Aims and outline of the thesis

This thesis presents the clinical and molecular studies in patients and families with various cardiovascular disorders, including thoracic aortic aneurysms and dissections, congenital heart disease and cardiomyopathies. Most patients were seen by a multidisciplinary team of experts from the departments of Clinical Genetics, Pediatric and Adult Cardiology, and Cardiothoracic and Vascular Surgery of the Erasmus MC, University Medical Center Rotterdam, with the support of colleagues from the departments of Molecular Genetics, Pathology and Radiology, now embedded within the Academic Center for Inherited Cardiovascular Diseases, the Academic Center for Congenital Heart Disease, and the European Reference Network on Rare Multisystemic Vascular Diseases (VASCERN).

The aim of the studies in this thesis was to identify new genes and pathways involved in cardiovascular disease, and to further characterize the clinical and genetics aspects of previously published and newly identified disorders.

Chapter 1 summarizes the genetic factors contributing to human cardiovascular disease. **Chapter 2** discusses the recommendations for cardiogenetic care in patients with thoracic aortic aneurysms and dissections, with special attention paid to genetic counseling in patients with Loeys-Dietz syndrome type 3 (a.k.a. aneurysms-osteoarthritis syndrome), and reports the identification of important pathways involved in aneurysm formation by gene expression profiling. **Chapter 3** describes the clinical and genetic studies in patients with left-sided congenital heart defects, broadening the phenotypic spectrum of mutations in the *NOTCH1* and *PKP2* gene. **Chapter 4** argues the role of *CALR3* in monogenic cardiomyopathy and reports the identification of two new genes, *ALPK3* and *ASNA1*, implicated in pediatric cardiomyopathy, providing new insights into disease mechanisms. **Chapter 5** discusses the significance and implications of our studies and outlines future perspectives.