

MUTATIONS IN PROPROTEIN CONVERTASE FURIN SHOW IMPAIRED TGFB SIGNALING IN ANEURYSM PATIENTS

TOWARDS POLYGENIC HYPOTHESIS FOR ANEURYSM DISEASE

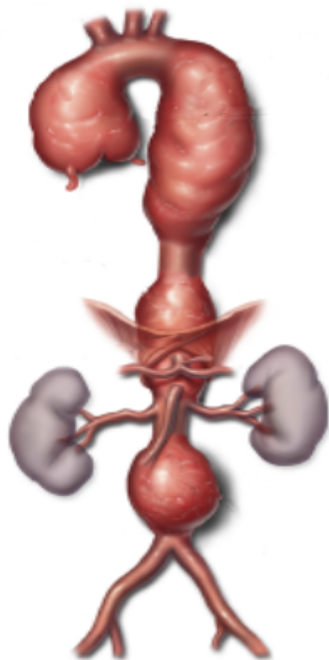
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Comparing abdominal and thoracic aortic aneurysms



**Thoracic
(TAAD)**

1:500 men
1:1500 women

**Abdominal
(AAA)**

1:20 men
1:100 women

Shared characteristics

Asymptomatic

Men > Women

> 60y

Smoking

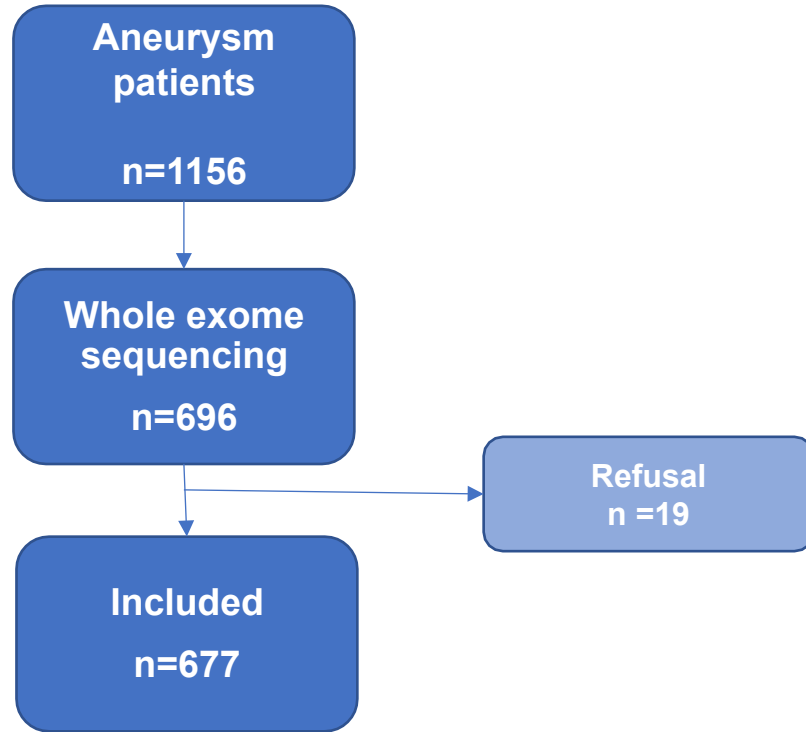
Hypertension

20-30% Familial

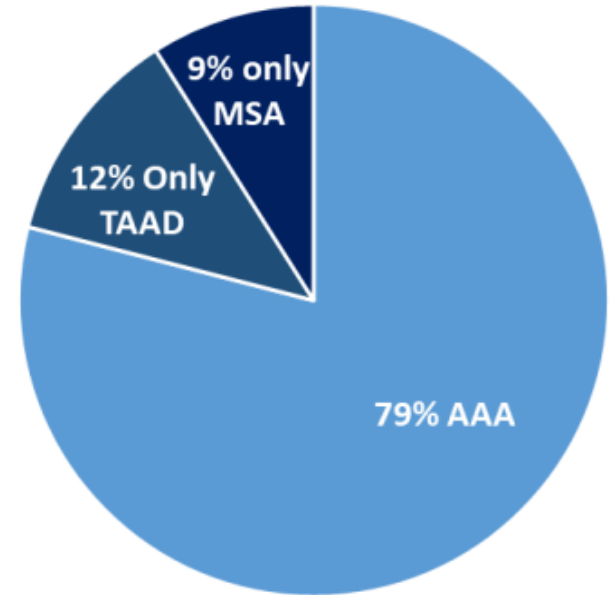
Value of identifying genetic contribution to AAA

- Predict outcome (genotype–phenotype)
- Distinguish which relatives have increased risk
- Direct family screening to relatives with genetic cause

Aneurysm patient cohort in this study

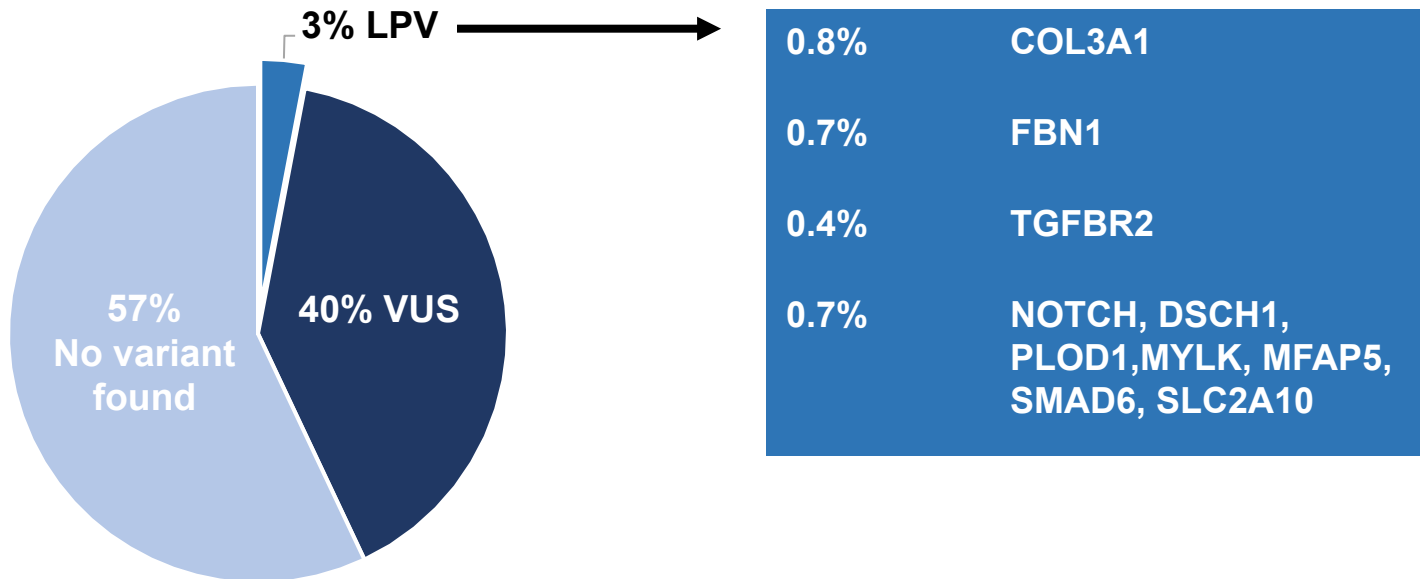


aneurysms in study population



**MSA: medium sized artery aneurysm*

(L)PV in aneurysm genes panel found in 3% of 677 abdominal aneurysm cases



Burden analysis vs candidate gene

- Burden analysis yields only a few significant hits, most known aneurysm genes are not significant
- Candidate gene approach: focus on TGFB signaling related genes
- Identified *FURIN* based on its regulation of TGFB



Proprotein convertase FURIN cleaves inactive precursor to mature protein

Profurin



Furin

Profibrillin



Fibrillin

Procollagen V



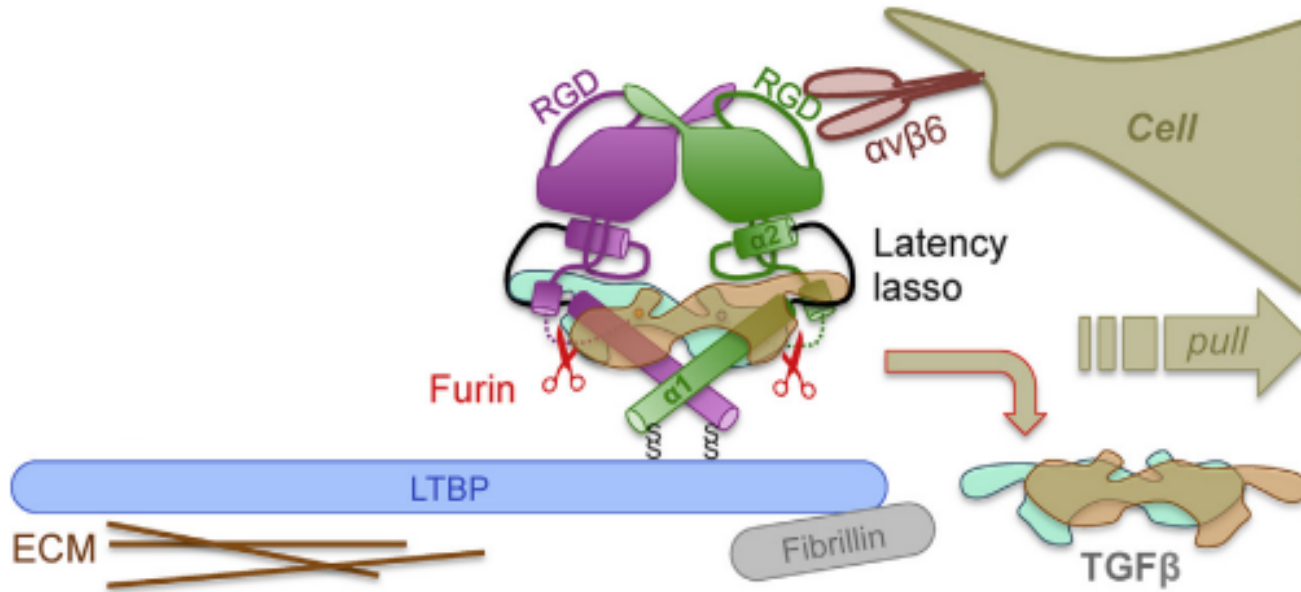
Collagen V

Pro-TGFB



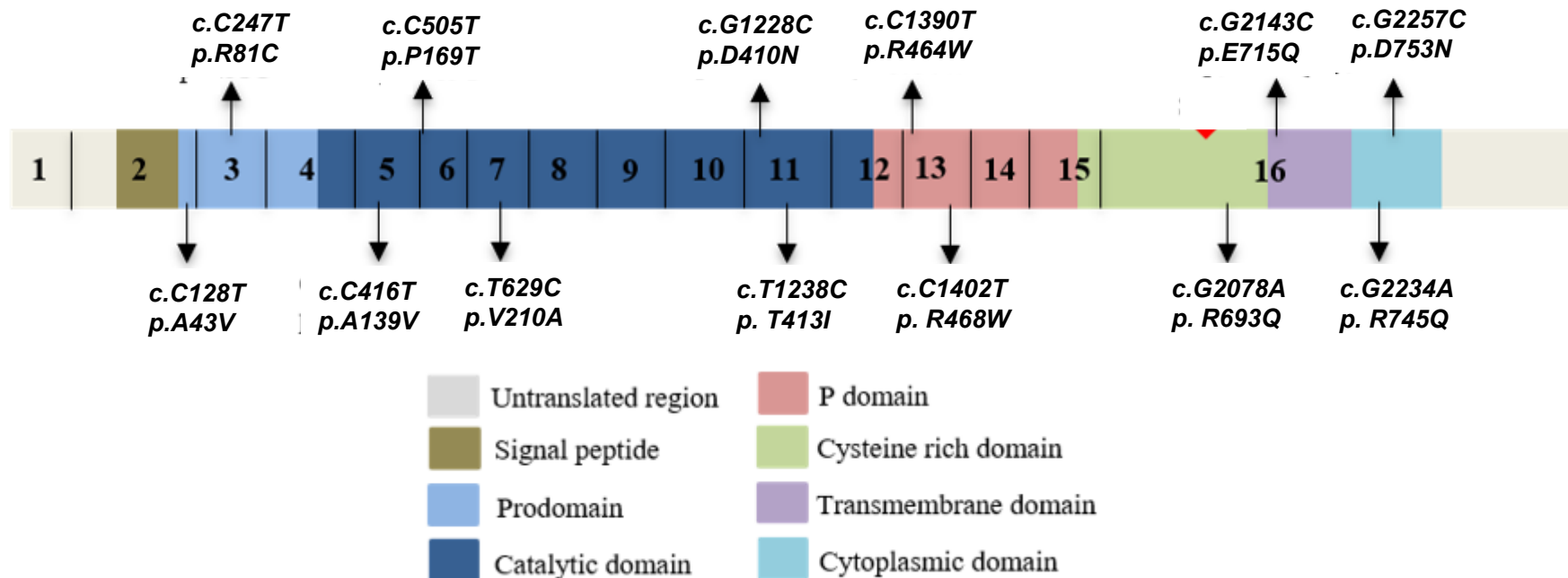
TGFB dimer

Cleavage of pro-TGFB by FURIN is essential for TGFB maturation

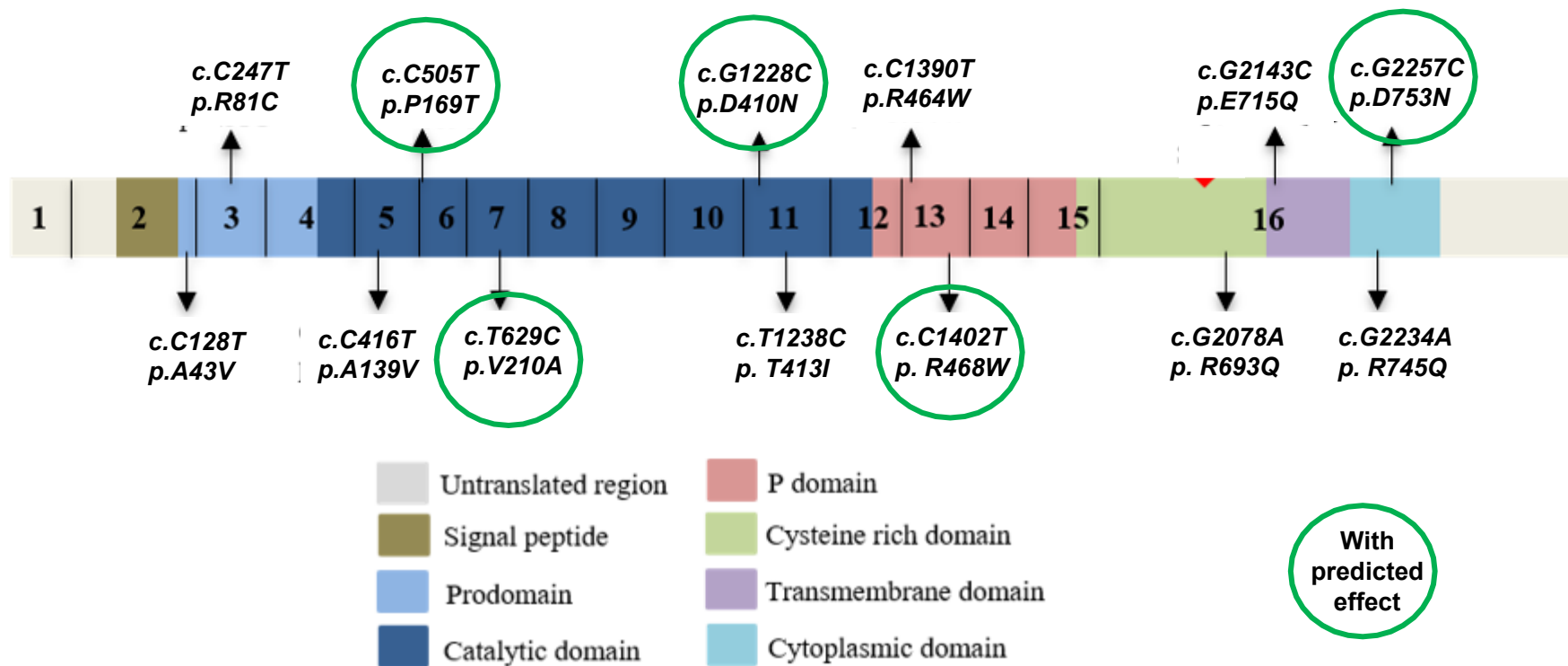


From D.B. Constam, Seminars in Cell and Developmental Biology 32 (2014) 85-97

13 *FURIN* variants identified in 24 unrelated patients

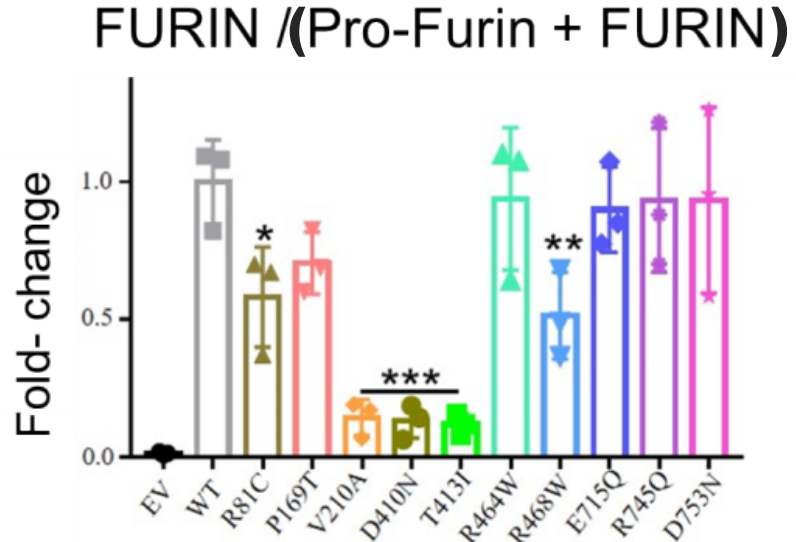
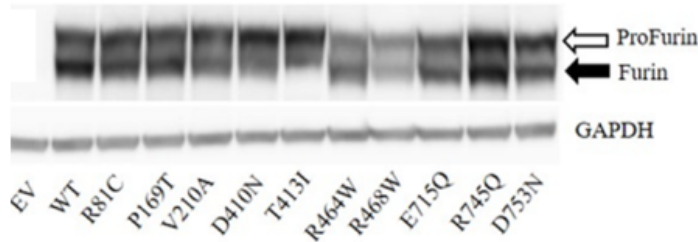


13 *FURIN* variants identified in 24 unrelated patients



Impaired auto catalytic maturation of recombinant FURIN

Constructs - HEK-293T cells

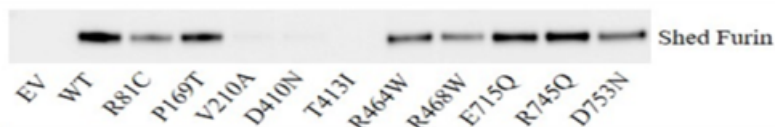


Predicted effect:

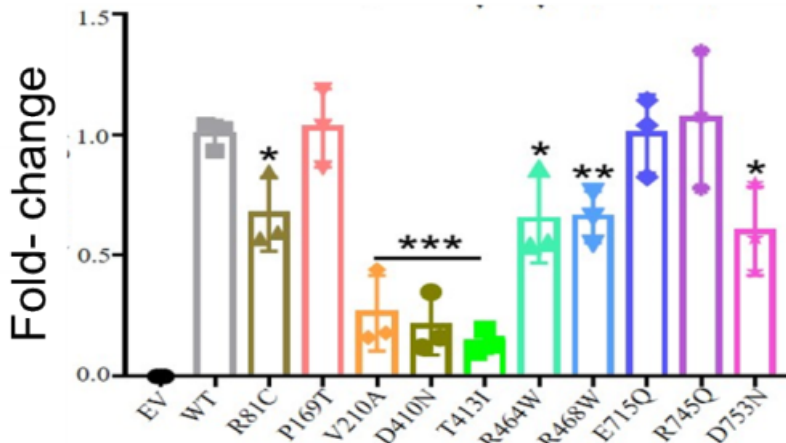
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FURIN shedding is impaired in recombinant cells

Constructs - HEK-293T cells



Shed FURIN/ Intracellular FURIN ratio

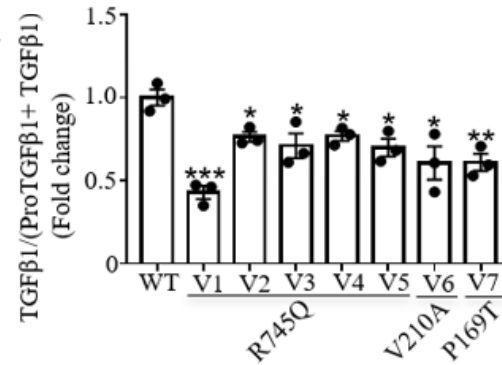
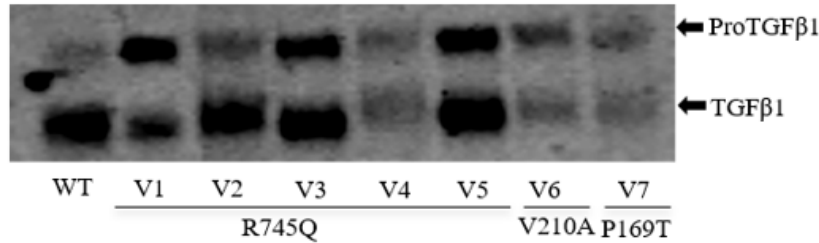


Predicted effect:

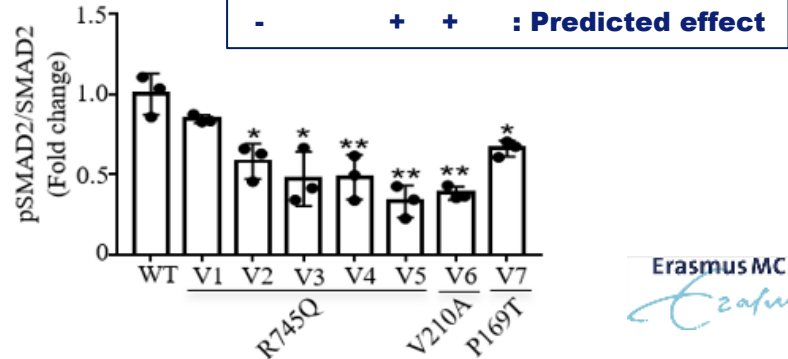
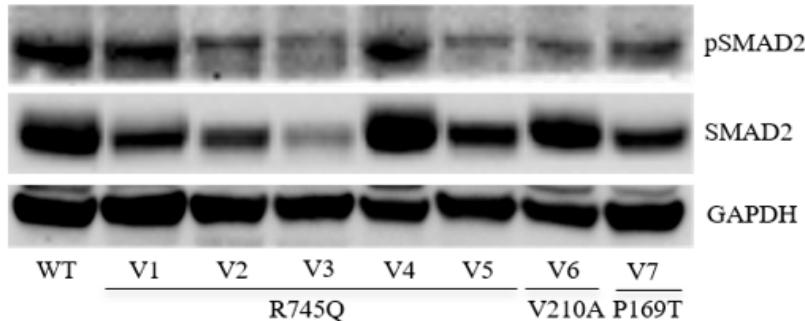
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Impaired intracellular TGF β signaling in fibroblasts of *FURIN* patients

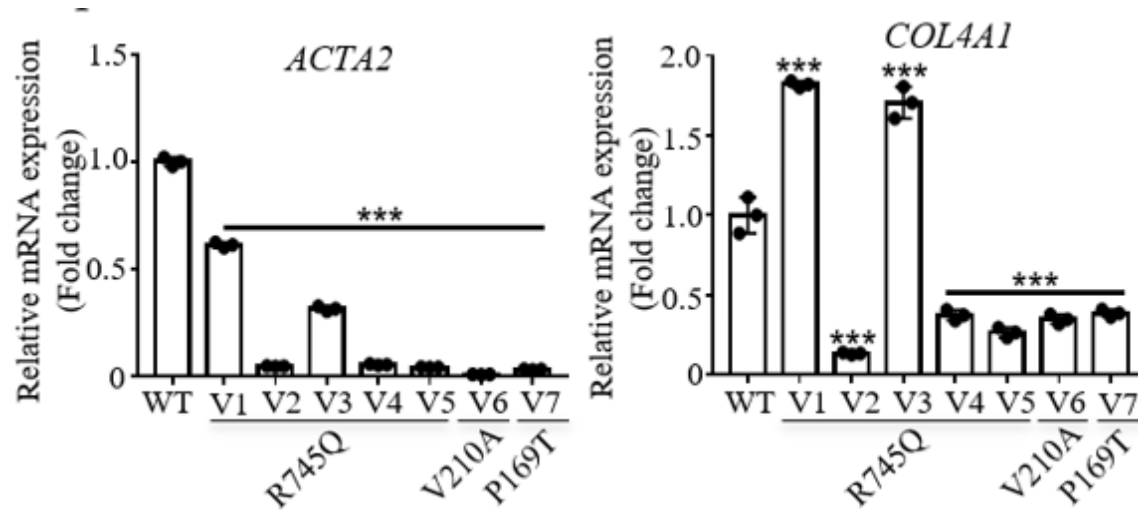
TGF β maturation



SMAD2 phosphorylation



TGFB target genes are variably affected in patient fibroblasts



Predicted effect

-

+

+

-

+

+

Interaction with other genetic factors: polygenic contribution

Conclusion

**FURIN contributes to susceptibility for aorta aneurysms
by impairing TGF β signaling**

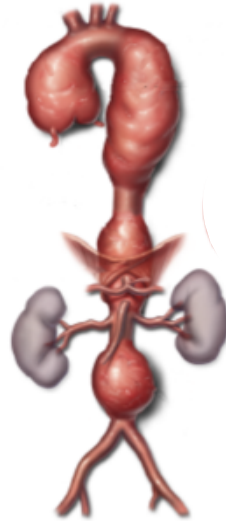
Aneurysms

Abdominal Aorta

Thoracic Aorta

Middle sized arteries

Dissections and rupture



Extravascular signs

Hypermobility

Scoliosis

Pectus excavatum

Skin extensibility

Increased risk for relatives

Towards polygenic hypothesis



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