70th ESCVS

7th IMAD

New genes in connective tissue disorders

Bart Loeys, MD, PhD

Antwerp University Hospital, Antwerp and Radboud University Medical Center, Nijmegen

UZA Kennis / Ervaring / Zorg

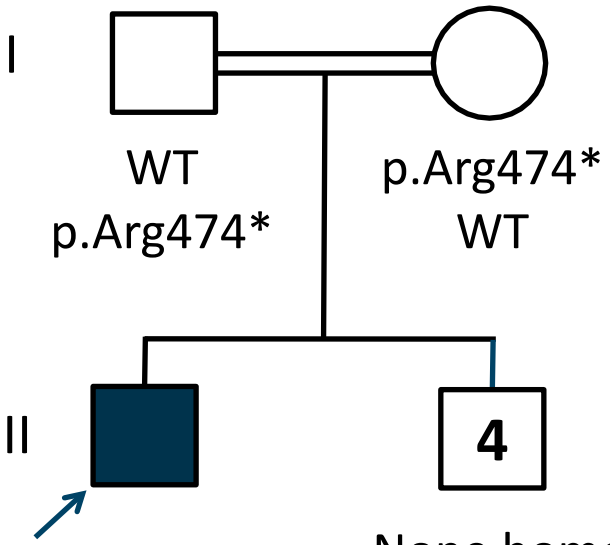
Universiteit Antwerpen

Radboudumc university medical center

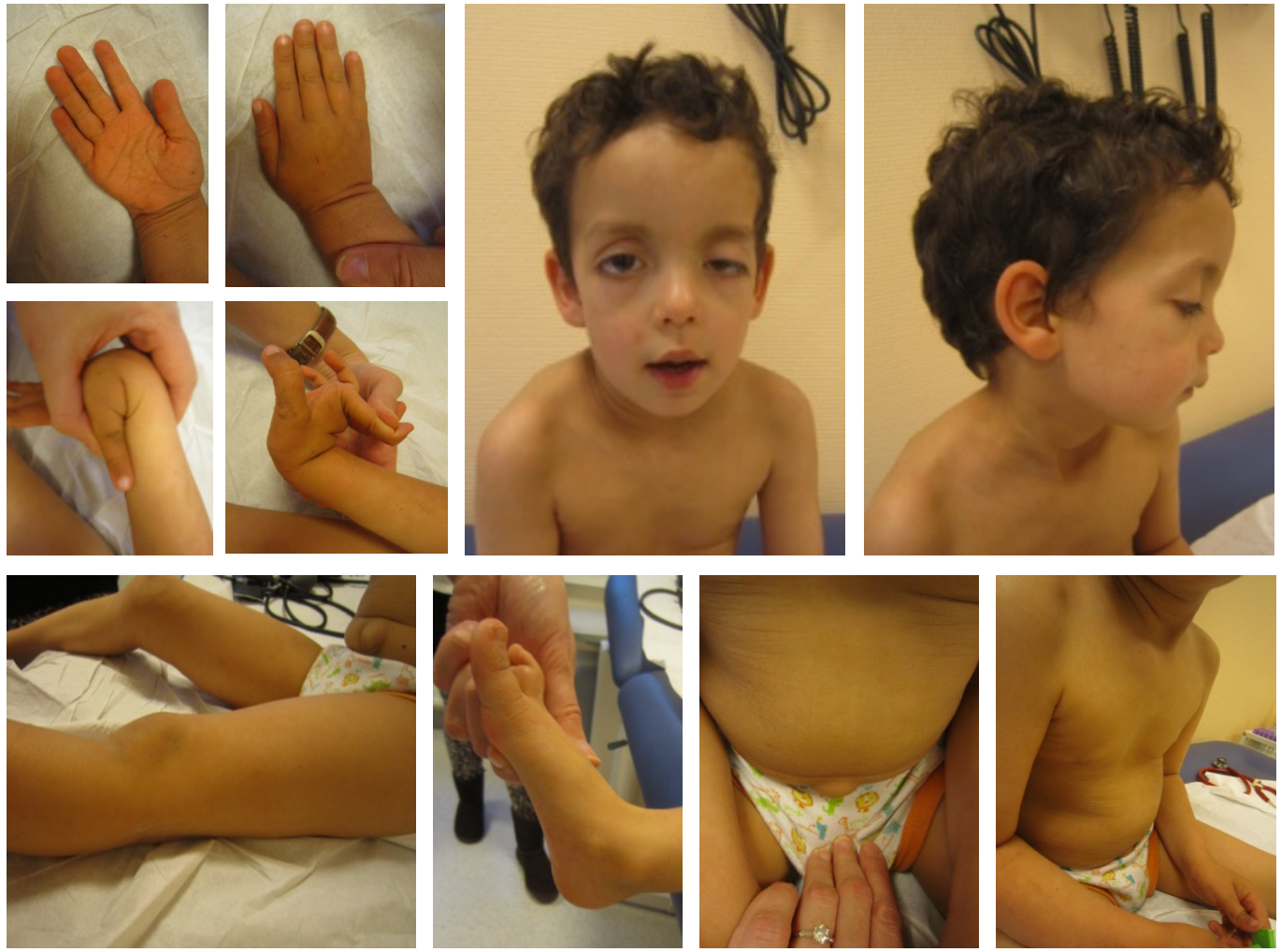
New genetic insights in aortopathy

- *IPO8 – the first recessive Loeys-Dietz syndrome*
- *THSD4 – another connective tissue player in aortic aneurysm*
- *PMEPA1 – marfanoid habitus with occasional aortopathy*

A new autosomal recessive LDS gene ?



IPO8



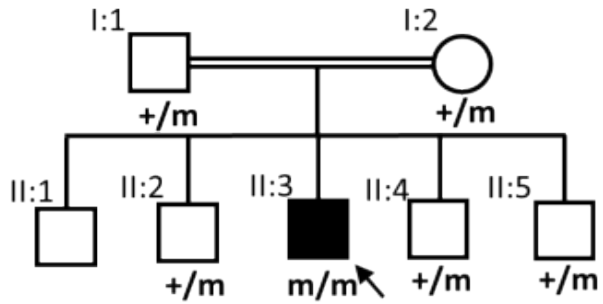
TRIO EXOME SEQUENCING

- Developmental delay - hypotonia
- Facial dysmorphism
- Joint hypermobility (Beighton 9/9)
- Bell shape thorax with pectus excavatum
- ASD - aortic root and ascendens dilatation

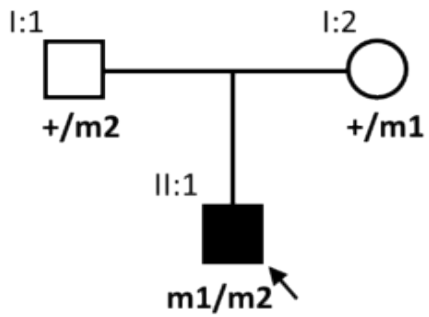
Referred by Isabelle Maystadt, Brussels

Recessive truncating *IPO8* variants

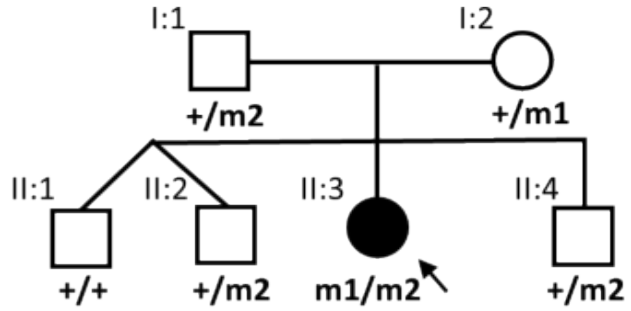
Family 1
p.(Arg474*) (m)



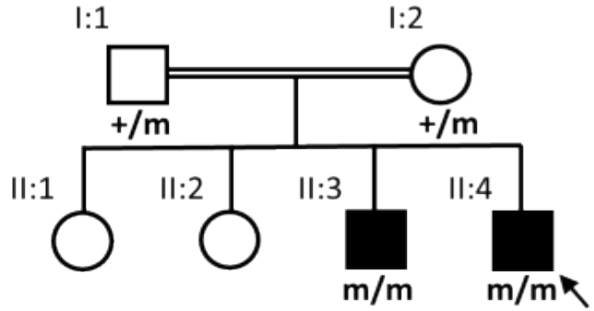
Family 2
p.(Val257Glufs*3) (m1)
p.(Val334Glyfs*19) (m2)



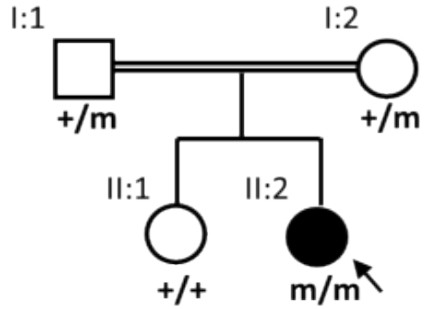
Family 3
p.(Lys447_Arg476del) (m1)
p.(Leu866Profs*12) (m2)



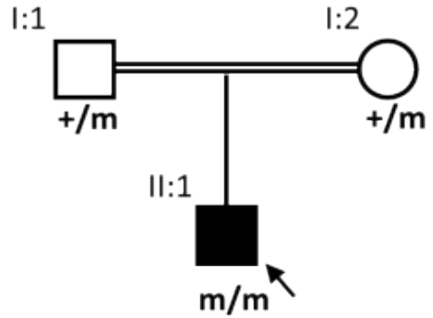
Family 4
p.(Trp259*) (m)



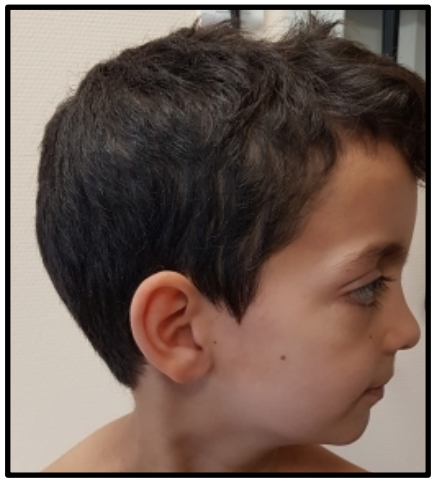
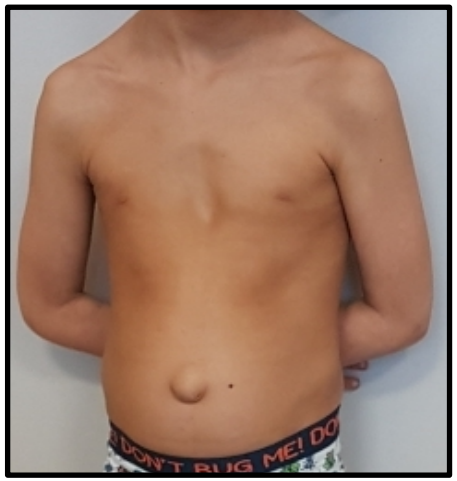
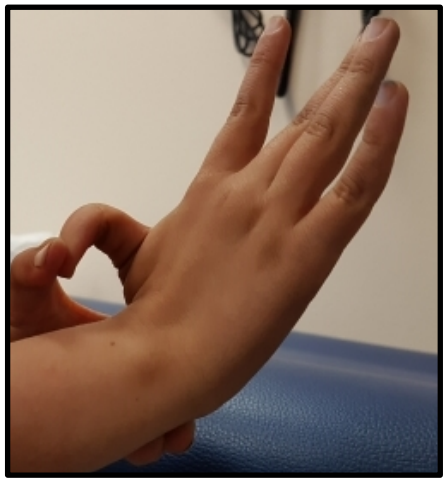
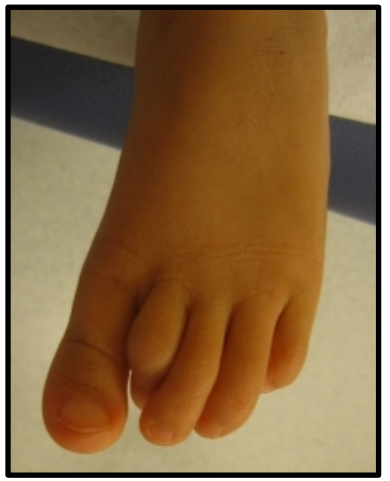
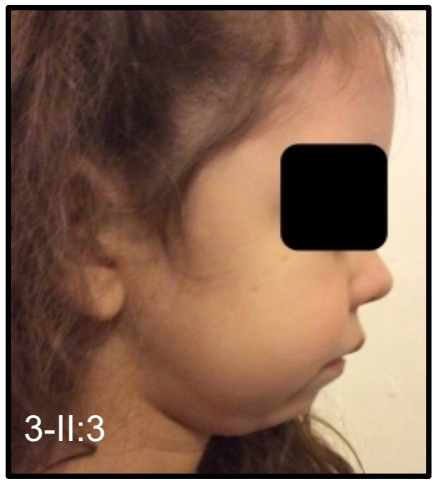
Family 5
p.(Leu783Valfs*5) (m)

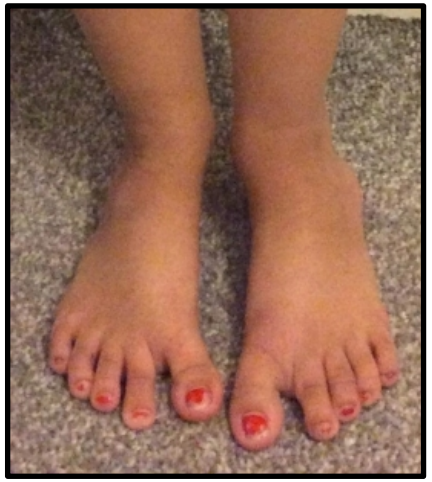
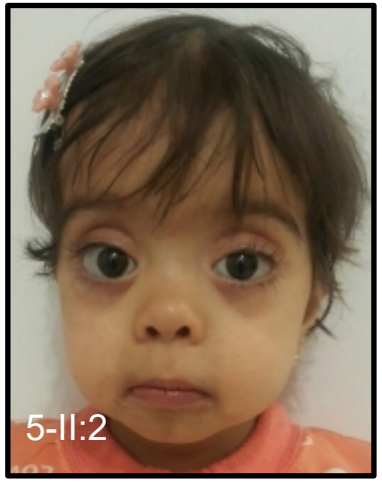


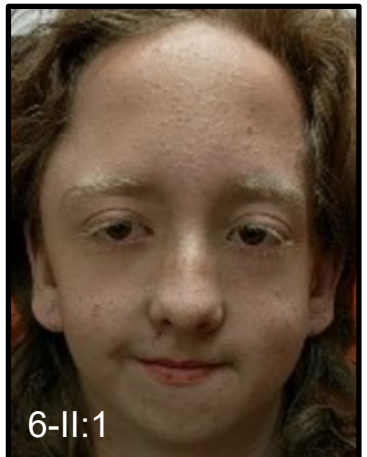
Family 6
p.(Thr967_Glu1006delinsLys) (m)

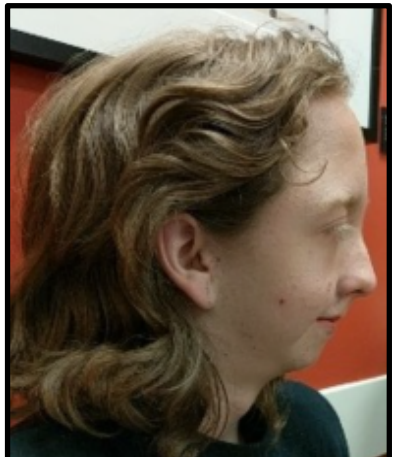


Van Gucht et al, AJHG, 2021



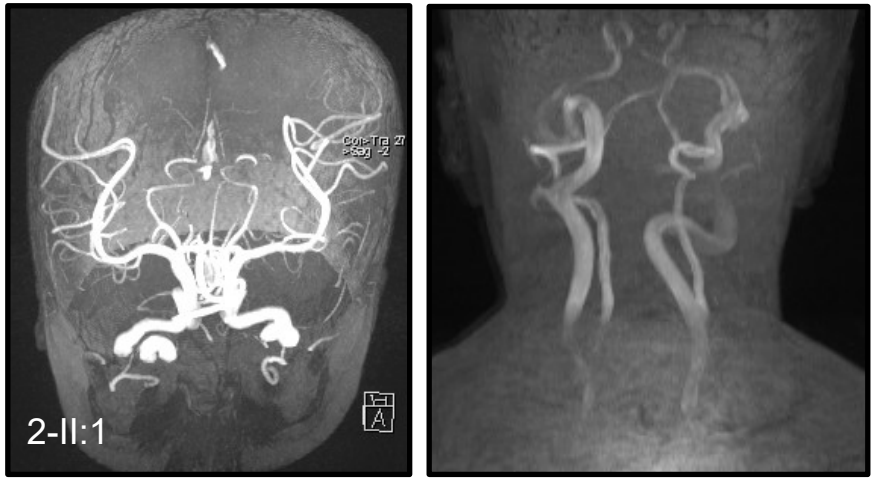


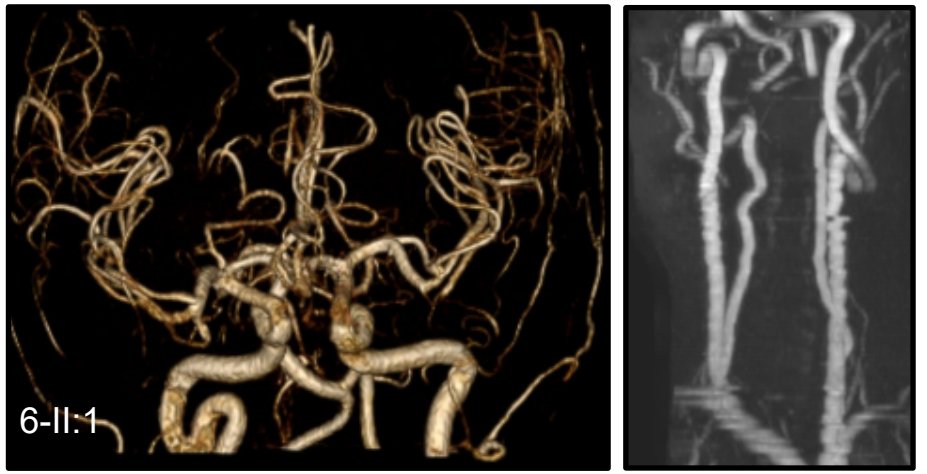
Loeys-Dietz like findings

- Hypertelorism
- Cleft palate/bifid uvula
- Pectus excavatum
- Cervical spine anomalies
- Arachnodactyly
- Joint hypermobility
- Motor developmental delay

Cardiovascular presentation

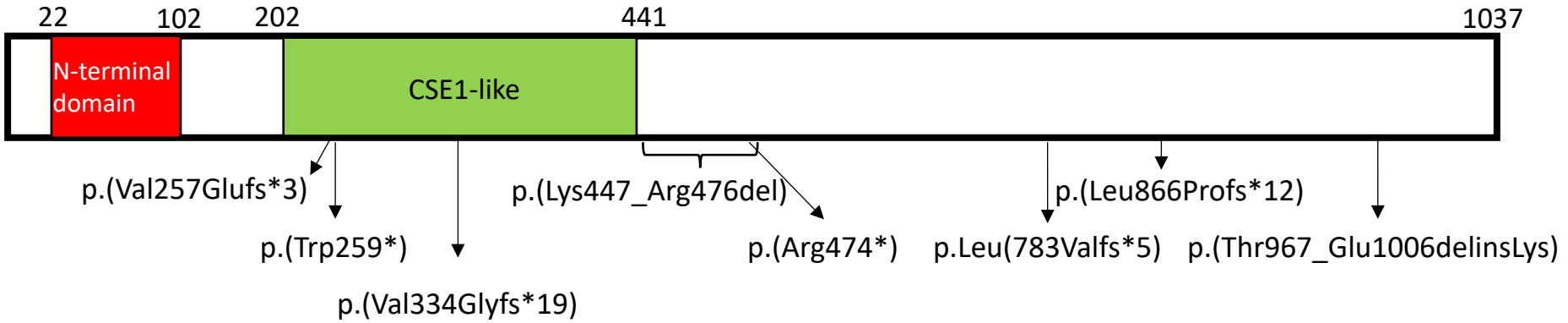
Age range: 9,3 years (4 – 19 years; n=7)
Aortic root aneurysm Z-score: 5,94 (range 3.5-10; n=6)
Ascending aorta aneurysm Z-score: 4,58 (range 2.7-8.7; n=6)
No dissections observed
Other aneurysms: com/int carotid arteries, cerebral arteries, pulmonary artery, coronary sinus
Other cardiovascular anomalies: ASD, VSD, PDA (n=7)
Arterial/aortic tortuosity: only 2 patients extensively imaged



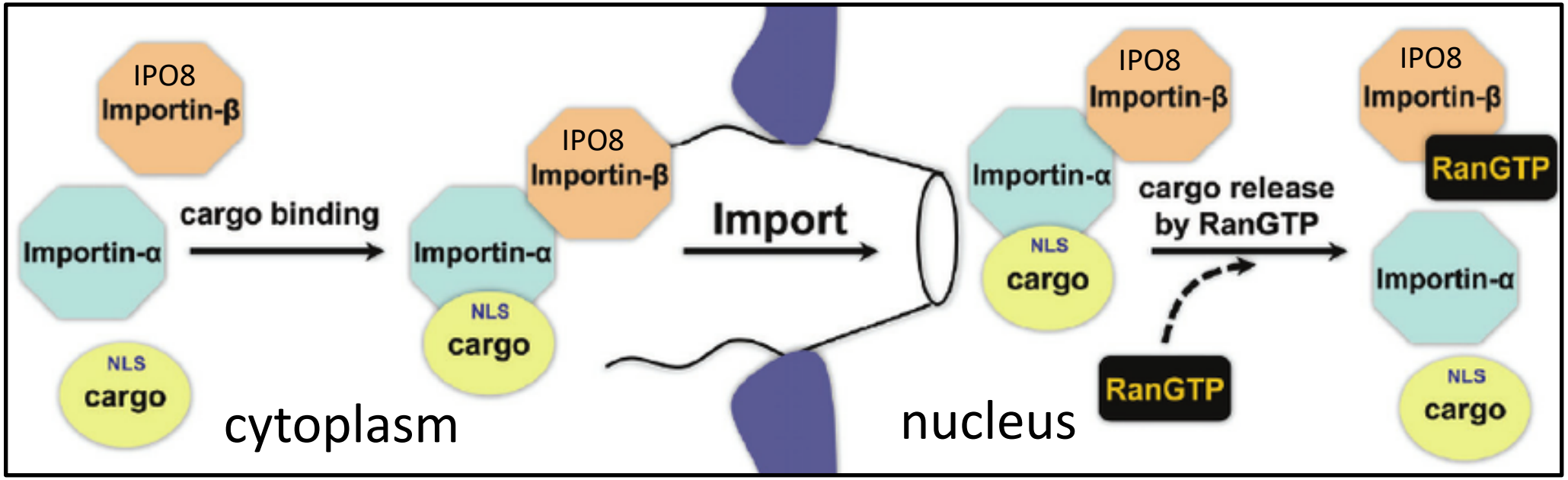


Van Gucht et al, AJHG, 2021

IPO8 (Importin-8)

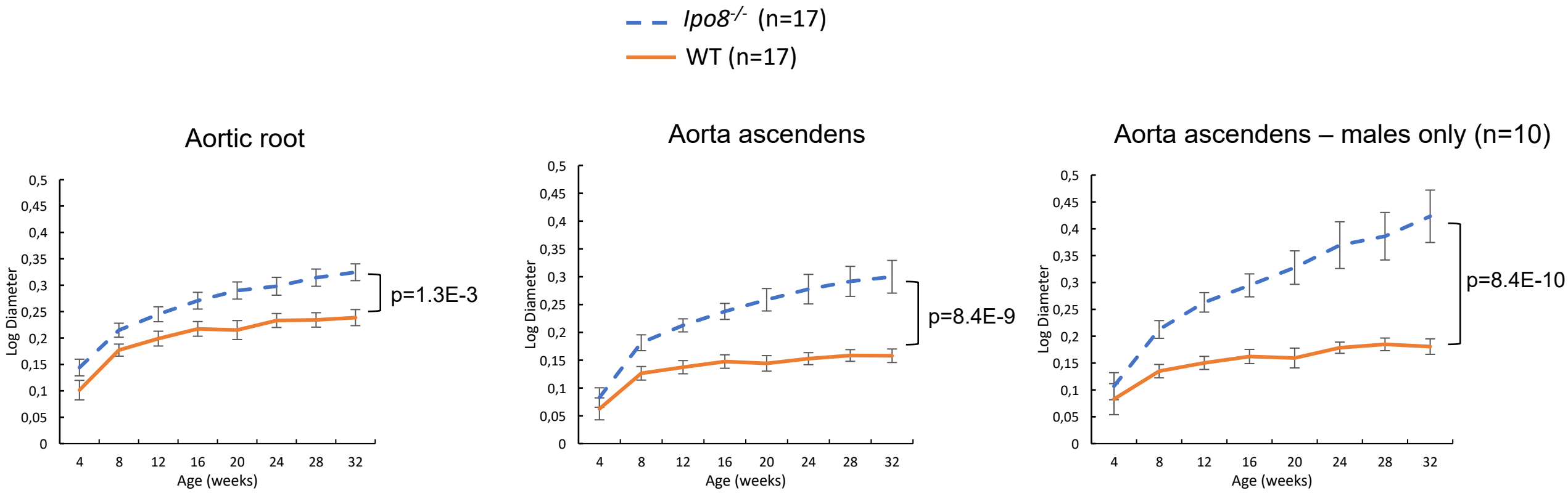


- Ubiquitously expressed; belongs to beta-importin family
- No IPO mutations linked to disease



- Possible cargo: mature miRNAs on AGO2, pSMAD3-SMAD4, possible ERK and c-Jun

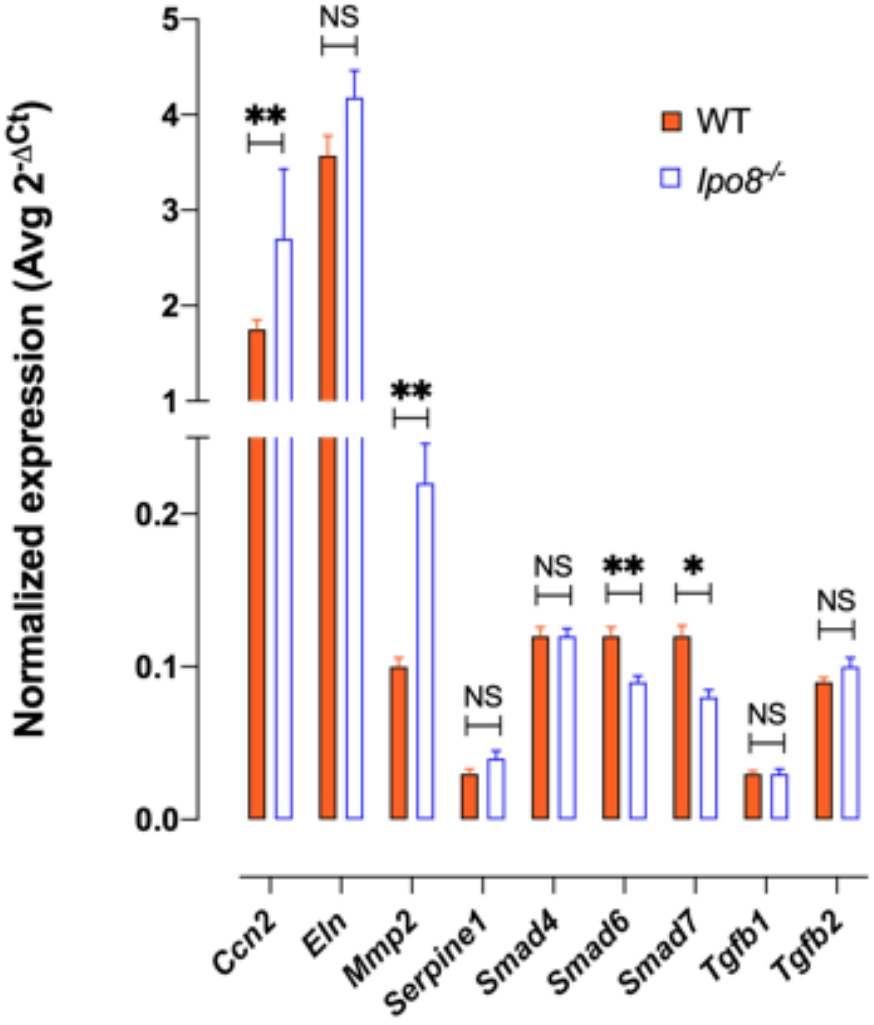
Echocardiography *Ipo8*$^{-/-}$ mice



Three homozygous mutant males (3/9, 33.3%) died from aortic rupture at the age of 32, 36, and 46 weeks

Van Gucht et al, AJHG, 2021

RT qPCR for TGFβ superfamily-related genes

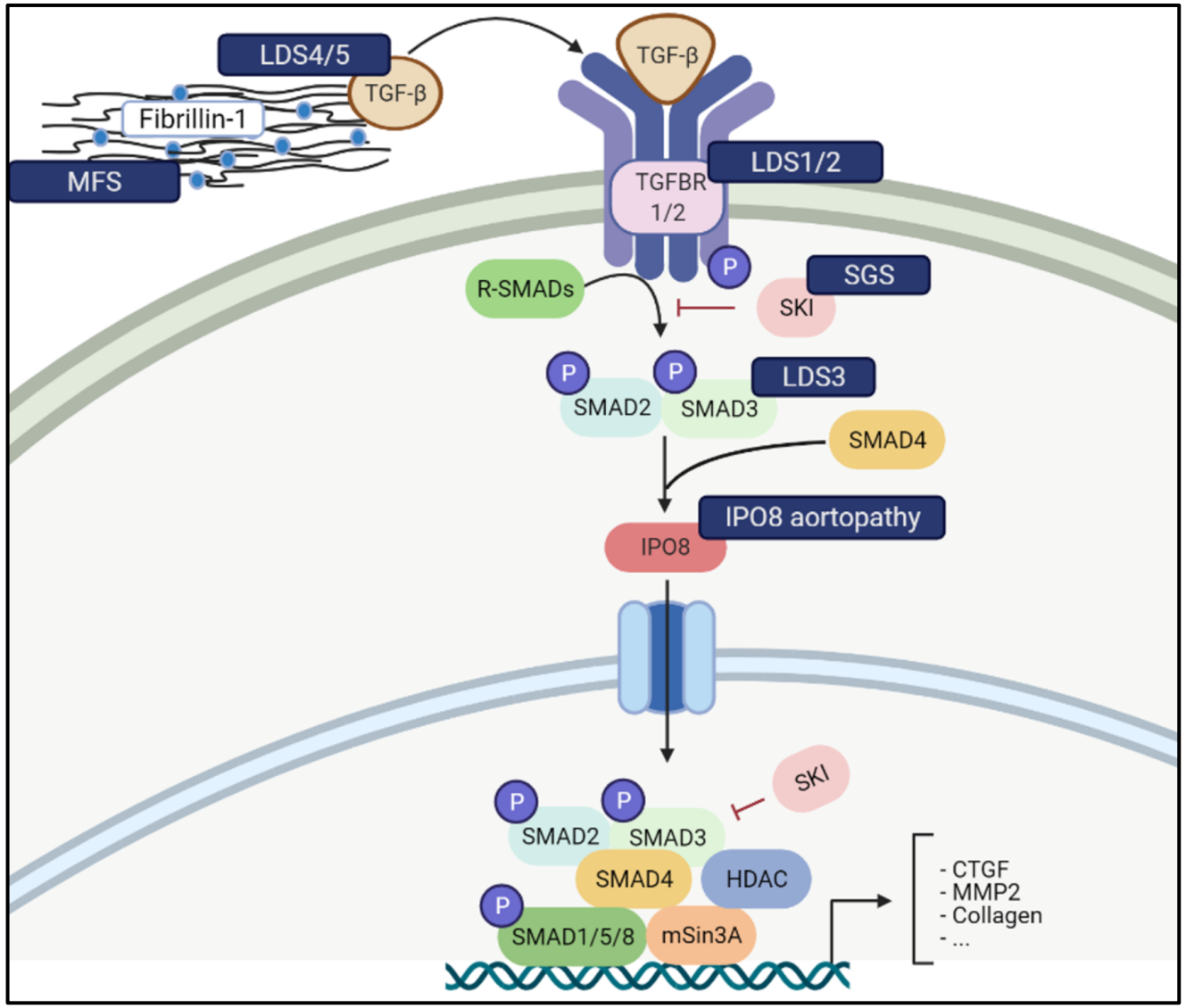


Downregulation of *Smad6/7*, so decreased inhibition of BMP/TGFβ signaling

Upregulation of *Ccn2 (Ctgf)* and *Mmp2*, prototypical downstream TGFβ signaling targets

Van Gucht et al, AJHG, 2021

First importin-β disorder: syndromic TAA caused by bi-allelic IPO8 loss-of-function variants



Phenotypical resemblance to Loeys-Dietz syndrome with early onset TAA

Ipo8$^{-/-}$ mouse model recapitulates human phenotype

Immunohistochemistry and RT-qPCR studies of murine *Ipo8*$^{-/-}$ aortic tissue reveal pathophysiological mechanisms that have previously been described in clinically overlapping TGFβ-related signalopathies

Downstream position of IPO8 offers unique target for therapeutic intervention

Van Gucht et al, AJHG, 2021

Published in final edited form as:

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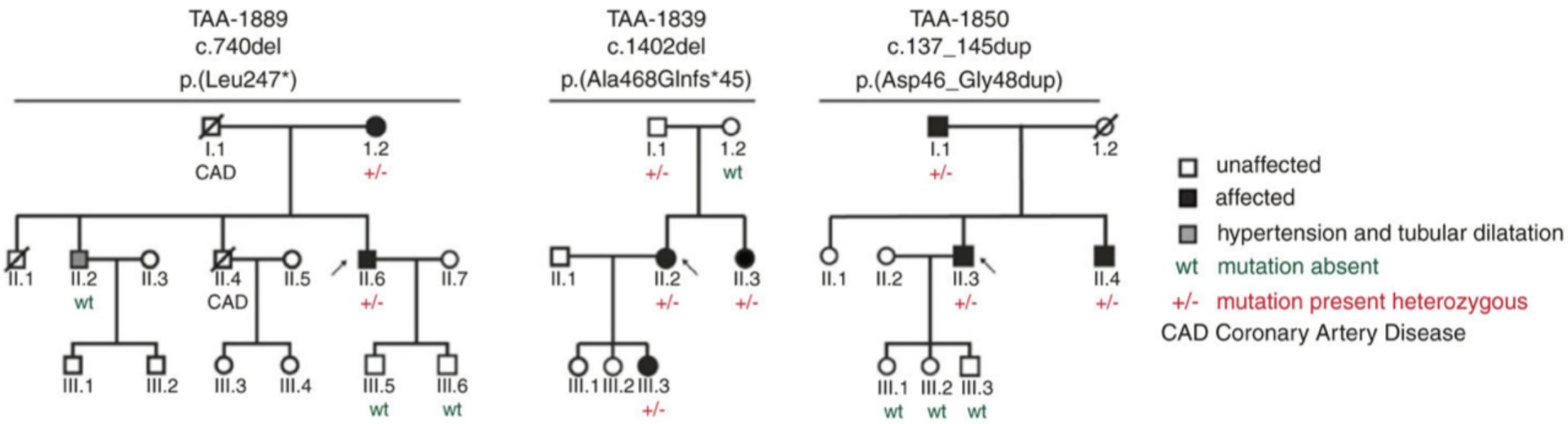
Pathogenic variants in *THSD4*, encoding the ADAMTS-like 6 protein, predispose to inherited thoracic aortic aneurysm

Sandy Elbitar, PharmD, PhD[1,2], Marjolijn Renard, PhD[3], Pauline Arnaud, PharmD, PhD[1,4,5], Nadine Hanna, PharmD, PhD[1,4,5], Marie-Paule Jacob, PhD[1], Dong-Chuan Guo, PhD[6], Ko Tsutsui, PhD[7], Marie-Sylvie Gross, MS[1], Ketty Kessler, PhD[8], Laurent Tosolini, MS[1], Vincenzo Dattilo, PhD[9], Sebastien Dupont, PhD[1], Jeremie Jonquet, MS[1], Maud Langeois, MS[5], Louise Benarroch, PhD[1,10], Melodie Aubart, MD, PhD[1,11], Youmna Ghaleb, PharmD, PhD[1,2], Yara Abou Khalil, PharmD[1,2], Mathilde Varret, PhD[1], Petra El Khoury, PharmD, PhD[1,2], Benoit Ho-Tin-Noé, PhD[1], Yves Alembik, MD[12], Sébastien Gaertner, MD[13], Bertrand Isidor, MD[14], Laurent Gouya, MD, PhD[5], Olivier Milleron, MD[5], Kiyotoshi Sekiguchi, PhD[7], Dianna Milewicz, MD, PhD[6], Julie De Backer, MD, PhD[3], Carine Le Goff, PhD[1], Jean-Baptiste Michel, MD, PhD[1], Guillaume Jondeau, MD, PhD[1,5], Lynn Y. Sakai, PhD[15], Catherine Boileau, PharmD, PhD[1,4,5], Marianne Abifadel, PharmD, PhD[1,2]

Sequencing of TAAD probands (n=1150)



II:6 age 43 -Type A aortic dissection
I:2 age 75 - asc ao replacement

II:2 age 48 - root 42mm (Z=3,2);
Asc 47 mm (Z=4,7)
I:1 age 80 - Ao ?
II:3 age 45 - root/asc – Z=0,9/2.3
III:3 age 16 - root/asc – Z=0,7/3.0

II:3 age 39 MI – Ao root 48mm (Z=4)/asc 35mm(Z=1.6)
I:4 age 44 aortic dissection
I:1 age 68 aortic surgery for ascending and abdominal Ao

Midlife aortic aneurysm and dissection

Family/variation p. notation/ variation c. notation	Patient	Sex	Variation status	Age at diagnosis/ height/weight	Aortic status	Other vascular manifestations	Other clinical manifestations
Family 1: TAA-1889 p.(Leu247*) c.740del	Proband II.6	M	+/ –	43 years/1m86/115 kg	Type A aortic dissection; aortic diameter prior to dissection NA	None	Mild pectus excavatum, dolichostenomelia, high-arched palate
	Brother II.4	M	NA	Died at 53 years/ 1m85/NA	Aortic diameter NA	None but CAD	NA
	Mother I.2	F	+/ –	75 years/NA/NA	Ascending aortic replacement; aortic diameter NA	None	COPD, lymphoma, arthritis
	Son III.5	M	– / –	24 years/NA/NA	No aortic dilatation	None	None
	Son III.6	M	– / –	25 years/NA/NA	No aortic dilatation	None	None
	Brother II.2	M	– / –	61 years/1m83/130 kg	AoR: 45 mm (Z = 1.5 SD); AAo: 46 mm (Z = 2.8 SD) (tubular dilation remained stable during a 3-year period after treatment of high blood pressure)	None	None
Family 2: TAA-1839 p. (Ala468Glnfs*45) c.1402del	Proband II.2	F	+/ –	48 years/1m70/77 kg	AoR: 42 mm (Z = 3.2 SD); AAo: 47 mm (Z = 4.7 SD)	None	Dolichostenomelia, hypertelorism, arthritis
	Daughter III.3	F	+/ –	16 years/1m70/68 kg	AoR: 28 mm (Z = 0.7 SD); AAo: 32 mm (Z = 3.0 SD) mild aortic regurgitation	None found but tortuosity	Scoliosis
	Sister II.3	F	+/ –	46 years/1m80/70 kg	AoR: 33 mm (Z = 0.9 SD); AAo: 36 mm (Z = 2.3 SD)	None	None
	Mother I.2	F	– / –	75 years/NA/NA	AoR: 37 mm	NA	NA
	Father I.1	M	+/ –	80 years/NA/NA	NA	NA	NA
Family 3: TAA-1850 p. (Asp46_Gly48dup) c.137_145dup	Proband II.3	M	+/ –	39 years/1m77/93 kg	AoR: 48 mm (Z = 4.0 SD); AAo: 35 mm (Z = 1.6 SD)	CAD (MI at 39 years)	Hypercholesterolemia, hypertension, active smoker
	Daughter III.1	F	– / –	16 years/1m67/NA	AoR: 30 mm (normal)	None	None
	Daughter III.2	F	– / –	12 years/NA/NA	No aortic dilatation	None	None
	Son III.3	M	– / –	17 years/NA/NA	AoR: 32 mm; AAo: 26 mm (normal)	None	None
	Brother II.4	M	+/ –	44 years/1m82/NA	Aortic dissection at 42 years (dilatation of the AAo present prior to dissection)	NA	NA
	Father I.1	M	+/ –	68 years/1m81/NA	Aortic diameter NA operated for aortic dilatation of AAo and abdominal aorta	NA	NA
Family 4: TAA-1817 p. (Tyr321Asn) c.961T>A	Proband	F	+/ –	64 years/1m67/56 kg	AoR: 44 mm (Z = 3.9 SD); Bentall surgery for aortic regurgitation at 61 years	None	Spontaneous pneumothorax
	Daughter	F	+/ –	25 years/1m78/62 kg	AoR: 30 mm (Z = 0.8 SD); AAo: 29 mm (Z = 1.3 SD)	None	None
Family 5: TAA-1819 p.(Arg781Trp) c.2341C>T rs767807136	Proband	M	+/ –	57 years/NA/NA	AoR: 50 mm (electively replaced) bicuspid aortic valve, hypertension	Raynaud syndrome	None
	Brother	M	– / –	84 years/NA/NA	Aortic diameter NA no clinical manifestation of TAA	None	None

12 mutation carriers:

Other vascular findings:

CAD 1X (smoker, hyperchol and hypertension !)

Tortuosity 1X

BAV 1X

Other clinical manifestations:

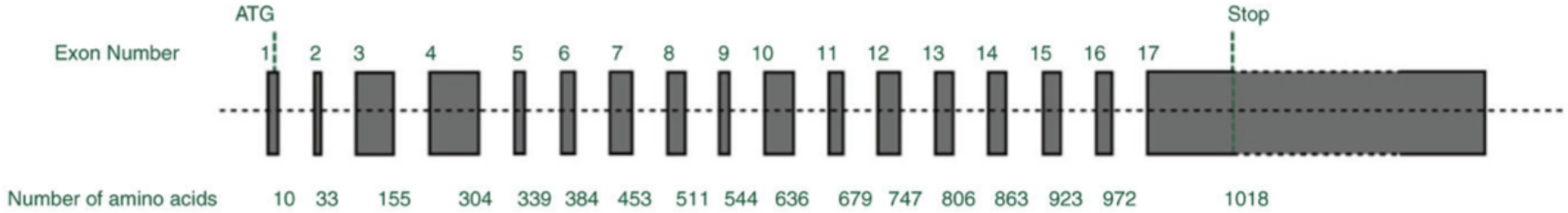
Dolichostenomelia 2X

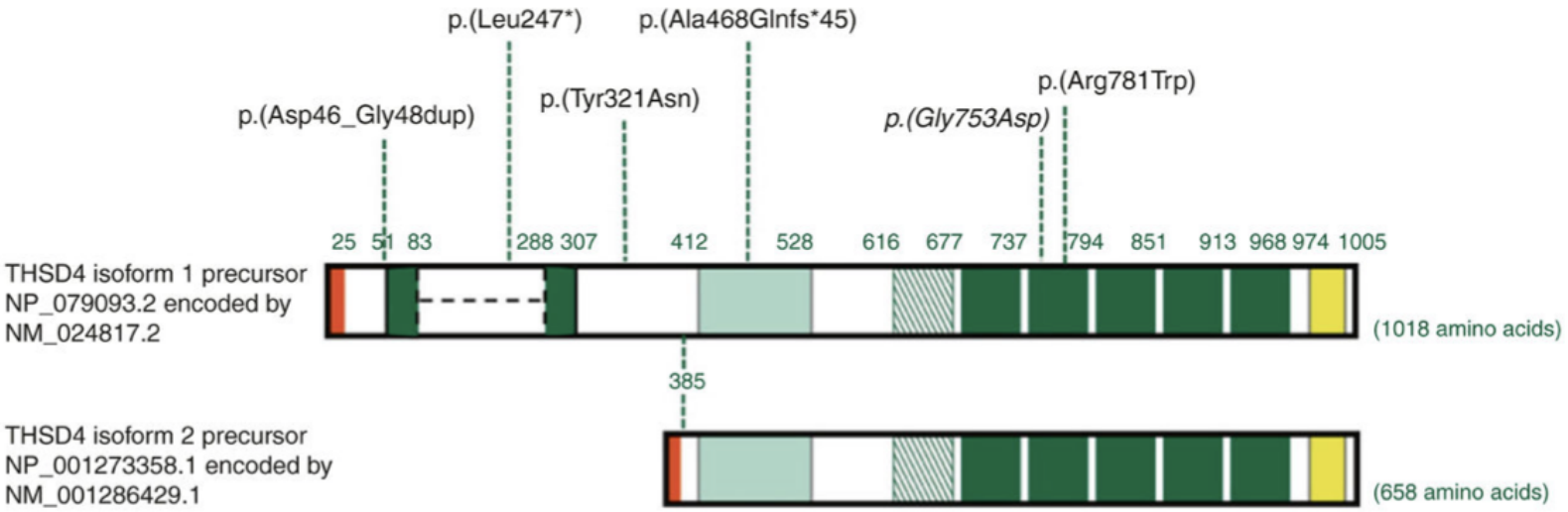
Pectus excavatum 1X

Pneumothorax 1X

Hypertelorism 1X

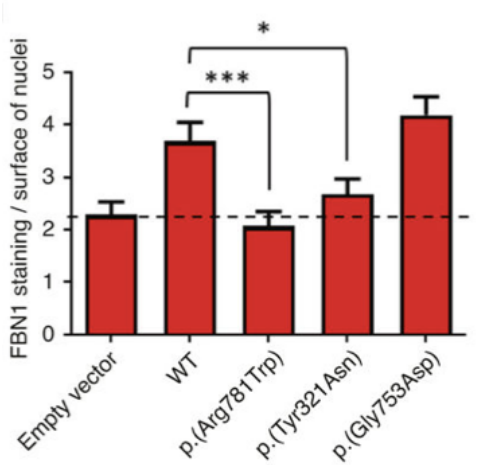
Raynaud 1X



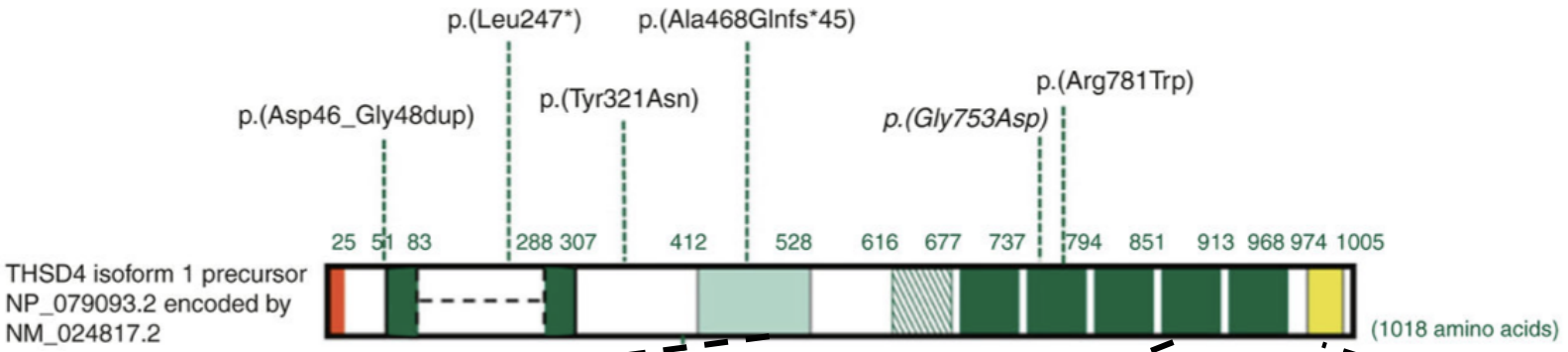


p.Gly753Asp

3 TAAD probands
Also gnomad: 45/125.528
No functional effect on microfibril assembly



THSD4 – Antwerp experience



CADD-scores 24-31
Each 2X in gnomad

p.(Thr483Ile)

+/-

-/-

Borderline aortic root (40 mm)

+/-

32 yrs: type A dissection
49 yrs: arteria lienalis aneurysm surgery

-/-

Normal echocardiography

p.(Gly859Arg)

+/-

53 yrs: David procedure aortic sinus 52 mm

+/-

23 yrs: borderline aortic sinus

Both presented Marfanoid features including mitral valve prolapse, tall stature, scoliosis, arachnodactyly and pes plani.

p.(Asn983Ser)

Early SCD

+/-

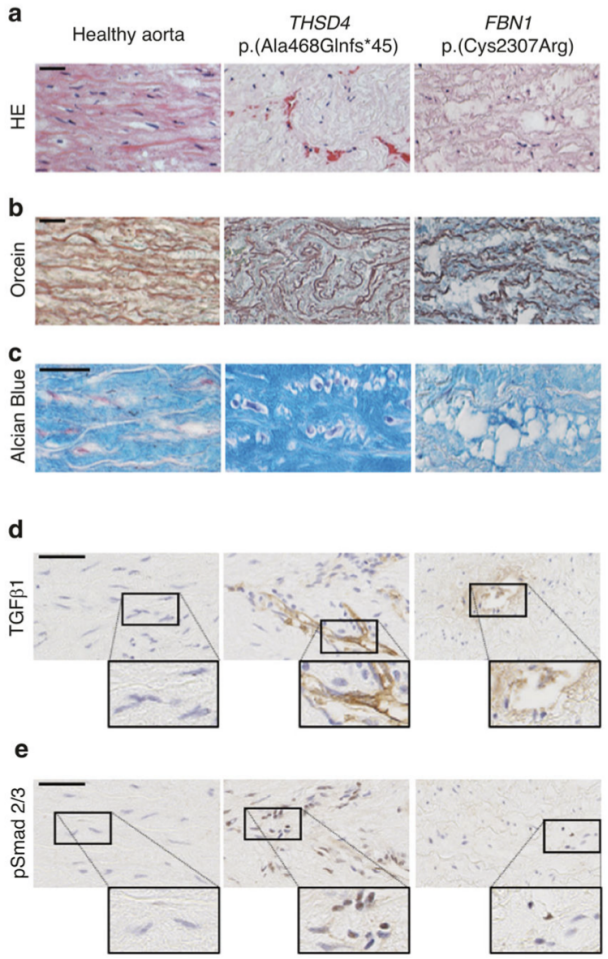
52 yrs: David procedure aortic sinus 48 mm

Aortic aneurysm

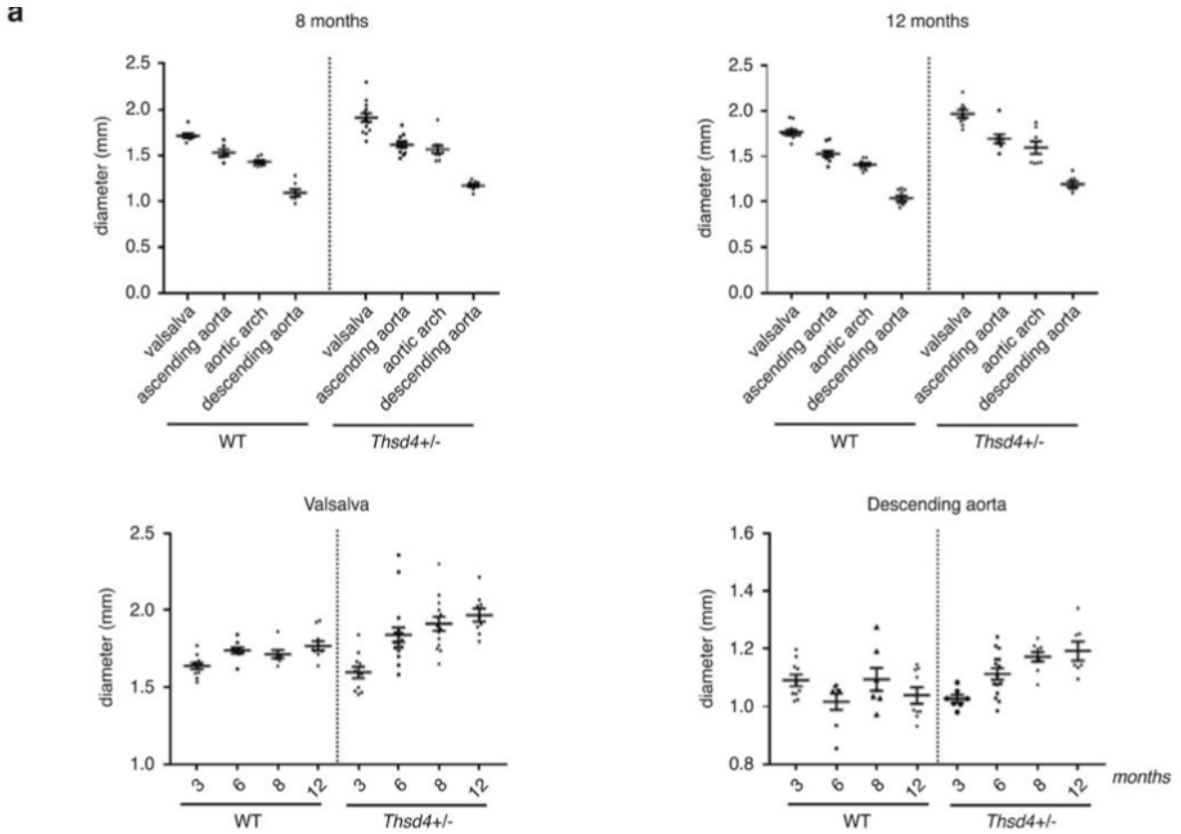
Pathogenesis

THSD4 encodes for ADAMTSL6 that promotes microfibril assembly and involved in TGF-beta signaling

Human aorta

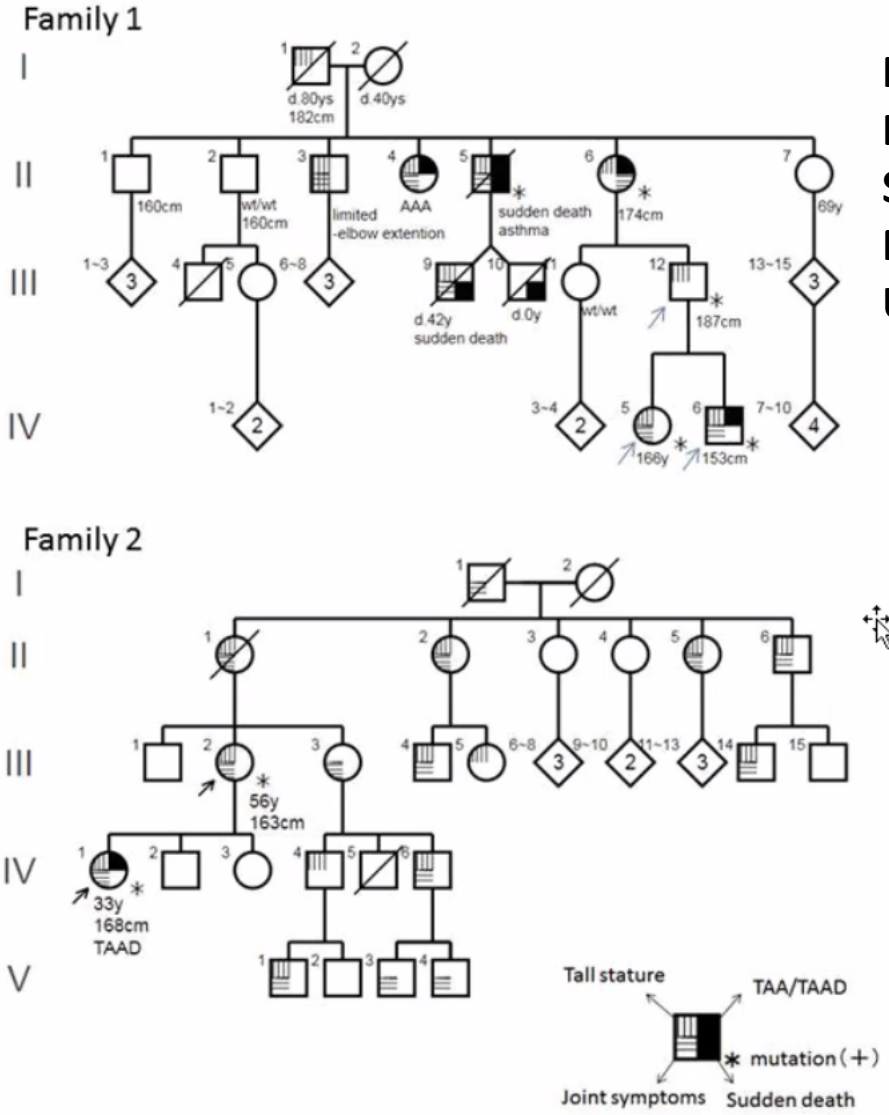


Thsd4$^{+/-}$ mouse

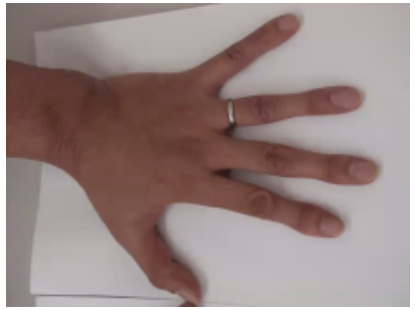


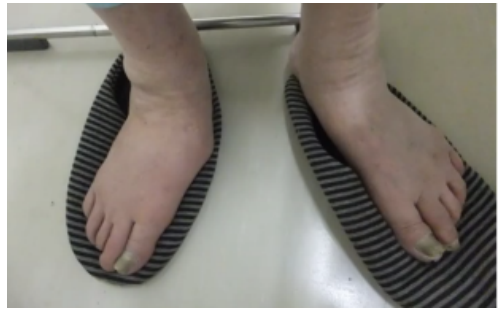
TMEPAI/PMEPA1

- First reported at the international MFS meeting in Amsterdam in 2019

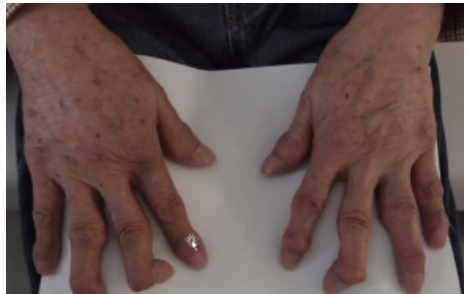


Proband: tall stature, joint hypermobility, pectus ex
Daughter: armspan, scoliosis,joint hypermobility, pectus exc, mitral valve prolaps
Son: armspan, joint hypermobility, arachnodactyly, aorta sinus (Z=2.3 – 11yrs)
Mother: osteo-arthritis knee (35 & 46 yrs), abdominal aneurysm surgery (73yrs)
Uncle: joint contractures and sudden cardiac death



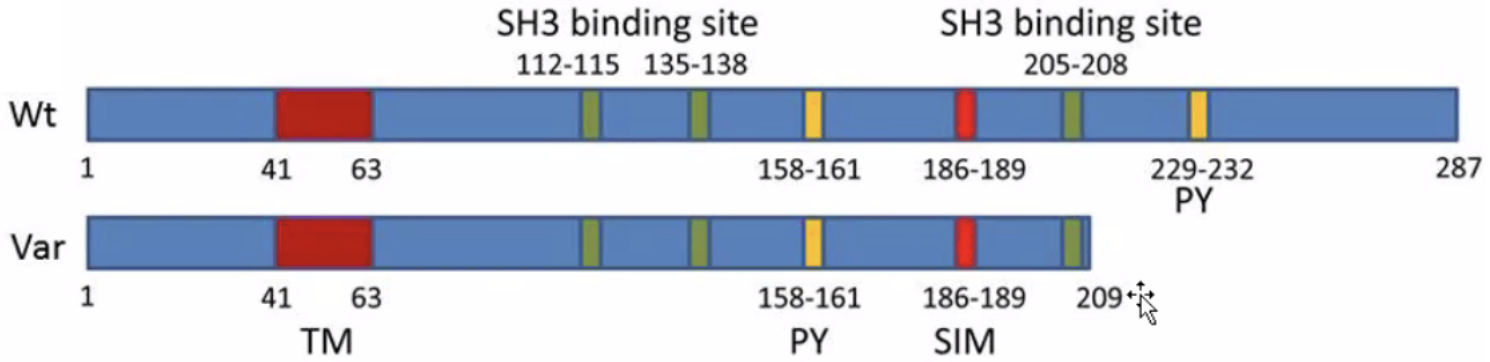


Proband: armspan, arachnodactyly, joint contractures, type B diss (33 yrs)
Mother: joint contractures, no aortic aneurysm (56 yrs)

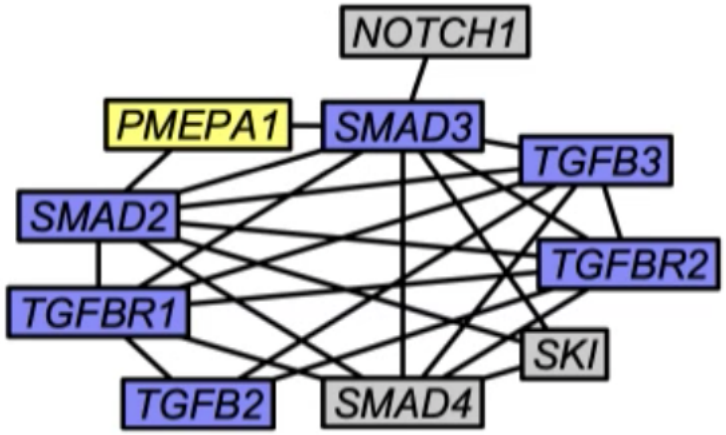


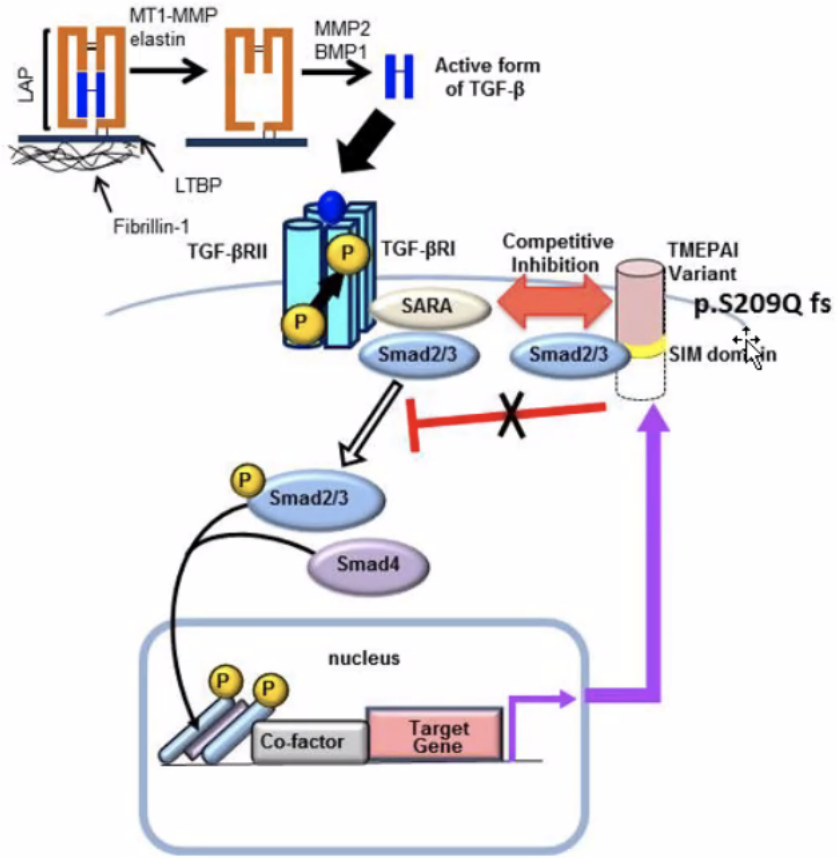
Morisaki H & Morisaki T et al, 2019

Prostate Transmembrane Protein, Androgen Induced 1 (PMEPA1)



p.Ser209Glnfs*3

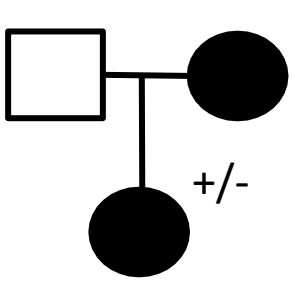




PMEPA1 regulates TGFbeta signalling

Antwerp experience

p.Pro207Glnfs*3

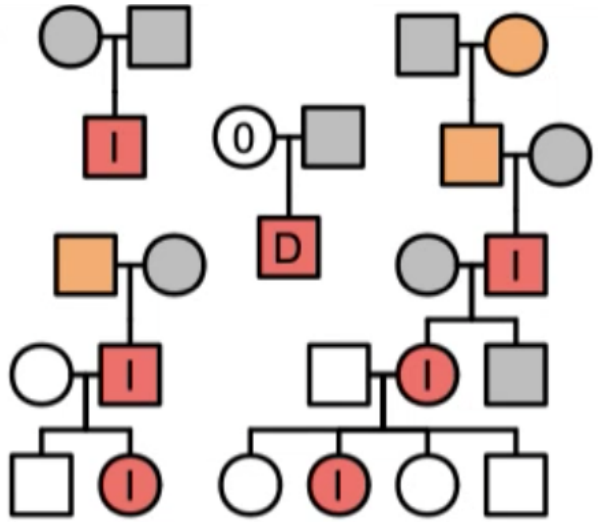


Myopia
Mitral valve prolapse
Joint hypermobility

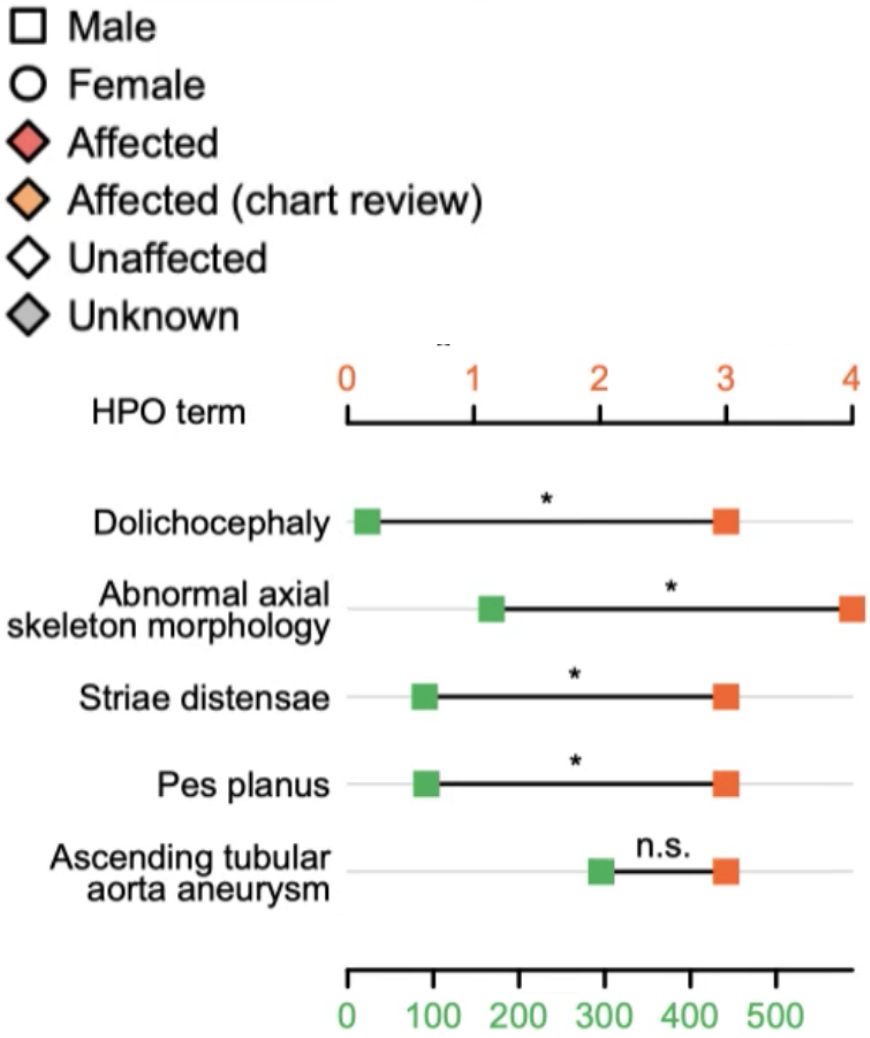
Arachnodactyly
Pectus deformity
Scoliosis
Pes planum
Atrial Septum defect
Pulmonary artery dilation
Ao root z-score=0,09

Courtesy of Julie Harvengt, Liege

UK experience



p.Ser209Glnfs*3
p.Ser209Alafs*61



Courtesy of Andre Mumford, Bristol

All truncating variants in last exon, caused by del or ins or cytosine in a stretch of 7 cytosines

Conclusions

- First recessive LDS gene and two novel aneurysm genes with connective tissue findings
- Newly discovered genes explain only small proportions of TAA patients
- Three new geneitc players: all have links to TGFbeta signalling

Thank you !

Antwerp cardiogenomics team