Genetic basis of cardiac ion channel diseases

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The intrinsic complexity and future perspectives of genetic research

The genetic background of many diseases is very complex due to the involvement of many genes and diverse modifiers. New techniques and databases may help us to understand the genetic basis of (cardiac) disorders.

Disorders of cardiac ion channels may lead to a heterogeneous group of diseases, also known as cardiac channelopathies. Loss-of-function or gain-of-function of cardiac ion channels may result in critical changes of the action potential in parts or throughout the heart, which may subsequently result in abnormal cardiac behaviour. Our understanding of channelopathies is complicated by several factors, among which the complexity of the clinical phenotypes. The phenotypic expression of channelopathies is often heterogeneous (both in severity and differences in disease features); where it may give a disastrous outcome in one patient, another may experience no or only minor complaints. Importantly, as malignant arrhythmias may only occur once or intermittently during life, day to day functioning of the heart is most often normal. This implies that only during certain conditions (such as psychological stress, exercise, auditory stimuli, hyperthermia, use of certain drugs, premature ventricular contractions, bradycardia etc.) and a simultaneously increased vulnerability of the heart, the channelopathy emerges and gives rise to ventricular arrhythmias, which may ultimately lead to syncope or sudden cardiac death.

Another complicating factor is that abnormal ion channel functioning may not only alter the cardiac action potential in different ways, but in rare cases may also give rise to other cardiac or extra-cardiac abnormalities: Frustaci and Priori et al.[1] showed that biopsy samples taken from *SCN5A* mutation-positive Brugada syndrome patients demonstrated myocardial cell degeneration and death, suggesting that abnormalities in the function of Na^+ channels may induce structural abnormalities and cell death. Another example is that reductions in *SCN5A* function are associated with dilated cardiomyopathy (DCM),[2-4] which leads to dilation of the cardiac chambers and congestive heart failure; transcriptional downregulation of *RyR2* mRNA expression has also been associated with DCM in a mouse model.[2,5] In addition, abnormal ion channel functioning has been described in multisystem disorders: mutations in *KCNJ2* are associated with Andersen syndrome,[6] a rare skeletal muscle disorder often associated with prolongation of the QT interval, with the classical triad of periodic paralysis, cardiac arrhythmias, and congenital dysmorphisms[7,8]; gain-of-function mutations in *CACNA1c* can cause Timothy syndrome,[9] which is characterized by multiorgan dysfunction, including lethal arrhythmias, congenital heart defects, immune deficiency, intermittent hypoglycemia, syndactyly, cognitive abnormalities, and autism.

Other difficulties in understanding cardiac channelopathies are the allelic heterogeneity and the diverse impact of the different mutations on channel function: variations in a single gene can cause a wide range of distinct clinical phenotypes. There are several examples of mutations that are associated with a highly variable clinical phenotype. One of the clearest cases concerns the *SCN5A* mutation 1795insD: patients carrying this mutation show sudden nocturnal death and signs of multiple arrhythmia syndromes including bradycardia, conduction delay, QT prolongation, and right precordial ST-elevation.[10] Another example is the E161K mutation in *SCN5A* that is discussed in chapter 3, which is associated with different combinations of cardiac conduction disease, Brugada syndrome and sick sinus syndrome.[11]

The contributions of other (yet-unknown) genetic and environmental factors also play a role in the final form or severity of the disease. This is foremost evident in the incomplete penetrance, which appears to be common in all forms of cardiac channelopathies.[12] Probably, delicate gene-gene interactions and co-existing abnormalities play an important role in determining the ultimate phenotype of the disease. Genetic factors other than the causal mutation itself that play a role in modulation of disease severity are starting to be uncovered. For instance, several cases of compound heterozygosity have been reported, where two mutations in the same gene or even in two different genes are responsible for the (most often severe) phenotype.[13-17] Furthermore, the combined effect of a mutation in *SCN5A* and polymorphisms in the atrial-specific gap junction protein connexin40 gene has been reported to cause familial atrial standstill.[18] The genetic factors modulating disease severity may also reside in the gene affected itself and even on the same allele: a common polymorphism in *SCN5A* (H558R) that attenuates the biophysical defect of a mutation on the same allele has been described.[19] As reported in chapters 4 and 5, variants in the promoter regions of genes can affect gene expression,[20] which may cause variability in phenotypic expression and thus might also explain the observed differences in disease penetrance and expression of channelopathies. The challenging next step in this research field is therefore the identification of genetic modifiers (such as single nucleotide polymorphisms, SNPs), which are expected to influence the susceptibility for arrhythmias.[20,21]

One should take into account that not all disease-causing mutations can be identified by current PCR-based exon-scanning methodologies, which are only able to identify point mutations or small insertions and deletions in coding regions or at splice junctions. These methods do not detect copy number variations of genes or large gene rearrangements such as large duplications and deletions (which may involve multiple exons), as discussed in chapter 8.[22] Also mutations in non-coding regions (such as introns or promoter regions) of candidate genes, as well as mutations in yet unknown genes can be responsible for the phenotype in the remaining mutation-negative patients. Therefore, mutation detection in the future should also focus on finding large gene rearrangements, copy number variations and mutations in non-coding regions, which may affect gene expression or could for instance abolish or create putative binding sites for spliceosomes, leading to alternative exon-splicing.

One is just starting to understand the data generated by the Human genome project and the SNP consortium. Researchers are working to identify and understand the function of disease-related genes. Technological advances now allow the systematic study of whole-genome sequences, so that research that may have taken years in the past now takes weeks to months, and will only improve in time. In a few years, computer chips containing specific aspects of the genetic makeup can be used for DNA analysis by using a single blood sample from a patient. The obtained genetic information may be used to predict the risk of developing certain (cardiac) diseases, allowing earlier diagnosis and possible prevention and to more accurately diagnose the cause of symptoms or diseases. This will also help researchers to more efficiently discover and develop safer, more effective medication aimed at the causes of diseases, not just their symptoms. Preliminary clinical studies already indicate the possibility for genotype-specific therapy in congenital Long QT syndrome (Table 1). One should however discuss whether presymptomatic screening is always ethically justified.

Although many cardiac channelopathies are quite rare, its understanding is essential to unravel the pathogenesis of arrhythmias. These studies are important both because they tell us about the uncommon patients who have genetic variants and because they (1) inform important basic biology and (2) suggest approaches to understand how common variation may modulate arrhythmia susceptibility even in "run-of-the-mill" cases. By knowing which genes are involved in disease, researchers can develop better medical treatments and prevention strategies that are specific for those gene defects. In the years to come, our increasing knowledge may lead to better targeted treatment of patients at risk.

Table 1: Overview of genotype-specific therapy based on abbreviations of the QT interval by agents or other interventions in congenital Long QT syndrome (LQTS).

LQTS subtype	Gene	Treatment
LQT1	*KCNQ1*	β-blockers Other anti-adrenergic therapies
LQT2	*KCNH2*	β-blockers Potassium supplementation
LQT3	*SCN5A*	Na^+ channel blockers in the presence of β-blockers or in combination with an ICD Pacemaker therapy (?)

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