Marfan syndrome (MFS) is a connective tissue disorder. Connective tissue is the cement of our body holding together our cells, tissues and organs. Connective tissue is found throughout our body and therefore diseases of connective tissue commonly affect different organ systems. The most typical signs of MFS are displacement of the lens in the eye and enlargement of the first part of the aorta. Next to these main signs, patients with MFS usually have a typical physical appearance: they are long and slender, have long and thin arms, legs and fingers and may suffer from scoliosis and chest anomalies. MFS is caused by a small defect in a gene called FBN1. This gene encodes the information on how to make an important protein of the connective tissue called fibrillin-1. Defects in the gene, may lead to a smaller amount or lesser quality of this protein.

In 2003 the Human Genome Project unravelled the complete human genetic code. This opened the door to the understanding and discovery of many new genetic medical conditions. Further research, allowed to investigate many genes simultaneously, but at the same time, required the interpretation of a lot of genetic information. Distinguishing those differences that are benign from those that actually predispose to certain diseases, became very challenging. In the first part of this thesis we focussed on this point. We wanted to improve the interpretation of those genetic variations that affect the FBN1 gene. For this purpose, we used the current guidelines from the American College of Medical Genetics (set up to distinguish benign from disease causing-variants) and modified some of the criteria to better match them to the FBN1 gene and to the disease, MFS.

Complications affecting the heart and blood vessels are the most life-threatening manifestations in MFS and impair life expectancy in these patients. Weakened connective tissue in the wall of the aorta, makes it less resistant to the constant forces exerted by a pumping heart. This weakness can lead to enlargement of the aorta and, ultimately, to a life-threatening aortic tear in the wall. Connective tissue is also present in the heart muscle and therefore patients with MFS may have a weakened heart muscle leading to enlargement and less well-functioning heart chambers and abnormal heartbeat (arrhythmia).

In a second part of this thesis we engaged in four more in-depth studies of some specific cardiovascular manifestations of MFS. First, we showed that male MFS patients have larger aortas than females, but that the rate of aortic enlargement is similar between them. Aortic enlargement rate was higher in those women which had at least one pregnancy in comparison to women who had never been pregnant. Furthermore, the fastest enlargement seemed to occur during pregnancy. Therefore appropriate surveillance during this period is crucial.

Second, since fibrillin-1 in MFS is more vulnerable to breaking, we expected to find higher quantities of protein fragments in the bloodstream. By measuring these fragments, we thought we might be able
to predict aortic enlargement and -tearing in MFS patients. For this study we included 86 patients and 40 healthy controls. Although we were able to detect several fragments of the fibrillin-1 protein in blood, we were unable to correlate the fragments to aortic enlargement or tearing. A significant finding was that in a small group of MFS patients with very stiff aortas (usually a sign of advanced disease), a certain fibrillin-1 fragment was very high. Since this group was very small, it could be interesting to further investigate this point in the future.

Third, in the same group of patients and healthy subjects, we looked at the presence of decreased heart function and arrhythmia. None of the healthy subjects had these problems, however, decreased heart function and arrhythmia, originating in the heart chamber, were present in 8% and almost 25% of the patients, respectively. The most important factors contributing to arrhythmia were enlargement of the left heart chamber and the presence of extra heartbeats. We concluded that monitoring of the heart function with cardiac ultrasound in all patients is recommended and that in case of palpitations or of an enlarged left chamber diameter, additional registration of the heart rhythm should be considered.

Fourth, we investigated whether obstructive sleep apnoea (OSA) increased the cardiovascular risk of patients with MFS. OSA is defined as an increased number of respiratory pauses during sleep. To study OSA we performed an in-hospital sleep study for 1 night in 40 patients. We observed that OSA was present in 42.5% of them and that this high prevalence was related to overweight. In fact, we found that despite the classical view of MFS patients as long and slender, 27.5% of our patients (55.6% if only adults >40 years were considered) actually had overweight. Some cardiovascular features, like high blood pressure, larger aortic diameters beyond the aortic arch and more frequent arrhythmia were more common in patients with OSA. However, we could not exclude that these findings could be related to other determining factors (like age or overweight itself). We think that those patients with overweight or those with symptoms of OSA (daytime sleepiness, snoring, breathing difficulties during sleep) should undergo an in-hospital sleep study. MFS patients should control their weight and overweight should be treated appropriately.

Finally, in the third part of the thesis we explored whether adding the drug losartan to conventional treatment with beta-blockers could better prevent aortic enlargement and -tearing and decreased heart function, than beta-blockers alone. Beta-blockers are medicines which reduce the heart rate and the blood pressure and, in this way, reduce the impact of blood circulation on a weakened aorta. Contrary to beta-blockers, losartan is thought to block one of the main disease-causing pathways in MFS and has proven to be very promising in mouse models. To study the effect of single versus combined treatment, we randomized 22 MFS patients to take either a beta-blocker and a placebo, or
a combined therapy of beta-blockers and losartan. After 3 years of treatment we observed that aortic enlargement and heart function were similar in both groups of patients. We therefore concluded that the combined therapy did not have a better effect than treatment with a beta-blocker alone. Although our study was very small, it was in line with the findings of other larger studies. Together they support the idea that combined therapy is not useful for all the patients, but might be reserved for certain cases.

Overall, the originality of this thesis lays on the study of less-common aspects of MFS. Next to offering a new and more accurate way of interpreting variants in FBN1, it has given further perspectives on several less-well studied clinical manifestations of MFS. Furthermore, it has contributed to new therapeutic insights. This thesis will serve as starting point of several larger research projects and constitutes therefore, a step towards a better and more personalized medicine.