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## Funding

Methusalem Grant from the Flemish government and Ghent University
(BOF15/MET-V/011)

VZW Fonds voor Hartchirurgie
(489644)

Baillet-Latour Grant for Medical Research, by European Union (RRF-2.3.1-21-2022-00003)

Concerted Research Action grant UGent
(BOF GOA019-21)

UZ GENT
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Fonds Baillet Latour
CENTER FOR MEDICAL GENETICS GHENT
FACULTY OF MEDICINE AND HEALTH SCIENCES

# From Mice to Humans: Elucidating Cardiovascular Complications of Marfan Syndrome

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Public defense to obtain the degree of
"Doctor in Health Sciences"

September 20th, 2024

## Summary

Marfan syndrome (MFS) is a rare genetic disease caused by defects in the fibrillin-1 protein. This protein plays a crucial role in the structure and maintenance of connective tissue, which provides support to many organ system in the body. Healthy connective tissue is important for bones, eyes, skin, lungs, nervous system, heart and blood vessels, which can all be affected by MFS. One of the most important consequences of MFS is a gradual enlargement of the aorta, which can lead to potentially fatal rupture of this large blood vessel.

Additionally, mitral valve prolapse, arrhythmia and cardiomyopathy are also complications of MFS that significantly contribute to the mortality in patients. Considering there is no cure for patients with MFS, researchers are continuously trying to find new ways to treat the disease by understanding how it develops and progresses.

The overall goal of this doctoral thesis was to investigate the complex mechanisms in MFS that contribute to these life-threatening cardiovascular manifestations in order to identify new and more effective treatments.

Our studies in *fibrillin-1* mutant mouse models that represent various stages of aortic disease progression in MFS, provide insight into the role of TGFβ signaling in aortic homeostasis and aortic dissection. Contrary to the traditional view that TGFβ drives MFS-associated aortic disease, our findings demonstrate a nuanced role where certain aspects of TGFβ signaling might have protective effects. We propose that in early stages of aortic disease progression, focal areas in the aortic wall where TGFβ signaling is reduced, play a key role in elastic lamellae degradation through mast cell recruitment and/or activation, thereby potentially contributing to aortic dissection. Additionally, we discuss the impact of sexual dimorphism on aortic disease progression in MFS, displaying a protective role for female sex hormones.

Finally, we provide an overview of the morphological changes observed in the hearts of patients with MFS. We document the presence of an intrinsic myocardial disease phenotype in patients with MFS, independent of clinical manifestations. We highlight myocardial remodeling and degenerative changes in MFS, including the presence of granulocytes. These insights will be valuable for future research studies into myocardial dysfunction and cardiomyopathy related to MFS.

To conclude, these studies may facilitate better patient-specific clinical surveillance and aid the development of new therapeutic interventions for aortic disease and myocardial dysfunction in MFS.

## Key publications

**Deleeuw V**, D'hulst S, Demolder A, et al. (2024). Mapping the Marfan Heart: Ultrastructural Evidence for Myocardial Remodeling and Cardiomyopathy. In preparation for Cardiovascular Research.

**Deleeuw, V.,** Carlson, E., Renard, M., et al. (2023). Unraveling the role of TGFβ signaling in thoracic aortic aneurysm and dissection using Fbn1 mutant mouse models. Matrix biology : journal of the International Society for Matrix Biology, 123, 17–33.

**Deleeuw, V.,** De Clercq, A., De Backer, J., et al. (2021). An Overview of Investigational and Experimental Drug Treatment Strategies for Marfan Syndrome. Journal of Experimental Pharmacology. 11;13:755-779.

## Curriculum vitae

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## PhD Manuscript