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Recent Genetic Discoveries Implicating Ion Channels in Human Cardiovascular Diseases

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Abstract

The term channelopathy refers to human genetic disorders caused by mutations in genes encoding ion channels or their interacting proteins. Recent advances in this field have been enabled by next-generation DNA sequencing strategies such as whole exome sequencing with several intriguing and unexpected discoveries. This review highlights important discoveries implicating ion channels or ion channel modulators in cardiovascular disorders including cardiac arrhythmia susceptibility, cardiac conduction phenotypes, pulmonary and systemic hypertension. These recent discoveries further emphasize the importance of ion channels in the pathophysiology of human disease and as important druggable targets.

INTRODUCTION

Ion channels are a ubiquitous class of proteins that confer selective ionic permeability to cell membranes and enable many diverse physiological processes including membrane excitability, synaptic transmission, signal transduction and cell volume regulation. Importantly, thousands of mutations in more than 60 genes encoding human ion channels have been associated with a group of heterogeneous conditions collectively dubbed channelopathies .

Scientific advances in elucidating the molecular basis of channelopathies have contributed to improved genetic diagnoses, development of genotype-phenotype correlations and inspiring new strategies for treatment of many rare disorders. Further, studying these experiments of nature can reveal new druggable targets that could have value in more common disease settings. This article will review some of the more compelling recent advances in discovering genetic defects that cause human cardiovascular disorders by affecting ion channel function. Many of the recent advances have been made possible by state-of-the-art genetic approaches including genome wide association studies (GWAS) and whole exome sequencing. Particular emphasis has been given to disorders of cardiac rhythm (arrhythmia) and blood pressure regulation.

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Genetic discoveries using exome sequencing

Paradigms for discovering genes responsible for Mendelian (i.e., single gene) disorders have evolved considerably in recent years. Before completion of the human genome project, the main approaches used in human genetics required the availability of large families, labor-intensive genotyping methods and complex statistical approaches just to approximate the location of the disease-causing gene. With the advent of next-generation DNA sequencing, there has been a renaissance in finding disease-associated genes. In particular, whole exome sequencing attempts to capture then sequence with multi-fold redundancy all coding exons in the genome [1,2]. This technical advance coupled with specific experimental designs and robust bioinformatics tools can be used to rapidly identify candidate mutations in a fraction of the time required by traditional approaches. The rapidity of this approach has led to deployment of exome sequencing in the clinic to make genetic diagnoses in rare disorders particularly in pediatric populations [3]. A critical challenge interpreting exome data is prioritizing the most likely disease-causing variants. Three examples discussed below highlight different successful strategies.

Crotti and colleagues used exome sequencing to identify mutations in two probands suffering severe forms of congenital long-QT syndrome (LQTS) manifesting as cardiac arrest during infancy but for whom no genetic causes had been found through conventional genetic testing [4••]. Mutations were discovered in two genes encoding identical peptides for the ubiquitous calcium ion binding protein calmodulin. Because the parents of the affected offspring were not affected by LQTS and the causative mutations were assumed to have arisen *de novo* in the probands, all variants inherited from the parents could be excluded and this greatly limited the number of variants that needed consideration. Although calmodulin itself is not an ion channel, the protein modulates the activity of L-type calcium channels, voltage-gated sodium channels, and the ryanodine-sensitive sarcoplasmic reticulum calcium release channel to name just a few physiologically relevant targets. Exome sequencing was similarly utilized by Marsman et al. to identify a mutation in a calmodulin gene (*CALM1*) in a two-generation Moroccan family segregating idiopathic ventricular fibrillation. In this situation, several candidate mutations were identified but only one variant in *CALM1* segregated with the phenotype and was deemed biologically plausible. Calmodulin gene mutations were also identified in catecholaminergic polymorphic ventricular tachycardia (CPVT) without QT interval prolongation using conventional methodologies [5] and efforts are underway by several groups to elucidate the molecular basis for genotype-phenotype relationships. Finally, a study by Boczek and colleagues featured a bioinformatics strategy predicated on known networks of interacting proteins and pathways [6]. Application of this approach led to the discovery of a novel *CACNA1C* mutation encoding a dysfunctional (gain-of-function) L-type calcium channel.

Exome sequencing has been widely applied to examine the prevalence and diversity of rare genetic variants in various populations. The National Heart, Lung and Blood Institute Grand Opportunity funded Exome Sequencing Project (ESP) cataloged variants in 6500 subjects [7]. Mining of these data has revealed surprisingly high rates of rare variants predicted to have deleterious effects within ion channel encoding genes previously associated with congenital arrhythmia susceptibility [8–10]. A similar observation was made in the NIH based exome cohort of 870 participants not previously selected for specific cardiac disorders [11]. In the NIH study, 360 variants were identified in genes, many of which encode ion channels, previously associated with arrhythmia predisposition and 4 subjects were later revealed to have LQTS. The explanation for these findings could be an underestimation of the population prevalence of these conditions, false positive detection, or mostly likely a combination of these two possibilities.

Peripheral nerve sodium channel implicated in cardiac conduction

Genome-wide association studies (GWAS) are designed to map genomic loci conferring risk for common, genetically complex diseases or physiological traits. This approach is predicated upon the “common disease-common variant” hypothesis that implies a major determinant of common diseases or traits in populations is conferred by a limited number of common genetic variants. Extremely high throughput and robust genotyping methods have enabled the wide application of the GWAS paradigm to cardiovascular phenotypes including indices of cardiac electrical function measured by the surface electrocardiogram (ECG). Following several informative studies seeking genomic determinants of the QT interval [12–14], a major risk factor for sudden cardiac death secondary to ventricular arrhythmias, recent work has deciphered the genetic landscape underlying the PR interval and QRS duration, proxies for conduction velocity across the atrioventricular node and the spread of conduction throughout the ventricles, respectively.

One intriguing and somewhat unexpected finding from recent GWAS has been the emergence of common variants in *SCN10A* as determinants of PR interval, QRS duration and heart rate response during atrial fibrillation [15–20]. Similar observations were made using a novel phenome-wide association study (PheWAS) design applied to electronic medical records [21•]. *SCN10A* encodes voltage-gated sodium channel $\text{Na}_v1.8$ (Fig. 1), which was originally identified in sensory neurons and subsequently was associated with inherited peripheral neuropathies [22,23]. The molecular basis for this genomic association was unknown until recently.

In an elegant and comprehensive study by van den Boogaard and colleagues, a genome-wide survey of transcription factor foot prints in heart highlighted potential mechanisms underlying the genomic association of *SCN10A* variants with cardiac conduction and unveiled intriguing new ideas about transcriptional regulation of cardiac sodium channel expression. Using chromatin immunoprecipitation coupled to next-generation sequencing (ChIP-Seq), van den Boogaard and colleagues discovered a transcriptional network involving transcription factors important for cardiac development and cardiac ion channel gene targets of their regulation [24•]. In particular, the T-box transcription factor TBX3 suppresses, whereas the related factor TBX5 enhances transcription of *SCN5A* and *SCN10A* in mouse heart by interacting with conserved binding sites located within these two neighboring genes. Further, the minor (less common) allele at a non-coding single nucleotide polymorphism (SNP) associated with cardiac conduction disrupts one of these TBX3/TBX5 binding sites. These findings provide strong evidence that *SCN5A* and *SCN10A* are co-regulated by T-box factors and that the GWAS signal for cardiac conduction may be explained by disruption of this transcriptional regulation.

SCN10A subsequently has become a focus of attention by two groups eager to elucidate a plausible physiological function for $\text{Na}_v1.8$ channels in mammalian heart [25,26]. A study by Yang and colleagues investigated the contribution of $\text{Na}_v1.8$ to sodium current in mouse cardiac myocytes. They found that expression of $\text{Na}_v1.8$ mRNA was highest in tissue from the right ventricle and both atria, and that a relatively specific blocker (A-803367) suppressed late sodium current in myocytes but had no effect on peak current. Genetic knockout of murine *Scn10a* also attenuate late sodium current in mouse cardiomyocytes. A-803367 also caused action potential shortening at slow pacing rates in both murine and rabbit ventricular myocytes consistent with suppression of late sodium current. These findings implicate $\text{Na}_v1.8$ as a contributor to myocyte sodium current. A different conclusion was reached by Verkerk et al. who investigated $\text{Na}_v1.8$ in murine cardiomyocytes and determined that protein and functional expression was primarily in intracardiac neurons rather than myocytes. While the basis for these different observations is unclear, it is worth pointing out that different mouse strains were employed by the two

groups. Whereas Verkerk and colleagues used inbred FVB/N mice, the experiments of Yang et al., were performed using mice having a mixed C57BL/6:129/sv genetic background in which the human cDNA for Nav1.5 had been inserted into the native murine locus [27].

SCN10A modulates risk of Brugada syndrome

The Brugada syndrome (BrS) is an inherited predisposition to sudden cardiac death from cardiac (ventricular) arrhythmias that occurs in persons without overt structural heart disease [28]. A characteristic ECG pattern of ST elevation confined to the right precordial leads may be present under baseline conditions or be evoked by pharmacological challenge with sodium channel blockers (e.g., procainamide, flecainide, ajmaline) [29] or fever [30] is often diagnostic of the condition. Mutations in the main cardiac sodium channel gene *SCN5A* account for approximately 30% of cases, whereas mutations in several other sodium channel interacting proteins, L-type calcium channel subunits and potassium channels account for some, but not all, of the remainder [31]. The inheritance pattern observed in BrS families most closely resembles autosomal dominant inheritance with incomplete penetrance, but some evidence points to a greater degree of genetic complexity [32].

Recent findings by Bezzina et al. using the GWAS paradigm support the involvement of *SCN10A* and a non-channel gene (*HEY2*) involved with cardiac development in the pathogenesis of BrS [33•]. Additionally, their study illustrated the compounding effect of multiple risk alleles at both loci in the risk for BrS. These discoveries suggest that inheritance in BrS is non-Mendelian or that *SCN10A* and *HEY2* are very strong genetic modifiers. Either way, these new data further highlight the emergence of *SCN10A* as an important cardiac arrhythmia susceptibility gene.

Potassium channel mutations in pulmonary artery hypertension

In what may be the first discovered lung vascular channelopathy, Ma *et al.* recently reported 6 novel heterozygous mutations in *KCNK3* encoding a twin-pore, acid-sensing potassium channel (K2p3.1, TASK-1; Fig. 1) in either familial or idiopathic pulmonary arterial hypertension [34••]. The initial discovery was made in an index family by exome sequencing. Most of the mutations were clustered near the two pore regions of the affected channel and were demonstrated to be loss-of-function alleles. Interestingly, function could be partially rescued for some mutants by a phospholipase A2 inhibitor (ONO-RS-082) previously shown to activate the wildtype channel. *KCNK3* is expressed in pulmonary arterial smooth muscle cells and may contribute to setting the resting membrane potential in these cells in an oxygen sensitive manner [35,36]. Loss-of-function mutations may evoke less polarized membranes that could plausibly evoke vasoconstriction leading to pulmonary hypertension.

Potassium and calcium channel mutations in primary aldosteronism

Hypertension is a major risk factor for stroke, atherosclerosis, heart and kidney failure. Primary aldosteronism represents one form of potentially curable hypertension caused by adrenal tumors that produce the mineralocorticoid hormone aldosterone. In pioneering work by the Lifton laboratory, exome sequencing of adrenal adenomas removed from patients with primary aldosteronism, revealed frequent (~40% tumors) recurrent mutations of *KCNJ5* encoding Kir3.4, a subunit of the G-protein gated inward rectifying potassium channel type 4 (GIRK4; Fig. 1) [37••]. Other reports soon followed confirming this discovery [38–45]. Most mutations were somatic (e.g., acquired during pathogenesis of the adenoma), but germline mutations were also identified in kindreds with heritable forms of aldosteronism associated with adrenal hyperplasia [37,46–48]. Two specific mutations within the ion selectivity region of the channel were discovered in most cases including a non-conservative substitution of a highly conserved glycine residue (G151R) within the signature motif

(GYG) of potassium-selective channels. Both mutations confer altered selectivity for sodium ions and enable the channel to conduct an aberrant inward current. This aberrant sodium current causes membrane depolarization of adrenal cells, activation of calcium channels with resulting calcium influx leading to aldosterone secretion and stimulated cell growth. Another inherited mutation of the Kir3.4 GYG motif (G151E) was found in subjects with a milder form of primary aldosteronism without adrenal hyperplasia [46]. Interestingly, this mutation causes more pronounced sodium selectivity and larger inward current, which seems paradoxical given the milder phenotype. However, the unregulated sodium conductance through the mutant channels impairs cell viability *in vitro* and this likely limits the potential for hyperplastic cell growth *in vivo*.

In a recent report by Scholl, et al., exome sequencing of aldosterone-producing adrenal adenomas also led to discovery of two recurrent somatic mutations in *CACNA1D*, the pore-forming subunit (Ca_v1.3; Fig. 1) of L-type voltage-gated calcium channel in a small subset of cases (12%) that did not have mutations in either *KCNJ5* or *CTNNB1* (another gene associated with this phenotype) [49]. *CACNA1D* mutations were also discovered that had arisen *de novo* in the germlines of two children with a novel genetic syndrome of primary aldosteronism combined with neurological deficits (seizures, complex neuromuscular abnormalities). Additional somatic *CACNA1D* mutations were reported by Azizian and colleagues [50]. Mutant channels evoked hyperpolarized shifts in the voltage-dependence of activation such that channels would be open at the resting membrane potential of adrenal granulosa cells (gain-of-function). Additionally, the kinetics of channel inactivation were slowed by these mutations. The gain-of-function in calcium conductance should trigger aldosterone secretion and stimulate cell growth in a manner similar to what was predicted for *KCNJ5* mutations.

CONCLUSIONS

During the past two years, new discoveries related to ion channels or interacting proteins have been implicated as causative for severe forms of congenital cardiac arrhythmia susceptibility, pulmonary artery hypertension and a form of curable systemic hypertension (primary aldosteronism). Additional investigations have highlighted the importance of non-coding variants in a peripheral nerve voltage-gated sodium channel gene as a determinant of cardiac conduction phenotypes. Many of these advances have been enabled by next-generation DNA sequencing technologies. Genetic discoveries implicating ion channel dysfunction continue to offer insight into the pathophysiology of a range of human cardiovascular diseases.

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HIGHLIGHTS

- Exome sequencing has enabled discovery of new channelopathies.
- Mutations in calmodulin have been defined as novel cardiac arrhythmia susceptibility genes.
- A peripheral nerve sodium channel emerged as an important contributor to cardiac conduction.
- Mutations in a twin-pore, acid-sensing potassium channel cause pulmonary artery hypertension.
- Somatic or germline mutations in potassium and calcium channels cause primary aldosteronism.

Voltage-gated Na channel (e.g., Na_v1.8)

Voltage-gated Ca channel (e.g., Ca_v1.3)

Twin-pore K channel
(e.g., TASK-1)

Inward rectifying K channel
(e.g., Kir3.4)

Fig 1.
General transmembrane topology of ion channels discussed in this article.