Genetic variants in calcium calmodulin pathway in association with cardiovascular disease

ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death all over the world and it affects an increasing number of people annually. Numerous risk factors are involved in the etiology of this complex disease. In addition to an unhealthy lifestyle, environmental factors, and other comorbidities, genetics also plays a role. The study of genetic variants associated with CVD is one of the main areas of interest nowadays. This is because it can aid in the identification of genetic biomarkers for prevention, prediction and treatment of patients affected by CVD.

Regulation of calcium signalling through calmodulin (CaM) is a key pathway involved in the physiology and molecular biology of the heart. CaM binds calcium and regulates calcium, playing a crucial role in several processes, such as cellular excitation-contraction coupling.

Research has shown that genetic variants, such as polymorphisms, can be factors predisposing to complex diseases. Thus, I hypothesized that studying and characterizing polymorphisms in the components of the CaM pathway could unravel how genetic traits influence CVD predispositions. In this thesis I focused on polymorphisms in 3 isoforms of CaM (CaM1, 2, 3) and proteins involved in its signalling, NOS (nitric oxide synthases) and CaMKs (calcium/calmodulin dependent protein kinases), in CVD. The analysis of the polymorphisms was performed on a cohort of 300 cardiopathic patients; a blood sample was collected and spotted on FTA cards. DNA was isolated and RLFP-PCR was performed in order to analyse the single nucleotide polymorphisms (SNP) of interest.

The comparison of the genetic and allelic frequencies between the group of interest and the European reference group, used as control, showed interesting results in increasing the risk to develop a specific CVD, specifically for the SNP rs1549758, rs61202009 in NOS3 and mainly for the SNP rs7214723 in CaMKK1. The significant and interesting results of this last SNP in the cardiopathic Italian population, I analysed it also in a dutch cohort population and carried out an in-depth study of the role of CaMKK1 (calcium calmodulin–dependent protein kinase kinase I) in the heart and blood vessels, through in vitro studies on human vascular smooth muscle cells. In this in vitro experiment I found that CaMKK1 is a novel regulator of phenotypic switching of hVSMC towards synthetic VSMCs, thereby providing CaMKK1 as a new therapeutic target to reduce vascular remodeling, as well as a new potential genetic biomarker in the contest of cardiovascular diseases.