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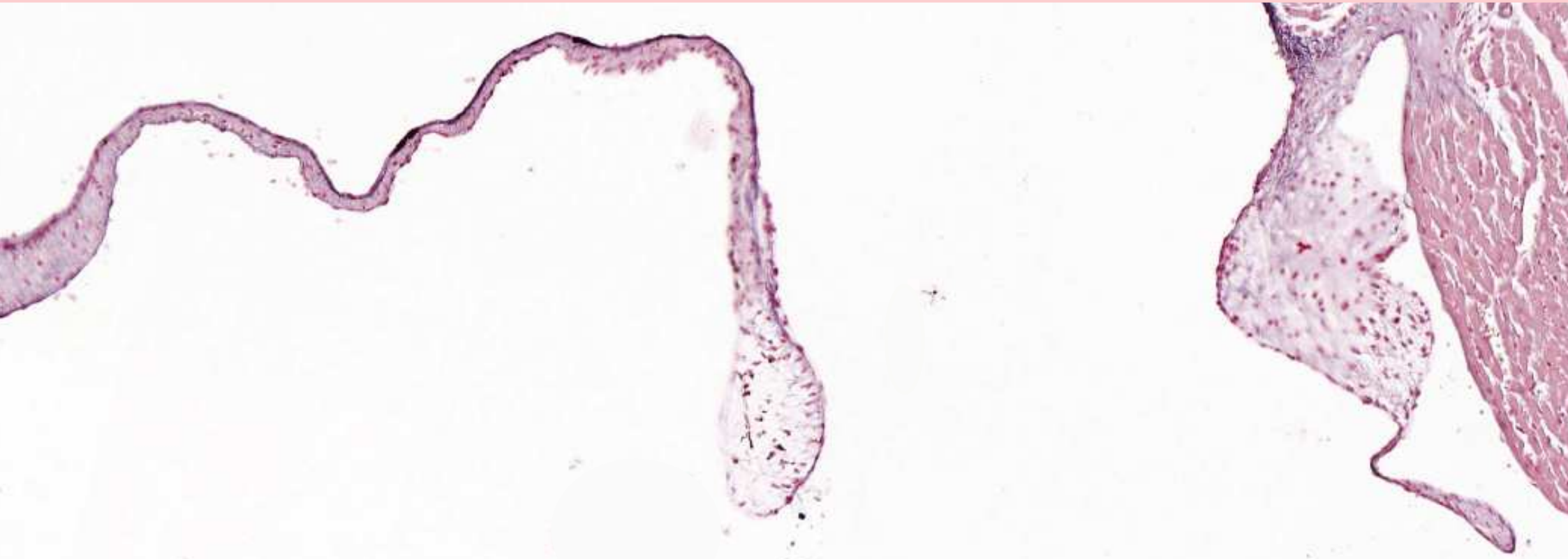
Leiden University Medical Center

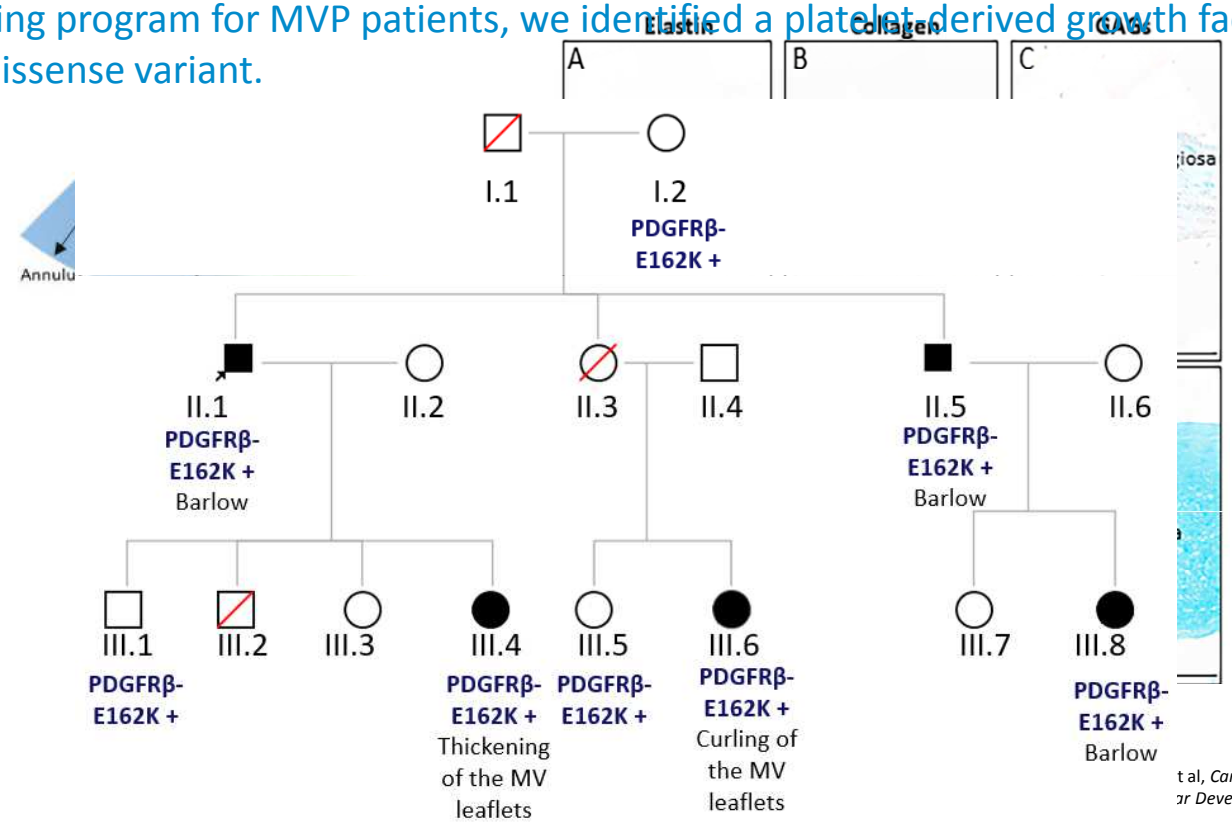
Mutation in PDGFRβ:
a potential new pathogenic variant for mitral valve prolapse

Yoska (H.W.) Wu, PhD candidate



Introduction

- Mitral valve prolapse (MVP) is a common valvular heart disease which can cause regurgitation and eventually can lead to heart failure symptoms and arrhythmias.
- MVP due to myxomatous degeneration is characterized by familial clustering.
- In a genetic screening program for MVP patients, we identified a platelet-derived growth factor receptor β (PDGFRβ)-E162K missense variant.



t al, *Cardiovascular Research*, 2020
ar Development and Disease, 2021

PDGFRβ

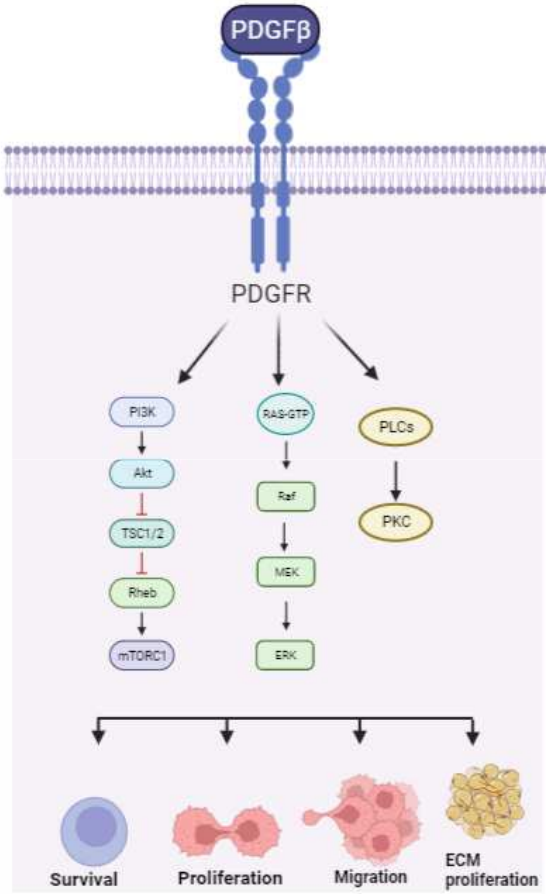
PDGFRβ is a receptor tyrosine kinase

Provides essential cues for

- efficient epicardial migration
- coronary vascular smooth muscle cell formation
- coronary vessel maturation

PDGFRβ-E162K

- Missense variant
- Transition from C to T in exon 4 (Glu162Lys-E162K)
- In the second Ig-like domain

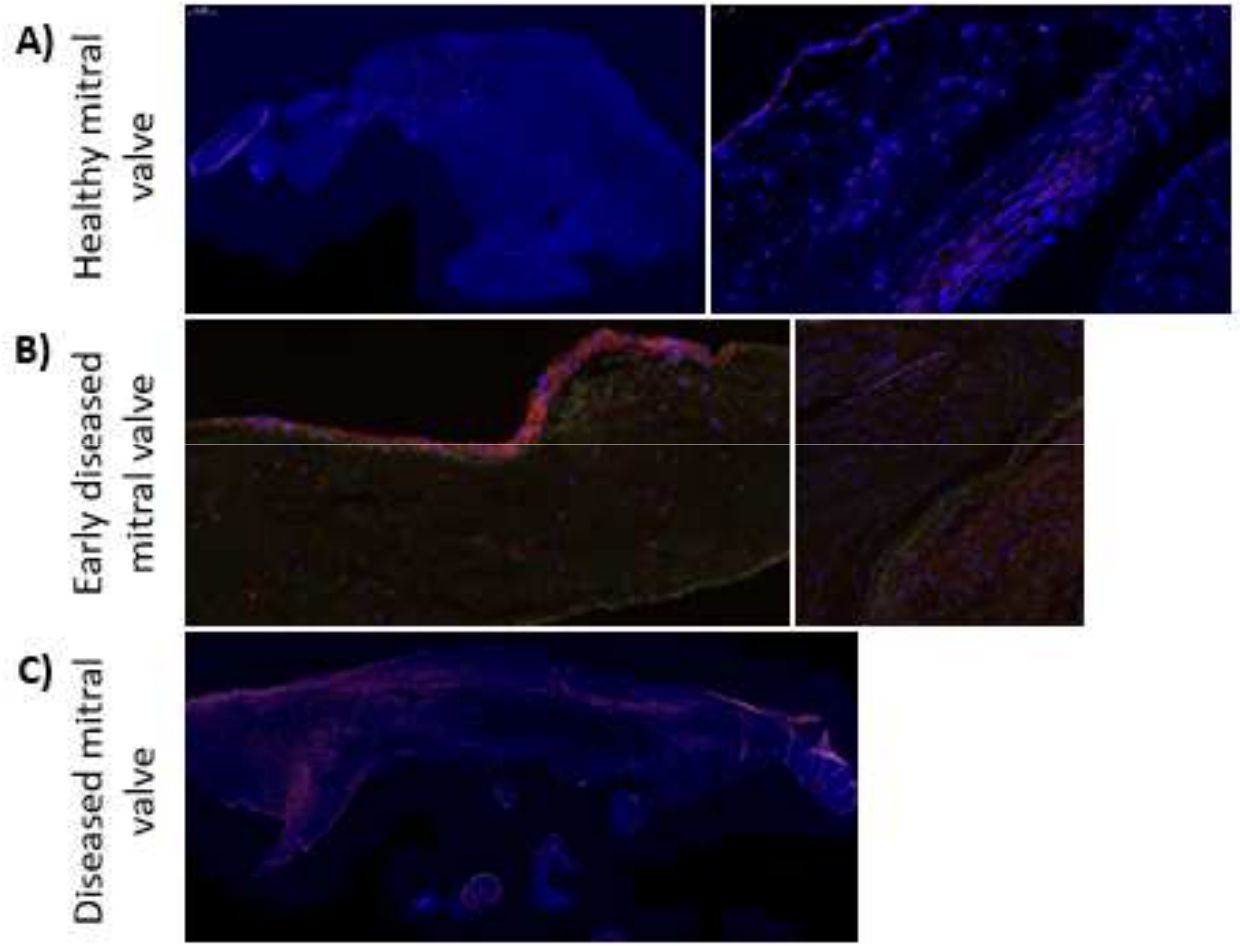


Smith et al., *Circulation Research*, 2011
Figure created using Biorender

PDGFRβ expression in human mitral valves

PDGFRβ

DAPI



AIM

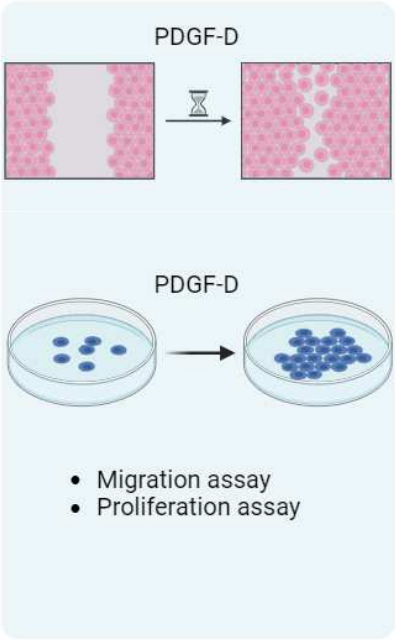
To investigate whether the PDGFRβ-E162K mutation is responsible for mitral valve abnormalities

Adams et al. *European Heart Journal*, 2010
Biorender

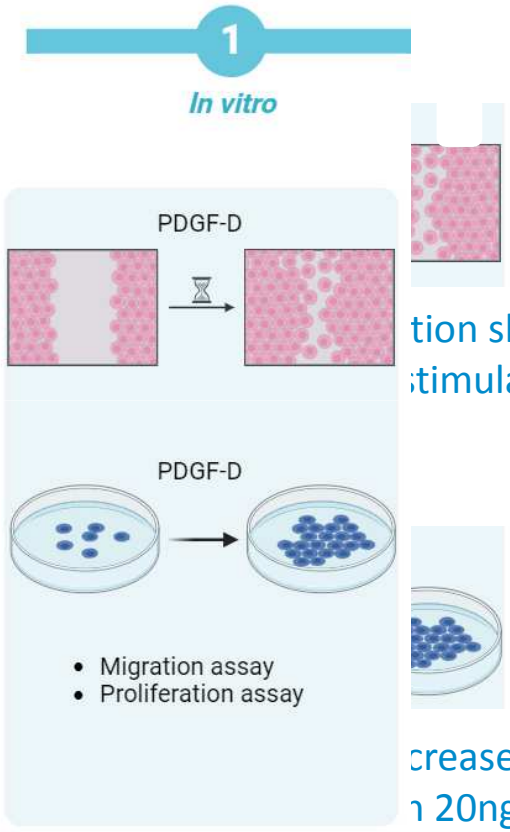
Methods

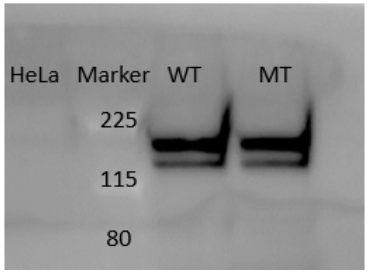
1

In vitro

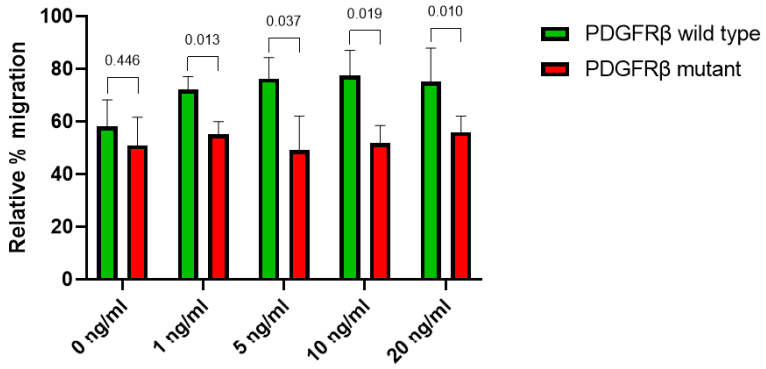


- Migration assay
- Proliferation assay

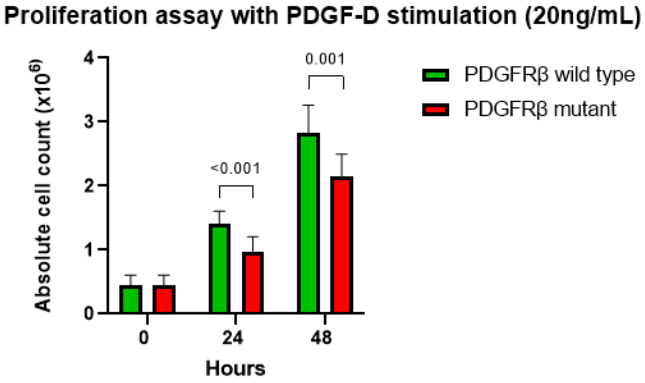




Scrat tion showed reduced migrati timulated with PDGF-D



Prolife creased proliferation in mu 20ng/mL PDGF-D



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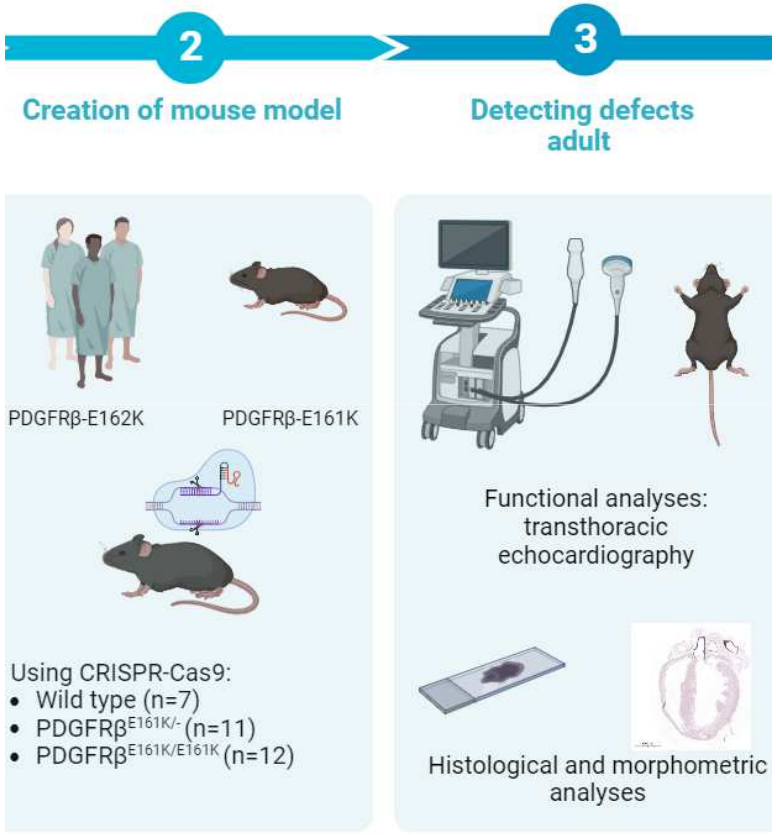
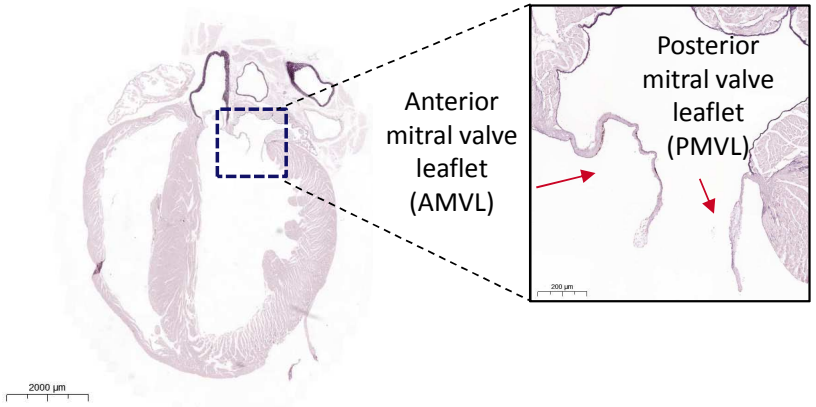
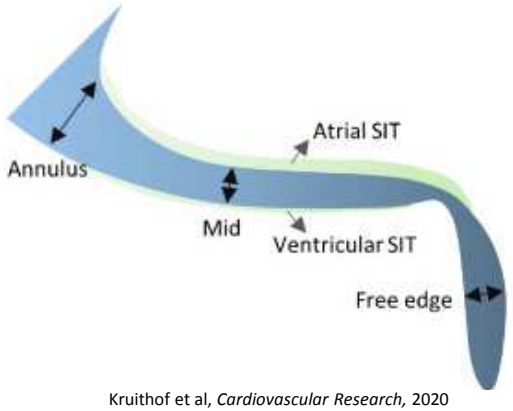
0.0559



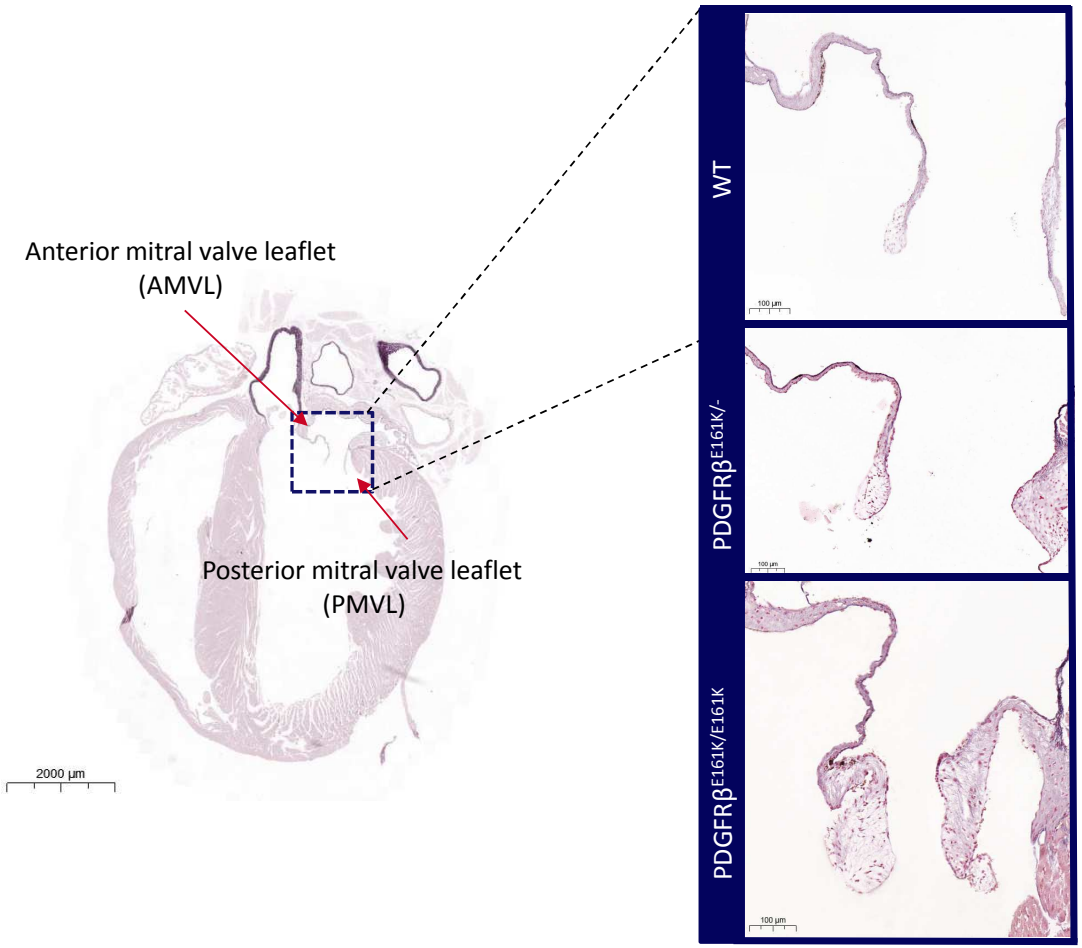
Histological analyses showing alterations reminiscent of myxomatous mitral valve

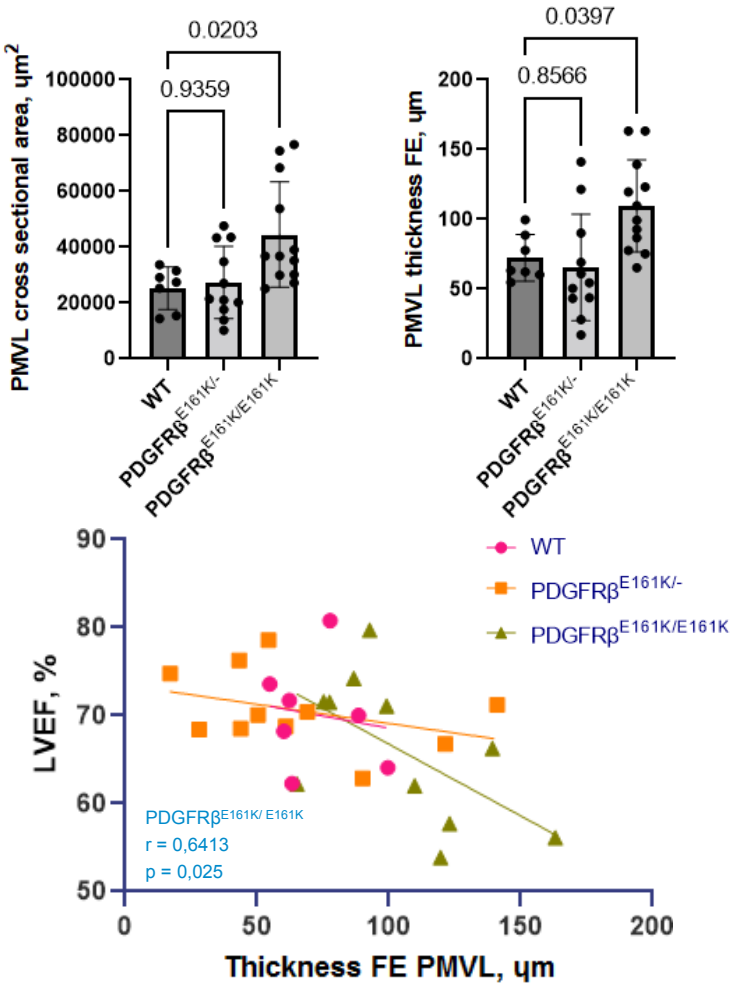


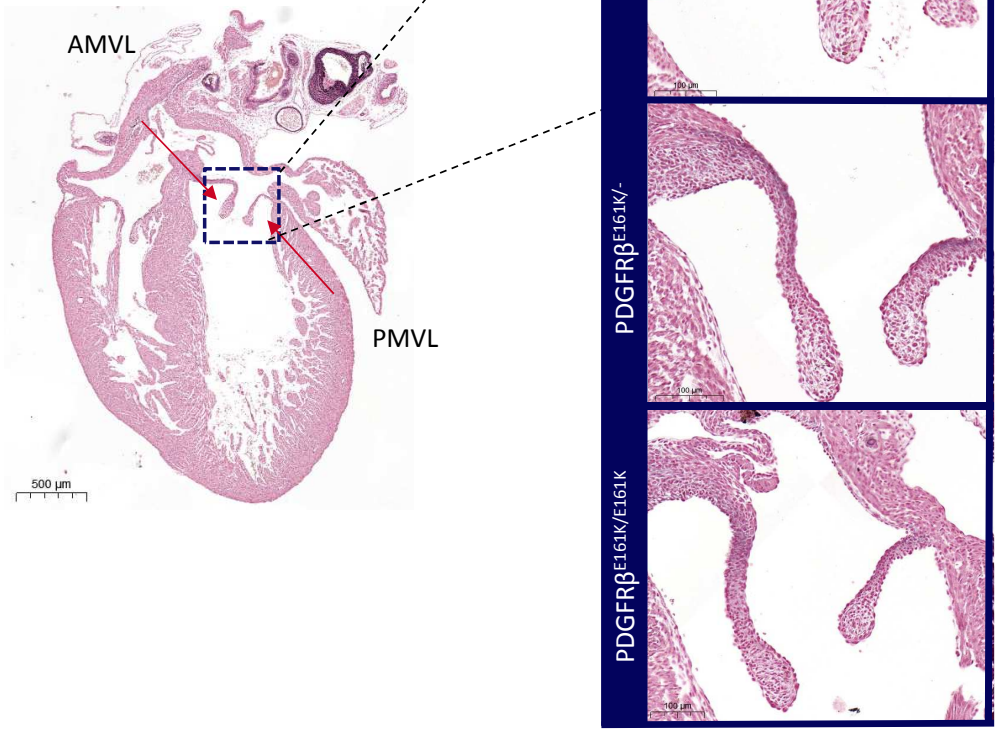


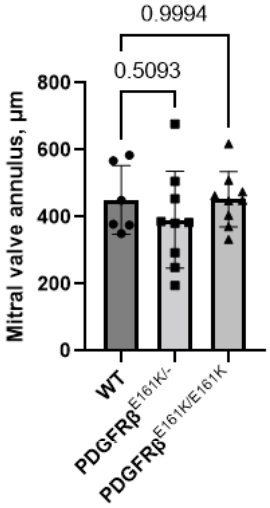
Kruithof et al, *Cardiovascular Research*, 2020

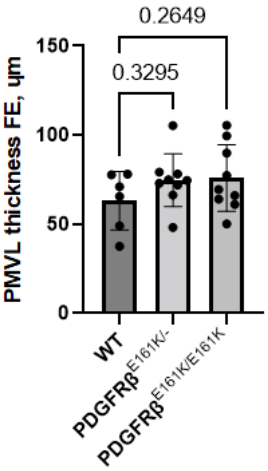
Morphometric analyses showing defects in mitral valve of homozygous hearts

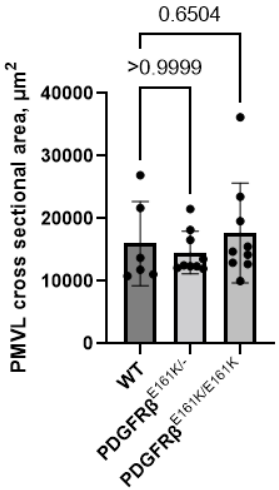




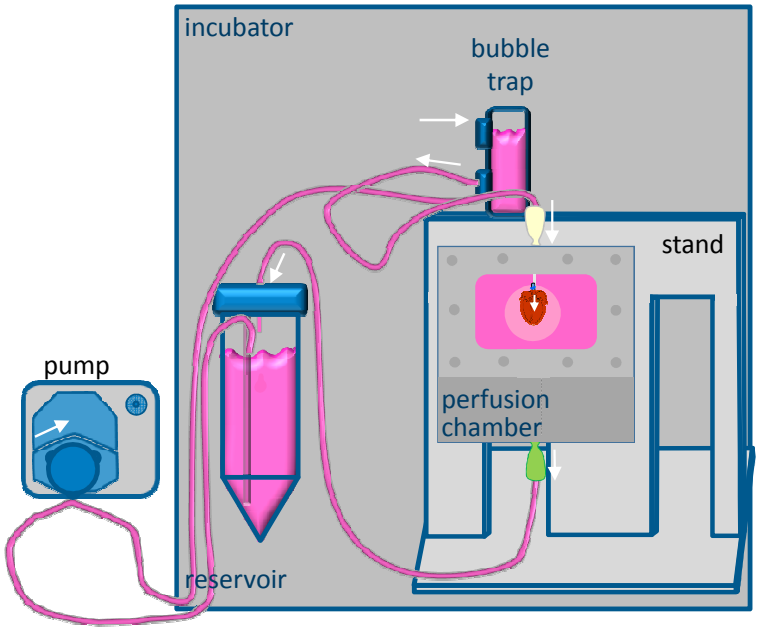

AMVL
PMVL
500 µm
Elastin (WRF
WT
PDGFRβE161K/-
PDGFRβE161K/E161K


0.9994
0.5093
Mitral valve annulus, µm
800
600
400
200
0
WT
PDGFRβE161K/-
PDGFRβE161K/E161K


0.2649
0.3295
PMVL thickness FE, µm
150
100
50
0
WT
PDGFRβE161K/-
PDGFRβE161K/E161K

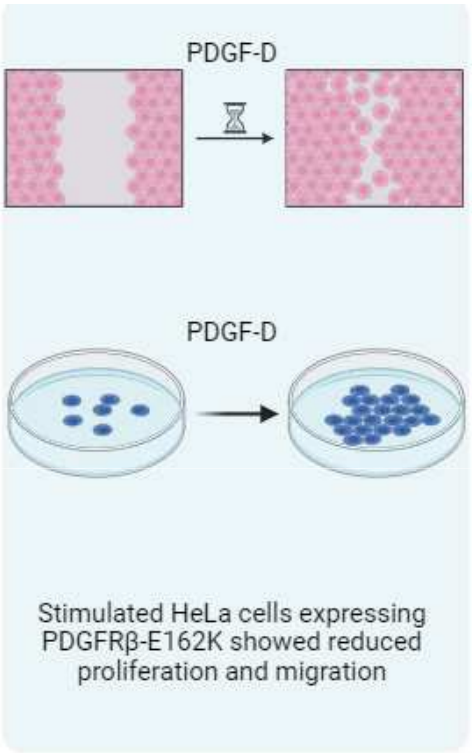

0.6504
>0.9999
PMVL cross sectional area, µm2
40000
30000
20000
10000
0
WT
PDGFRβE161K/-
PDGFRβE161K/E161K

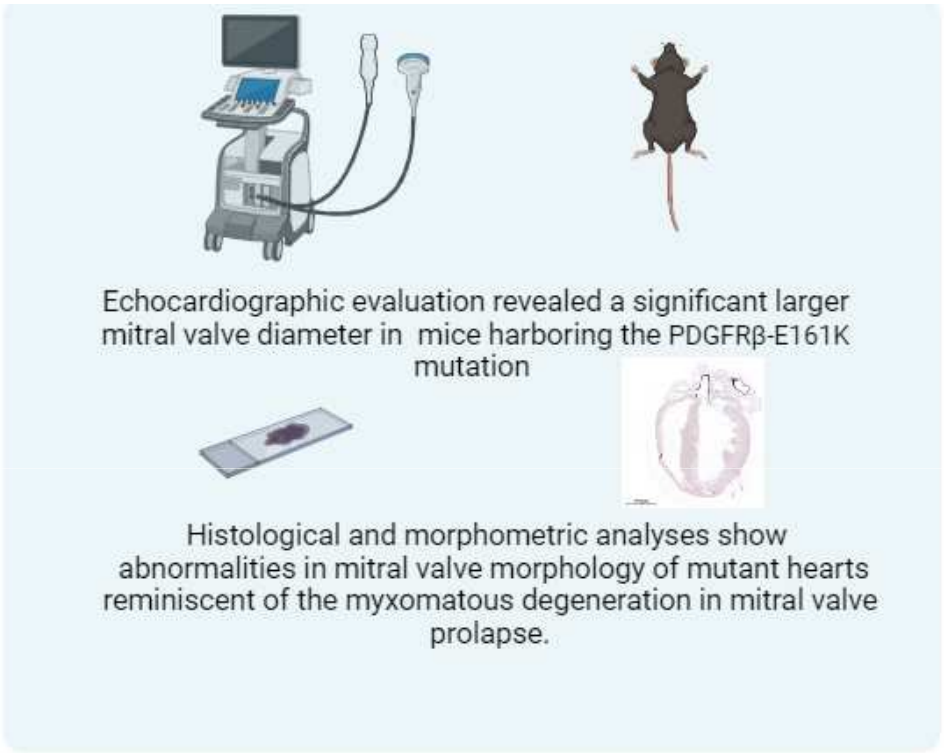
Current experiments

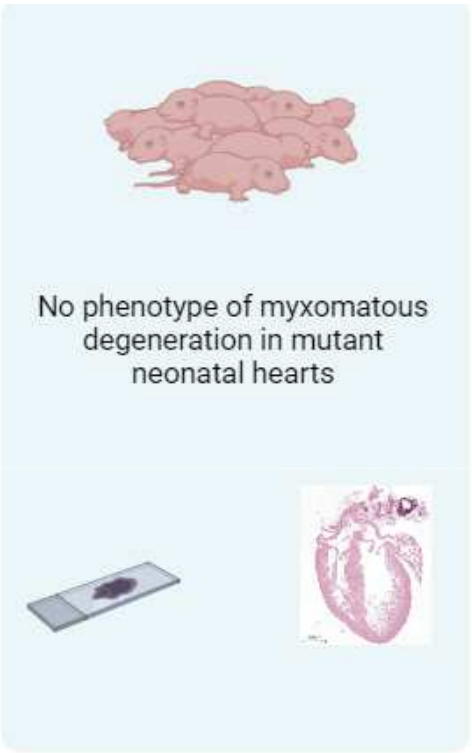


Kruithof et al., *Journal of Visualized Experiments*, 2015

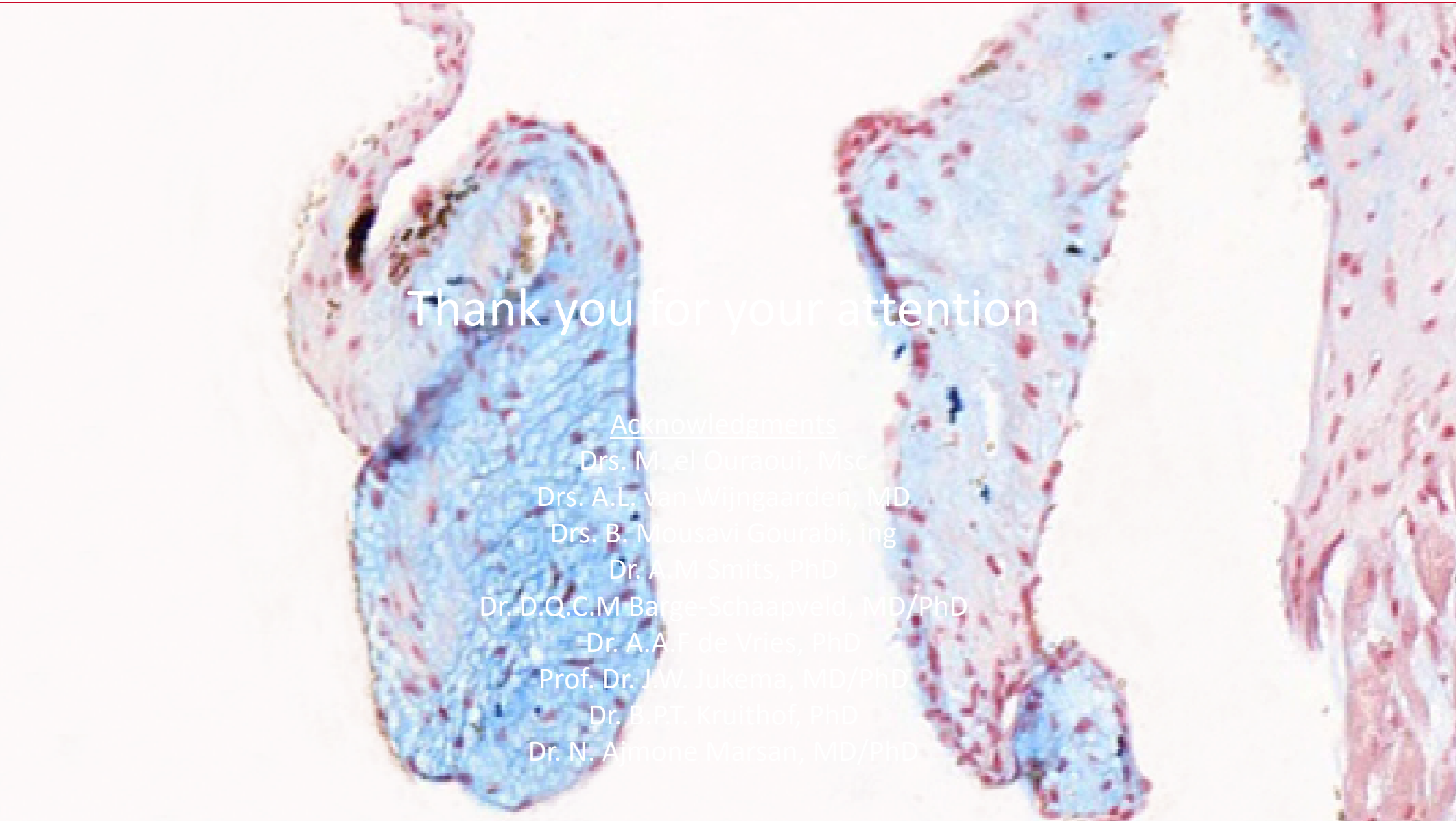
Conclusions







- **The PDGFRβ-E162K variant is associated with familial MVP and alters the function of PDGFRβ.**
- **Mice harboring this mutation display mitral valve defects with a larger mitral valve annulus and larger and thicker PMVL.**
- **These defects were not expressed in mutant neonatal hearts, indicating that it is acquired during life.**



Thank you for your attention

Acknowledgments

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