Genetics of Thoracic Aortic Aneurysms & Aortic Valve Disease

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SERIOUS MEDICINE. EXTRAORDINARY CARE.

No disclosures

Objectives

1. Review the genetic causes of heritable thoracic aortic aneurysm disease

2. Demonstrate how timely genetic testing can direct patient care and decrease mortality by impacting surveillance, type & timing of aortic surgery and medical treatments

3. Review the limited data on the genetics of bicuspid aortic valve disease and identify some of the “high risk” markers

Heritable Thoracic Aortic Aneurysm Disease

Extracellular matrix proteins

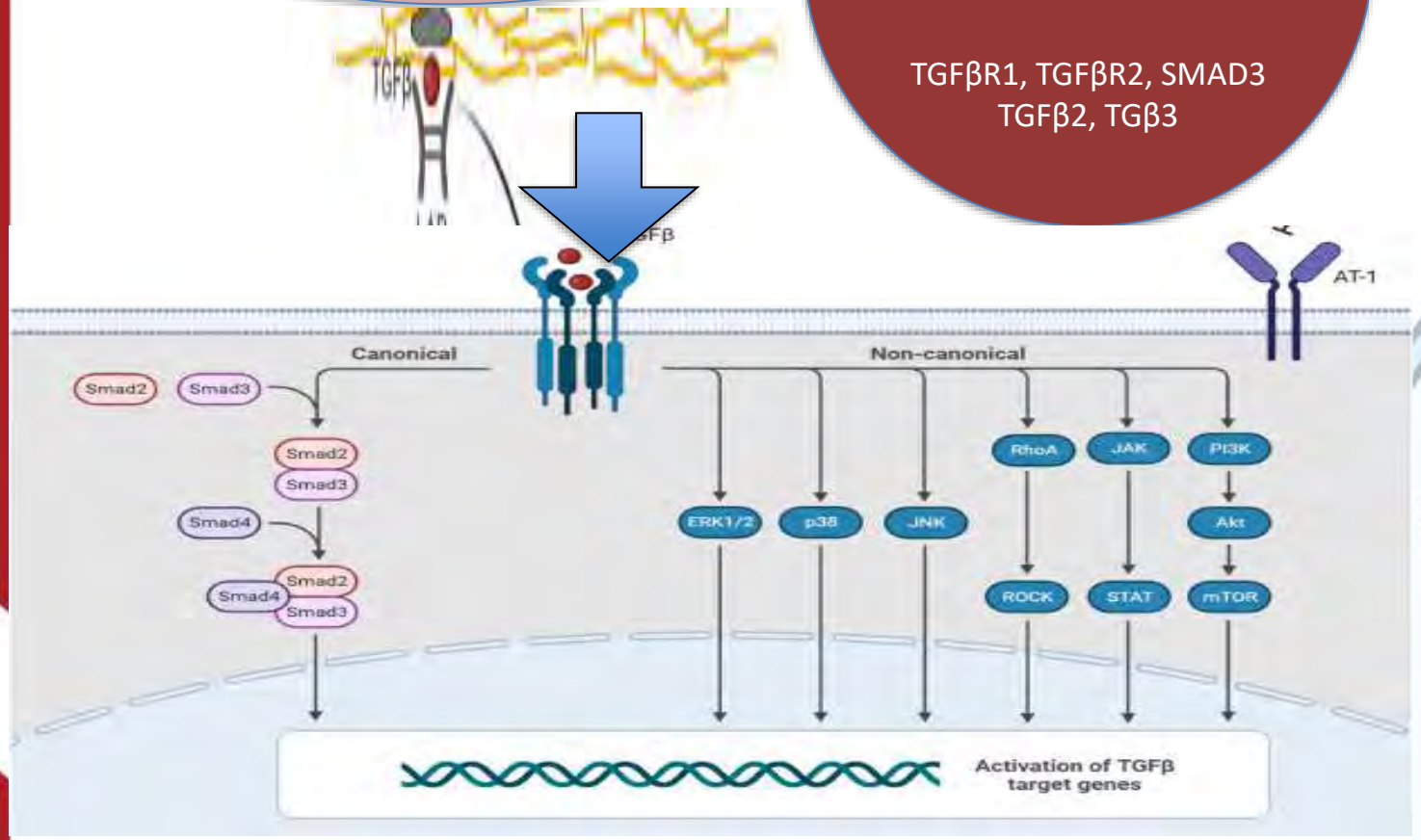
FBN1, LOX, COL3A1

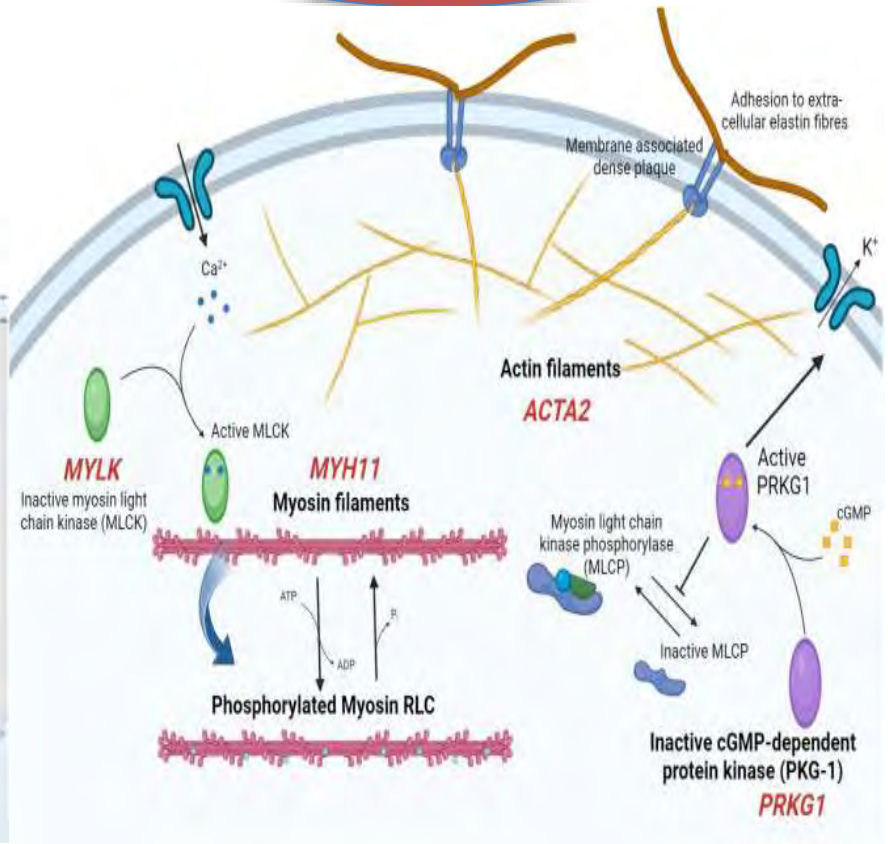
Proteins Involved in TGFβ signaling pathway

TGFβR1, TGFβR2, SMAD3
TGFβ2, TGβ3

Proteins involved in smooth muscle contraction

ACTA2, MYH11, PRKG1, MYLK



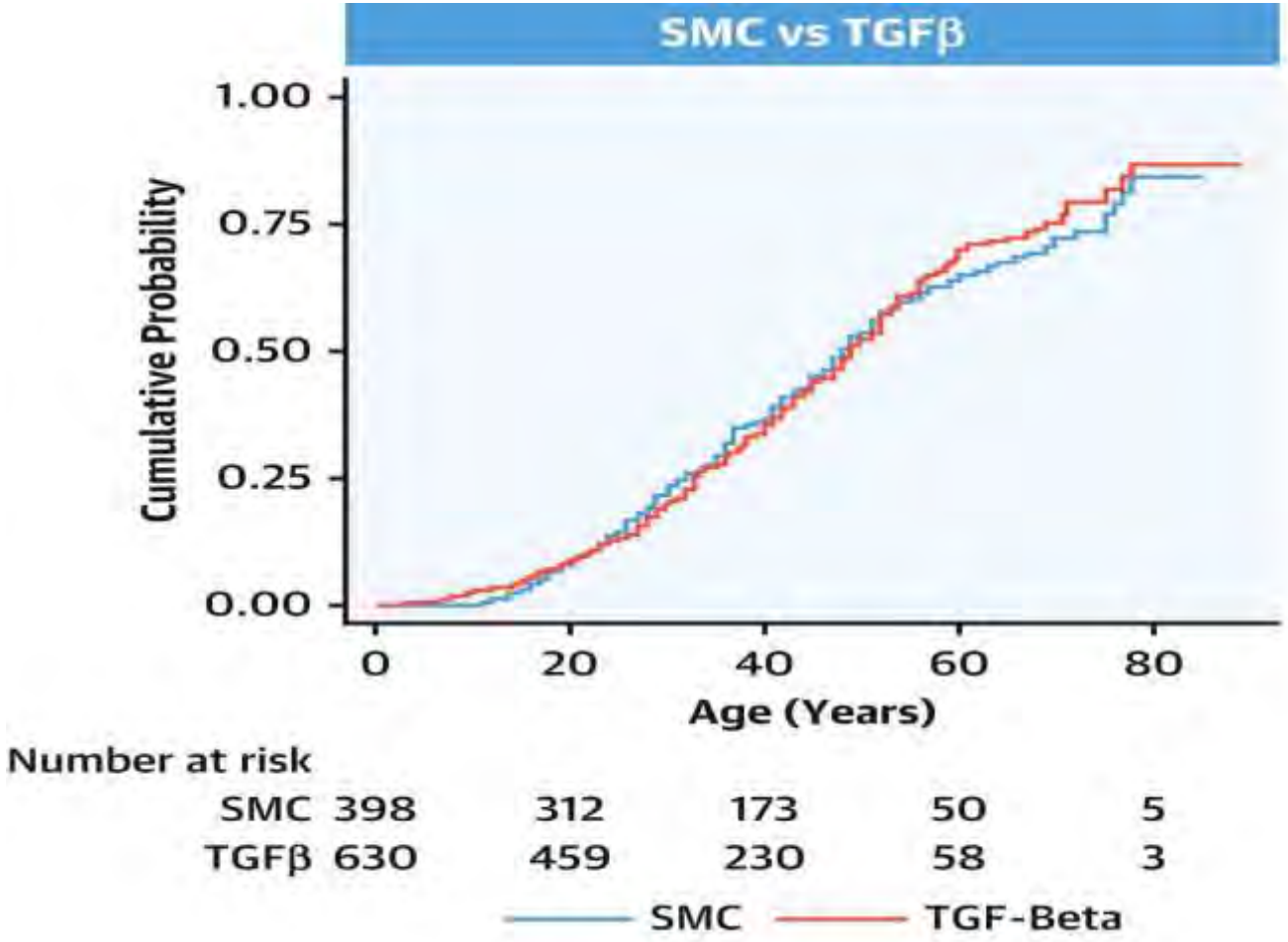


Montalcino Aortic Consortium Registry

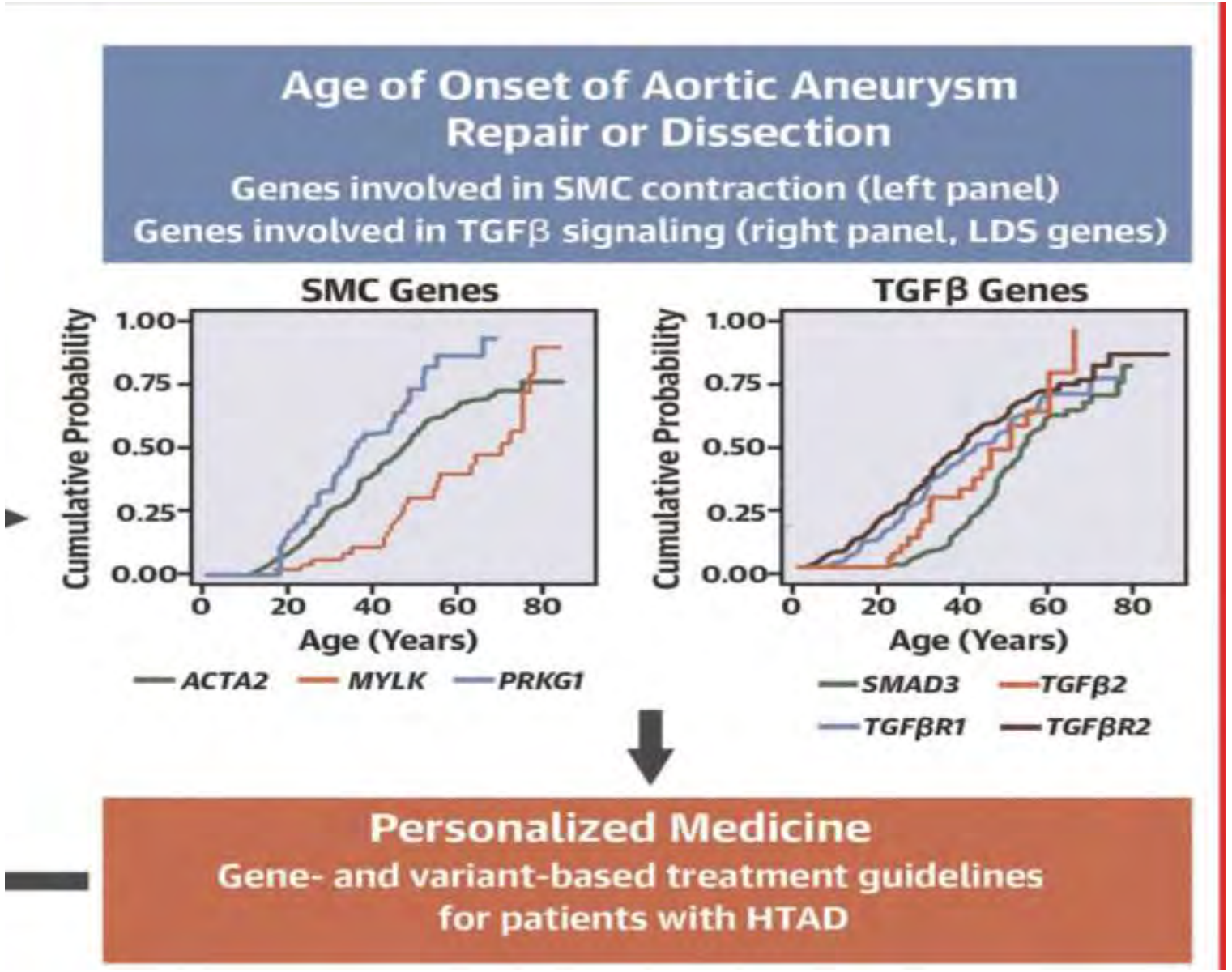
Genetic Aortic Disorders Association Canada
L'Association Canadienne des Maladies Génétiques de l'Aorte

- UTHealth Houston
- University of Washington
- University of Washington in St. Louis
- Texas Children's Hospital
- University of Sydney
- University of Nebraska
- Ghent University, Belgium
- Baylor College of Medicine
- Great Ormond Hospital, UK
- Massachusetts General Hospital
- University of Michigan
- University Health Network
- University of Calgary
- HOAG Memorial Hospital
- University of Kentucky
- St. Francis Hospital & Heart Center (NY)
- The Heart Hospital (TX)
- University of Barcelona (Spain)

Comparative Risks of Initial Aortic Events Associated With Genetic Thoracic Aortic Disease

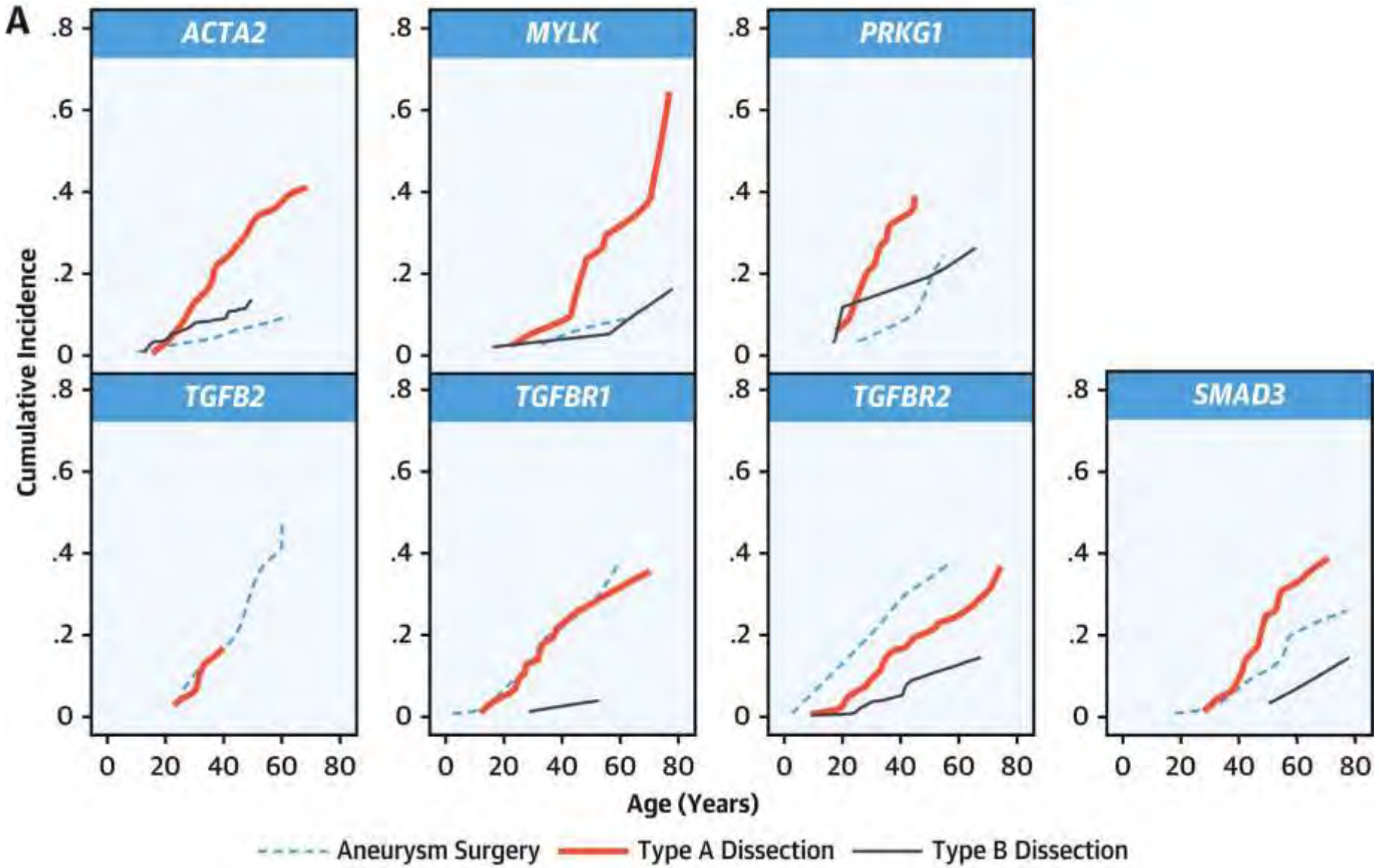


Regelado et al. JACC 2022 Aug 30;80(9):857-869.



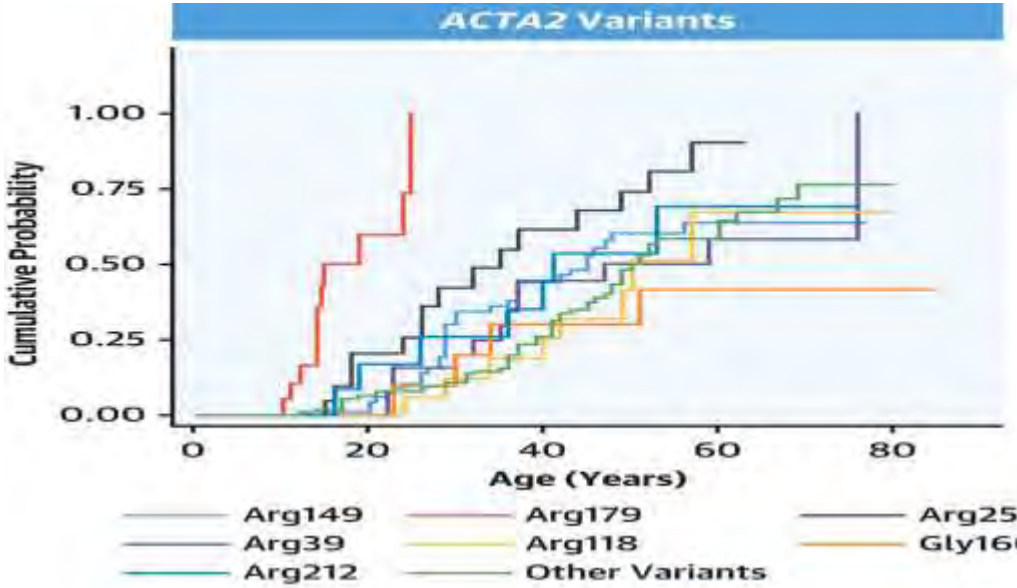
Regelado et al. JACC 2022 Aug 30;80(9):857-869.

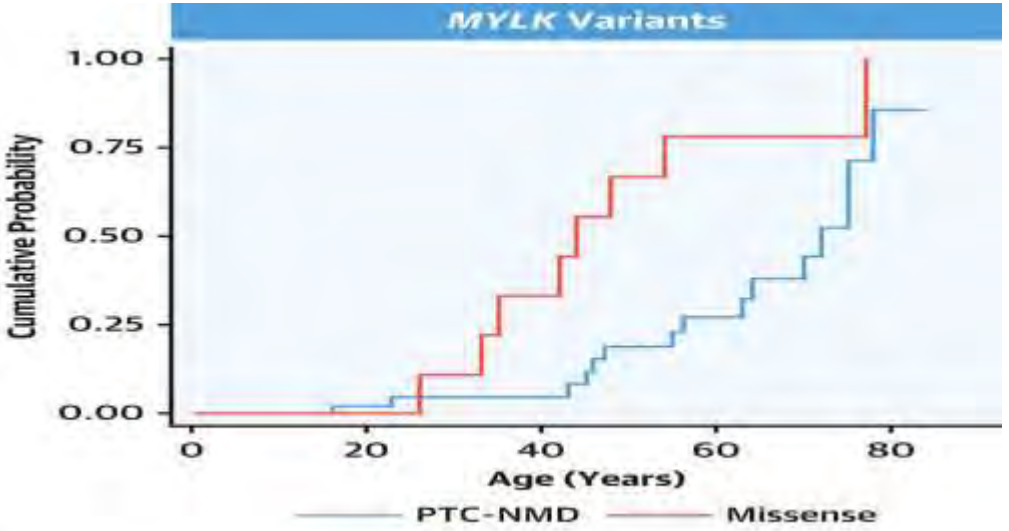
Clinical Presentation By Gene

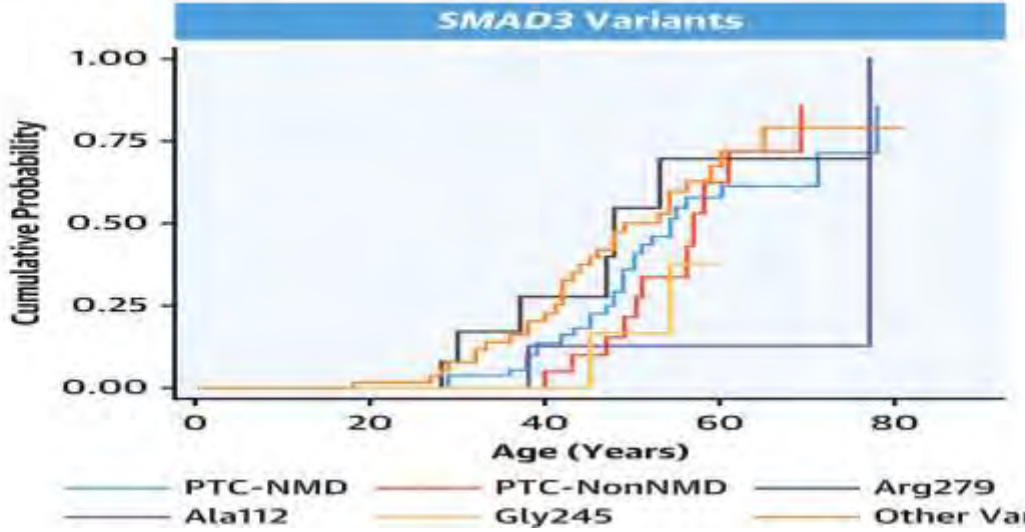


Regelado et al. JACC 2022 Aug 30;80(9):857-869.

Aortic Event by Genetic Variant

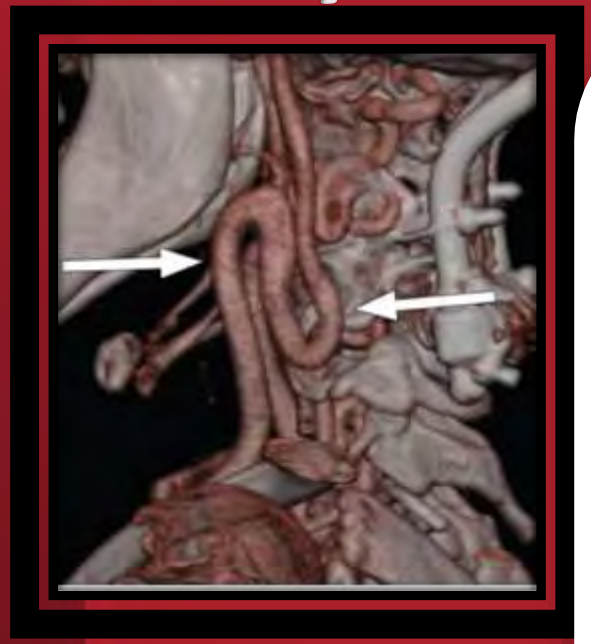


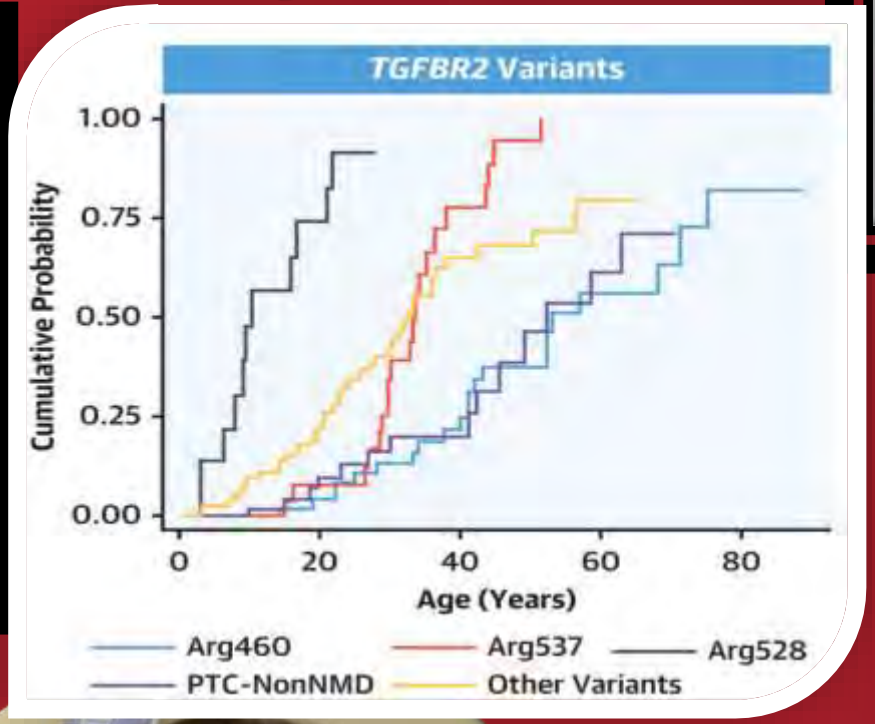


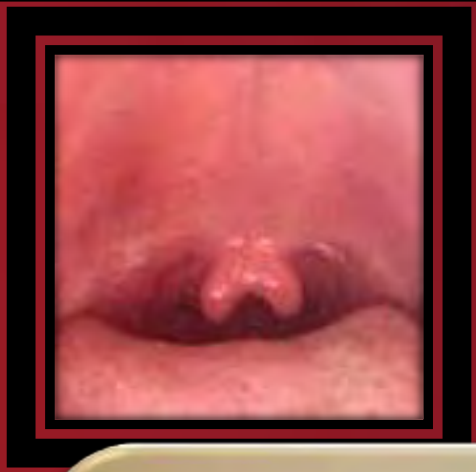


Regelado et al. JACC 2022 Aug 30;80(9):857-869.

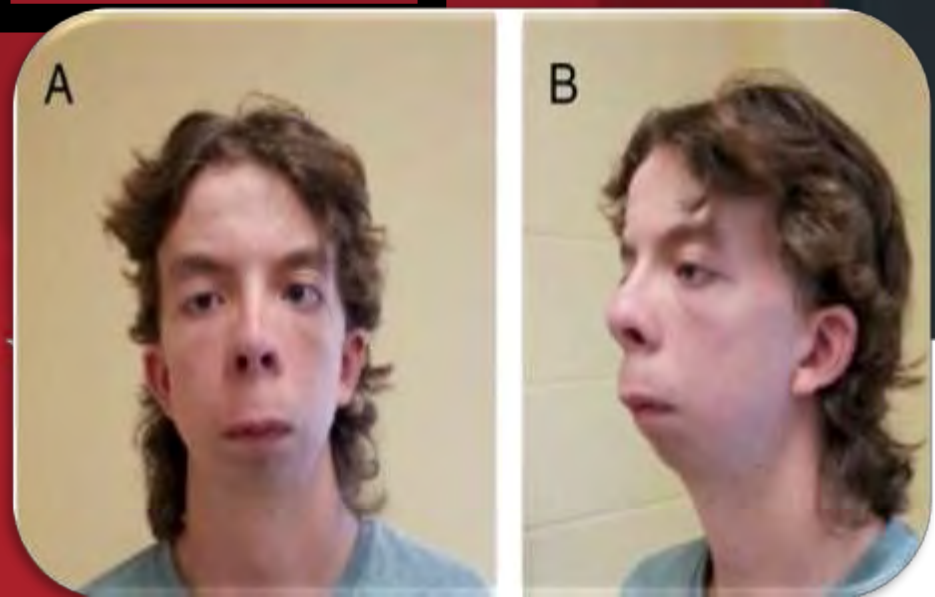
“Loeys Dietz” Syndrome

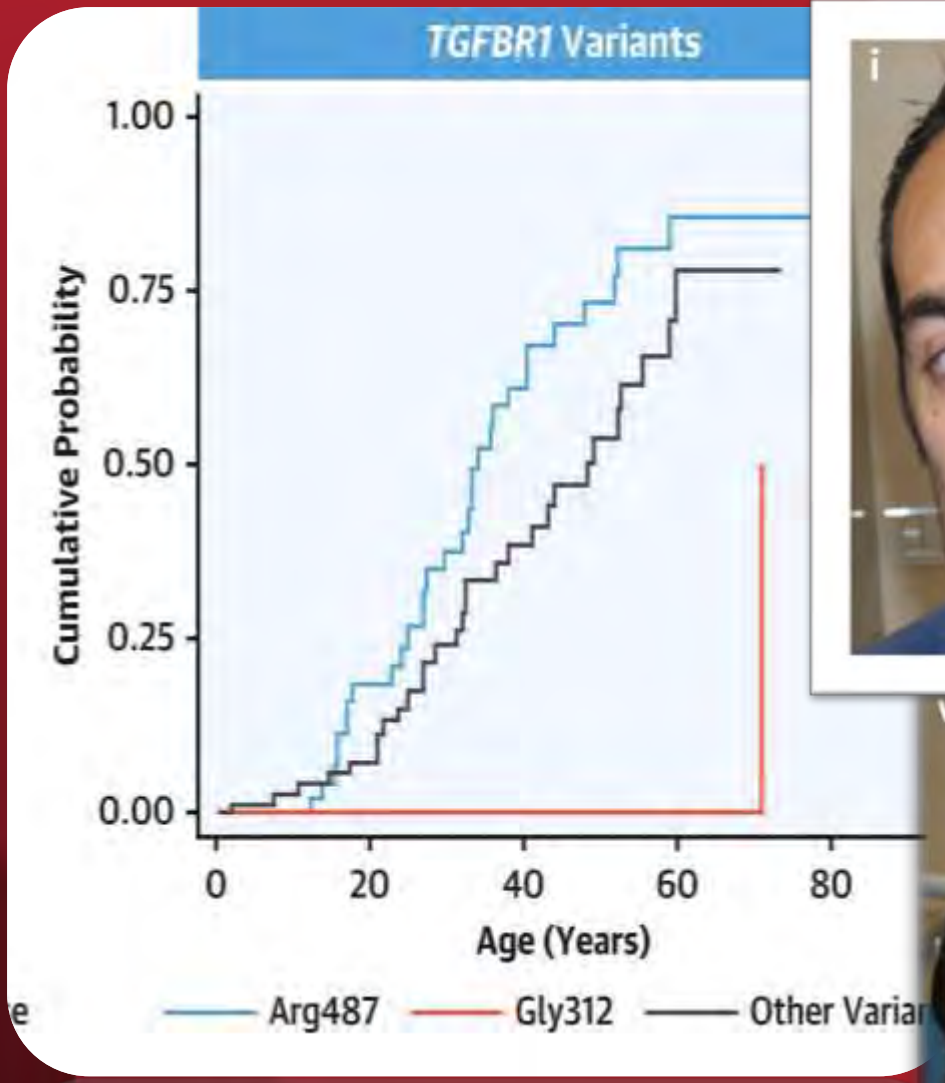


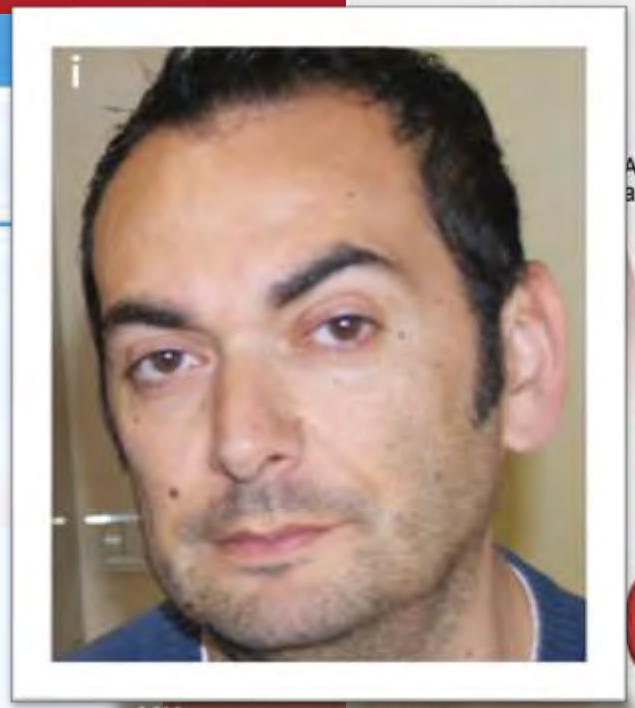




- Broad or bifid uvula
- Retrognathia
- Hypertelorism
- MSK contractures
- Cervical spine instability
- Arterial tortuosity




TGFBR1 Variants
1.00
0.75
0.50
0.25
0.00
Cumulative Probability
0
20
40
60
80
Age (Years)
Arg487
Gly312
Other Varian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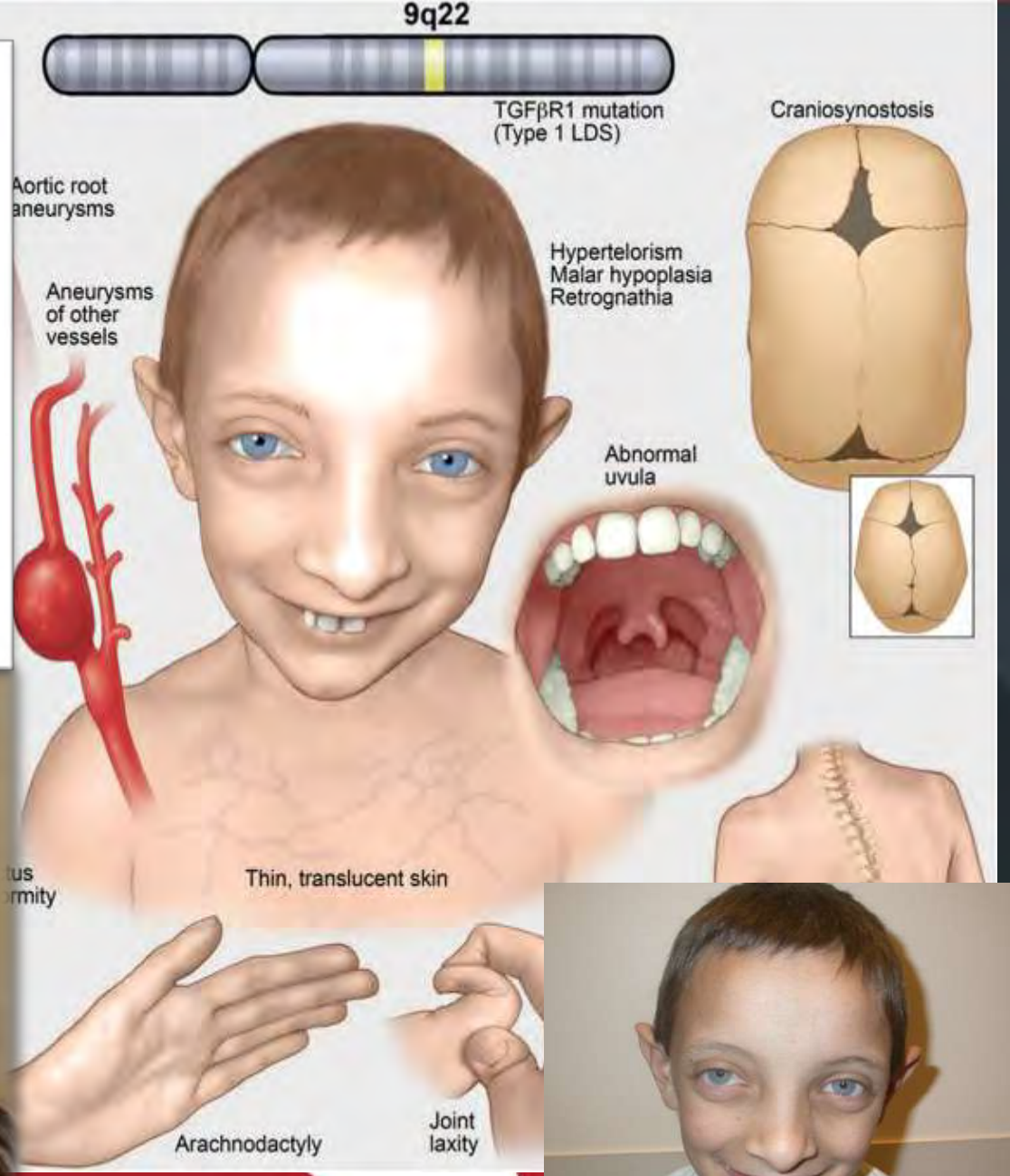
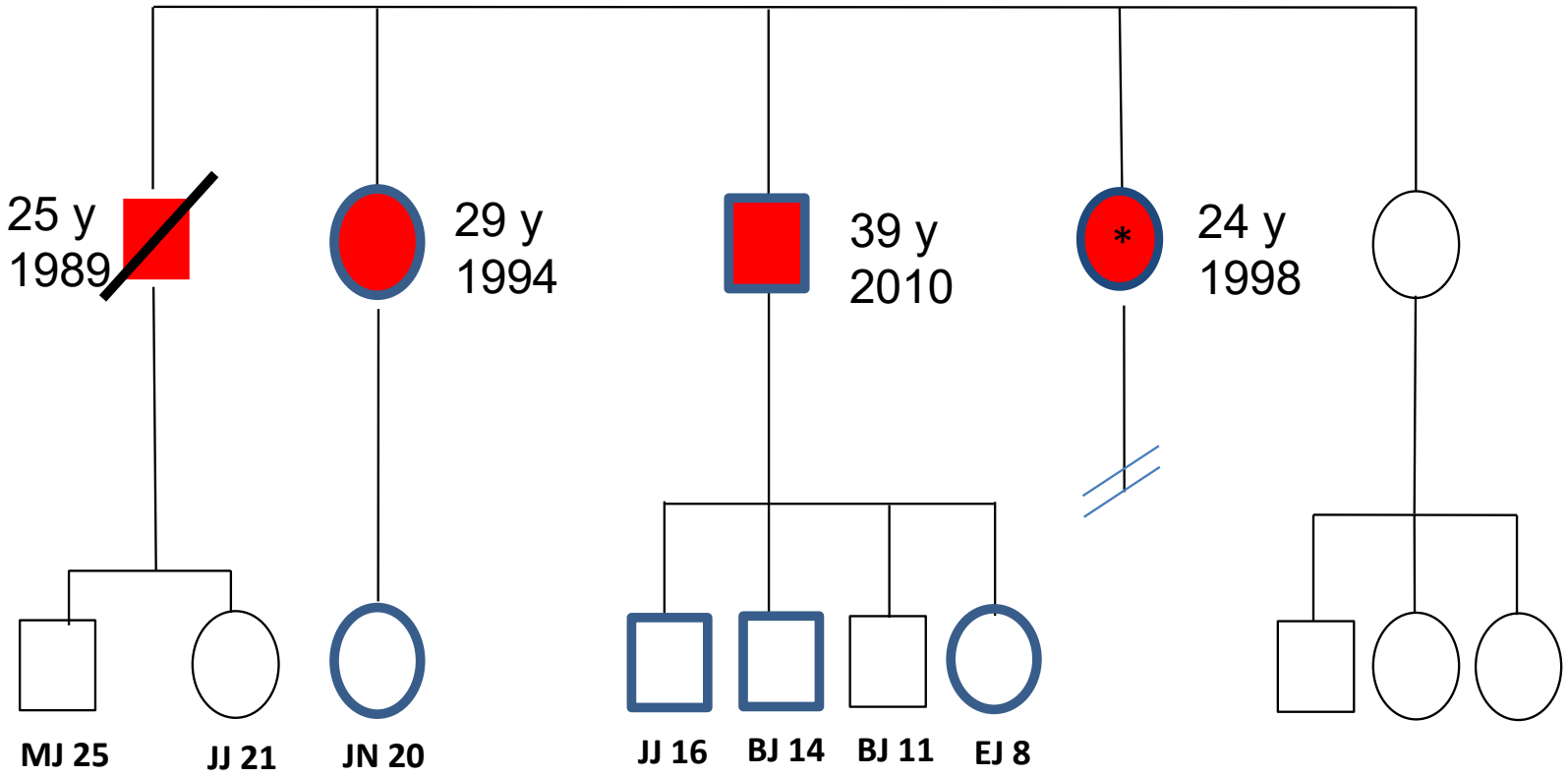

9q22
TGFβR1 mutation
(Type 1 LDS)
Craniosynostosis
Aortic root
aneurysms
Aneurysms
of other
vessels
Hypertelorism
Malar hypoplasia
Retrognathia
Abnormal
uvula
Thin, translucent skin
Arachnodactyly
Joint
laxity

Medical History

Aortic dissection from AAo to iliac bifurcation s/p Bentall (1998)

Recurrent bowel obstructions

Recurrent “TIAs”



Mother

- CVA at 40 with no risk factors
- MGF: very fit. Unexplained sudden death at 52 (“dropped dead on the living room floor”)
- MGM: Parkinson’s disease, stroke late in life, died of brain cancer at 83

Father

- Youngest of 8 children, none have cardiac history
- Died at 54 of brain cancer
- PGF: heart failure in mid 80s
- PFM: old age, 90+

ACTA2 & Premature Atherosclerotic Coronary Artery Disease

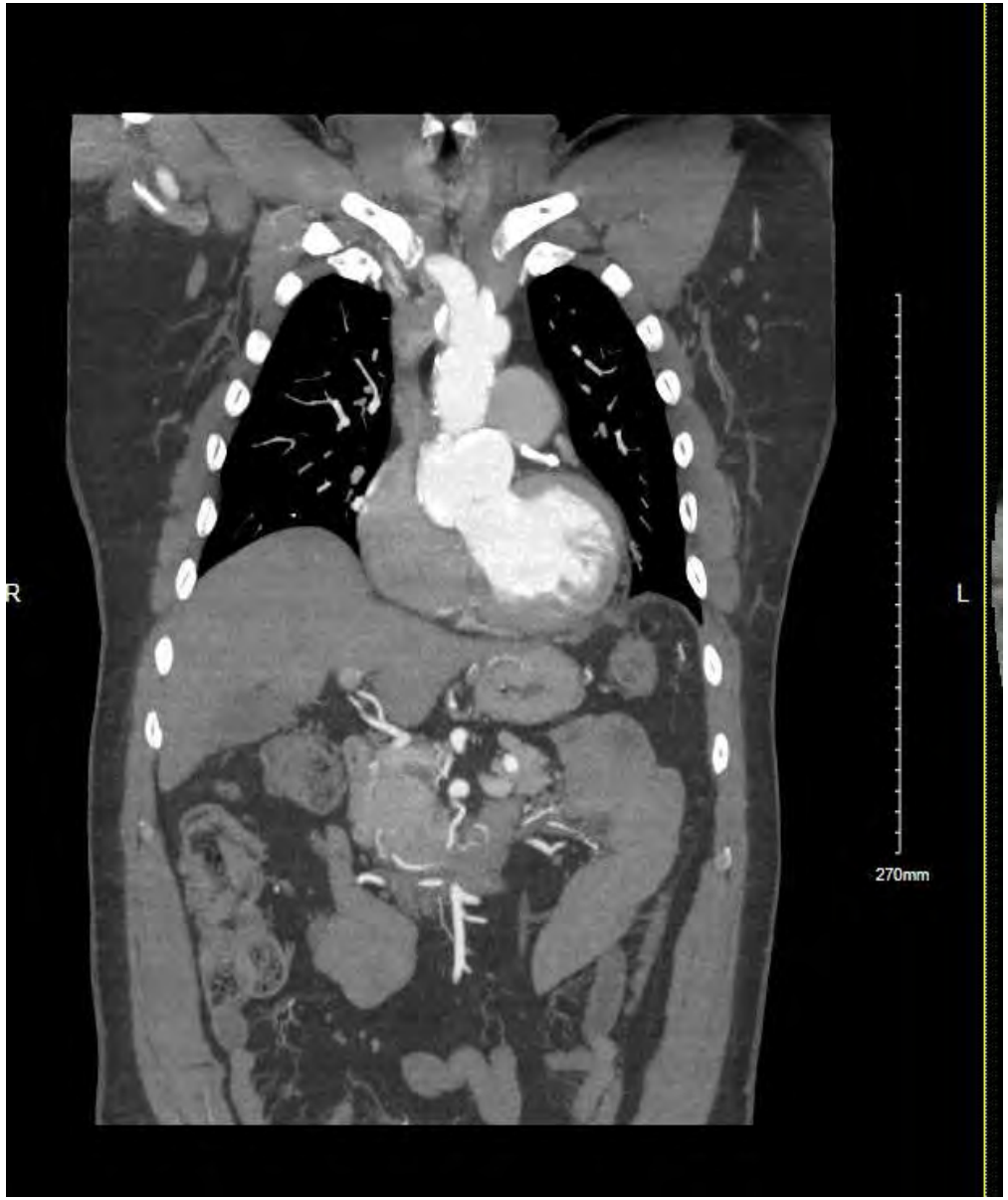
A

ACTA2 exons	Mutation	No.	TAAD	Stroke	CAD
2	p.R39H	13	8	3*	2
3	p.P72Q	3	3	0	0
4	p.N117T	4	3	1	0
	p.R118Q	15	8	1	6
5	[illegible]	4	2	0	0
	p.R149C	[illegible]	24	4	12
6	p.V154A	4	2	0	0
	p.G160D	6	5	0	0
	p.R185Q	5	2	0	3
7	p.R212Q	4	2	1*	1
	p.P245H	1	1	1	0
	p.I250L	1	1	1	0
	p.R258C/H	15	10	7*	0
8	p.R292G	5	4	0	0
9	p.T326N	7	4	1	2
	p.T353N	2	1	1	1

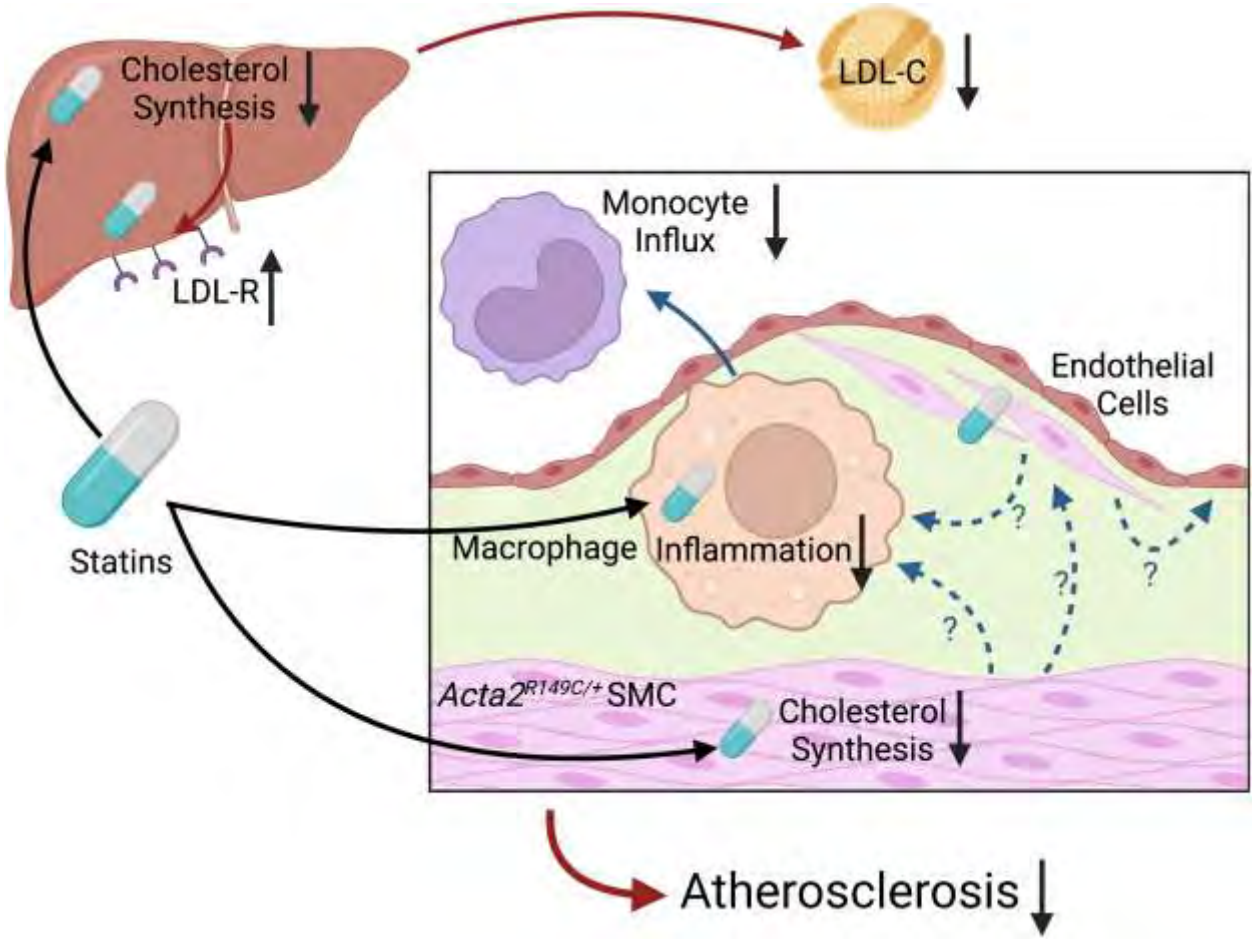
Mutations occur in more than 15 individuals in which more than 25% of *ACTA2* carriers have strokes

Mutations occur in more than 15 individuals in which more than 25% of *ACTA2* carriers have CAD

ACTA2R149 Aortopathy & CAD

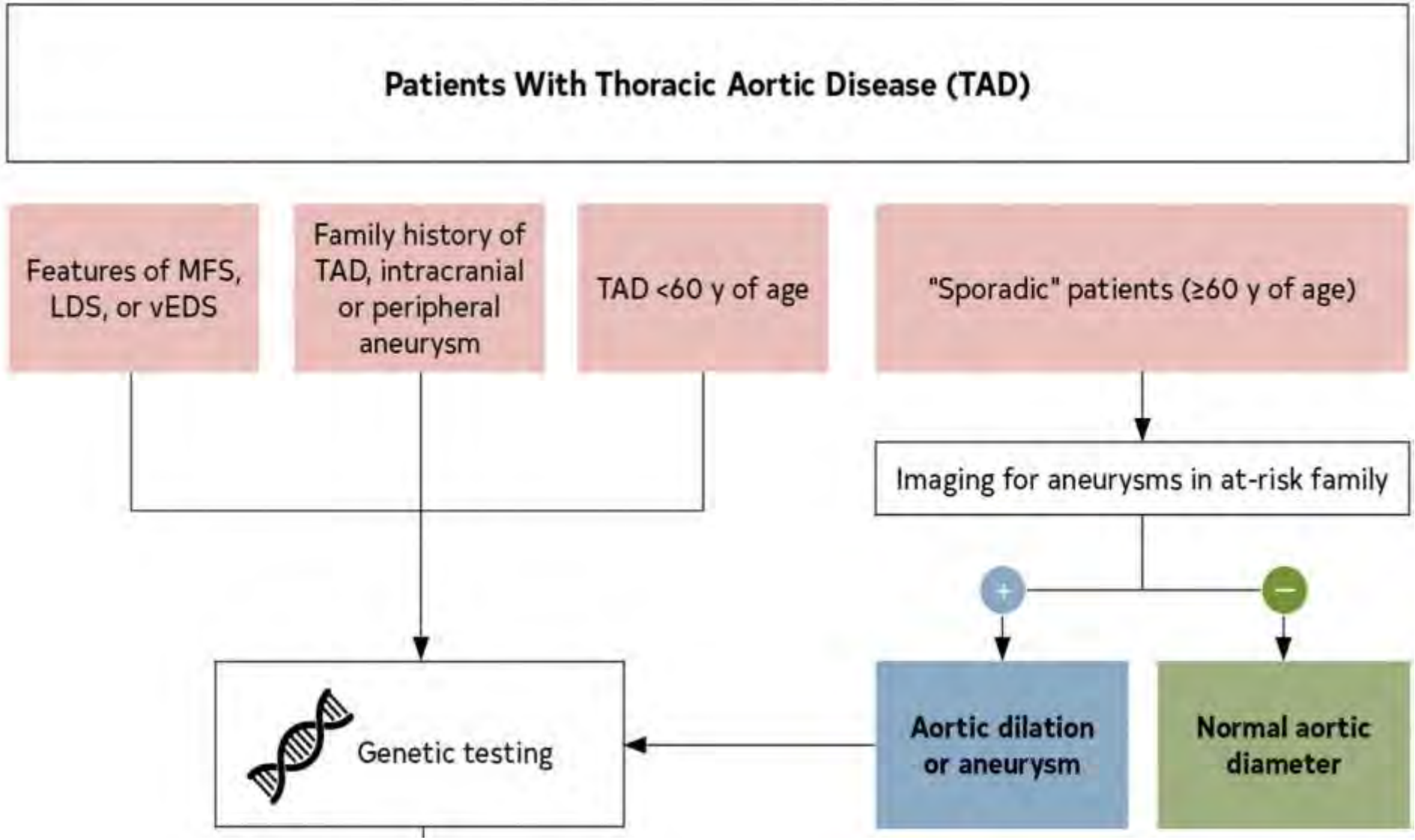


Statins suppress atherosclerosis In ACTA2 R149 Mice



Eur Heart J, Volume 44, Issue 29, 1 August 2023, Pages 2727–2729, https://doi.org/10.1093/eurheartj/ehad364

2022 Aortic Guidelines For Genetic Testing



2022 ACC/AHA guideline for the diagnosis and management of aortic disease J Thorac Cardiovasc Surg 2023 Jun 28

Genetic Testing

RESULT: UNCERTAIN

Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
ACTA2	c.337A>G (p.Asn113Asp)	heterozygous	Uncertain Significance

About this test

This diagnostic test evaluates 35 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

Aortopathy Team

Surgical Recommendations

COR	Genetic Variant	High Risk Features*	Aortic Diameter (cm)
1	TGFBR1	No	≥ 4.5
1	TGFBR2	No	≥ 4.5
2b	TGFBR1	Yes	≥ 4.0
2a	TGFBR2	Yes	≥ 4.0
2a	SMAD3	-	≥ 4.5
2b	TGFB2	-	≥ 4.5
2b	TGFB3	-	≥ 5.0
2a	ACTA2	No	≥4.5
2b	ACTA2	Yes	≥4.2
2b	PRKG1		≥ 4.0

*certain specific pathogenic variants, women with TGFBR2 and small body size, severe extra aortic Features, family history of dissection (especially at young age or relatively small aortic size, Aortic growth rate > 0.3 cm/year

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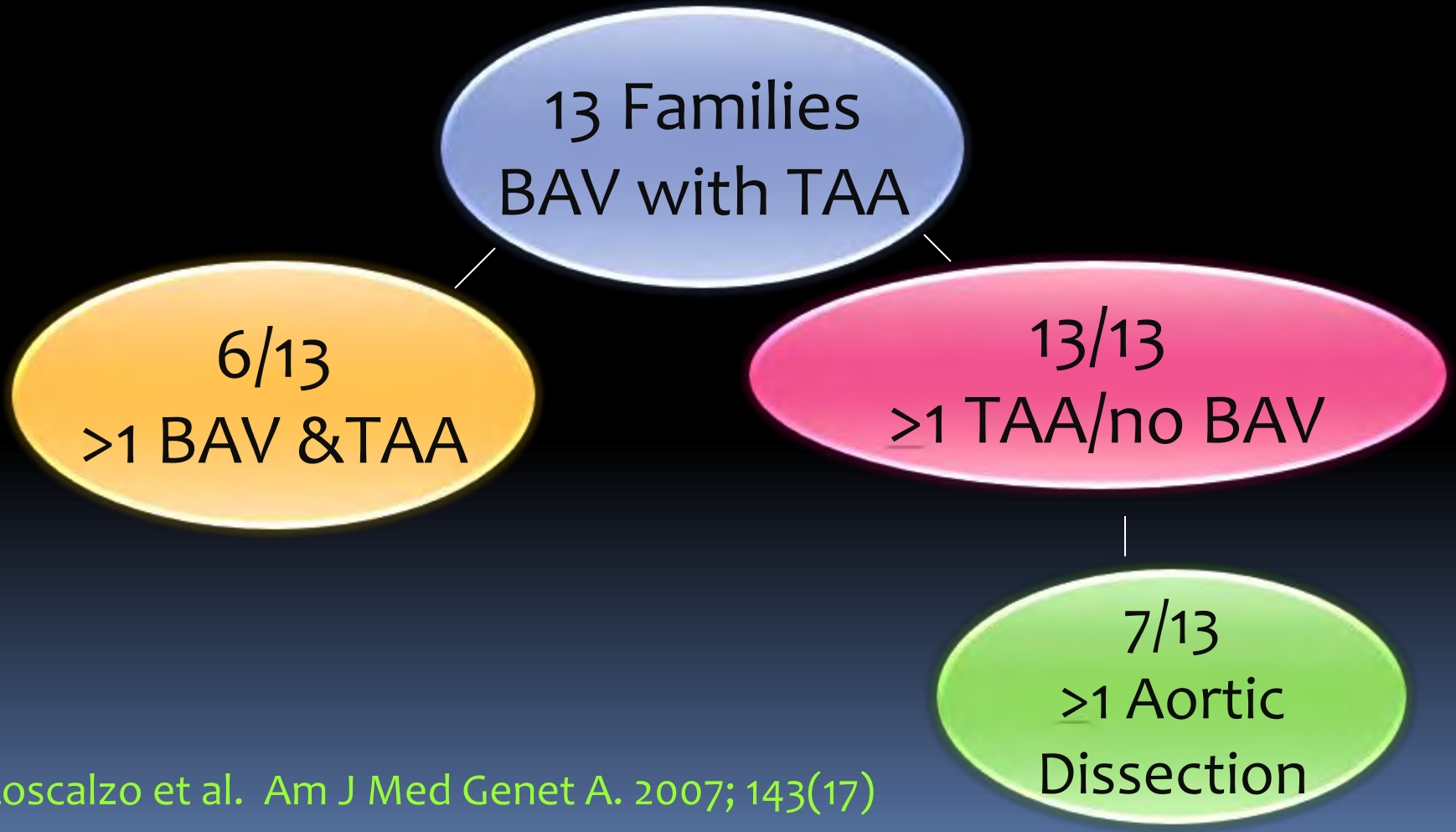
Bicuspid Aortic Valve And Thoracic Aortic Aneurysm



Loscalzo et al. Am J Med Genet A. 2007; 143(17)

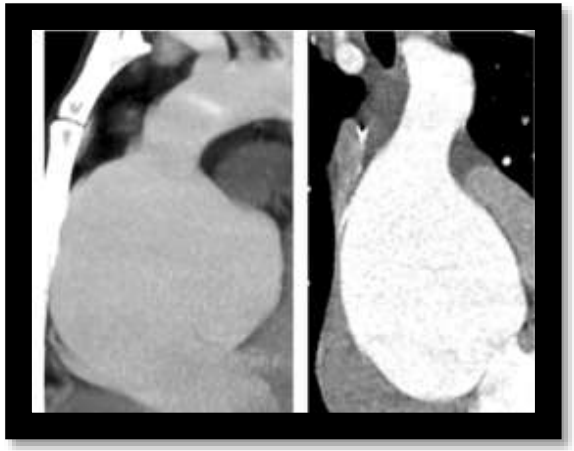
Bicuspid Aortic Valve

Isolated Bicuspid Valve with BAV aortopathy

- 1-2% of the population
- 5% lifetime risk of aortic dissection
- Maximal site of dilation is ascending aorta
- Aortic stenosis may be present
- Associated with other left heart obstructive lesions
- Family history of BAV without dissection
- Genetic testing on a research basis

Isolated Bicuspid Valve with HTAAD gene

- 10 % of the population (TGFBR1&2, FLNA A, ACTA2)
- >50% lifetime risk of aortic dissection
- Maximal site of dilation is aortic sinuses
- Aortic stenosis not present – normal functioning or isolated aortic insufficiency
- Family history of aortic dissection
- Genetic testing warranted



Conclusions

1. 20% of patients with sporadic aortic aneurysms will have a genetic basis to their disease

2. Genetic mutation has a greater impact than aortic size on risk of aortic dissection

3. Genetic testing can direct vascular imaging, affect timing of surgery , impact medical therapy and prevent death from dissection in other affected family members

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