Review Article

Effects of Mutations and Genetic Overlap in Inherited Long-QT and Brugada Arrhythmia Syndromes

Christina-Maria Kotta, Aris Anastasakis, Christodoulos Stefanadis

First Department of Cardiology, University of Athens Medical School, Hippokration Hospital, Athens, Greece

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Address:
Christina-Maria Kotta

14, Paloumbioti St.
114 76 Athens, Greece
e-mail: mckotta@hotmail.com

The functional characterisation of causative mutations behind the inherited long-QT and Brugada arrhythmia syndromes has been the focus of much research that has attempted to link the genotype to the phenotype. This article will examine our current knowledge of the effects of mutations, as well as the genetic and phenotypic overlap in inherited arrhythmia syndromes.

Long-QT syndrome

Long-QT syndrome (LQTS) is an inherited cardiac disease that is characterised by prolongation of the QT interval on the electrocardiogram and is associated with syncopal episodes, dangerous ventricular arrhythmias of the *torsades de pointes* type, and a high risk of sudden death on a substrate of a structurally normal heart.[1] Today we know that LQTS is an inherited autosomal dominant arrhythmogenic disease that is caused by mutations in the genes of cardiac ion channels and their subunits.[2-5] According to the genes involved, the type of syndrome is labelled as LQT1, LQT2, etc. (Table 1).

Brugada syndrome

Brugada syndrome (BrS) is an inherited cardiac disease that is characterised electrocardiographically by ST-segment elevation in the right precordial leads V_1-V_3, with or without right bundle branch block, and is associated with syncopal episodes and a high risk of sudden death on a substrate of a structurally normal heart.[6-9] The syndrome is inherited in an autosomal dominant manner and is estimated to be responsible for 4-12% of total sudden deaths, and for up to 20% of sudden deaths with a "normal" heart.[8-10] In addition, it is estimated to account for 40-60% of the cases of ventricular fibrillation that were previously characterised as idiopathic.[11,12] Up to now, mutations in the *SCN5A* gene, which encodes the cardiac Na^+ ion channel and constitutes the I_{Na} current, appear to form the main genetic substrate of the syndrome and are detected in about 18-30% of patients, with a higher prevalence in the purely familial forms of the syndrome (Table 1).[13-17]

Structure of the cardiac ion channels

The cardiac ion channels are macromolecular protein complexes of the cellular membrane, which, by responding to differences in transmembrane potential, change their stereochemical structure. These stereochemical changes, though small, lead to the opening of a pore through which, within fractions of a second, millions of

Table 1. The main genes of long-QT syndrome and Brugada syndrome.

Type	Gene	Chromosome	Protein	Function	Frequency	Reference
LQT1	*KCNQ1*	11p15.5	$K_v7.1$ α	I_{Ks} ↓	~30-35%	77
LQT2	*KCNH2*	7q35-36	$K_v11.1$ α	I_{Kr} ↓	~25-30%	2
LQT3	*SCN5A*	3p21-23	$Na_v1.5$ α	I_{Na} ↑	~5-7%	3
LQT5	*KCNE1*	21q22.1-22.2	minK β	I_{Ks} ↓	~1%	80
LQT6	*KCNE2*	21q22.1-22.2	MiRP1 β	I_{Kr} ↓	~1%	79
BrS1	*SCN5A*	3p21-23	$Na_v1.5$ α	I_{Na} ↓	~18-30%	13

↑↓ – Increase or decrease in cardiac current in the case of mutation, respectively.

ions enter or leave the cell, creating a current of some picoamperes.[18] The process of cellular depolarisation and repolarisation is carried out via four successive, discrete stages of changes in the stereochemical condition of the channels, which are specific to each channel.[19] Nevertheless, all voltage-dependent channels have several structural and functional characteristics in common, such as a voltage sensor that detects the changes in potential, the pore, which in response to the sensor opens and closes, allowing or preventing the flow of ions, and the ion selection filter.[18,19]

Functional consequences of the mutations

The functional cardiac currents are the result of the perfectly coordinated expression of the biophysical, biochemical, and biogenic properties of their channels.[20] Obviously, even small changes in the structures of the channels as a result of mutations are capable of influencing and damaging these complex functional properties. This influence may result in a partial or complete loss of functionality, or an additional, greater than normal functionality. Thus, as a first approximation, the mutations are classified into those that lead to *gain-of-function* and those that result in *loss-of-function*.

LQTS

In LQTS we know that mutations in the genes for the K^+ channels (LQT1,2,5,6) lead to loss-of-function, materially reducing the intensity of the I_{Kr} and I_{Ks} currents, and hence the "repolarisation reserve", while changes in the gene for the Na^+ channel (LQT3) lead to gain-of-function, increasing the intensity of the I_{Na} channel, and hence depolarisation.[21]

In the case of mutations of the cardiac K^+ channels, their pathological action is exerted via two main mechanisms. The first concerns the ability of subunits to assemble into tetramers, resulting in a dramatic reduction (~50%) in the available functional channels and a corresponding dramatic decrease in flow. This phenomenon is defined as *haploinsufficiency*.[22,23] The second mechanism concerns mutations that lead to structural anomalies in the subunits, which most often alter the kinetics or the conduction of the channel. This mechanism is defined as *dominant-negative suppression*.[24-28]

In contrast to the mutations of the cardiac K^+ channels, mutations of the *SCN5A* gene in LQTS have a common mechanism and lead to gain-of-function, mainly through imperfect deactivation of the channels, or destabilisation or slowing of the deactivation process.[29] In each case, the result is the presence of late inward I_{Na} depolarisation currents in the plateau phase of the cardiac action potential, which, even though of low intensity, prolong its duration. This prolongation leads to the appearance of premature afterdepolarisations.[30,31]

BrS

In BrS the mutations in the Na^+ channel gene (*SCN5A*) cause reduced functionality and a decrease in the I_{Na} current.[32-35] Some mutations lead to completely non-functional channels, while others alter their biophysical properties.[35] Frame-shift, nonsense, and splice mutations lead to completely non-functional channels, reducing by half the available functional channels (haploinsufficiency).[13,36,37] Many missense mutations have also been described that appeared to reduce the permeability and conductivity of the Na^+ channel, or to lead to channels with altered biophysical properties.[38] The result in each case is a decrease in the I_{Na} current (Figure 1).

Clinical significance of the mutation type

LQTS

Mutations that, because of topology (carboxy-terminal end), are associated with a milder ('*forme fruste*')

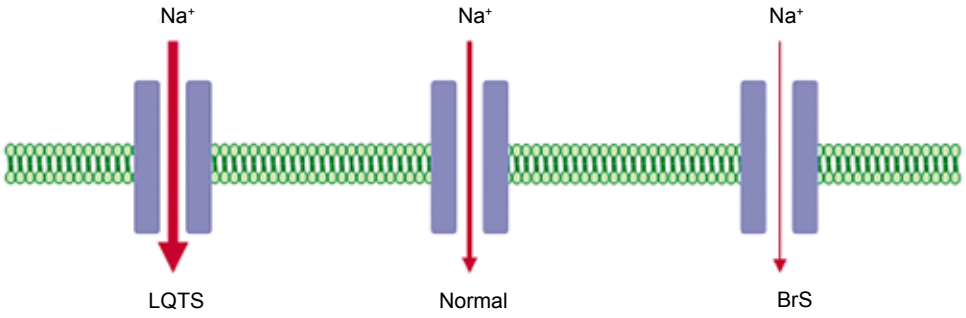

Figure 1. Gain- and loss-of-function of the Na+ channels in long-QT syndrome and Brugada syndrome, with an increase and decrease in cardiac I_{Na} current, respectively.

phenotype and clinical course have been described in types LQT1, LQT2, and LQT5.[39-41] A recent study of LQT1 patients showed that patients who carried transmembrane (which mainly affect the channel's pore and voltage sensor), missense (which lead to channels with altered biophysical properties), or dominant-negative suppression mutations, independently have a significantly increased risk of cardiac events of all kinds, compared to those who have carboxy-terminal, non-missense or haploinsufficiency mutations.[42]

BrS

A recent study of patients with mutations in the *SCN5A* gene showed that the level of loss-of-function caused by each mutation partially reflects the clinical phenotype.[43] Mutations that cause complete loss-of-function (nonsense) have been found to be associated with a significantly higher incidence of syncope and more severe conduction disturbances (prolongation of QRS on challenge and PR on challenge and rest) compared to mutations that cause reduced function (many of them missense). Research into this matter is currently ongoing so that the genetic data can serve as a new risk stratification index in the future.

Genetic overlap with other arrhythmogenic syndromes

Discrete mutations of the genes of cardiac ion channels have been described that, by affecting in various ways the cardiac repolarisation currents I_{Ks}, I_{Kr}, I_{K1} and the depolarisation I_{Na} current, form the pathological substrate of discrete syndromes. Thus, mutations in these genes are also implicated, apart from LQTS and BrS, in short QT syndrome (SQTS), in forms of familial atrial fibrillation, in systemic conduction disease, in idiopathic ventricular fibrillation, and in congenital sick sinus syndrome (Figure 2).[44-45]

The recognition that mutations that cause loss-of-function of the K^+ channels lead to the clinical phenotype of LQTS, while others, which cause gain-of-function, lead to the clinical phenotype of SQTS, starts to bring some kind of sense to the matter.[21,44-46] Accordingly, it is understandable how mutations that cause loss-of-function of the Na^+ channel lead to the clinical phenotype of BrS, while others, which cause gain-of-function, lead to the clinical phenotype of LQTS.[21,33,35] This relatively simple interpretation has validity, but becomes more complicated in light of other findings.

At the heart of the question of genetic overlapping lies mainly the *SCN5A* gene. Discrete mutations of the gene, most of which cause loss-of-function, form the common genetic denominator in various syndromes, but in addition these same mutations appear to lead in some cases to different phenotypes, which, even within the same family, can be manifested in a mixed, combined, or exclusive form (Figure 3).[55-64] Furthermore, data from recent studies have also implicated subclinical mutations of the gene in ventricular fibrillation during the first hours of acute myocardial infarction.[65,66] In many cases, the functional character of these mutations in cellular expression systems *in vitro* has been shown to affect a wide assortment of the channel's biophysical properties at the same time, with simultaneous multilevel loss-of-function, resulting in various clinical manifestations. An example is the mutation 1795 insD, which leads to the coexistence of LQTS and BrS, which is almost incomprehensible on the clinical level.[59]

Nevertheless, what these functional studies do

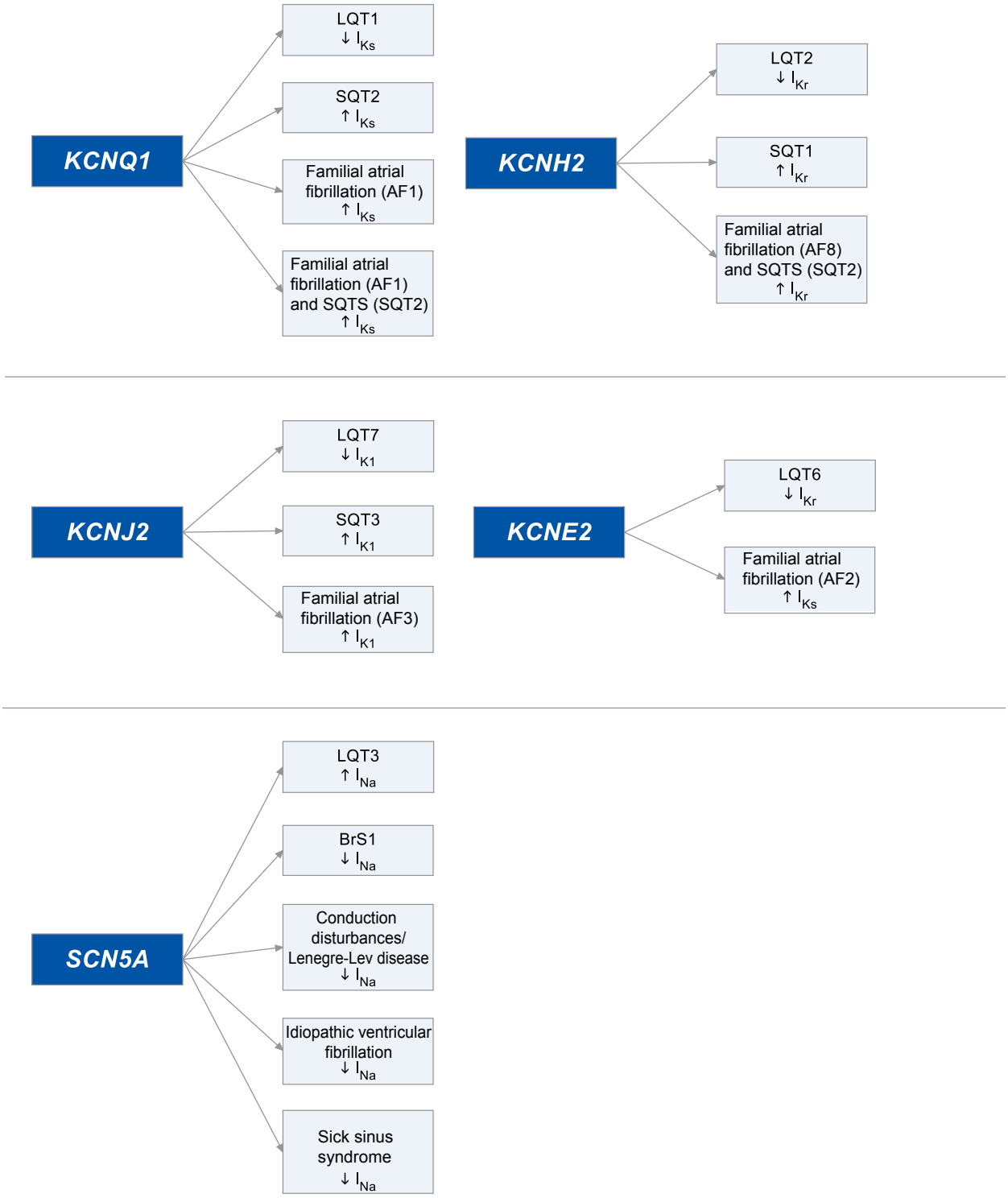

Figure 2. Genetic overlap of the genes of the cardiac channels *KCNQ1*,[44,47,48,77] *KCNH2*,[2,45,49] *KCNJ2*,[46,50,78] *KCNE2*,[51,79], *SCN5A*.[3,13,52-55] ↑↓ – increase or decrease of current in the case of mutation, respectively.

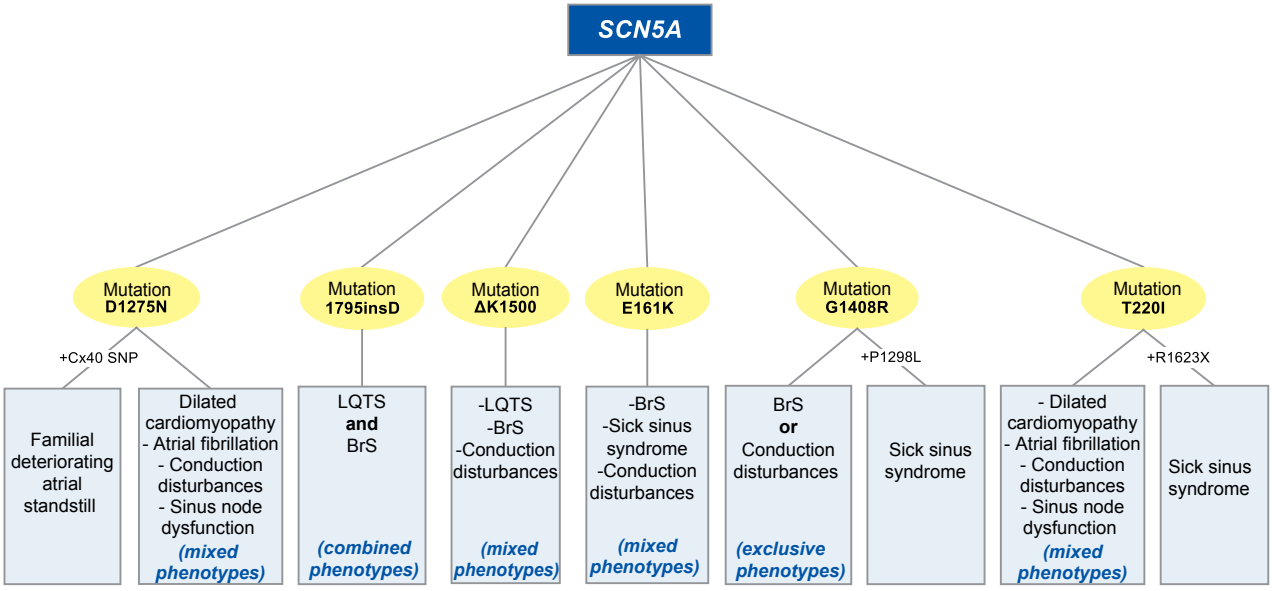

Figure 3. Genetic overlap of the *SCN5A* gene via the D1275N,[56-58] 1795insD,[59-61] ΔK1500,[62] E161K,[63] G1408R,[55,64] T220I[55,58] mutations. Mixed phenotypes – one or more or all of the above. Combined phenotypes – all of the above. Exclusive phenotypes – one of the above. +Cx40 SNP – the phenotype is manifested only when there coexists a specific polymorphism of the connexin 40 gene. +P1298L/+R1623X – the phenotype is manifested only when these mutations also coexist (compound heterozygotes).

not explain is how various combinations of mixed and exclusive phenotypes can appear among people who are carriers of the same mutation of the *SCN5A* gene. The same question also essentially applies to the varying degrees of penetrance and expressivity that the diseases often exhibit among patients who are carriers of discrete mutations of the other genes of the cardiac channels, which lead to classical forms of the syndromes without significant genetic overlapping. The factors of sex and age are often reported not to contribute to these differences.[62] Thus, the picture that starts to take shape is one where the main genetic substrate is the central axis of the clinical outcome, but the way and the extent to which it is expressed depend to a significant degree on other factors.[67,68]

By the term "modifying factors" we mean mainly those environmental and genetic factors whose effects shape the clinical outcome. The prevailing view is that environmental factors are probably mainly responsible for the paroxysmal manifestations of familial syndromes, while genetic factors are mainly implicated in the interpersonal variations between patients with a common main pathological substrate.[67] The genetic modifying factors mainly concern the single nucleotide polymorphisms (SNPs), which are normally responsible for about 90% of our genetic diversity.[68]

Genetic modification via SNPs is applied either via the interaction with the main pathological substrate by the same gene, or by a different gene, while, according to the case, this interaction may either exacerbate the final pathological expression or mitigate it.[68] An indicative example of the exertion of modifying action by the same gene is the SNP H558R of *SCN5A*, where its presence in homozygous form (R558) in combination with any of the mutations T512I, M1766L, and R282H of *SCN5A*, significantly mitigates their pathological expression (less loss of I_{Na}).[69-71] Even though the molecular mechanisms behind these effects are not known, such types of phenomenon appear also to contribute significantly to the degree of penetrance and to the selective phenotypical expressions of the diseases.[68]

The quest for a genetic variant with a modifying action beyond that of the pathological reference gene opens up a vast array of possibilities, and our knowledge of this matter is still woefully scanty. To get some kind of picture, we can turn to a recent study that showed that certain SNPs of the genes of the α_2 and β_1 adrenergic receptors are associated with an increased symptomatology and risk of cardiac events among patients with LQTS who have the same pathological mutation of LQT1.[72]

An understanding of the nature of genetic modifying factors is the next central goal in the understanding of inherited arrhythmogenic syndromes. To achieve this goal it is likely that our gaze will need to be less focused. The role of mutations of cardiac ion channels appears to extend beyond the myocytes of the ventricles and to those of the atria, to the specialised cells of the conduction system, the sinus node, and the Purkinje fibres, where they exert their effect through interactive and feedback processes with dozens of other proteins that compose a complex, and in places specialised, cellular environment. This theory also has another dimension, that of a possible cellular remodelling as a result of the cardiac ion channel mutations' additive pathological effect. Finally, the view has been expressed that these mutations probably also disturb the architecture of the intracellular environment, leading locally to foci of fibrosis, apoptosis, and cell death.[63,73,74] This seems to concern mainly the Na^+ channels, which have complex natural roles in the atria, the ventricles, and the conduction system.[74]

Mutations of the *SCN5A* gene have recently been implicated in cases of mixed phenotypes, with concomitant idiopathic dilated cardiomyopathy (Figure 3).[57,58] In addition, in some cases of patients with a clinical BrS phenotype, some of whom were carriers of mutations of the *SCN5A* gene and had a "normal" heart on non-invasive clinical examination, the histology of samples from endomyocardial biopsy revealed structural lesions.[75,76] To what extent this genetic substrate contributes to the development of structural changes, or whether the two exist independently and in combination are responsible for the clinical phenotype, remains to be elucidated.[73]

Clinical and basic research into inherited cardiac diseases still has to overcome many challenges, and it seems that this will require a combination of approaches. The continual feedback of information from bench to bedside, and *vice versa*, composes the continuously cycling collaboration that, even today, is leading to the provision of better health services[81] and on which progress and understanding of these diseases mainly depends. With each step we take towards the future, this information steadily acquires added value.

References

1. Schwartz PJ, Periti M, Malliani A. The long Q-T syndrome. Am Heart J. 1975; 89: 378-390.
2. Curran ME, Splawski I, Timothy KW, Vincent GM, Green ED, Keating MT. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. Cell. 1995; 80: 795-803.
3. Wang Q, Shen J, Splawski I, et al. SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. Cell. 1995; 80: 805-811.
4. Splawski I, Shen J, Timothy KW, et al. Spectrum of mutations in long-QT syndrome genes. KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. Circulation. 2000; 102: 1178-1185.
5. Chiang CE, Roden DM. The long QT syndromes: genetic basis and clinical implications. J Am Coll Cardiol. 2000; 36: 1-12.
6. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol. 1992; 20: 1391-1396.
7. Brugada J, Brugada R, Brugada P. Right bundle-branch block and ST-segment elevation in leads V1 through V3: a marker for sudden death in patients without demonstrable structural heart disease. Circulation. 1998; 97: 457-460.
8. Brugada J, Brugada P, Brugada R. The syndrome of right bundle branch block ST segment elevation in V1 to V3 and sudden death—the Brugada syndrome. Europace. 1999; 1: 156-166.
9. Brugada P, Brugada R, Brugada J. Sudden death in patients and relatives with the syndrome of right bundle branch block, ST segment elevation in the precordial leads V(1) to V(3) and sudden death. Eur Heart J. 2000; 21: 321-326.
10. Benito B, Brugada R, Brugada J, Brugada P. Brugada syndrome. Prog Cardiovasc Dis. 2008; 51: 1-22.
11. Gussak I, Antzelevitch C, Bjerregaard P, Towbin JA, Chaitman BR. The Brugada syndrome: clinical, electrophysiologic and genetic aspects. J Am Coll Cardiol. 1999; 33: 5-15.
12. Grace AA. Brugada syndrome. Lancet. 1999; 354: 445-446.
13. Chen Q, Kirsch GE, Zhang D, et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. Nature. 1998; 392: 293-296.
14. Antzelevitch C, Brugada P, Brugada J, Brugada R. Brugada syndrome: from cell to bedside. Curr Probl Cardiol. 2005; 30: 9-54.
15. Napolitano C, Priori SG. Brugada syndrome. Orphanet J Rare Dis. 2006; 1: 35.
16. Schulze-Bahr E, Eckardt L, Breithardt G, et al. Hum Mutat. 2003; 21: 651-652.
17. Kotta CM, Anastasakis A, Gatzoulis K, Manolis AS, Stefanadis C. Novel sodium channel SCN5A mutations in Brugada syndrome patients from Greece. Int J Cardiol. 2010; 145: 45-48.
18. Ackerman MJ, Clapham DE. Ion channels—basic science and clinical disease. N Engl J Med. 1997; 336: 1575-1586.
19. Sansom MS. Ion channels: structure of a molecular brake. Curr Biol. 1999; 9: R173-175.
20. Delisle BP, Anson BD, Rajamani S, January CT. Biology of cardiac arrhythmias: ion channel protein trafficking. Circ Res. 2004; 94: 1418-1428.
21. Roden DM, Lazzara R, Rosen M, Schwartz PJ, Towbin J, Vincent GM. Multiple mechanisms in the long-QT syndrome. Current knowledge, gaps, and future directions. The SADS Foundation Task Force on LQTS. Circulation. 1996; 94: 1996-2012.
22. Keating MT, Sanguinetti MC. Molecular and cellular mecha-

nisms of cardiac arrhythmias. Cell. 2001; 104: 569-580.
23. Tristani-Firouzi M, Chen J, Mitcheson JS, Sanguinetti MC. Molecular biology of K(+) channels and their role in cardiac arrhythmias. Am J Med. 2001; 110: 50-59.
24. Sanguinetti MC, Curran ME, Spector PS, Keating MT. Spectrum of HERG K+-channel dysfunction in an inherited cardiac arrhythmia. Proc Natl Acad Sci U S A. 1996; 93: 2208-2212.
25. Wollnik B, Schroeder BC, Kubisch C, Esperer HD, Wieacker P, Jentsch TJ. Pathophysiological mechanisms of dominant and recessive KVLQT1 K+ channel mutations found in inherited cardiac arrhythmias. Hum Mol Genet. 1997; 6: 1943-1949.
26. Bianchi L, Shen Z, Dennis AT, et al. Cellular dysfunction of LQT5-minK mutants: abnormalities of IKs, IKr and trafficking in long QT syndrome. Hum Mol Genet. 1999; 8: 1499-1507.
27. Bianchi L, Priori SG, Napolitano C, et al. Mechanisms of I(Ks) suppression in LQT1 mutants. Am J Physiol Heart Circ Physiol. 2000; 279: H3003-3011.
28. Brunner M, Peng X, Liu GX, et al. Mechanisms of cardiac arrhythmias and sudden death in transgenic rabbits with long QT syndrome. J Clin Invest. 2008; 118: 2246-2259.
29. Wang DW, Yazawa K, George AL, Bennett PB. Characterization of human cardiac Na+ channel mutations in the congenital long QT syndrome. Proc Natl Acad Sci U S A. 1996; 93: 13200-13205.
30. Kass RS, Moss AJ. Long QT syndrome: novel insights into the mechanisms of cardiac arrhythmias. J Clin Invest. 2003; 112: 810-815.
31. Grant AO. Molecular biology of sodium channels and their role in cardiac arrhythmias. Am J Med. 2001; 110: 296-305.
32. Tan HL, Bezzina CR, Smits JP, Verkerk AO, Wilde AA. Genetic control of sodium channel function. Cardiovasc Res. 2003; 57: 961-973.
33. Bezzina CR, Rook MB, Wilde AA. Cardiac sodium channel and inherited arrhythmia syndromes. Cardiovasc Res. 2001; 49: 257-271.
34. Balser JR. Sodium "channelopathies" and sudden death: must you be so sensitive? Circ Res. 1999; 85: 872-874.
35. Viswanathan PC, Balser JR. Inherited sodium channelopathies: a continuum of channel dysfunction. Trends Cardiovasc Med. 2004; 14: 28-35.
36. Baroudi G, Napolitano C, Priori SG, Del Bufalo A, Chahine M. Loss of function associated with novel mutations of the SCN5A gene in patients with Brugada syndrome. Can J Cardiol. 2004; 20: 425-430.
37. Keller DI, Barrane FZ, Gouas L, et al. A novel nonsense mutation in the SCN5A gene leads to Brugada syndrome and a silent gene mutation carrier state. Can J Cardiol. 2005; 21: 925-931.
38. Vatta M, Dumaine R, Antzelevitch C, et al. Novel mutations in domain I of SCN5A cause Brugada syndrome. Mol Genet Metab. 2002; 75: 317-324.
39. Berthet M, Denjoy I, Donger C, et al. C-terminal HERG mutations: the role of hypokalemia and a KCNQ1-associated mutation in cardiac event occurrence. Circulation. 1999; 99: 1464-1470.
40. Donger C, Denjoy I, Berthet M, et al. KVLQT1 C-terminal missense mutation causes a forme fruste long-QT syndrome. Circulation. 1997; 96: 2778-2781.
41. Ohno S, Zankov DP, Yoshida H, et al. N- and C-terminal KCNE1 mutations cause distinct phenotypes of long QT syndrome. Heart Rhythm. 2007; 4: 332-340.
42. Moss AJ, Shimizu W, Wilde AA, et al. Clinical aspects of type-1 long-QT syndrome by location, coding type, and biophysical function of mutations involving the KCNQ1 gene. Circulation. 2007; 115: 2481-2489.
43. Meregalli PG, Tan HL, Probst V, et al. Type of SCN5A mutation determines clinical severity and degree of conduction slowing in loss-of-function sodium channelopathies. Heart Rhythm. 2009; 6: 341-348.
44. Bellocq C, van Ginneken AC, Bezzina CR, et al. Mutation in the KCNQ1 gene leading to the short QT-interval syndrome. Circulation. 2004; 109: 2394-2397.
45. Brugada R, Hong K, Dumaine R, et al. Sudden death associated with short-QT syndrome linked to mutations in HERG. Circulation. 2004; 109: 30-35.
46. Priori SG, Pandit SV, Rivolta I, et al. A novel form of short QT syndrome (SQT3) is caused by a mutation in the KCNJ2 gene. Circ Res. 2005; 96: 800-807.
47. Chen YH, Xu SJ, Bendahhou S, et al. KCNQ1 gain-of-function mutation in familial atrial fibrillation. Science. 2003; 299: 251-254.
48. Hong K, Piper DR, Diaz-Valdecantos A, et al. De novo KCNQ1 mutation responsible for atrial fibrillation and short QT syndrome in utero. Cardiovasc Res. 2005; 68: 433-440.
49. Hong K, Bjerregaard P, Gussak I, Brugada R. Short QT syndrome and atrial fibrillation caused by mutation in KCNH2. J Cardiovasc Electrophysiol. 2005; 16: 394-396.
50. Xia M, Jin Q, Bendahhou S, et al. A Kir2.1 gain-of-function mutation underlies familial atrial fibrillation. Biochem Biophys Res Commun. 2005; 332: 1012-1019.
51. Yang Y, Xia M, Jin Q, et al. Identification of a KCNE2 gain-of-function mutation in patients with familial atrial fibrillation. Am J Hum Genet. 2004; 75: 899-905.
52. Schott JJ, Alshinawi C, Kyndt F, et al. Cardiac conduction defects associate with mutations in SCN5A. Nat Genet. 1999; 23: 20-21.
53. Probst V, Kyndt F, Potet F, et al. Haploinsufficiency in combination with aging causes SCN5A-linked hereditary Lenègre disease. J Am Coll Cardiol. 2003; 41: 643-652.
54. Akai J, Makita N, Sakurada H, et al. A novel SCN5A mutation associated with idiopathic ventricular fibrillation without typical ECG findings of Brugada syndrome. FEBS Lett. 2000; 479: 29-34.
55. Benson DW, Wang DW, Dyment M, et al. Congenital sick sinus syndrome caused by recessive mutations in the cardiac sodium channel gene (SCN5A). J Clin Invest. 2003; 112: 1019-1028.
56. Groenewegen WA, Firouzi M, Bezzina CR, et al. A cardiac sodium channel mutation cosegregates with a rare connexin 40 genotype in familial atrial standstill. Circ Res. 2003; 92: 14-22.
57. McNair WP, Ku L, Taylor MR, et al. SCN5A mutation associated with dilated cardiomyopathy, conduction disorder, and arrhythmia. Circulation. 2004; 110: 2163-2167.
58. Olson TM, Michels VV, Ballew JD, et al. Sodium channel mutations and susceptibility to heart failure and atrial fibrillation. JAMA. 2005; 293: 447-454.
59. Bezzina C, Veldkamp MW, van Den Berg MP, et al. A single Na(+) channel mutation causing both long-QT and Brugada syndromes. Circ Res. 1999; 85: 1206-1213.
60. Veldkamp MW, Viswanathan PC, Bezzina C, Baartscheer A, Wilde AA, Balser JR. Two distinct congenital arrhythmias evoked by a multidysfunctional Na(+) channel. Circ Res.

2000; 86: E91-97.
61. Clancy CE, Rudy Y. Na(+) channel mutation that causes both Brugada and long-QT syndrome phenotypes: a simulation study of mechanism. Circulation. 2002; 105: 1208-1213.
62. Grant AO, Carboni MP, Neplioueva V, et al. Long QT syndrome, Brugada syndrome, and conduction system disease are linked to a single sodium channel mutation. J Clin Invest. 2002; 110: 1201-1209.
63. Smits JP, Koopmann TT, Wilders R, et al. A mutation in the human cardiac sodium channel (E161K) contributes to sick sinus syndrome, conduction disease and Brugada syndrome in two families. J Mol Cell Cardiol. 2005; 38: 969-981.
64. Kyndt F, Probst V, Potet F, et al. Novel SCN5A mutation leading either to isolated cardiac conduction defect or Brugada syndrome in a large French family. Circulation. 2001; 104: 3081-3086.
65. Hu D, Viskin S, Oliva A, et al. Genetic predisposition and cellular basis for ischemia-induced ST-segment changes and arrhythmias. J Electrocardiol. 2007; 40: S26-29.
66. Hu D, Viskin S, Oliva A, et al. Novel mutation in the SCN5A gene associated with arrhythmic storm development during acute myocardial infarction. Heart Rhythm. 2007; 4: 1072-1080.
67. Priori SG. Inherited arrhythmogenic diseases: the complexity beyond monogenic disorders. Circ Res. 2004; 94: 140-145.
68. Scicluna BP, Wilde AA, Wilde AW, Bezzina CR. The primary arrhythmia syndromes: same mutation, different manifestations. Are we starting to understand why? J Cardiovasc Electrophysiol. 2008; 19: 445-452.
69. Viswanathan PC, Benson DW, Balser JR. A common SCN5A polymorphism modulates the biophysical effects of an SCN5A mutation. J Clin Invest. 2003; 111: 341-346.
70. Ye B, Valdivia CR, Ackerman MJ, Makielski JC. A common human SCN5A polymorphism modifies expression of an arrhythmia causing mutation. Physiol Genomics. 2003; 12: 187-193.
71. Poelzing S, Forleo C, Samodell M, et al. SCN5A polymorphism restores trafficking of a Brugada syndrome mutation on a separate gene. Circulation. 2006; 114: 368-376.
72. Schwartz PJ, Vanoli E, Crotti L, et al. Neural control of heart rate is an arrhythmia risk modifier in long QT syndrome. J Am Coll Cardiol. 2008; 51: 920-929.
73. Saffitz JE. Structural heart disease, SCN5A gene mutations, and Brugada syndrome: a complex ménage à trois. Circulation. 2005; 112: 3672-3674.
74. Lehnart SE, Ackerman MJ, Benson DW, et al. Inherited arrhythmias: a National Heart, Lung, and Blood Institute and Office of Rare Diseases workshop consensus report about the diagnosis, phenotyping, molecular mechanisms, and therapeutic approaches for primary cardiomyopathies of gene mutations affecting ion channel function. Circulation. 2007; 116: 2325-2345.
75. Frustaci A, Priori SG, Pieroni M, et al. Cardiac histological substrate in patients with clinical phenotype of Brugada syndrome. Circulation. 2005; 112: 3680-3687.
76. Coronel R, Casini S, Koopmann TT, et al. Right ventricular fibrosis and conduction delay in a patient with clinical signs of Brugada syndrome: a combined electrophysiological, genetic, histopathologic, and computational study. Circulation. 2005; 112: 2769-2777.
77. Wang Q, Curran ME, Splawski I, et al. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. Nat Genet. 1996; 12: 17-23.
78. Plaster NM, Tawil R, Tristani-Firouzi M, et al. Mutations in Kir2.1 cause the developmental and episodic electrical phenotypes of Andersen's syndrome. Cell. 2001; 105: 511-519.
79. Abbott GW, Sesti F, Splawski I, et al. MiRP1 forms IKr potassium channels with HERG and is associated with cardiac arrhythmia. Cell. 1999; 97: 175-187.
80. Splawski I, Tristani-Firouzi M, Lehmann MH, Sanguinetti MC, Keating MT. Mutations in the hminK gene cause long QT syndrome and suppress IKs function. Nat Genet. 1997; 17: 338-340.
81. Fowler SJ, Cerrone M, Napolitano C, Priori SG. Genetic testing for inherited cardiac arrhythmias. Hellenic J Cardiol. 2010; 51: 92-103.