Inherited cardiac disorders include primarily electrical diseases, such as Brugada Syndrome (BS), and structural cardiomyopathies, often causing sudden cardiac death at young age. The identification of effective risk stratification criteria is high priority for correct patient management. It has been increasingly recognized that different genetic variants can contribute to phenotype modulation (Roden 2004, Bezzina 2013). However, genetic data are scarcely considered for risk stratification, because correlation between genotype and clinical phenotype is often inconclusive. In a pilot study we identified genetic variants associated with the occurrence of arrhythmic events in a cohort of BS patients (Sommariva 2012), which in perspective may improve clinical practice.

The first goal of our project is to exploit high throughput technologies to expand our knowledge on the molecular bases by identifying new disease genes and pathogenetic variants. Accordingly, we recently identified new BS candidate genes by next generation sequencing (Di Resta 2015). Selected variants will be functionally studied in _in vitro_ models including patient-derived iPS cells. In addition, genetic and clinical data will be correlated by multivariate analysis in order to evaluate genotype contribution to the expression of the pathological phenotype and the predisposition to malignant arrhythmias.

Our second goal is to identify markers of early cardiac involvement for the diagnosis of asymptomatic patients, which is a relevant clinical issue since the first symptom may be sudden death. To this purpose, the dosage of tissue-specific cell free circulating DNA based on specific methylation patterns will be investigated (Lehmann-Werman 2016).

Thanks to the close interaction between geneticists and cardiologists, this project will improve knowledge of the underlying genetic bases, thus increasing diagnostic power and improving familial counseling and clinical management.

References


