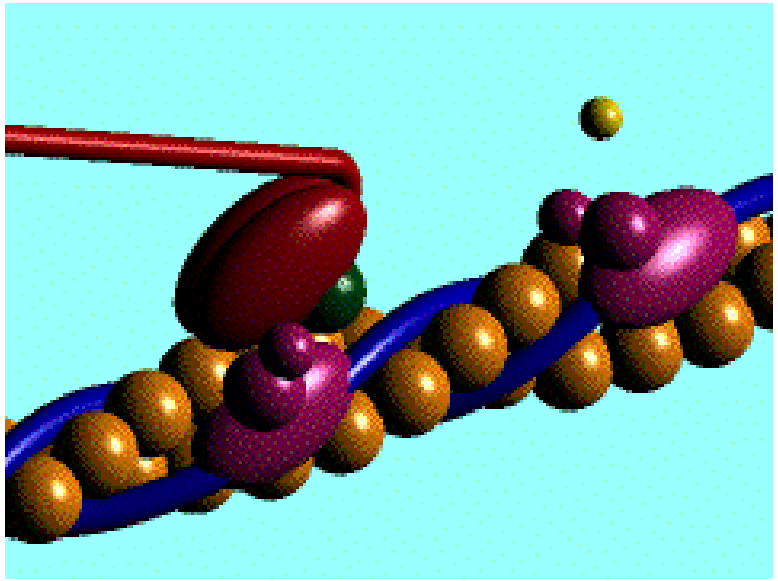
Figure 2 | **Signalling pathways involved in familial thoracic aortic aneurysms (TAA).** The proteins encoded by genes in which mutations cause familial TAA are indicated with a green asterisk. **a** | Mechanical stimuli activate

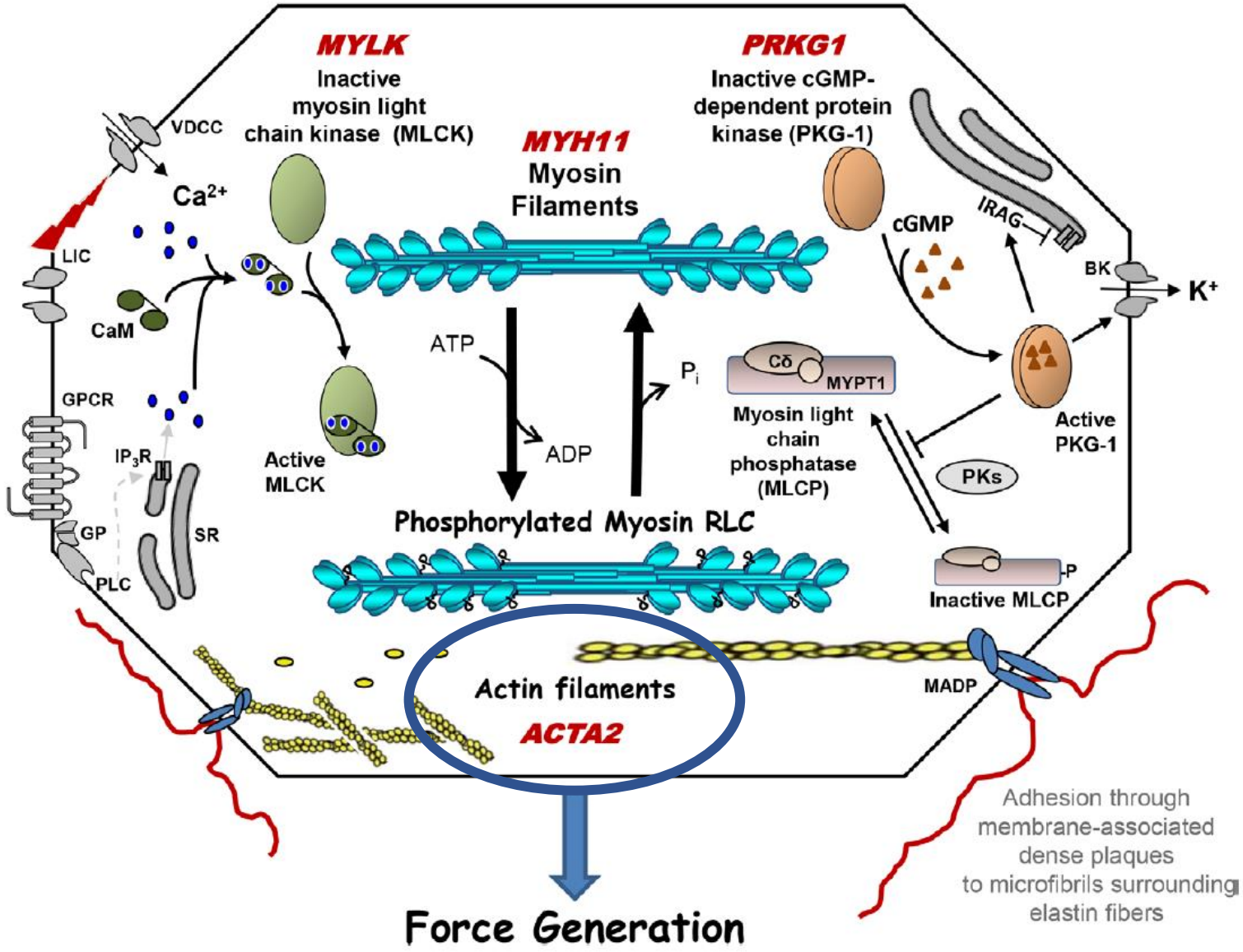
Nonsyndromic Hereditary Thoracic Aortic Disease

- Autosomal dominant inheritance
- Decreased penetrance, variable expression
- Minimal systemic features
- 20% of pts have a first-degree relative w/ TAAD
- Caused by genetic variants that disrupt a protein in SMC contractile unit and alter smooth muscle cell force generation



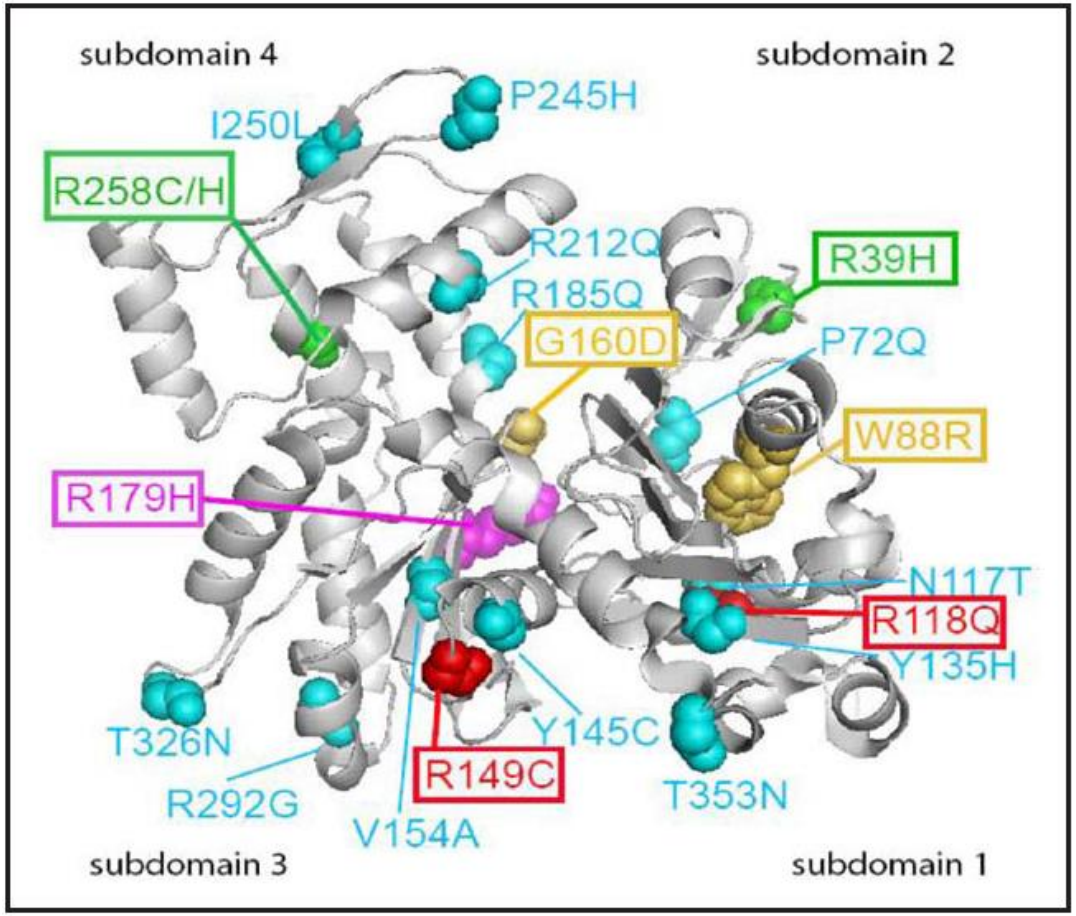
Smooth Muscle Cell Contraction

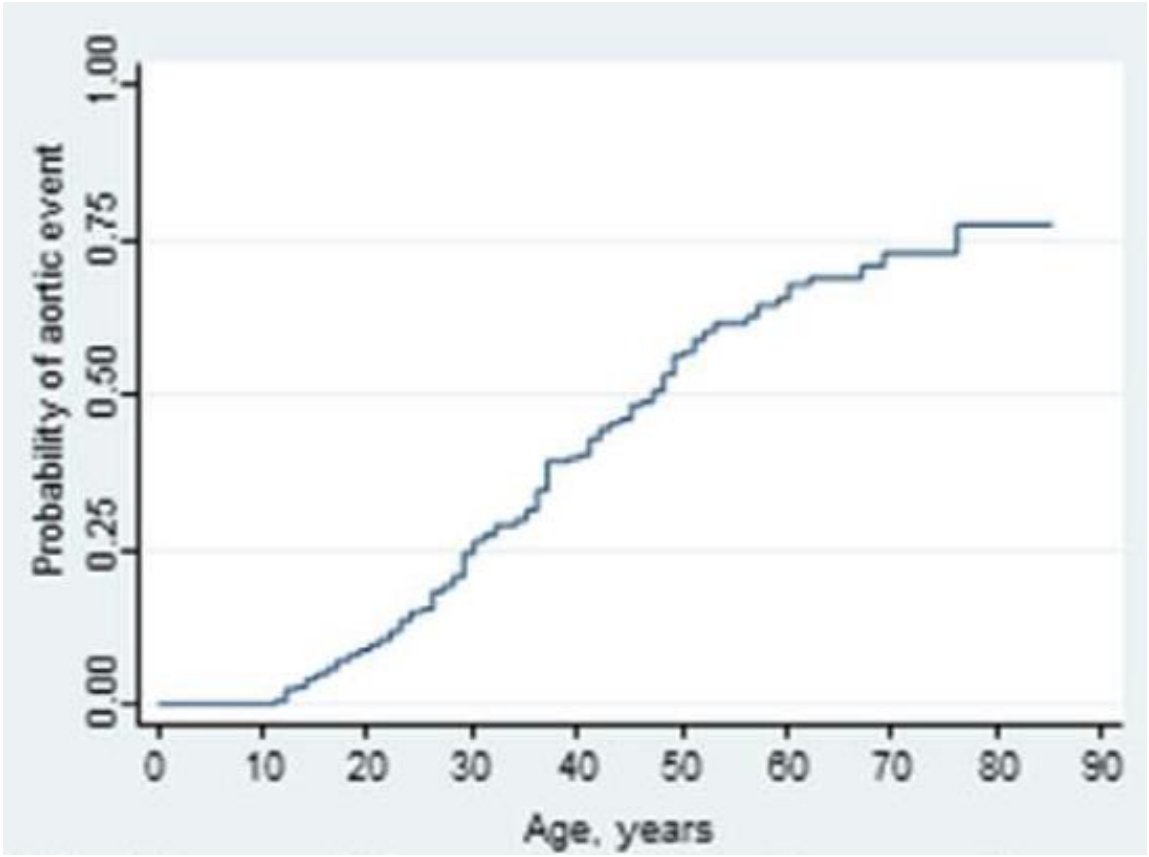




Milewicz, et al. Arterioscler Thromb Vasc Biol 2017

ACTA2-Associated Aortic Disease

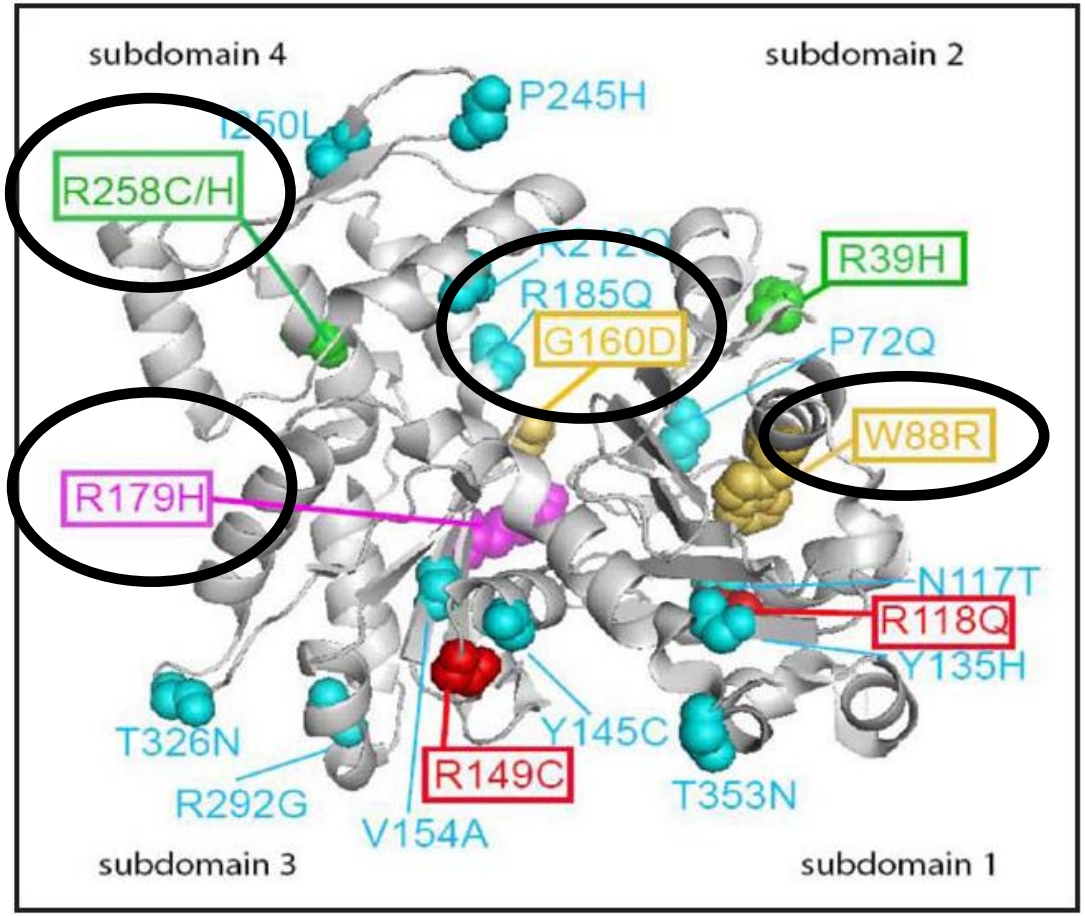


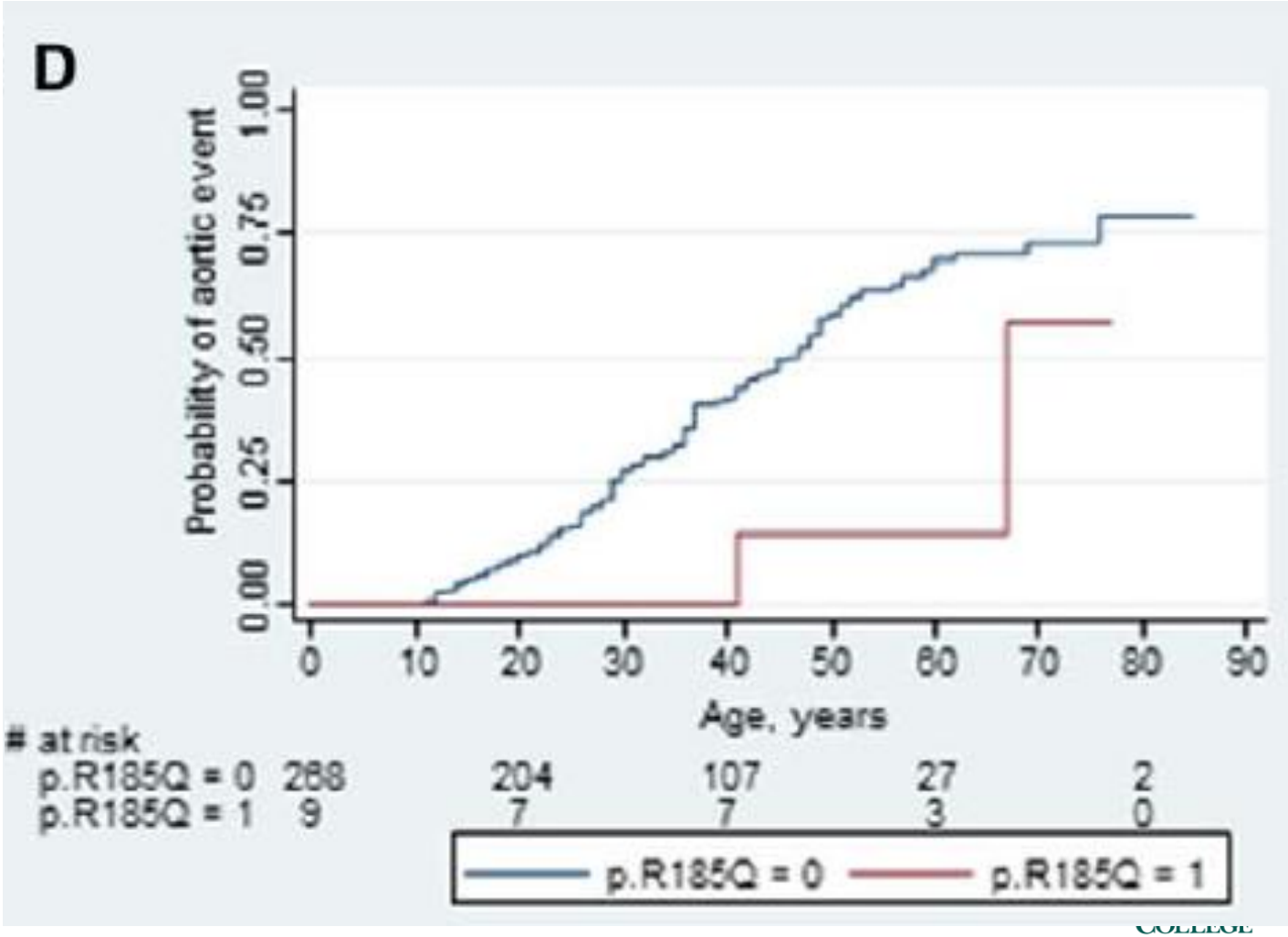


Median Age at Aortic Event = 36 y/o
33% Dissected at Dimension < 5.0 cm

Regalado, et al. Circ Cardiovasc Genet 2015

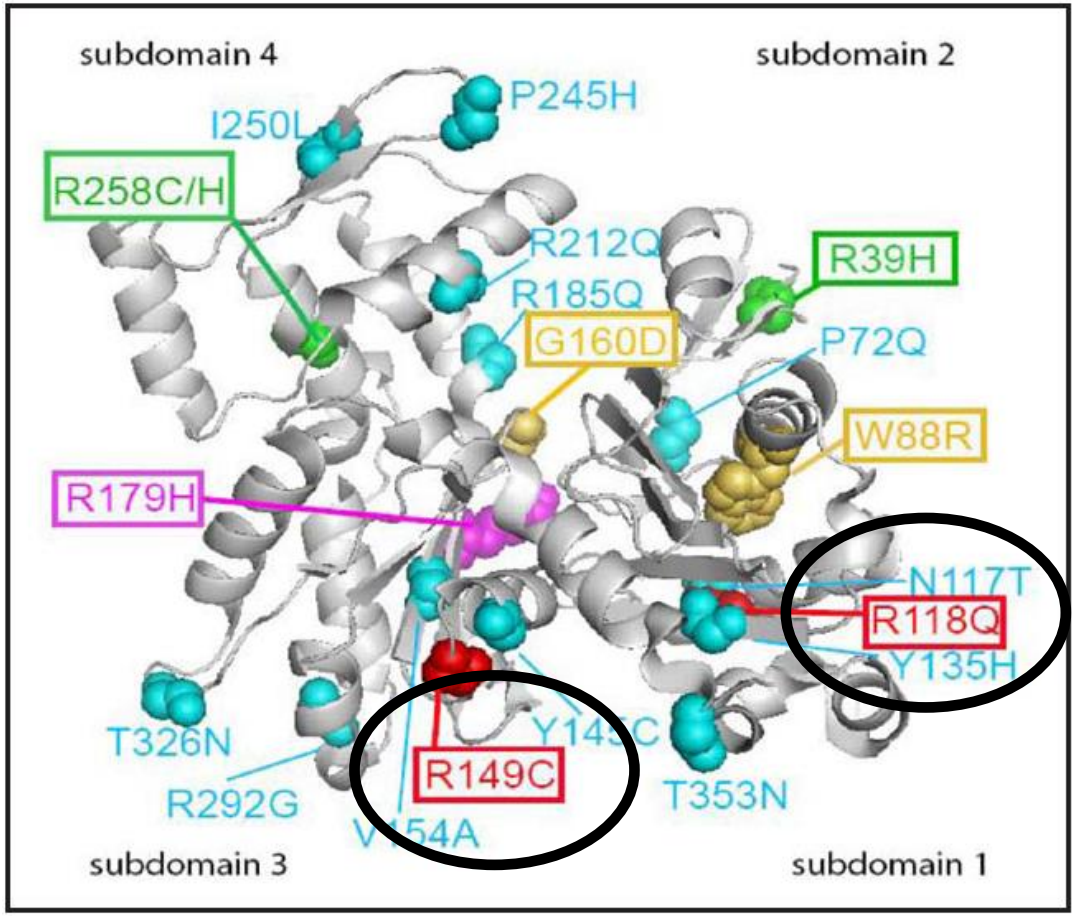
ACTA2-Associated Aortic Disease





Regalado, et al. Circ Cardiovasc Genet 2015

ACTA2-Associated Aortic Disease



R149 and R118

- Predispose to early onset coronary artery disease

Regalado, et al. Circ Cardiovasc Genet 2015

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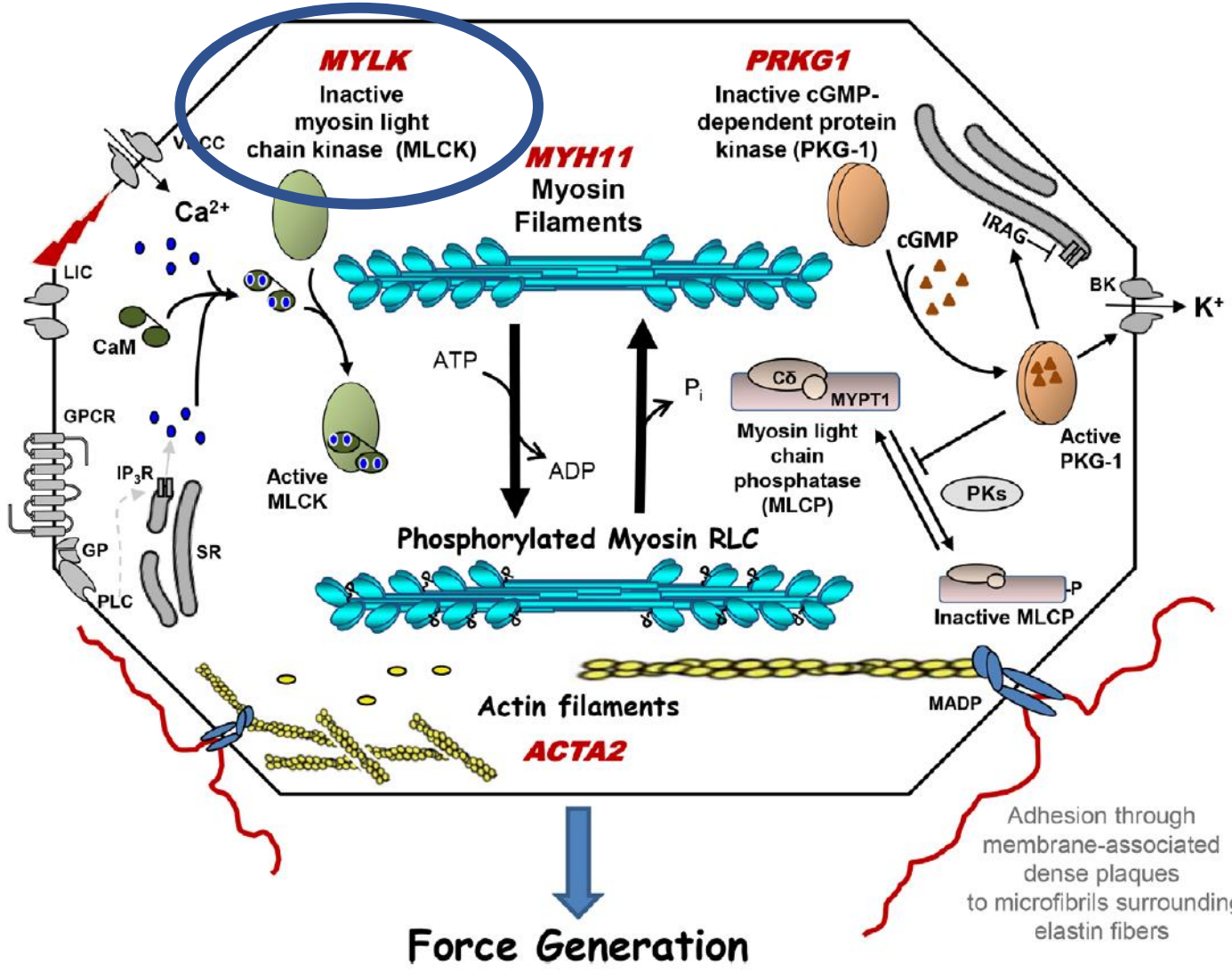
Smooth Muscle Cell Contraction



Milewicz, et al. Arterioscler Thromb Vasc Biol 2017

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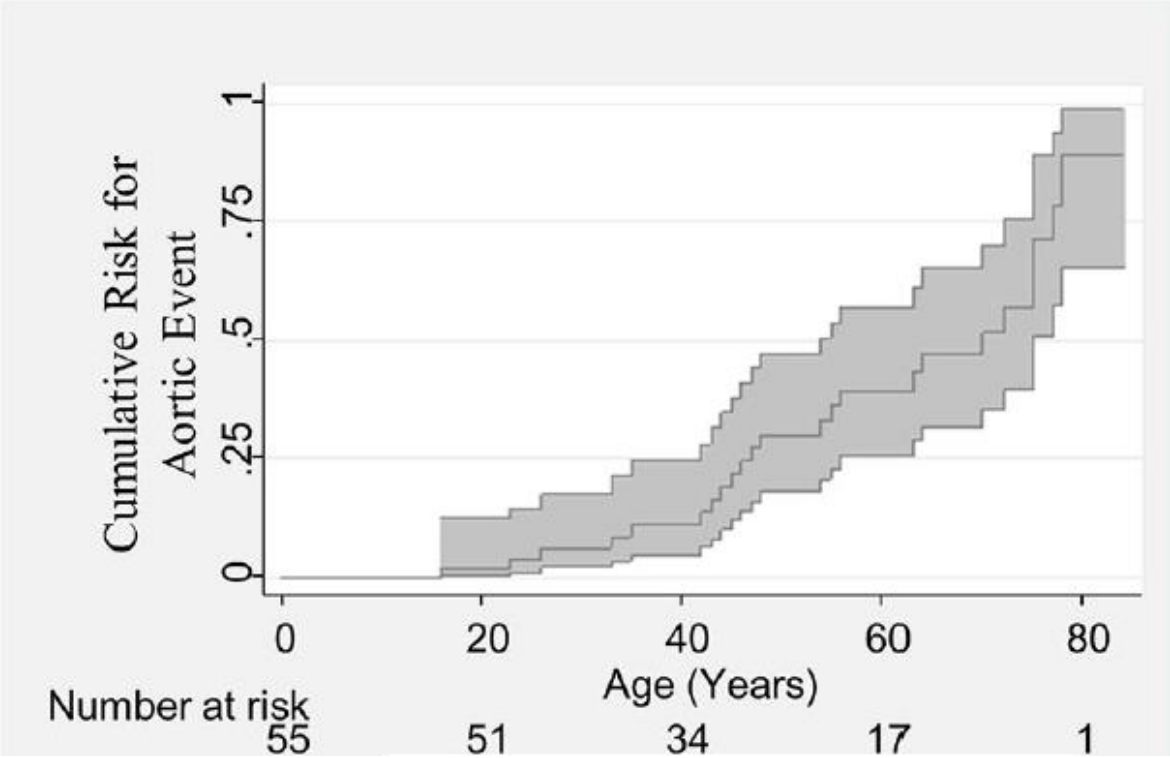
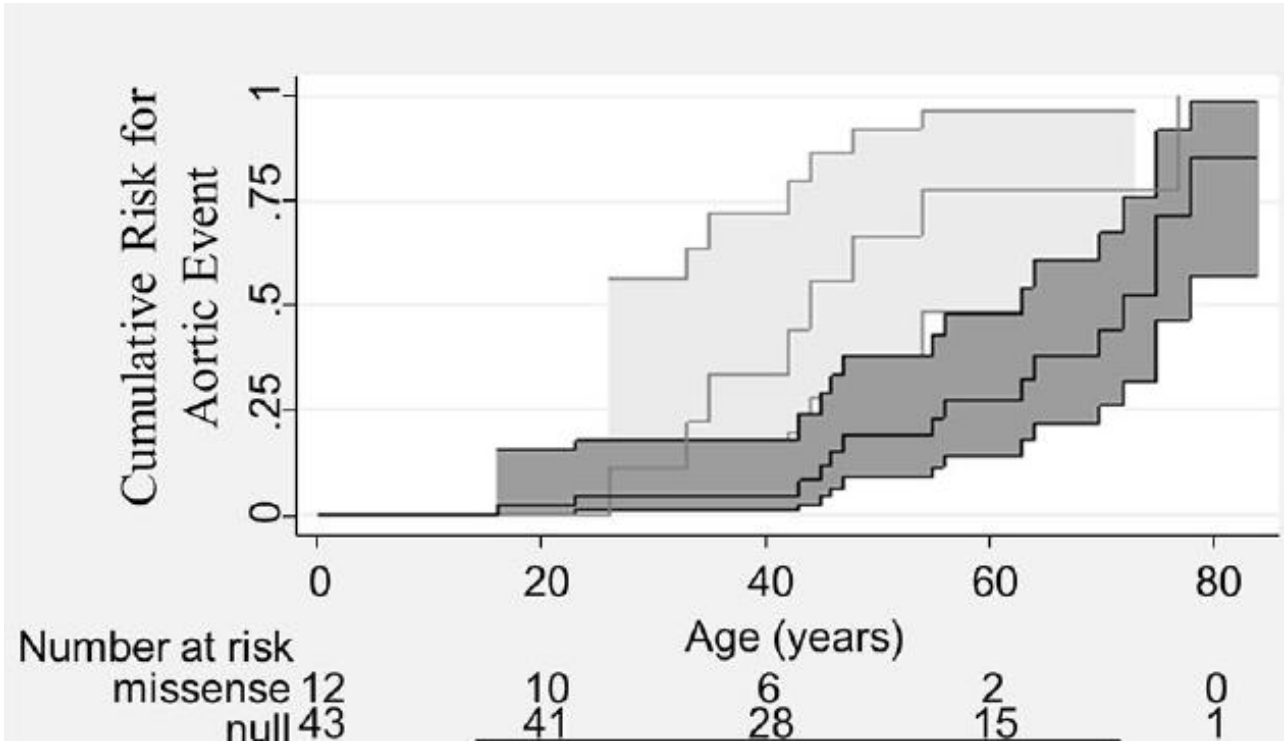
MYLK-Associated Aortic Events

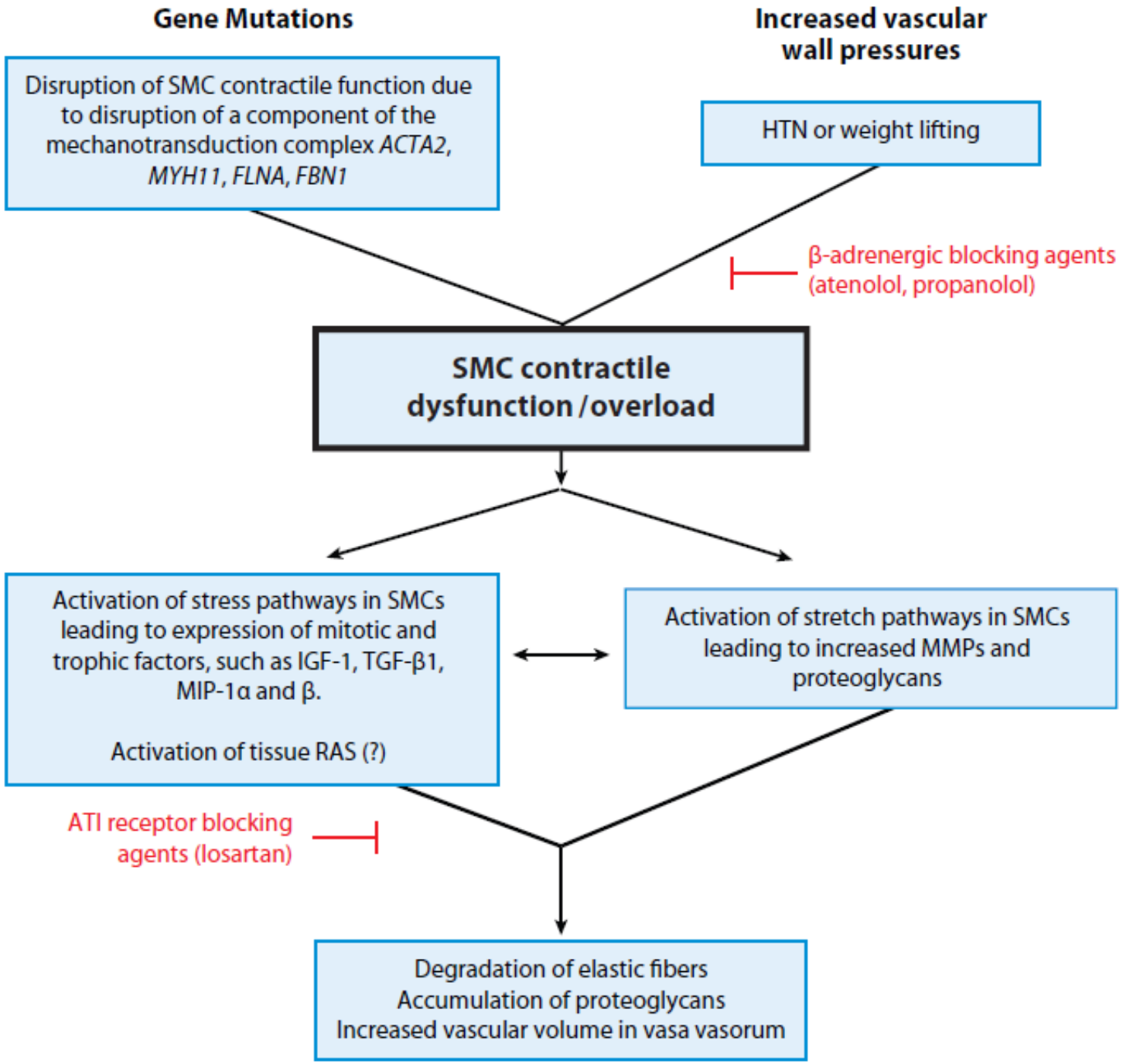
Overall Risk



Missense vs. Null Variants



Wallace, et al. Genet Med, 2019



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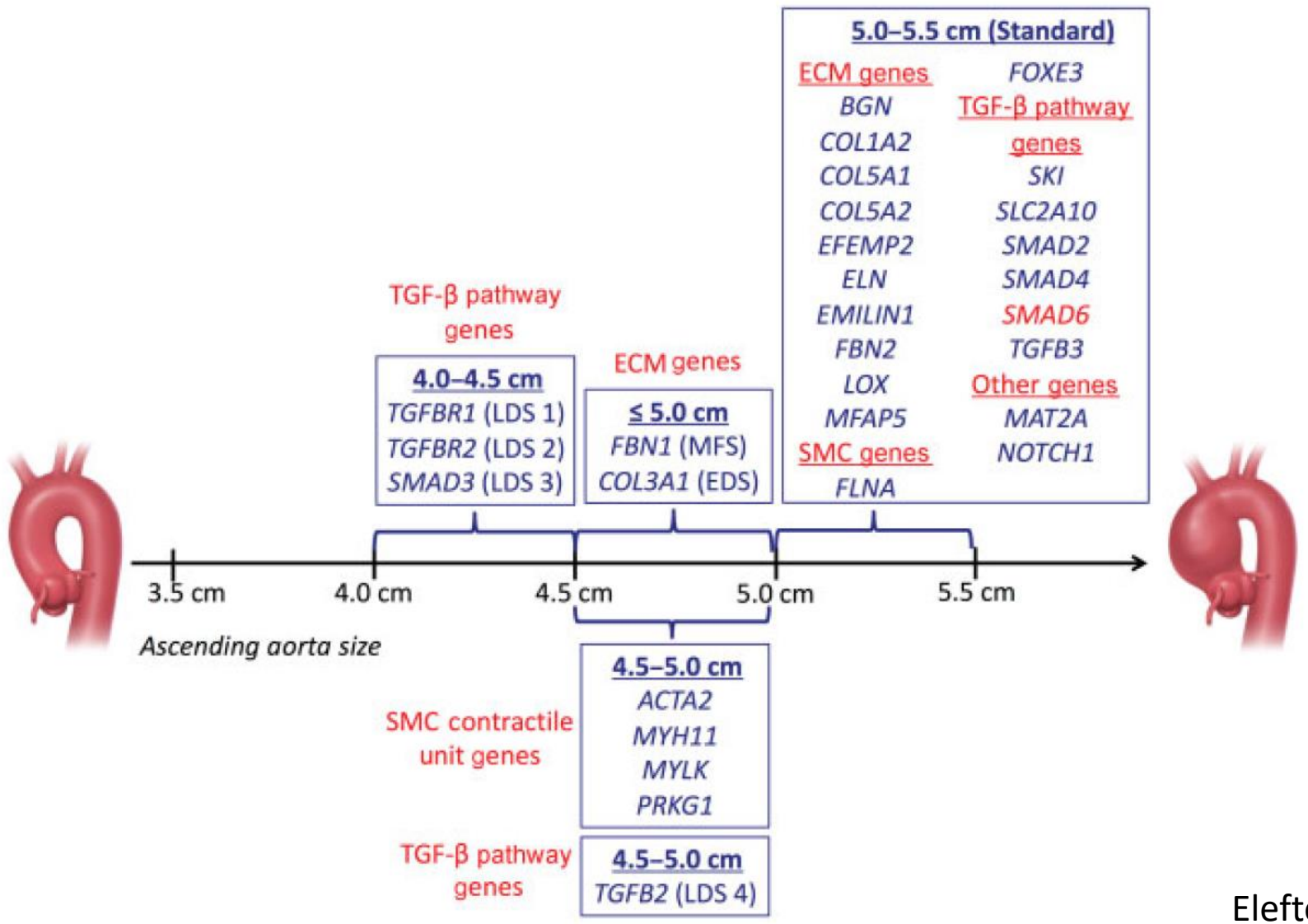
Gene-based Timing of Prophylactic ARR

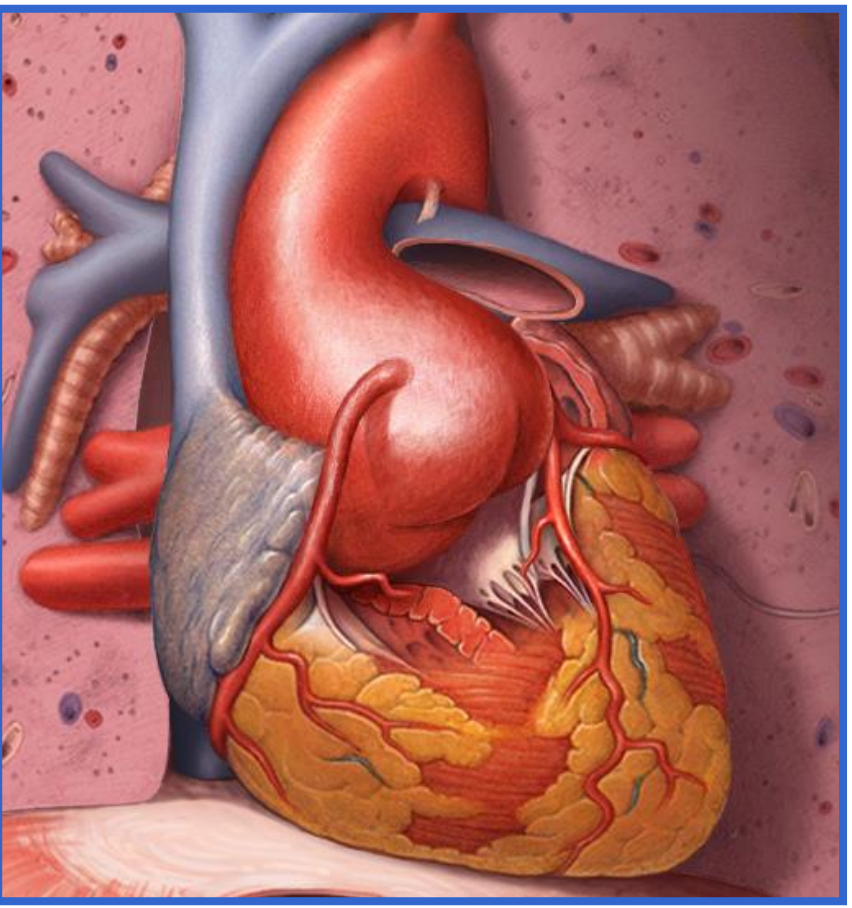


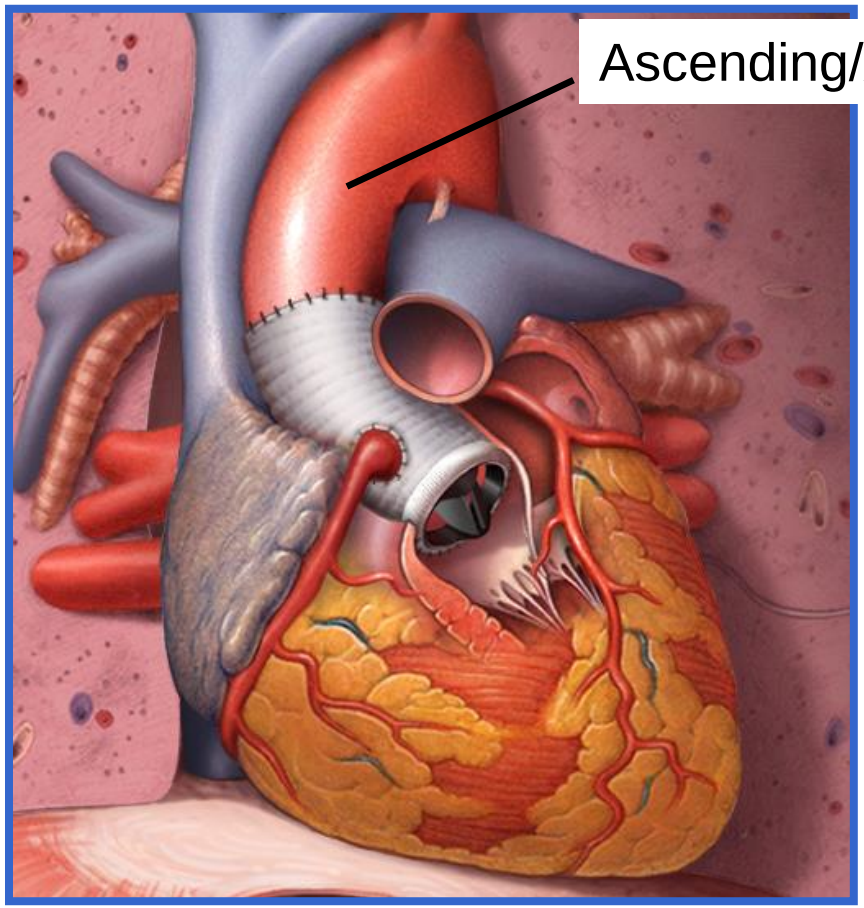
Elefteriades, et al. Aorta 2018

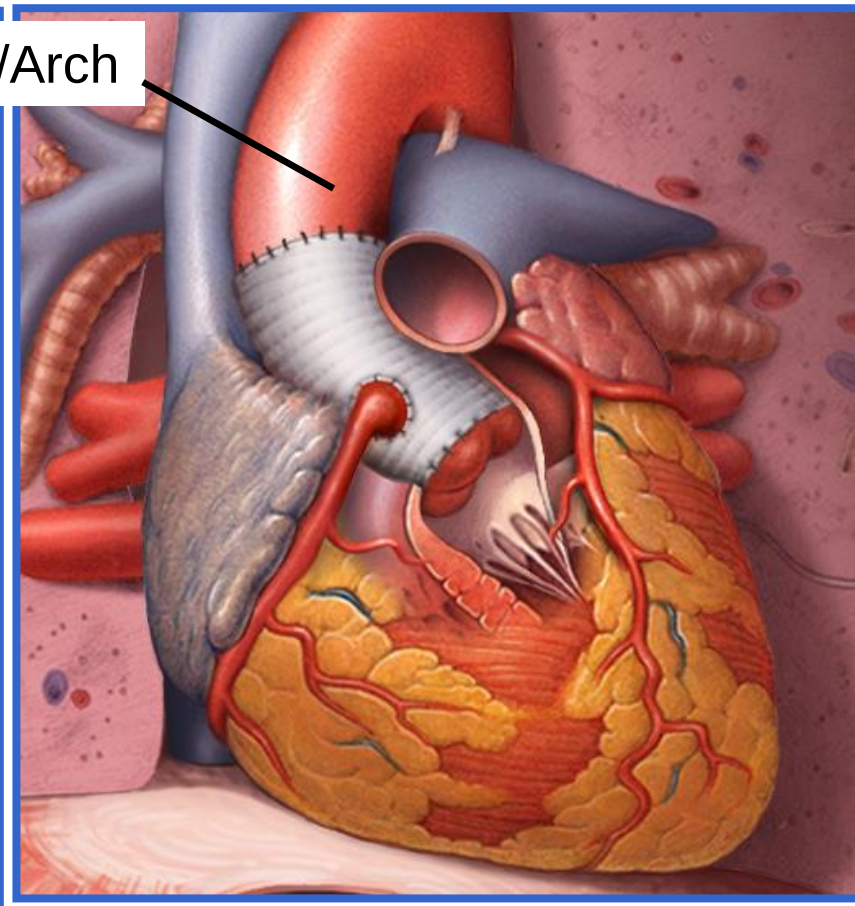
Aortic Root Replacement

Composite Mechanical Valve

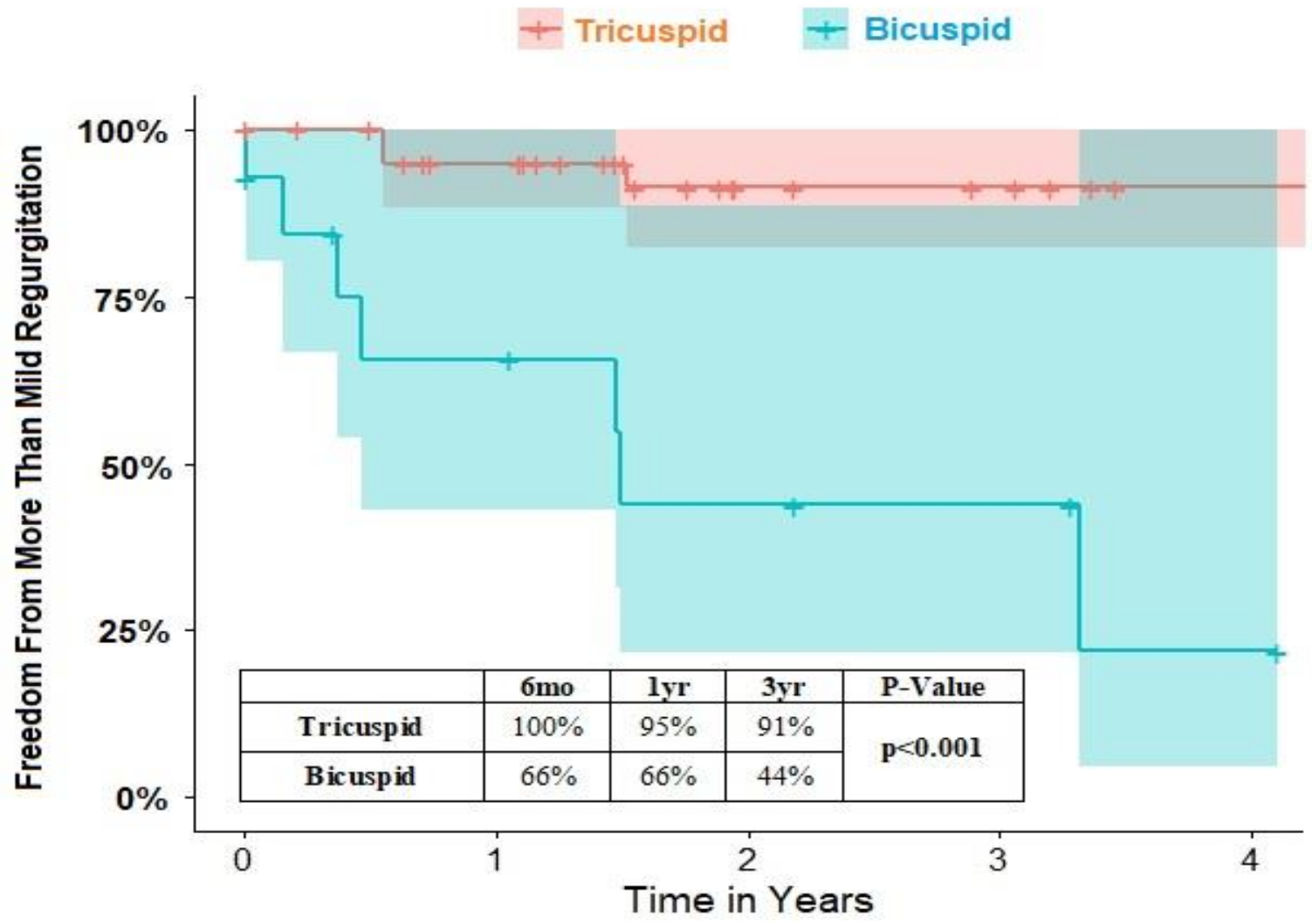
Valve Sparing







HHI/MCW Valve-sparing ARR Outcomes



	6mo	1yr	3yr	P-Value
Tricuspid	100%	95%	91%	p<0.001
Bicuspid	66%	66%	44%	

HHI/MCW Aortopathy Clinic

Indications for Referral

- Systemic features of connective tissue disorder (i.e. pectus, scoliosis, wrist/thumb sign, cleft palate, club feet, etc.)
- Family history of thoracic aneurysms or dissections
- Aortic dissection < 60 years of age
- Ascending aortic aneurysm diagnosed < 50-60 years of age

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HHI/MCW Aortopathy Clinic

1. Patient/family evaluated by Cardiology & Genetics (Med-Peds providers)
2. Custom HTAD gene panel (> 20 genes)

- If positive genetic testing (≈ 20-30%) → Gene-specific management
  - Medical therapy (beta-blocker or ARB), activity restrictions
  - Surveillance imaging (+/- head/neck imaging)
  - Timing of aortic aneurysm repair

- If negative testing or variant of unknown significance (≈ 70-80%)
  - Imaging of first-degree relatives
  - Whole Exome Sequencing

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Summary

- Evolving understanding of how genetic variants result in hereditary thoracic aortic disease

- Identifying causative HTAD genetic variant critical for:
  - Screening for aortic and vascular complications
  - Guide medical and surgical management
  - Identifying at-risk family members

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