

# Can gene variants help in risk prediction?

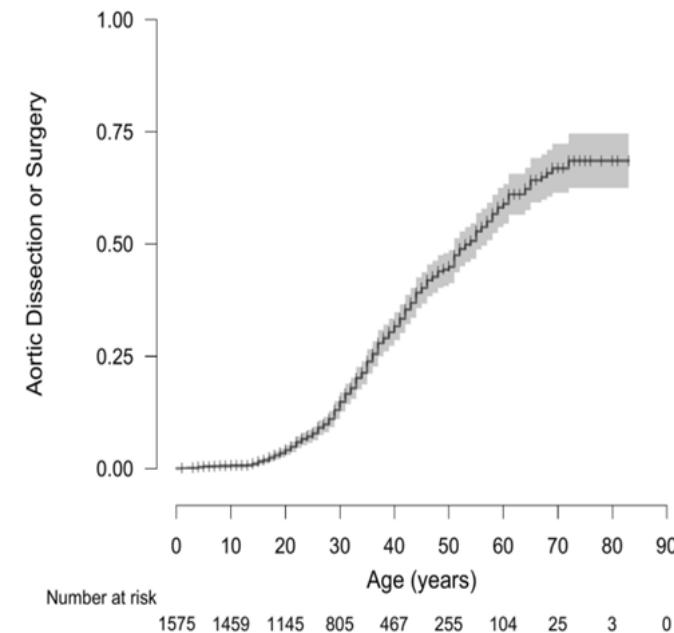
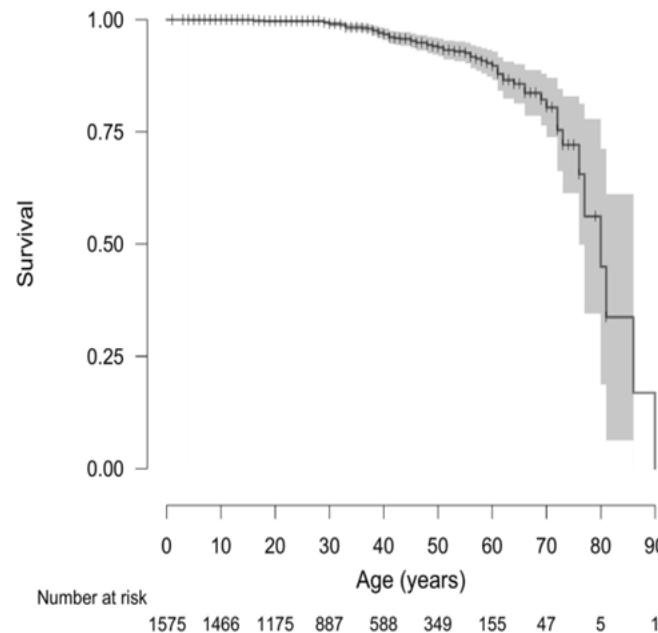
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# Methods



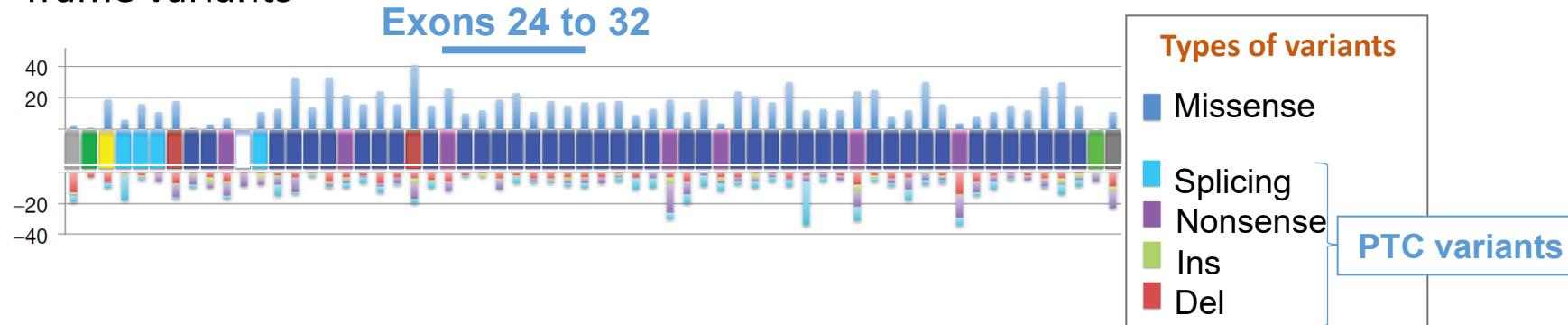
- 1575 patients, **probands and relatives**
  - Multidisciplinary follow-up in CRMR « MFS and related diseases », Bichat hospital
  - Molecular analysis: pathogenic variants in the *FBN1* gene
- Variant categorization
  - **In-frame** = missense, small in-frame insertions/deletions
  - **PTC** = nonsense, out-of-frame insertions/deletions, splice site variations, exon(s) deletions/duplications

# All FBN1 pathogenic variants

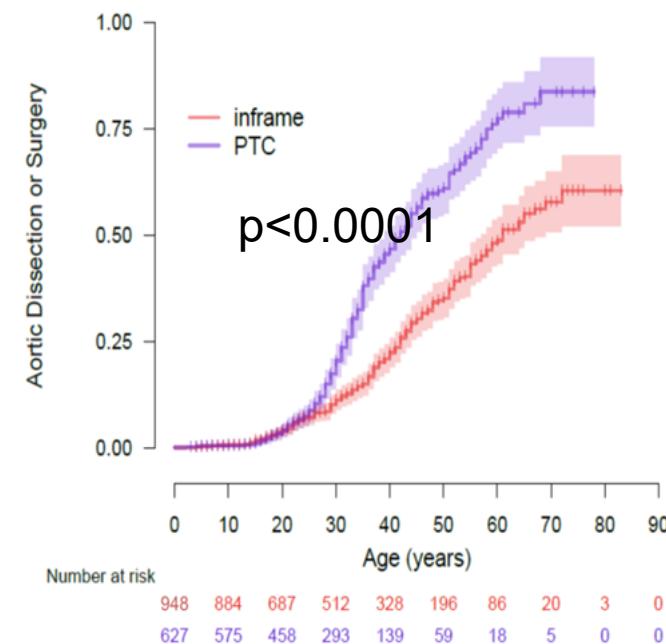
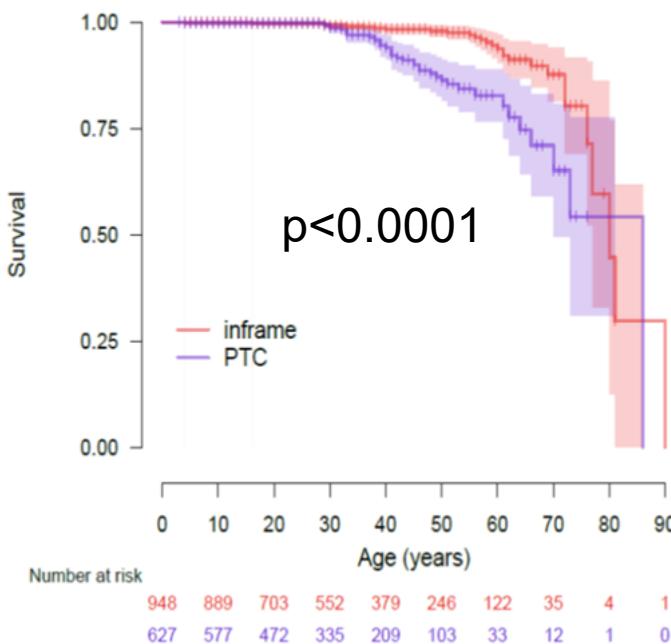


# Genotype-phenotype correlations

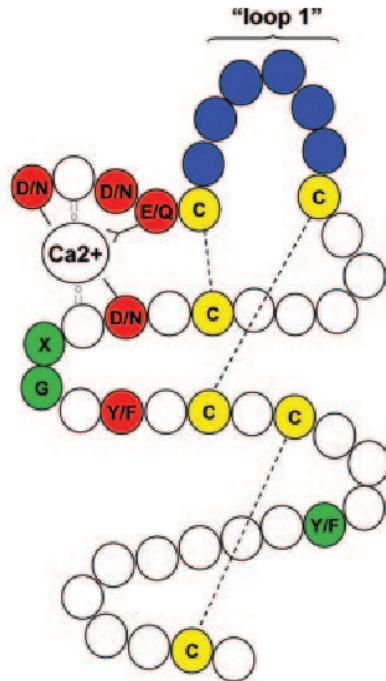
- Pathogenic variants within the **neonatal region** (exons 24 to 32) → more severe phenotypes including neonatal MFS
- In-frame variants changing the **cysteine content** in fibrillin-1 associated with more **ophtalmological** manifestations
- **PTC variants** associated to **more severe cardiovascular phenotypes** than in-frame variants



# PTC vs Inframe

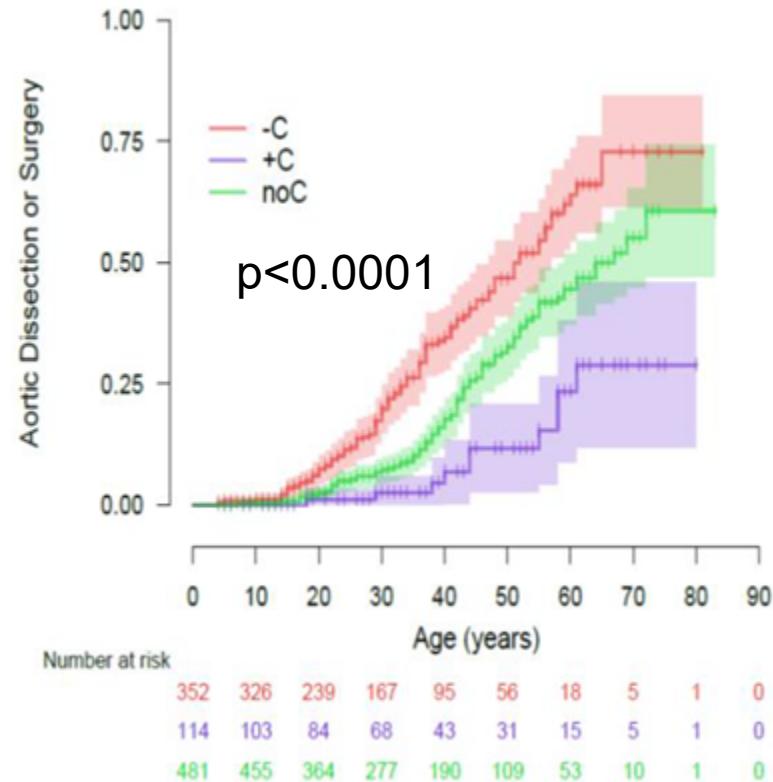
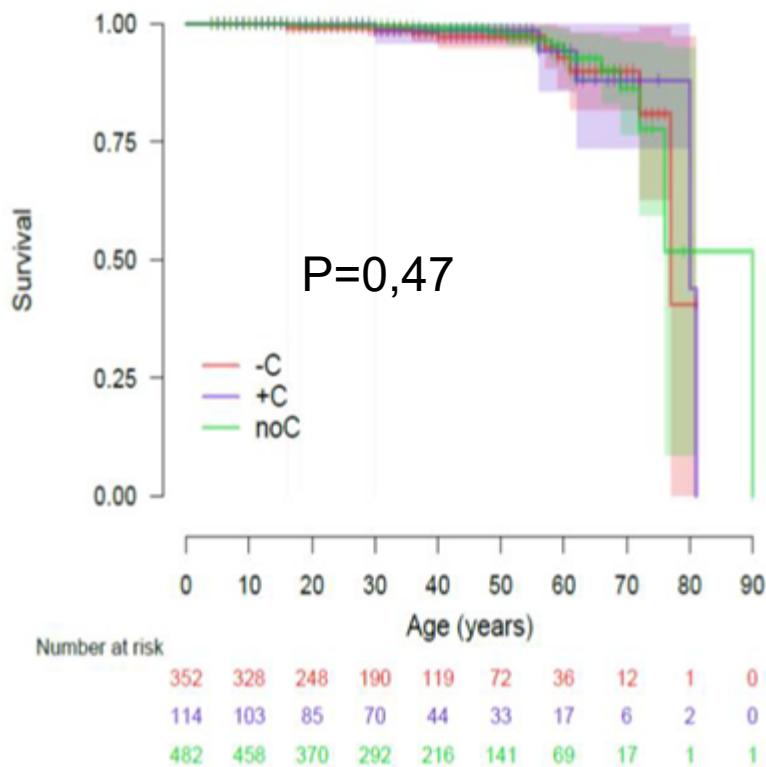


# Results

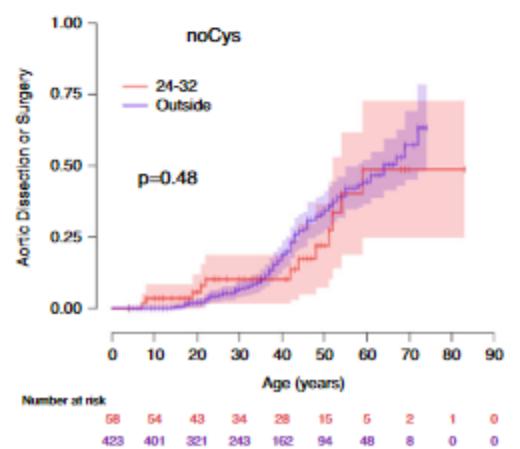
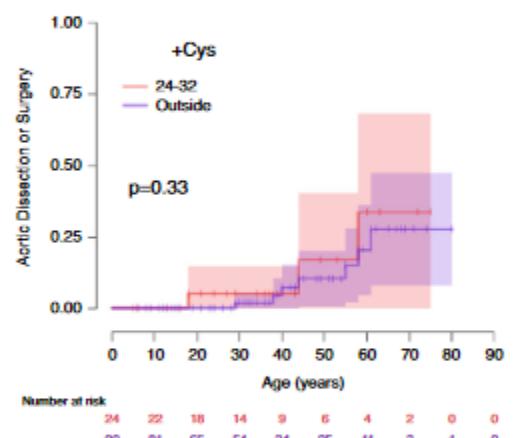
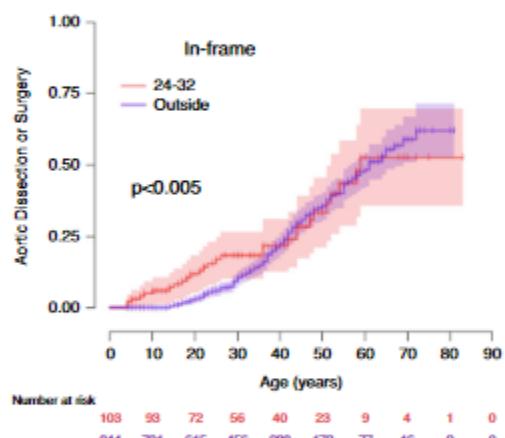
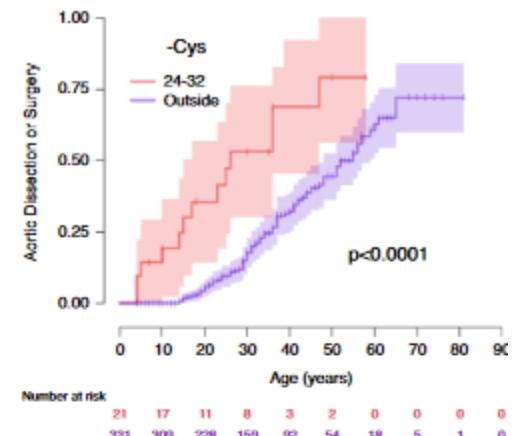
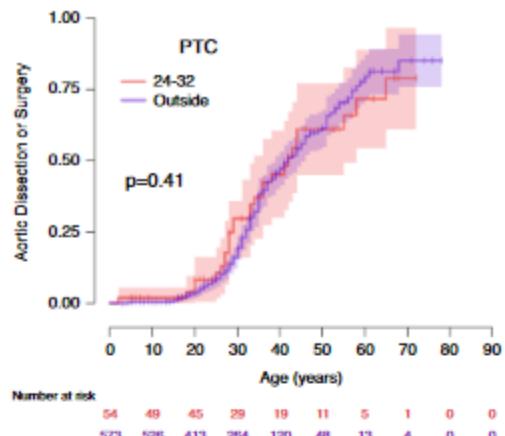


- Pathogenic in-frame variants (*disulfide bond*)
  - « -Cys » variants → very severe phenotype (CV, ophth. and SK)
  - « +Cys » variants → fewer aortic events and globally less severe forms, except for ophthalmological features
  - « noCys » variants → intermediate aortic risk, less EL surgery

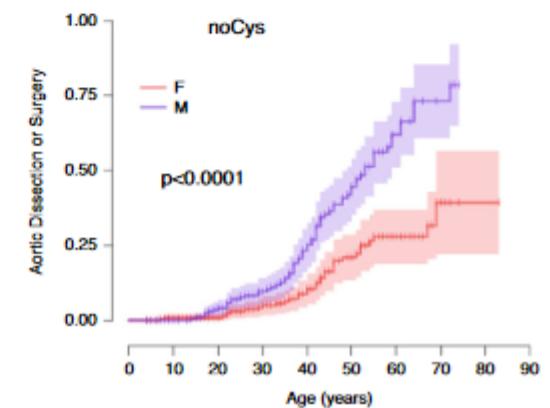
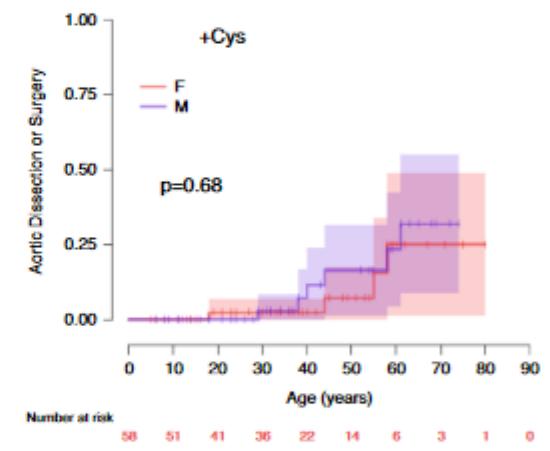
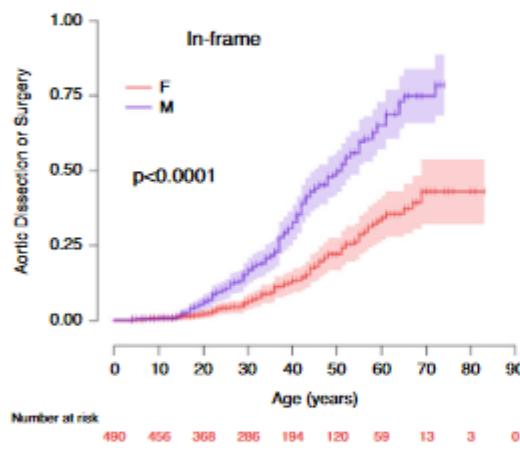
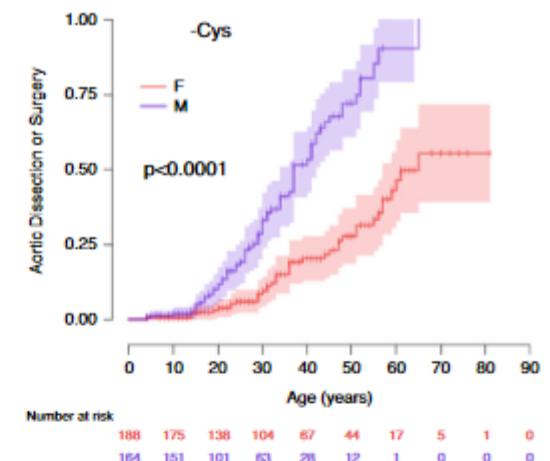
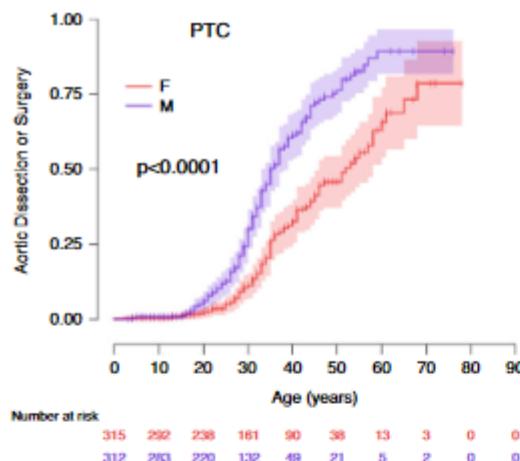
# Inframe



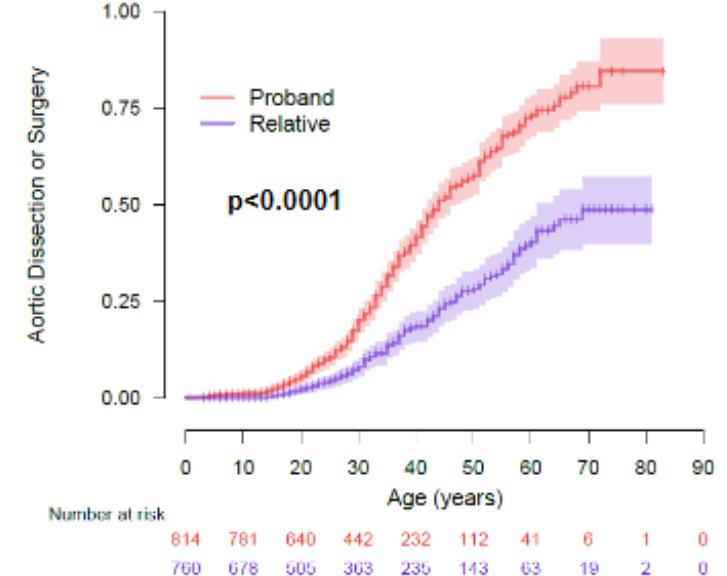
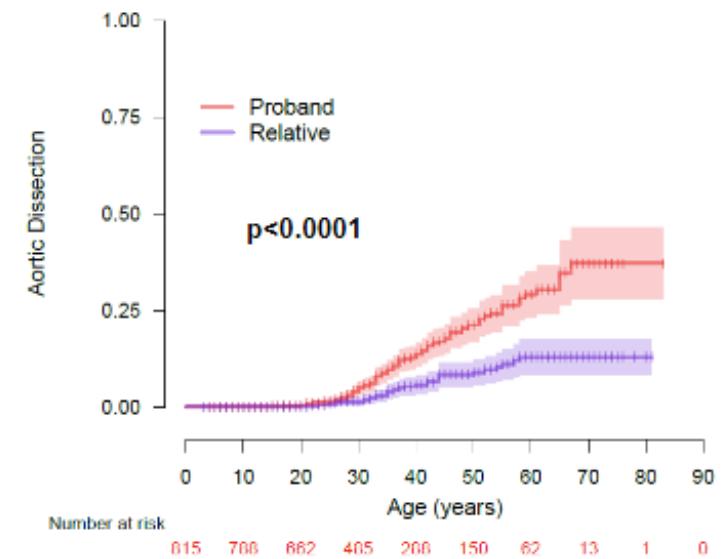
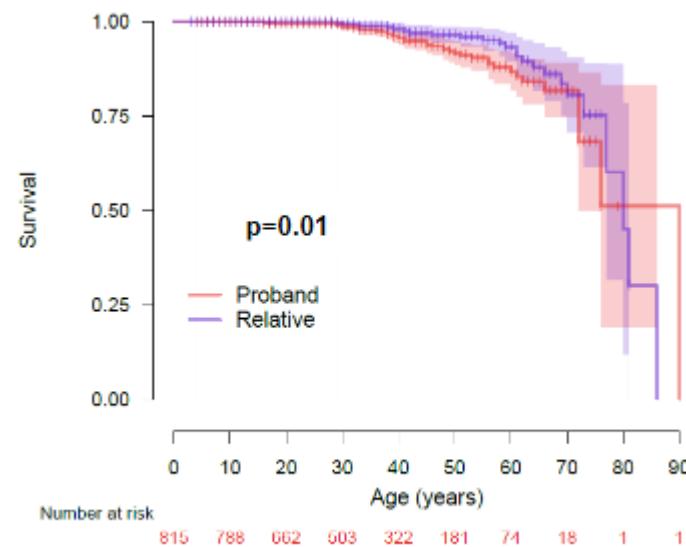
24-32



# Males more severe



# Probands more severe



FBN1

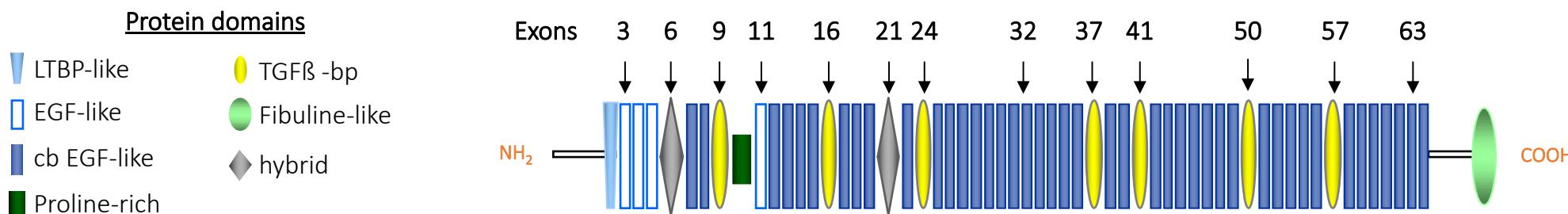
# Conclusion

- YES: variant gives indication on the aortic risk
  - Among other factors
- Translation in aortic root surgery prophylaxis diameter modification ?
  - No: Needs aortic risk as a function of aortic diameter...
  - More/less aggressive ?

**FBN1**

Characteristic	Domain Affected			
	cbEGF-like	Hybrid	TB	EGF-like
<i>N (%)</i>	663 (70)	99 (10)	98 (10)	47 (6)
<i>Age yr, mean (SD)</i>	34.7 (18.0)	34.3 (18.3)	37.1 (20.1)	32.7 (18.0)
<i>Males, N (%)</i>	315 (48)	50 (50)	48 (49)	23 (49)
<i>Familial, N (%)</i>	463 (70)	83 (83)	72 (73)	32 (68)
<i>Proband, N (%)</i>	338 (51)	33 (33)	48 (49)	24 (51)
<i>Cardiovascular</i>				
Aortic root diameter, mean (SD)	37.6 (6.6)	36.2 (6.7)	37.1 (6.6)	35.7 (7.3)
Aortic dissection, N (%)	48 (7)	9 (9)	3 (3)	3 (6)
Preventive aortic surgery, N (%)	122 (18)	15 (15)	15 (15)	4 (9)
Mitral valve surgery, N (%)	42 (6)	6 (6)	2 (2)	1 (2)

EGF-like, epidermal growth factor-like domains; cbEGF-like, calcium-binding EGF like domains; TB, transforming growth factor-protein-like domains.



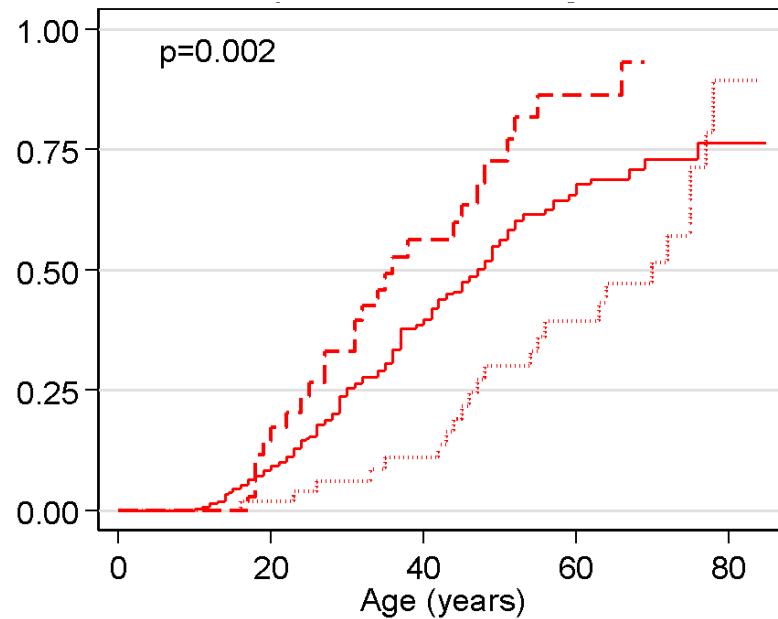
# Clinical features in patients with vs. without dissection



	No aortic dissection	Aortic dissection	
<b>N</b>	311	92 (69 type A)	
<b>Females (%)</b>	173 (56%)	46 (50%)	0.28
<b>Age at diagnosis</b>	31 (20)	41 (17)	<0.001
<b>Death (%)</b>	13 (4.2%)	27 (30%)	<0.001
<b>Clinical features</b>			
<b>Tortuosite Ao (%)</b>	34/189 (18)	23/67 (34)	0.01
<b>Tortuo.vert.carot (%)</b>	82/174 (47)	35/49 (71)	0.003
<b>Hypertel (%)</b>	58/244 (24)	28/64 (44)	0.003
<b>Bifid or broad uvula (%)</b>	65/2628 (25)	27/69 (39)	0.02
<b>Arched palate</b>	110/263 (42)	29/72 (40)	0.9
<b>Wide scars (%)</b>	61/263 (23)	32/69 (46)	<0.001
<b>Translucent skin (%)</b>	98/273 (36)	32/69 (46)	0.1
<b>Craniosynostosis</b>	19/207 (9)	7/70 (10)	0.8
<b>Systemic score</b>	4.0 (3.1)	4.4 (3.4)	0.3
<b>&gt;=7</b>	46/237 (19)	14/62 (23)	0.6
<b>ExtraAo. Arterial event (%)</b>	22/299 (7)	14/88 (16)	0.02

# Genes

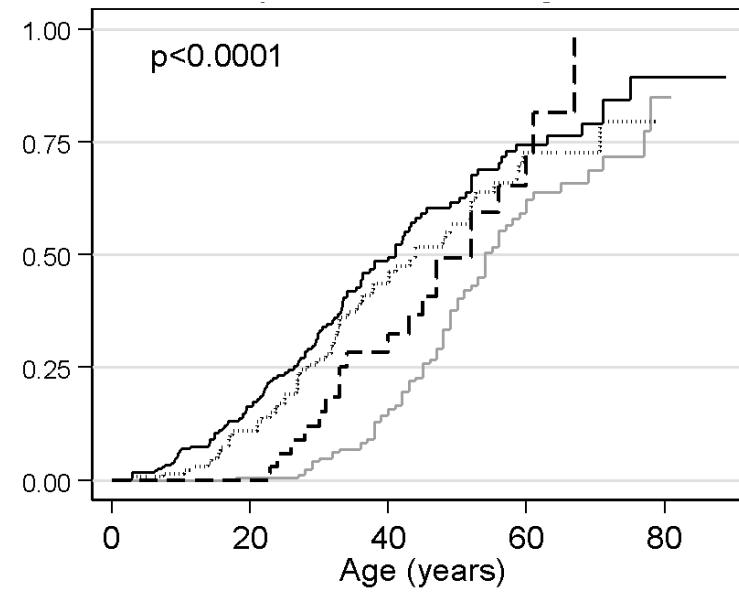
SMC genes



Number at risk					
ACTA2	306	231	127	31	4
MYLK	55	51	34	17	1
PRKG1	37	30	12	2	0

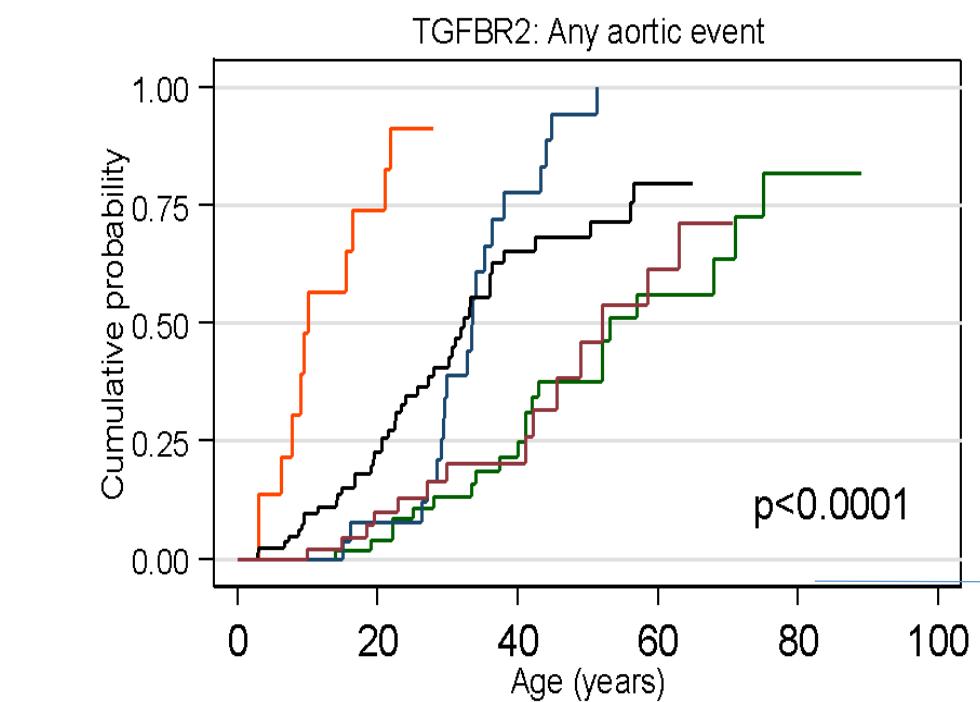
— ACTA2 ······ MYLK - - - PRKG1

TGFB genes



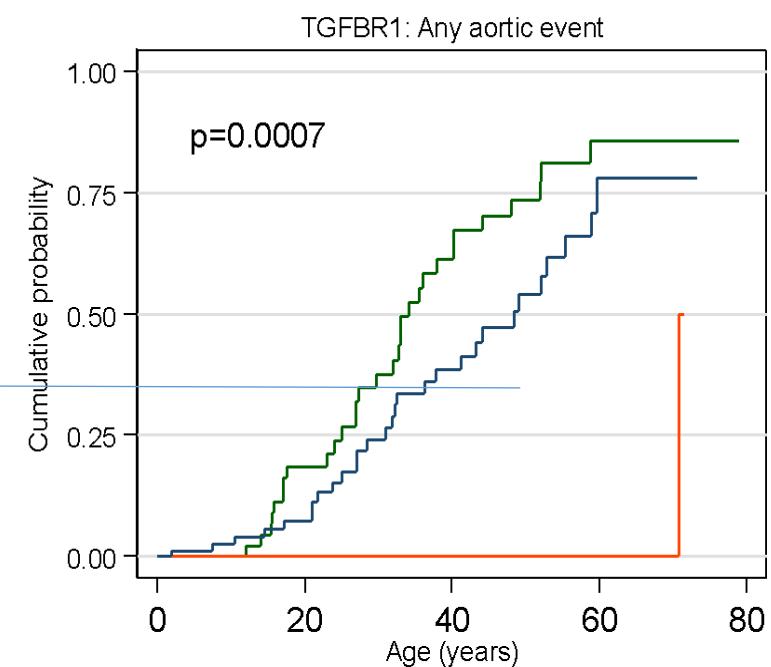
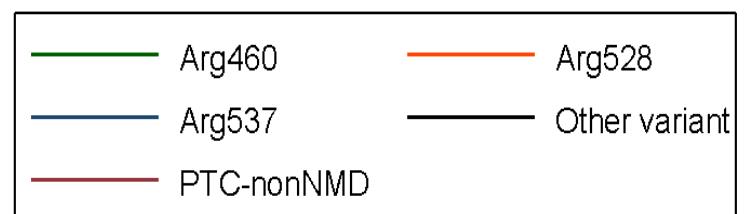
Number at risk					
SMAD3	211	182	113	28	1
TGFB2	42	34	18	5	0
TGFBR1	141	92	44	11	0
TGFBR2	236	151	55	14	2

— SMAD3 - - - TGFBR2 ······ TGFBR1 — TGFBR2



Number at risk

Arg460	57	45	25	7	2	0
Arg528	15	3	0	0	0	0
Arg537	29	22	4	0	0	0
Other variant	85	50	12	3	0	0
PTC-nonNMD	50	31	14	4	0	0



Number at risk

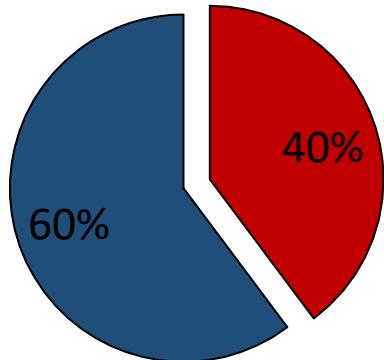
Arg487	46	32	13	3	0
Gly312	14	12	7	5	0
Other variant	81	48	24	3	0



Thank you

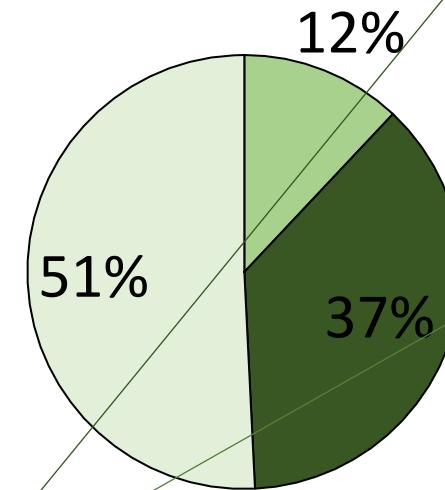
# Population

All (N=1576)  
Aortic event by 40 to 80 yr: 32% to 69%  
F: 20% to 55%, M: 44% to 82%  
EL surgery: 25%  
Scoliosis: 45%



PTC (N=627, 40%)  
Aortic event by 40 to 80 yr: 47% to 83%  
F: 32% to 79%, M: 61% to 89%  
EL surgery: 13%  
Scoliosis: 52%

Cysteine loss (N=353, 22%)  
Aortic event by 40 to 80 yr: 35% to 73%  
F: 20% to 55%, M: 52% to 100%  
EL surgery: 43%  
Scoliosis: 45%



Inframe (N=949, 60%)  
Aortic event by 40 to 80 yr: 23% to 60%  
F: 13% to 43%, M: 33% to 78%  
EL surgery: 33%  
Scoliosis: 41%

No cysteine change: (N=482, 31%)  
Aortic event by 40 to 80 yr: 18% to 61%  
F: 11% to 39%, M: 25% to 79%  
EL surgery: 23%  
Scoliosis: 43%