Genetics and cardiac channelopathies

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Abstract: Sudden cardiac death is a major contributor to mortality in industrialized nations; in fact, it is the cause of more deaths than acquired immune deficiency syndrome, lung and breast cancer, and stroke together. Frequently, the autopsy becomes the principal diagnostic tool because macroscopic and microscopic analyses reveal the underlying cause of death. However, a significant number of sudden cardiac deaths remain unexplained. These cases are referred to as "natural" or arrhythmogenic. In the young, in up to 50% of sudden cardiac death cases, sudden death is the first and only clinical manifestation of an inherited cardiac disease that had remained undetected by conventional clinical investigations. To improve diagnosis, genetic testing has recently been added to these clinical tools. During the last two decades, there has been considerable progress in the understanding about genetics of sudden cardiac death. With that new information, the probands and their family members can make an informed decision regarding their care and know whether and to what extent they are at risk of suffering from the disease. Thus, genetic technology and expertise have become essential for the diagnosis of some forms of inherited cardiac diseases and to provide a basis for subsequent prevention strategies. This review focuses on recent advances in the understanding of cardiopathies owing to genetic investigations. ***Genet Med* 2010:12(5):260–267.**

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Sudden cardiac death (SCD) is responsible for ~1 million deaths annually in the developed world,[1] which makes arrhythmias as one of the most significant causes of death and disease in the general population. Most cases of SCD are related to an underlying ischemic heart disease. Because ischemic heart disease is not prevalent in the young, in these cases, SCD may often be related to a familial, inherited, or genetic disease.[2,3]

A careful cardiac investigation during the autopsy can provide a definitive diagnosis in structural heart diseases, be it by the identification of a culprit coronary lesion or heart muscle disease, which explain the episode. However, a significant number of SCD cases remain unexplained after a comprehensive medicolegal investigation. These autopsies are usually labeled as negative, natural, or arrhythmogenic. In these negative autopsies, especially in the young, a genetic disease causing an electrical disturbance (ion channelopathy) should be immediately suspected. Because of the familial nature of the disease, the identification of these genetic defects carry important implications for relatives who are at potential risk of also having a fatal cardiac condition.[4,5]

Several mutations in genes that encode cardiac ion channels and structural proteins have already been associated with fatal and nonfatal arrhythmias, although the basic mechanisms have yet to be fully elucidated.[6] Genetic testing has therefore become a new tool in clinical cardiology. As such, when the clinical diagnosis is clear, genetic testing may help confirm the disease and identify genetic carriers in the family. A genetic study may even be of help in borderline phenotypes, because sometimes it becomes the only means of diagnosing a potentially fatal disease. However, when the clinical phenotype is not clear (i.e., sudden unexplained death), genetic testing continues to be a fishing expedition, which can only be performed for research but not for clinical purposes, because it is not cost effective.

Despite some significant overlaps, inherited cardiac diseases associated with SCD can be classified into two broad groups (Fig. 1)[7]:

a. Primary electrical diseases, or channelopathies, in which the arrhythmogenic substrate is found in the electrical properties of the heart, and
b. Cardiomyopathies, in which structural abnormalities such as hypertrophy, dilatation, or fatty and/or fibrotic infiltration, are responsible for inducing the arrhythmia.

In this review, we focus on the genetic basis of the primary electrical diseases or ion channelopathies.

ION CHANNEL DISEASES

Ion channels are integral membrane proteins that are responsible for ion conduction across the cell membrane. Ion channel subunits are multimeric proteins formed by different subunits, which are usually encoded by separate genes. Ion channel subunits are formed by pore-forming α-subunits, which mediate ion currents, and regulatory β-subunits. In the heart, as in other excitable tissues, the generation of the action potential results from the complex balance of several ion currents. When this balance is disrupted by the altered current generated by a faulty ion channel (due to a genetic mutation), there may be a risk for electrical instability (arrhythmias in the heart or epilepsy in the brain). Channelopathy is thus defined as an inherited syndrome caused by mutations in genes encoding for ion channels, their subunits, or associated proteins.[8–13]

Several mutation-associated cardiac diseases, affecting sodium (Na^+), potassium (K^+), or calcium (Ca^{2+}) ion currents, have been described affecting either the generation of the action potential or calcium homeostasis. Cardiac channelopathies may be clinically identified only by the presence of some characteristic electrocardiographic (ECG) abnormalities.[14–16] These are not always present in genetic carriers, because the diseases often have a low penetrance.[17–20] In these situations, genetic studies may be key to providing a lead toward an etiology for the unexplained symptoms.[21]

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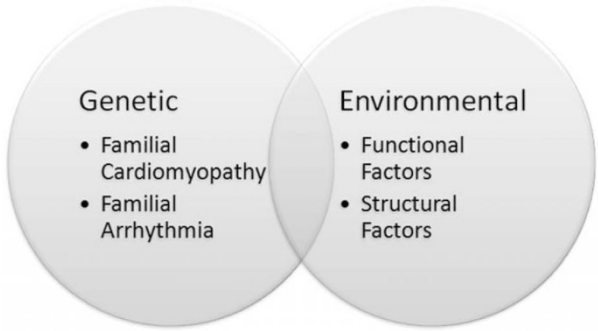

Fig. 1. Arrhythmogenic factors. Arrhythmogenesis depends on the critical interaction between environmental and genetic factors. The equilibrium prevents the arrhythmias. Alteration of only one may already induce arrhythmogenesis.

Diseases associated with sodium channel dysfunction

The α-subunit of the cardiac isoform of the sodium channel is known as Nav1.5 and is encoded by the *SCN5A* gene. Nav1.5 is a membrane protein that contains 2015 or 2016 residues (depending on the splice variant) for an approximate molecular weight of 227 kDa. It consists of four homologous domains, known as DI to DIV, joined by so-called linkers. These three linkers in addition to the N-terminus and the C-terminus of the protein are cytoplasmic. Each domain, DI to DIV, contains six transmembrane helices (namely S1–S6) linked by intracellular or extracellular loops. S5 and S6 in each of the domains form the pore-lining helices, and the extracellular loop between them is the longest among extracellular segments of Nav1.5.

Malfunctioning of cardiac Na^+ channels is the cause of some primary arrhythmia syndromes. Among others, four diseases have been associated to genetic mutations that affect Na^+ channel function: Brugada syndrome (BrS), Lev-Lenègre syndrome (familial progressive conduction disease), long QT syndrome (LQTS), and familial atrial fibrillation (AF). Certain mutations can give rise to different phenotypes with enhanced or reduced channel function and even combinations of phenotypes[8] (Table 1).

Brugada syndrome

BrS is a hereditary disease responsible for ventricular fibrillation and SCD in the young. The disease is characterized by the presence of right ventricular conduction abnormalities and coved-type ST-segment elevation in the anterior precordial leads (V1–V3). Patients with BrS have a structurally normal heart, although minor structural alterations have been described in some cases.[17–20] The prevalence of BrS is estimated to be ~35/100,000 person/year. Although the mean age of onset of events is ~40 years, SCD can affect individuals of any age, particularly men (75%). Of those patients affected, 20–50% has a family history of SCD.

The disease exhibits an autosomal dominant pattern of transmission and variable penetrance.[13,22] Most mutations occur in genes related to Na^+ channels, although other channels may also be implicated in BrS.[23] Between 20 and 25% of patients affected by BrS have mutations in the *SCN5A* gene,[24] which encodes the α-subunit of the cardiac Na^+ channel. To date, there are >200 *SCN5A* BrS-related mutations described. These mutations lead a loss of Na^+ channel function through several mechanisms.[8,12,13,24–28] Modulation of the phenotype may be related to the presence of environmental factors (i.e., inducers like fever, or medications) or additional genetic factors. A combination of two BrS mutations, each of which can produce functional but biophysically defective sodium channels, is associated with a more severe phenotype.[29] Similarly, several promoter polymorphisms have been described in *SCN5A*, which may also affect Na^+ channel function. A haplotype of six polymorphisms in the *SCN5A* promoter has been functionally linked to a reduced expression of the sodium current. This variant was found among patients of Asian origin and could explain the different clinical phenotypes and increased incidence of BrS in certain geographic regions in the Southeast Asia.[30–33]

The second gene linked to BrS is *GPD1-L*, a Na^+ channel-associated mutation also responsible of sudden death (SD) in neonates.[34] *GPD1-L* encodes for a glycerol-3-phosphate dehydrogenase-like protein of 351 amino acids. It has been shown that mutations in *GPD1-L* impair the surface membrane expression of the ion channel and reduce inward Na^+ current.[35] Other recently described minor contributors to BrS are mutations in the genes *SCN1B* (sodium channel beta-1 subunit) and *SCN3B* (beta-3 subunit of the cardiac sodium channel).[36,37]

Lev-Lenègre syndrome

Lev-Lenègre syndrome is a progressive cardiac conduction disease characterized by gradually developed ventricular fibrosis of the conduction system, which may lead to arrhythmias or asystolia.[38] The first locus for the disease was reported in 1995, on chromosome 19q13.2–13.3.[39] In 1999, the first mutations causing the disease were associated with *SCN5A*.[24] Mutations in *SCN5A* lead to a reduction in Na^+ current, reducing the velocity of the impulse conduction.[11]

Long QT syndrome

LQTS is a cardiac channelopathy characterized by a QT segment prolongation, responsible for ventricular tachyarrhythmias with associated episodes of syncope and SD.[40] LQTS is one of the leading causes of SD among young people. It can be congenital or acquired, generally in association with drugs and electrolyte imbalance (hypokalemia, hypocalcemia, and hypomagnesemia).[41] The clinical presentation can be variable, ranging from asymptomatic patients to episodes of syncope and SD caused by ventricular tachyarrhythmias (*torsade de pointes*) in a structurally normal heart.[40,42] Prolongation of the QT interval may arise because of a decrease in the K^+ repolarization currents or to an inappropriate delay in the entry of Na^+ into the myocyte.

Until now, 12 different types of LQTS have been described, most of them associated to K^+ channel disorders (potassium channel encoding genes). However, a 10–15% of the LQTS cases are related to mutations in *SCN5A* (Type 3 LQTS).[38] Patients with Type 3 LQTS present arrhythmias associated with bradycardia and symptoms at rest, especially during sleep. Type 3 LQT patients do not respond as well to β-blockers, and the presence of a long QT3 mutation is a sign of high risk for events. LQTS Type 10 is caused by a mutation in the *SCN4B* gene, which encodes the β4-subunit of the cardiac Na^+ channel (Nav4b).[43] This mutation induces a positive change in the inactivation of Na^+ channels, which increases Na^+ current and delays the repolarization in a similar fashion to Type 3 LQTS.

Atrial fibrillation

AF is defined as an unpredictable activation of the atria, characterized by irregular fibrillatory ECG waves causing an irregular ventricular response, which manifests clinically as an irregular pulse. AF is one of the most common and yet challenging arrhythmias encountered in clinical practice. The prev-

Table 1 Ion channels diseases

Channel	Disease	Inheritance	Locus	Gene
Sodium	LQT 3	Autosomal dominant	3p21–24	*SCN5A*
	LQT 10	Autosomal dominant	11q23.3	*SCN4B*
	BrS	Autosomal dominant	3p21–p24	*SCN5A*
		Autosomal dominant	3p22.3	*GPD1-L*
		Autosomal dominant	19q13.1	*SCN1B*
		Autosomal dominant	11q24.1	*SCN3B*
	Lev-Lenègre syndrome	Autosomal dominant	19q13.2	?
		Autosomal dominant	3p21	*SCN5A*
	AF	Autosomal dominant	3p21	*SCN5A*
		Autosomal dominant	19q13.1	*SCN1B*
		Autosomal dominant	11q23.3	*SCN2B*
Sodium related	LQT 9	Autosomal dominant	3p25	*Cav3*
	LQT 12	Autosomal dominant	20q11.2	*SNTA1*
Potassium	LQT 1	Autosomal dominant	11p15.5	*KCNQ1*
	LQT 2	Autosomal dominant	21p22.1–p22.2	*KCNH2*
	LQT 5	Autosomal dominant	7q35–q36	*Mink (KCNE1)*
	LQT 6	Autosomal dominant	21p22.1–p22.2	*MiRP1(KCNE2)*
	LQT 7	Autosomal dominant	17q23.1–q24.2	*KCNJ2*
	LQT 1	Autosomal recessive	11p15.5	*KCNQ1*
	LQT 5	Autosomal recessive	21q22.1	*Mink (KCNE1)*
	SQT 1	Autosomal dominant	7q35	*HERG (KCNH2)*
	SQT 2	Autosomal dominant	11p15.5	*KCNQ1*
	SQT 3	Autosomal dominant	17q23	*KCNJ2*
	AF	Autosomal dominant	10q22	?
		Autosomal dominant	6q14–q16	?
		Autosomal dominant	10p11–q21	?
		Autosomal dominant	5p15	?
		Autosomal dominant	11p15.5	*KCNQ1*
		Autosomal dominant	12p13	*KCNA5*
		Autosomal dominant	21q22	*KCNE2*
		Autosomal dominant	17q23	*KCNJ2*
	AF and BrS	Autosomal dominant	11q13–q14	*MiRP2 (KCNE3)*
	AF and SQT	Autosomal dominant	7q35	*KCNH2*
Potassium related	LQT 11	Autosomal dominant	7q21–q22	*AKAP9*
Calcium	BrS and SQT	Autosomal dominant	2p13.3	*CACNA1C*
	BrS and SQT	Autosomal dominant	10p12.33	*CACNB2b*
	Timothy syndrome	Autosomal dominant	12p13.3	*CACNA1C*
	CPVT 1	Autosomal dominant	1q42.1-q43	*RYR2*
	CPVT 2	Autosomal recessive	1p13.3	*CASQ2*
Calcium related	LQT 4	Autosomal dominant	4q25-q27	*ANKB (ANK2)*

alence of 1% among the general population increases to 10% among individuals older than 80 years and it is responsible for over one third of all cardioembolic episodes.[44] Similarly, environmental factors have been reported to be particularly important in the onset and course of the condition.[45,46]

Although familial forms had remained mostly unknown, the identification, in 1997, of a genetic locus causing familial AF[47] defined AF as a genetic disease with an autosomal dominant pattern of inheritance and initiated a deeper research into the understanding of the pathophysiology of this inherited form of the arrhythmia.

To date, most of the genes associated to AF encode K^+ channel proteins (*KCNQ1*, *KCNE2*, *KCNE3*, *KCNA5*, *KCNJ2*, and *KCNH2*).[48] However, AF has also been associated with mutations in *SCN5A*[6,49] and recently to sodium channel beta-subunits *SCN1B* and *SCN2B*,[50] in patients with AF. These findings further support the hypothesis that decreased sodium current enhances AF susceptibility. A combined phenotype of long QT3 and AF has also been described, obviously caused by a gain of function mutation.[51]

Diseases associated with potassium channel dysfunction

The potassium channels most relevant to heart diseases are the slowly activating delayed rectifier cardiac K^+ channel and the voltage-gated inwardly rectifying K^+ channel. The α-subunits of the cardiac isoforms of these two potassium channels are known as KvLQT1 and KCNH2, respectively. Potassium channels allow repolarization currents to counteract the preceding depolarization process.[27,52] Mutations in the genes that encode the K^+ channels may give rise to three types of disease: LQTS, short QT syndrome (SQTS), and AF (Table 1).

Long QT syndrome

LQTS is a cardiac channelopathy mainly caused by repolarization abnormalities related to K^+ channels. Several mutations have been reported in K^+ channels, all of which are related to a loss of function.[42] Fifty to sixty percent of the clinical cases of LQTS are associated to mutations located on six different K^+ channel genes.[53,54] Inheritance can follow an autosomal dominant (Romano-Ward syndrome) or recessive (Jervell and Lange-Nielsen syndrome) transmission pattern.[55]

The most common form of the LQTS, known as Type 1 LQTS,[56,57] is caused by mutations in *KCNQ1*. The gene product of *KCNQ1*, namely KvLQT1, encodes for the α-subunit of the slowly activating delayed rectifier cardiac K^+ channel, I_{Ks}. To date, 40–50% of the cases of prolonged QT interval are associated to mutations in *KCNQ1*.[58,59] KvLQT1 forms a complex with the protein encoded by the *KCNE1* gene (MinK, β-subunit of the K^+ channel), which regulates I_{Kr} and I_{Ks} activity.[60,61] Five mutations have been reported in the *KCNE1* gene,[62] which induce 2–5% of the cases (i.e., LQTS Type 5).

KCNH2 (human-ether-a-go-go-related gene) encodes for the α-subunit of a voltage-gated inwardly rectifying K^+ channel that mediates the rapidly activating component of I_{Kr} in the heart. Mutations in *KCNH2* lead to loss of function of the K^+ channel and account for 35–45% of cases of the so-called Type 2 LQTS.[63–65] *KCNH2* associates with *KCNE2*, a gene which encodes MiRP1, β-subunit of the rapidly activating component of I_{Kr}. KCNE2 causes Type 6 LQTS, a very rare syndrome ($<$1%) which leads to loss of channel function.[66]

LQTS Type 7, or Tawil-Anderson syndrome, is caused by loss of function mutations in *KCNJ2*. This gene encodes I_{K1} (Kir2.1), an inward rectifying K^+ channel.[67] The incidence is very low (only eight natural variants have been described to date) and rarely associated with syncopes or SD[68]; however, episodes of polymorphic or bidirectional tachycardia may occur.[69]

Short QT syndrome

Short QT syndrome is a clinically malignant entity[2] characterized by a short QT interval ($<$330 milliseconds), with tall, symmetric and peaked T waves leading to ventricular arrhythmias and SD.[70] It may cause SD in neonates, because clinical manifestations may appear early in life. Most patients have a family history of SD with an autosomal dominant pattern of transmission and a high penetrance.[71]

Mutations of three K^+ channels have been related to SQTS due to enhanced function and, therefore, shortened repolarization. Type 1 SQTS has been associated with the *KCNH2* gene (human-ether-a-go-go-related gene), which induces a fast activation of K^+ currents, with enhanced I_{Kr} function and shortened ventricular action potentials.[15] The mutation described may present with AF in some families.[72]

The SQTS Type 2 has been linked to mutations in *KCNQ1*.[71–73] The mutation enhances the function of the K^+ channel, leading to a shortening of the action potential with AF.[72] Curiously enough, a rare entity caused by a *KCNQ1* mutation has been described, which is manifested as bradycardia in utero, and short QT and AF in the neonatal period.[73]

The SQTS Type 3 is caused by a mutation in *KCNJ2* gene, which accelerates the Phase 3 of the cardiac action potential.[74] This form of short QT has a characteristic ECG pattern, described as an abrupt and sharp termination of the T wave.

Atrial fibrillation

AF is the most common arrhythmia observed in clinical practice. Several loci have been mapped and most of them encode for subunits of potassium channels.[48] In 2003, the identification of a locus on chromosome 11 in a four-generation family and the subsequent identification of *KCNQ1* as responsible for the disease provided the first link of the genetic form of the arrhythmia with an ion channelopathy.[45] The analysis of KvLQT1 (*KCNQ1*) identified a missense mutation resulting in the amino acid change S140G. Electrophysiological studies revealed a gain of function in I_{ks} current when the mutated channel was expressed with the β-subunits MinK and MirP1. This gain of function explained well the shortening of the action potential duration and effective refractory period, which are thought to be the culprits of the disease.[45] The role of *KCNQ1* in AF has recently advanced,[75] with identification of a mutation in *KCNQ1*, (R14C) in an interesting family with AF. The mutant protein only showed increase I_{Ks} upon cell stretch with a hypotonic solution opening a new and stimulating debate on the role of genetic-environmental interaction in the development of the disease. In 2005, Hong et al.,[73] described a gain of function mutation in codon 141, responsible for a severe form of AF, in utero and SQTS.

Defects in genes encoding for potassium currents were further confirmed responsible for AF with the identification of gain of function mutations in *KCNE2*,[76] in *KCNH2* (causing AF and short-QT-syndrome)[72] and in Kir2.1.[77] A genetic defect has been described in *KCNE3* [78]; however, the functional analysis did not demonstrate a different biophysical effect caused by the mutant genetic defect, indicating that it could be a rare polymorphism. In summary, the biophysical findings therefore indicated a role of gain-of-function mutations in potassium channels in AF highlighting the pathophysiological role of shortened atrial action potentials. When Olson et al.[79] described a loss-of-function mutation in *KCNA5*, the gene that encodes Kv1.5,

the debate became more stimulating because it initiated the hypothesis that a prolongation of the action potential can also be a basic mechanism for development of AF.

Diseases associated with calcium channel dysfunction

The voltage-gated calcium channel subunit alpha, Cav1.2, encoded by *CACNA1C*, is a 2221 amino acid protein with a molecular weight of 250 kDa. It is a membrane protein with a similar topology to the α-subunit of the sodium channel: it consists of four homologous domains (DI to DIV), joined by cytosolic linkers. Each domain also contains six transmembrane helices. On the other hand, the Ryanodine receptor 2, encoded by *RyR2*, and the calsequestrin 2, encoded by the *RyR2* and *CASQ2*, respectively, locate at the sarcoplasmic reticulum. The Ryanodine receptor 2 is a huge protein of 4965 residues that has 12 transmembrane helices and a variety of domains, whereas *CASQ2* is a small protein of 399 residues (46 kDa).

Calcium ions are involved in phase 2 of cardiac action potential and also increase the output of calcium from the sarcoplasmic reticulum, which functions primarily as a storehouse of calcium in the skeletal muscle, to trigger cardiac contraction. The role of calcium channels in inherited arrhythmia syndromes has only recently been demonstrated.[80] To date, a Ca^{2+} channel dysfunction can produce three different diseases—a combination of BrS with shorter than normal QT interval, Timothy syndrome (TS), and Polymorphic Ventricular Tachycardia (Table 1).

Combination of BrS and shorter than normal QT intervals

Mutations in L-type Ca^{2+} channel (*CACNA1C*) or its β2b-subunit (*CACNB2b*) have been reported in BrS patients associated with a shorter than normal QT-interval (>330 milliseconds but <360 milliseconds in male probands), which is to be expected in the presence of decreased calcium inward current. The diseases associated with mutations in *CACNA1C* and *CACNB2b* follow an autosomal dominant pattern of transmission. These mutations (A39V and G490R in *CACNA1C* and S481L in *CACNB2b*) induce a loss of calcium channel function, which in the case of the A39V mutant is most likely caused by defective trafficking to the cell membrane.[81,82]

Timothy syndrome

TS is an uncommon disease characterized by the presence of a multiorgan dysfunction, which includes severe arrhythmias with the highest associated mortality.[83] TS is also named LQT Type 8,[84] caused by mutations in *CACNA1C*.[85] Two mutations have been reported in *CACNA1C* gene, which induce a gain of function with an altered I_{Ca} with a loss of voltage-dependent channel leading to a prolongation of action potential and QT interval.[85] The effect of the TS mutation on other L-channel gating mechanisms has yet to be investigated.[83,86–88] Some groups explore mechanisms by which beta-adrenergic stimulation modulates arrhythmogenesis in order to identify potential targets for antiarrhythmic therapy.[89]

Polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a familial arrhythmogenic disorder characterized by the presence of SCD sometimes associated with bidirectional polymorphic ventricular tachycardia. Patients show a normal resting ECG although adrenergic stimulation (vigorous exercise, fear) may induce syncope and/or SCD (30–50% by the age of 20–30 years) in a structurally normal heart.[90–92]

Two genetic forms have been identified responsible for CPVT. First, an autosomal dominant form caused by mutations (>120 have been identified to date) in the *RyR2* gene (1q42–q43), encoding the ryanodine receptor (CPVT Type 1).[93] Second, a recessive form, caused by mutations in calsequestrin (*CASQ2*) (CPVT Type 2), located on 1p13–p21.[94–96] These genes are key players in the storage and calcium release from the sarcoplasmatic reticulum to the cytosol. Both genes are therefore implicated in the mediation of excitation-contraction coupling. In general, mutations lead to increased intracellular Ca^{2+}, leading to late depolarizations which predispose to arrhythmias.[95]

Diseases associated with dysfunction of ion channel-associated proteins

Mutations in proteins involved in the trafficking of ion channels into the cell membrane have also been identified as key factors leading to cardiac arrhythmias. For instance, the *ANK2* gene encodes the ankyrin-B protein, which attaches membrane proteins such as the Na^+/K^+ ATPase pump, the Na^+/Ca^{2+} exchanger, and the inositol triphosphate receptor, to cytoskeletal structures.[97] Five mutations in *ANK2* have been described as responsible for LQT Type 4, characterized by fatal ventricular arrhythmias.

Caveoline-3 (*Cav3*) is a scaffolding protein implicated in membrane trafficking and positioning of the ion channels in the sarcoplasmatic membrane. Five reported mutations in *Cav3* are responsible for an enhancement of Na^+ channel function, leading to LQT Type 9.[98]

Syntrophins are cytoplasmic submembranous proteins that are components of the dystrophin associated protein complex.[99] The cytoskeletal protein syntrophin-α1 (*SNTA1*) is known to interact with the cardiac sodium channel (Nav1.5). The reported mutations in *STNA1* cause gain-of function of Nav1.5 with increased late I_{Na}, similar to the LQT3.[100,101]

Atrial natriuretic peptide precursor encodes atrial natriuretic peptide. Atrial natriuretic peptide modulates ionic currents in cardiac myocytes and can play a role in shortening of the atrial conduction time, which could be a potential substrate for atrial reentrant arrhythmias. In 2008, Hodgson-Zingman et al.[102] identified a frame shift mutation in atrial natriuretic peptide precursor in a large family with AF.

The latest gene to be linked to AF is the one identified by Zhang et al.[103] The clinical phenotype was characterized by a neonatal onset, with autosomal recessive inheritance. They identified a mutation in *NUP155*, which encode a member of the nucleoporins. Although still unknown, the mechanism by which *NUP155* may be associated with AF could be related to modulation of calcium handling proteins and ion channel and expression of its possible target genes, like *HSP70*. This gene is located in 5p13 and had been also associated with SD in the family.

GENETIC TESTING AND PERSONALIZED MEDICINE

The relevance of the sequencing of the human genome in the understanding of a wide range of diseases cannot be understated. In particular, genetics and genetic-molecular technology have had a great impact in research of cardiovascular diseases. In these past years, thanks to research in genetics, we have identified several disease-associated genes. Obviously, the research findings in the probands have clinical implications not only for them but also for their family members. The classic paradigm of dealing with a patient with signs and symptoms for

a disease has been changed with the advent of genetics, as now we are able to identify individuals at risk (genetic carriers), usually family members, who have just a genetic variation. As a result, a new area has emerged in clinical cardiology, cardiovascular genetics, which has to deal with a new level of complexity, not with patients but with families.

Because of the inherited scenario, it is imperative that the family is approached and studied after the death of the loved one from a suspected genetic disease. The previous knowledge of an electrical disease in the proband or the family member may help find an etiology for the sudden death, may provide closure to the family, and may enable the adoption of protective measures to prevent a second SCD. Therefore, clinical investigation is important in this situation. When the clinical tools have not been sufficient, genetic investigation and the identification of a potential disease-related mutation may be extremely important; the identification of the mutation in a family member will confirm that he or she is also at risk for the genetic disease and may receive preventive therapies. Those without the familial mutation are spared from that familial disease. This is critical and useful information.

It is also obvious that the suspicion of a familiar disease will bring anxiety and concern to the families who are learning that they may be also at risk while still mourning. Therapeutic decisions in asymptomatic genetic carriers are difficult, and physicians, patients, and family members will have to cope with complex new information. Multidisciplinary teams that incorporate cardiologists, geneticists, and genetic counselors are crucial to answer potential concerns, to be expeditious in the clinical and genetic investigations, and to approach the several unknowns that still remain. These teams have been recently organized through clinical cardiovascular genetics centers and are available in any major university center.

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In Memoriam: Remembrance of Barton Childs, 1916–2010

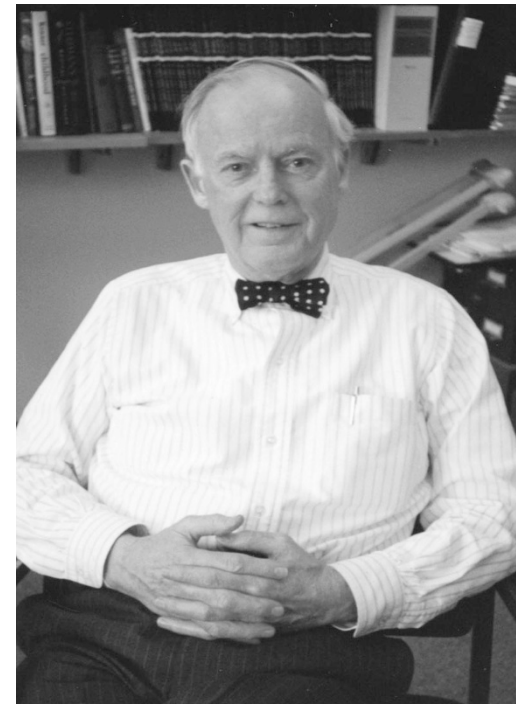
Barton Childs – eminent pediatrician, geneticist, and educator – died on 18 February 2010 at Johns Hopkins Hospital. He was 93. A tireless proponent for understanding the importance of individuality, Barton was his own best example. He was a leap-year baby, born on 29 February 1916 in Chicago, where he was raised by adoptive parents. He received his A.B. from Williams College in 1938 and that year entered the Johns Hopkins University School of Medicine, beginning an association of more than 70 years with an institution he loved. He completed his residency in Pediatrics on the Harriet Lane service of the Johns Hopkins Hospital in 1948, following three years of active duty in the U. S. Army during World War II.

Thereafter, he was away from Hopkins only for a research fellowship at Boston Children's Hospital in 1948-49 and, most important, a one-year Commonwealth Fellowship in 1952-53 at University College London, where he interacted with some of the giants of genetics including Lionel Penrose, JBS Haldane, and Harry Harris. Barton was stimulated to pursue a career in genetics by exposure to children with developmental defects. At the time, many viewed that decision as one that would divert a promising young clinician into a lifetime spent in the backwaters of medicine. How wrong they were.

One could characterize Barton's career during the next six decades as being dedicated to advancing our understanding of the role of the genes in health and disease across all areas of medicine. That passion drove him to the very end; he was a regular attendee and active participant in journal clubs, house staff conferences, and graduate student activities until the last few months of his life. To be his colleague was to be recurrently challenged, supported, and enlightened.

Barton's involvement in genetics education was not simply an appendage to his scientific and clinical work in pediatrics and genetics. It was, rather, central to his mission to integrate genetics into all of health care in a manner that would bind health professionals and the public in a partnership where genetic perspectives inform decisions about personal and public health, with prevention as the ultimate goal.

Barton was, therefore, as interested in genetics education for school children and the public as for medical students, residents, and practicing physicians, and he lent his expertise to the development of educational programs for all of those audiences. He was at pains to distinguish education from training, the latter an exposure to facts and procedures, the former rooted in enduring concepts such as variation and evolution that could serve as the basis for life-long learning. For his contributions to genetics education, Barton received the 1996 Award for Excellence in Human Genetics Education from the American Society of Human Genetics (ASHG), an apt complement to his 1973 Allan Award from ASHG, which recognized his scientific contributions to human genetics.



David Valle, MD and
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