Genetic variants in calcium calmodulin pathway in association with cardiovascular disease

Societal impact

CVD still represents one of the major challenges for public health, being the number one cause of death world-wide. However, several therapeutical approaches introduced toward the end of the 20th century have not yet halted the epidemic of CVD. Instead, the burden of cardiovascular conditions has risen to become the top cause of morbidity, and mortality worldwide. CVD is highly complex and multifactorial: multiple factors coexist increasing the risk of developing CVD. Lifestyle, environmental factors, other comorbidities, and genetics all play role in its etiology. Vascular remodelling, i.e. hypertension, atherosclerosis, vascular stiffness and calcification have become the main public health problem in the Western world. In this context, the identification of genetic variants associated with higher risk and susceptibility to develop a specific CVD, provides a crucial source of targets for the prevention, prediction and follow up of CVD patients.

In my thesis, I focused on the identification of variants in genes involved in the Ca^{2+} CaM pathway, in association with the risk of developing CVD. My aim was to find new potential biomarkers that are present already at birth and can cooperate with canonical markers developing in the course of the disease (e.g. troponin). Applying a combined "nature and nurture" approach will contribute to improving the health status of people across countries and reduce the economic impact that CVD has on healthcare systems.

In this study I have identified 4 genetic variants in the Ca^{2+} CaM pathway significantly associated with CVD. This not only led to recognising the crucial role of intracellular Ca^{2+} signalling in CVD, but also provides novel targets for future research and treatment avenues for CVD. Among these targets, SNP rs7214723 in *CAMKK1* is a new target and it is especially promising, and my research unravelling its role in VSMC biology brings the goal of novel therapies closer to being achieved.

In conclusion, my research described in this thesis lays the foundation for a novel role of the rs7214723 variant in the Ca^{2+} CaM pathway, providing a new biomarker for the diagnosis, prevention and treatment of CVD. Early diagnosis and preventive treatment is a cost-effective strategy to reduce the high levels of CVD morbidity and mortality, and their associated high economic burden. The association of only one single genetic variant with a complex disease such as CVD is not sufficient for a robust predictive model and needs further research. Yet, my results are promising and have the potential to lead to novel theragnostic strategies targeting CaMKK1 in the heart and vasculature. Finally, I propose further analysis of genes involved in the Ca^{2+} CaM pathway to link them to specific CVDs, such as hypertension, arterial stiffness, vascular calcification and heart disease.