Genetic modifiers in familial cardiac rhythm disorders
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CHAPTER 1

INTRODUCTION

Sudden cardiac death (SCD) is one of the most prevalent causes of death in Western societies. It underlies 20% of total mortality, and 50% of cardiovascular mortality\(^1\). In young individuals (below 40 years of age) SCD often occurs in the setting of disorders displaying Mendelian inheritance\(^2\), with the cardiomyopathies\(^3\) and primary electrical disorders\(^4\) being the most prevalent. Here, the inheritance of very rare genetic variants with large effects potentially increases risk for SCD substantially\(^5\). The primary electrical disorders have been linked primarily to mutations in genes encoding ion channel subunits or their interacting proteins (Figure 1)\(^6\). On the other hand, the cardiomyopathies are caused by mutations affecting genes coding for the contractile apparatus and structural components of the cardiomyocyte such as the sarcomere and desmosomes\(^6\).

Genotype-phenotype studies in these disorders have clearly established that they are not spared from the phenomena of reduced penetrance and variable expression typical of Mendelian diseases\(^7\). For instance, in the primary arrhythmia syndromes, extensive variability in clinical manifestations is often observed among family members carrying an identical ion channel gene mutation, with some individuals exhibiting overt abnormalities on the electrocardiogram (ECG) and suffering potentially fatal arrhythmias, whereas others do not display any ECG changes and do not develop rhythm disturbances throughout life. Probands and families with these Mendelian disorders, harboring known disease-causing mutations, likely provide a permissive, genetically sensitized setting for the identification of novel genes and pathways modulating cardiac (electrical) function.

FOCUS OF THIS DISSERTATION

In this thesis we employ the phenotypic variability evidenced among probands and their relatives with Mendelian cardiac disorders to identify genetic modifiers of disease expression. We focused on two distinct groups of disorders associated with increased risk of SCD, namely the primary electrical disorders (Long QT Syndrome, Brugada Syndrome, Conduction Disease) and hypertrophic cardiomyopathy (HCM). The aim of this thesis was to identify such genetic modifiers using both linkage and (family based) association analyses. Both a candidate SNP / gene approach as well as a genome-wide unbiased approach were used in the study of common genetic variants as possible modifiers of disease severity.

In chapter 2, we reviewed the available literature on the genetic and allelic architecture of SCD. In this review we focused on the common genetic variation that has been recently identified through genome-wide association studies to modulate risk of SCD and
to modulate heart rate and ECG indices of conduction (PR-interval, QRS-duration) and repolarization (QTc-interval) as intermediate phenotypes of SCD.

In chapter 3 we investigated the role of five common candidate SNPs in the renin-angiotensin-aldosterone system in families with HCM who carried one of three functionally-equivalent mutations in the \textit{MYBPC3} gene. These SNPs were previously suggested to modify the extent of hypertrophy in HCM.

In chapters 4-6, we focused on genetic modifiers of primary electrical disease. In chapter 4 we studied a large set of individuals (probands and, where available, their family-members) carrying a mutation in the \textit{KCNH2} gene and presenting clinically with Long QT syndrome type 2. Here we comprehensively investigated the effect of haplotype-tagging SNPs in and around 18 candidate genes on the QTc-interval. In this analysis, for the first time we took the effect of \textit{KCNH2} mutation type and location in our analysis for modifiers of QTc-interval.

In the last two chapters we studied a very large Dutch kindred with the \textit{SCN5A} mutation 1795insD. An extensive genealogical search allowed us to trace this family back to the eighteenth century, enabling the construction of a highly extended pedigree. Individuals
in this kindred present with manifestations of Long QT syndrome, Brugada syndrome and progressive conduction disease occurring either in isolation or in combinations thereof. In chapter 5, we performed linkage and association analysis with heart rate and ECG indices of conduction and repolarization using haplotype-tagging SNPs in and around 18 candidate genes. These genetic studies pointed us to the calcineurin/Nfat pathway as a possible modifier of the PR-interval in the setting of sodium channelopathy. We subsequently provided further insight into the possible role of this pathway by conducting a series of functional studies in mice that are knock-in for the homologous \textit{Scn5a} mutation (\textit{Scn5a}^{1798insD/+/ mice}). Finally, we performed a genome-wide association study (GWAs) in this family (chapter 6) uncovering novel interesting candidate genes that can provide insight into novel pathways regulating heart rate and the cardiac conduction and repolarization processes.
Reference List


