Identification of genetic factors underlying cardiac disorders causing sudden cardiac death
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Research into the genetic basis of inherited cardiac disorders associated with sudden cardiac death in the young has progressed rapidly in recent years, such that clinical genetic testing is now routinely employed for many conditions to identify causative genetic defects. Yet, with few exceptions, knowledge of the disease-causing genetic defect has a relatively modest impact on the ability to predict important clinical aspects such as the age of onset of the disease, its rate of progression, or the development of major cardiac events such as sudden cardiac death.

Studies in affected families have shown a large variability in disease symptoms and severity among relatives carrying the familial genetic defect. These observations have made it clear that, like most inherited disorders, allocating the inherited cardiac disorders exclusively to one genetic defect is an oversimplification of biological phenomena. It is likely that the inheritance of other genetic factors, commonly referred to as genetic modifiers, underlies at least in part this clinical variability.

Supported by a generous donation by the Horstingstuit Foundation, the Inherited Cardiac Disorders group of the Amsterdam UMC (co-led by Prof. Connie Bezzina and Prof. Arthur Wilde) in collaboration with colleagues at other Dutch UMCs, shall sequence the genome in 500 individuals with inherited cardiac disease with the aim of identifying such genetic modifiers. This will be done in a large set of patients carrying the same genetic defect (founder mutation). The fact that studied individuals carry the same founder mutation is thought to facilitate the identification of genetic modifiers.

The identification of genetic modifiers will improve the clinical care of patients with inherited cardiac disorders as it will lead to a refined, personalized, risk prediction and clinical management. When successful, the proposed approach can provide a template for studies in other areas of inherited (cardiac) disorders.