ABOUT SCN5A MUTATIONS CHRONOLOGICAL PUBLICATIONS

1992

Gellens ME, George AL Jr, Chen LQ, Chahine M, Horn R, Barchi RL, Kallen RG.Primary structure and functional expression of the human cardiac tetrodotoxin-insensitive voltage-dependent sodium channel. Proc Natl Acad Sci U S A 1992 Jan 15;89(2):554-8

Department of Medicine, University of Pennsylvania, Philadelphia 19104.

The principal voltage-sensitive sodium channel from human heart has been cloned, sequenced, and functionally expressed. The cDNA, designated hH1, encodes a 2016-amino acid protein that is homologous to other members of the sodium channel multigene family and bears greater than 90% identity to the tetrodotoxin-insensitive sodium channel characteristic of rat heart and of immature and denervated rat skeletal muscle. Northern blot analysis demonstrates an approximately 9.0-kilobase transcript expressed in human atrial and ventricular cardiac muscle but not in adult skeletal muscle, brain, myometrium, liver, or spleen. When expressed in Xenopus oocytes, hH1 exhibits rapid activation and inactivation kinetics similar to native cardiac sodium channels. The single channel conductance of hH1 to sodium ions is about twice that of the homologous rat channel and hH1 is more resistant to block by tetrodotoxin (IC50 = 5.7 microM). hH1 is also resistant to mu-conotoxin but sensitive to block by therapeutic concentrations of lidocaine in a use-dependent manner.

1995

George AL Jr, Varkony TA, Drabkin HA, Han J, Knops JF, Finley WH, Brown GB, Ward DC, Haas M Assignment of the human heart tetrodotoxin-resistant voltage-gated Na+ channel alpha-subunit gene (SCN5A) to band 3p21. Cytogenet Cell Genet 1995;68:67-70

Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN.

The chromosomal location of SCN5A, the gene encoding the principal voltage-gated Na+ channel expressed in human heart, has been determined by three independent methodologies: somatic cell hybrid mapping, chromosomal microdissection-polymerase chain reaction, and fluorescence in situ hybridization. The SCN5A gene was assigned to the short arm of chromosome 3 (band 3p21) by all three approaches. These data are further evidence that striated muscle Na+ channel genes are dispersed in the genome.

Wang Q, Shen J, Splawski I, Atkinson D, Li Z, Robinson JL, Moss AJ, Towbin JA, Keating MT. SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. Cell 1995 Mar 10;80(5):805-811.

University of Utah Health Sciences Center, Salt Lake City 84112.

Long QT syndrome (LQT) is an inherited disorder that causes sudden death from cardiac arrhythmias, specifically torsade de pointes and ventricular fibrillation. We previously mapped three LQT loci: LQT1 on chromosome 11p15.5, LQT2 on 7q35-36, and LQT3 on 3p21-24. Here we report genetic linkage between LQT3 and polymorphisms within SCN5A, the cardiac sodium channel gene. Single strand conformation polymorphism and DNA sequence analyses reveal identical intragenic deletions of SCN5A in affected members of two unrelated LQT families. The deleted sequences reside in a region that is important for channel inactivation. These data suggest that mutations in SCN5A cause chromosome 3-linked LQT and indicate a likely cellular mechanism for this disorder.

Schwartz PJ, Priori SG, Locati EH et al. Long QT syndrome patients with mutations of the SCN5A and HERG genes have differential responses to Na^+ channel blockade and to increases in heart rate: implications for gene-specific therapy. Circulation 1995;92:3381-3386.

Bennett PB, Yazawa K, Makita N, George AL Jr. Molecular mechanism for an inherited cardiac arrhythmia. Nature 1995 Aug 24;376(6542):683-5
Comment in: Nature. 1995 Aug 24;376(6542):640.

Department of Pharmacology, Vanderbilt University Medical Center, Nashville, Tennessee 37232, USA.

In the congenital long-QT syndrome, prolongation of the cardiac action potential occurs by an unknown mechanism and predisposes individuals to syncope and sudden death as a result of ventricular arrhythmias. Genetic heterogeneity has been demonstrated for autosomal dominant long-QT syndrome by the identification of multiple distinct loci, and associated mutations in two candidate genes have recently been reported. One form of hereditary long QT (LQT3) has been linked to a mutation in the gene encoding the human heart voltage-gated sodium-channel alpha-subunit (SCN5A on chromosome 3p21). Here we characterize this mutation using heterologous expression of recombinant human heart sodium channels. Mutant channels show a sustained inward current during membrane depolarization. Single-channel recordings indicate that mutant channels fluctuate between normal and non-inactivating gating modes. Persistent inward sodium current explains prolongation of cardiac action potentials, and provides a molecular mechanism for this form of congenital long-QT syndrome.

Wang Q, Shen J, Li Z, Timothy K, Vincent GM, Priori SG, Schwartz PJ, Keating MT. Cardiac sodium channel mutations in patients with long QT syndrome, an inherited cardiac arrhythmia. Hum Mol Genet 1995 Sep;4(9): 1603-7

Howard Hughes Medical Institute, University of Utah Health Sciences Center, Salt Lake City 84112, USA.

Long QT syndrome (LQT) is an inherited cardiac disorder that causes syncope, seizures and sudden death from ventricular tachyarrhythmias. We used single-strand conformation polymorphism (SSCP) and DNA sequence analyses to identify mutations in the cardiac sodium channel gene, SCN5A, in affected members of four LQT families. These mutations include two identical intragenic deletions and two missense mutations. These data suggest that SCN5A mutations cause LQT. The location and character of these mutations suggest that this form of LQT results from a delay in cardiac sodium channel fast inactivation or altered voltage-dependence of inactivation.

1996

Nakajima T, Kaneko Y, Taniguchi Y, Nagai R. [Long QT syndrome] Nippon Rinsho 1996 Mar;54(3):776-81

[Article in Japanese]
Second Department of Internal Medicine, Gunma University School of Medicine, Japan.

Romano-Ward syndrome, one of familial long QT syndromes, is an inherited disorder that causes sudden death from cardiac arrhythmias, specifically torsade de pointes and ventricular fibrillation. By linkage analyses, three LQT loci were previously mapped: LQT1 on chromosome 11p15.5, LQT2 on 7q35-36, LQT3 on 3p21-24. It was recently brought to light that LQT2 and LQT3 were caused by mutations of the gene encoding cardiac ion channels. Mutations in HERG on chromosome 7q35-36, encoding potassium channels (Ikr), cause LQT2, and block of Ikr is a known mechanism for drug-induced prolongation of cardiac action potentials, which provides a mechanistic link between LQT2 and certain forms of acquired LQT. Mutations in SCN5A on chromosome 3p21, encoding the human heart voltage-gated sodium-channel alpha-subunit, cause LQT3. Mutant channels show a sustained inward sodium current during membrane depolarization, which explains prolongation of cardiac action potentials.

Wang Q, Li Z, Shen J, Keating MT. Genomic organization of the human SCN5A gene encoding the cardiac sodium channel. Genomics 1996 May 15;34(1):9-16

Howard Hughes Medical Institute, University of Utah Health Sciences Center, Salt Lake City, Utah, 84112, USA.

The voltage-gated cardiac sodium channel, SCN5A, is responsible for the initial upstroke of the action potential. Mutations in the human SCN5A gene cause susceptibility to cardiac arrhythmias and sudden death in the long QT syndrome (LQT). In this report we characterize the genomic structure of SCN5A. SCN5A consists of 28 exons spanning approximately 80 kb on chromosome 3p21. We describe the sequences of all intron/exon boundaries and a dinucleotide repeat polymorphism in intron 16. Oligonucleotide primers based on exon-flanking sequences amplify all SCN5A exons by PCR. This work establishes the complete genomic organization of SCN5A and will enable high-resolution analyses of this locus for mutations associated with LQT and other phenotypes for which SCN5A may be a candidate gene.

1998

Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, Potenza D, Moya A, Borggrefe M, Breithardt G, Ortiz-Lopez R, Wang Z, Antzelevitch C, O'Brien RE, Schulze-Bahr E, Keating MT, Towbin JA, Wang Q. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. Nature 1998 Mar 19;392(6673):293-6

Department of Pediatrics (Cardiology), Baylor College of Medicine, Houston, Texas 77030, USA.

Ventricular fibrillation causes more than 300,000 sudden deaths each year in the USA alone. In approximately 5-12% of these cases, there are no demonstrable cardiac or non-cardiac causes to account for the episode, which is therefore classified as idiopathic ventricular fibrillation (IVF). A distinct group of IVF patients has been found to present with a characteristic electrocardiographic pattern. Because of the small size of most pedigrees and the high incidence of sudden death, however, molecular genetic studies of IVF have not yet been done. Because IVF causes cardiac rhythm disturbance, we investigated whether malfunction of ion channels could cause the disorder by studying mutations in the cardiac sodium channel gene SCN5A. We have now identified a missense mutation, a splice-donor mutation, and a frameshift mutation in the coding region of SCN5A in three IVF families. We show that sodium channels with the missense mutation recover from inactivation more rapidly than normal and that the frameshift mutation causes the sodium channel to be non-functional. Our results indicate that mutations in cardiac ion-channel genes contribute to the risk of developing IVF.

Janse MJ, Wilde AA. Molecular mechanisms of arrhythmias. Rev Port Cardiol 1998 Oct;17 Suppl 2:II41-6

Department of Clinical and Experimental Cardiology, University of Amsterdam, The Netherlands.

Most arrhythmias occur in patients with structural heart disease, where anatomical factors play an important role. Patients without structural heart disease may also suffer from arrhythmias, and recently the genetic basis for such so-called idiopathic arrhythmias has been elucidated. In the congenital long QT syndrome, characterized by a prolonged QT interval, torsade de pointes and sudden death, three aberrant ionic currents have been identified, resulting in a prolongation of the ventricular action potential, which in its turn may cause early afterdepolarization and torsade de pointes. In LQTS1, mutations in the KvLQT1 gene reduce the slow component of the delayed rectifier Iks; in LQTS, mutations in the Human Ether a-go-go Related Gene (HERG) reduce the rapid component of the delayed rectifier Iks. Both potassium currents are important determinants of repolarization: a reduction in outward currents carried by K+ ions prolongs the action potential. In LQTS3, there are mutation in the NA+ channel gene (SCN5A) which causes the channel to inactivate incompletely; the persistent inward current carried by Na+ ions also prolongs the action potential. In the Brugada syndrome, characterized by right bundle branch block, ST elevation in V1-V3 and sudden death, mutations have been observed in the Na+ channel gene, but it is as yet unclear which functional changes in the NA+ channel are responsible for the typical ECG changes and the arrhythmias. Various cardiac disorders may lead to changes in gene expression that modify channel function. In hypertrophy, the ventricular action potential is prolonged by a decrease in the inward rectifier and the transient outward current. After prolonged episodes of rapid electrical activity, the atrial action potential is shortened, because of a reduction in the Iks type calcium current. Finally, many carriers of mutated genes display no abnormalities on the ECG. It is conceivable that such individuals may show excessive QT prolongation when taking cardiac or noncardiac drugs (such as neuroleptics, antidepressants, antihistamines, antimicrobials, antimalarials) that block potassium currents.

Benhorin J, Goldmit M, MacCluer JW, Blangero J, Goffen R, Leibovitch A, Rahat A, Wang Q, Medina A, Towbin J, Kerem B. Identification of a new SCN5A mutation, D1840G, associated with the long QT syndrome. Mutations in brief no. 153. Online. Hum Mutat 1998;12(1):72

Heiden Department of Cardiology, Bikur Cholim Hospital, Jerusalem, Israel.

The long QT syndrome (LQT) is an inherited cardiac disorder that can cause sudden cardiac death among apparently healthy young individuals due to malignant ventricular arrhythmias. LQT was found to be caused by mutations in four genes LTQ1, LQT2, LQT3 and LQT5, and linkage was reported for an additional locus, LQT4, on chromosome 4q25-27. We have studied a large (n=131) LQT-affected Jewish kindred and identified tight linkage between the LQT-affected

status and LQT3 (lod score 6.13, with an estimated recombination fraction of zero). We identified a new point-mutation, A to G substitution at nucleotide 5519 of the SCN5A gene, changing the aspartate 1840 to glycine, D1840G. This is a non-conservative change of an amino acid completely conserved in sodium channels from Molusca to human. The mutation was identified in all affected individuals (n=23), and not identified in all the unaffected family members (n=40), and not in 200 chromosomes of healthy control individuals. The mutation was identified in 3/12 individuals with equivocal phenotype, thus, providing an accurate dignostic tool for all family members. This mutation is currently being used in a cellular electrophysiological model, to characterize the function of the mutated sodium channel in this syndrome.

1999

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;85:1206-13.

Clancy CE, Rudy Y Linking a genetic defect to its cellular phenotype in a cardiac arrhythmia. *Nature* 1999 Aug 5;400(6744):566-9

Cardiac Bioelectricity Research and Training Center, Department of Physiology and Biophysics, Case Western Reserve University, Cleveland, Ohio 44106-7207, USA.

Advances in genetics and molecular biology have provided an extensive body of information on the structure and function of the elementary building blocks of living systems. Genetic defects in membrane ion channels can disrupt the delicate balance of dynamic interactions between the ion channels and the cellular environment, leading to altered cell function. As ion-channel defects are typically studied in isolated expression systems, away from the cellular environment where they function physiologically, a connection between molecular findings and the physiology and pathophysiology of the cell is rarely established. Here we describe a single-channel-based Markovian modelling approach that bridges this gap. We achieve this by determining the cellular arrhythmogenic consequences of a mutation in the cardiac sodium channel that can lead to a clinical arrhythmogenic disorder (the long-QT syndrome) and sudden cardiac death.

Schott JJ, Alshinawi C, Kyndt F, Probst V, Hoorntje TM, Hulsbeek M, Wilde AA, Escande D, Mannens MM, Le Marec H. Cardiac conduction defects associate with mutations in SCN5A. Nat Genet 1999 Sep;23(1):20-1

Rook MB, Bezzina Alshinawi C, Groenewegen WA, van Gelder IC, van Ginneken AC, Jongsma HJ, Mannens MM, Wilde AA. Human SCN5A gene mutations alter cardiac sodium channel kinetics and are associated with the Brugada syndrome. Cardiovasc Res 1999 Dec;44(3):507-17

Laboratoire de Physiopathologie et de Pharmacologie Cellulaires et Moleculaires, INSERM CJF96-01, France.

Department of Medical Physiology, Utrecht University, The Netherlands.

BACKGROUND: Primary dysrhythmias other than those associated with the long QT syndrome, are increasingly recognized. One of these are represented by patients with a history of resuscitation from cardiac arrest but without any structural heart disease. These patients exhibit a distinct electrocardiographic (ECG) pattern consisting of a persistent ST-segment elevation in the right precordial leads often but not always accompanied by a right bundle branch block (Brugada syndrome). This syndrome is associated with a high mortality rate and has been shown to display familial occurrence. METHODS AND RESULTS: Pharmacological sodium channel blockade elicits or worsens the electrocardiographic features associated with this syndrome. Hence, a candidate gene approach directed towards SCN5A, the gene encoding the alpha-subunit of the cardiac sodium channel, was followed in six affected individuals. In two patients missense mutations were identified in the coding region of the gene: R1512W in the DIII-DIV cytoplasmic linker and A1924T in the C-terminal cytoplasmic domain. In two other patients mutations were detected near intron/exon junctions. To assess the functional consequences of the R1512W and A1924T mutations, wild-type and mutant sodium channel proteins were expressed in Xenopus oocytes. Both missense mutations affected channel function, most notably a 4-5 mV negative voltage shift of the steady-state activation and inactivation curves in R1512W and a 9 mV negative voltage shift of the steady-state activation curve in A1924T, measured at 22 degrees C. Recovery from inactivation was slightly prolonged for R1512W channels. The time dependent kinetics of activation and inactivation at -20 mV were not significantly affected by either mutation. CONCLUSIONS: Two SCN5A mutations associated with the Brugada syndrome, significantly affect cardiac sodium channel characteristics. The alterations seem to be associated with an increase in inward sodium current during the action potential upstroke.

PMID: 10690282 [PubMed - indexed for MEDLINE]

2000

Makita N, Shirai N, Wang DW, Sasaki K, George AL Jr, Kanno M, Kitabatake Cardiac Na(+) channel dysfunction in Brugada syndrome is aggravated by beta(1)-subunit. *Circulation* 2000 Jan 4-11;101(1):54-60

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BACKGROUND: Mutations in the gene encoding the human cardiac Na(+) channel alpha-subunit (hH1) are responsible for chromosome 3-linked congenital long-QT

syndrome (LQT3) and idiopathic ventricular fibrillation (IVF). An auxiliary beta(1)-subunit, widely expressed in excitable tissues, shifts the voltage dependence of steady-state inactivation toward more negative potentials and restores normal gating kinetics of brain and skeletal muscle Na(+) channels expressed in Xenopus oocytes but has little if any functional effect on the cardiac isoform. Here, we characterize the altered effects of a human beta(1)-subunit (hbeta(1)) on the heterologously expressed hH1 mutation (T1620M) previously associated with IVF. METHODS AND RESULTS: When expressed alone in Xenopus oocytes, T1620M exhibited no persistent currents, in contrast to the LQT3 mutant channels, but the midpoint of steady-state inactivation (V(1/2)) was significantly shifted toward more positive potentials than for wild-type hH1. Coexpression of hbeta(1) did not significantly alter current decay or recovery from inactivation of wild-type hH1; however, it further shifted the V(1/2) and accelerated the recovery from inactivation of T1620M. Oocyte macropatch analysis revealed that the activation kinetics of T1620M were normal. CONCLUSIONS: It is suggested that coexpression of hbeta(1) exposes a more severe functional defect that results in a greater overlap in the relationship between channel inactivation and activation (window current) in T1620M, which is proposed to be a potential pathophysiological mechanism of IVF in vivo. One possible explanation for our finding is an altered alpha-/beta(1)-subunit association in the mutant.
MeSH Terms:

Brugada R, Brugada J, Antzelevitch C, Kirsch GE, Potenza D, Towbin JA, Brugada P. Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. Circulation 2000 Feb 8;101(5):510-5

Department of Cardiology, Baylor College of Medicine, Houston, Texas, USA.

BACKGROUND: A mutation in the cardiac sodium channel gene (SCN5A) has been described in patients with the syndrome of right bundle branch block, ST-segment elevation in leads V1 to V3, and sudden death (Brugada syndrome). These electrocardiographic manifestations are transient in many patients with the syndrome. The present study examined arrhythmic risk in patients with overt and concealed forms of the disease and the effectiveness of sodium channel blockers to unmask the syndrome and, thus, identify patients at risk. METHODS AND RESULTS: The effect of intravenous ajmaline (1 mg/kg), procainamide (10 mg/kg), or flecainide (2 mg/kg) on the ECG was studied in 34 patients with the syndrome and transient normalization of the ECG (group A), 11 members of 3 families in whom a SCN5A mutation was associated with the syndrome and 8 members in whom it was not (group B), and 53 control subjects (group C). Ajmaline, procainamide, or flecainide administration resulted in ST-segment elevation and right bundle branch block in all patients in group A and in all 11 patients with the mutation in group B. A similar pattern could not be elicited in the 8 patients in group B who lacked the mutation or in any person in group C. The follow-up period

(37+/-33 months) revealed no differences in the incidence of arrhythmia between the 34 patients in whom the phenotypic manifestation of the syndrome was transient and the 24 patients in whom it was persistent (log-rank, 0.639). CONCLUSIONS: The data demonstrated a similar incidence of potentially lethal arrhythmias in patients displaying transient versus persistent ST-segment elevation and right bundle branch block, as well as the effectiveness of sodium channel blockers to unmask the syndrome and, thus, identify patients at risk.

PMID: 10662748 [PubMed - indexed for MEDLINE]

Priori SG, Napolitano C, Giordano U, Collisani G, Memmi M. Brugada syndrome and sudden cardiac death in children. Lancet 2000 Mar 4;355(9206):808-9

In five children from the same family who died after unexplained cardiac arrest, Brugada syndrome syndrome was suspected based on the transient manifestation of the typical electrocardiogram pattern in one of them. A mutation in the cardiac sodium-channel confirmed the diagnosis of Brugada syndrome, which suggests that this disease may cause sudden death in children.

Kambouris NG, Nuss HB, Johns DC, Marban E, Tomaselli GF, Balser JR A revised view of cardiac sodium channel "blockade" in the long-QT syndrome. *J Clin Invest* 2000 Apr;105(8):1133-40

Department of Anesthesiology, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA.
Mutations in SCN5A, encoding the cardiac sodium (Na) channel, are linked to a form of the congenital long-QT syndrome (LQT3) that provokes lethal ventricular arrhythmias. These autosomal dominant mutations disrupt Na channel function, inhibiting channel inactivation, thereby causing a sustained ionic current that delays cardiac repolarization. Sodium channel-blocking antiarrhythmics, such as lidocaine, potently inhibit this pathologic Na current (I(Na)) and are being evaluated in patients with LQT3. The mechanism underlying this effect is unknown, although high-affinity "block" of the open Na channel pore has been proposed. Here we report that a recently identified LQT3 mutation (R1623Q) imparts unusual lidocaine sensitivity to the Na channel that is attributable to its altered functional behavior. Studies of lidocaine on individual R1623Q single-channel openings indicate that the open-time distribution is not changed, indicating the drug does not block the open pore as proposed previously. Rather, the mutant channels have a propensity to inactivate without ever opening ("closed-state inactivation"), and lidocaine augments this gating behavior. An allosteric gating model incorporating closed-state inactivation recapitulates the effects of lidocaine on pathologic I(Na). These findings explain the unusual drug sensitivity of R1623Q and provide a general and unanticipated mechanism for understanding how Na channel-blocking agents may suppress the pathologic, sustained Na current induced by LQT3 mutations.

Deschenes I, Baroudi G, Berthet M, Barde I, Chalvidan T, Denjoy I, Guicheney P, Chahine M. Electrophysiological characterization of SCN5A mutations causing long QT (E1784K) and Brugada (R1512W and R1432G) syndromes. Cardiovasc Res 2000 Apr;46(1):55-65
Comment in: Cardiovasc Res. 2000 Apr;46(1):14-6.

Laval Hospital, Research Center, 2725, Chemin Sainte-Foy, Sainte-Foy, Quebec, Canada.
Familial long QT syndrome (LQTS) and Brugada syndrome are two distinct human hereditary cardiac diseases known to cause ventricular tachyarrhythmias (torsade de pointes) and idiopathic ventricular fibrillation, respectively, which can both lead to sudden death. OBJECTIVE: In this study we have identified and electrophysiologically characterized, in patients having either LQTS or Brugada syndrome, three mutations in SCN5A (a cardiac sodium channel gene). METHOD: The mutant channels were expressed in a mammalian expression system and studied by means of the patch clamp technique. RESULTS: The R1512W mutation found in our first patient diagnosed with Brugada syndrome produced a slowing of both inactivation and recovery from inactivation. The R4132G mutation found in our second patient who also presented Brugada syndrome, resulted in no measurable sodium currents. Both Brugada syndrome patients showed ST segment elevation and right bundle-branch block, and had experienced syncopes. The E1784K mutation found in the LQTS showed a persistent inward sodium current, a hyperpolarized shift of the steady-sate inactivation and a faster recovery from inactivation. CONCLUSION: The different clinical manifestations of these three mutations most probably originate from the distinct electrophysiological abnormalities of the mutant cardiac sodium channels reported in this study.

PMID: 10727653 [PubMed - indexed for MEDLINE]

Akai J, Makita N, Sakurada H, Shirai N, Ueda K, Kitabatake A, Nakazawa K, Kimura A, Hiraoka M. A novel SCN5A mutation associated with idiopathic ventricular fibrillation without typical ECG findings of Brugada syndrome. FEBS Lett 2000 Aug 11;479(1-2):29-34

Etiology and Pathogenesis Research Unit, Medical Research Institute, Tokyo Medical and Dental University, Japan.

Mutations in the human cardiac Na+ channel alpha subunit gene (SCN5A) are responsible for Brugada syndrome, an idiopathic ventricular fibrillation (IVF) subgroup characterized by right bundle branch block and ST elevation on an electrocardiogram (ECG). However, the molecular basis of IVF in subgroups

lacking these ECG findings has not been elucidated. We performed genetic screenings of Japanese IVF patients and found a novel SCN5A missense mutation (S1710L) in one symptomatic IVF patient that did not exhibit the typical Brugada ECG. Heterologously expressed S1710L channels showed marked acceleration in the current decay together with a large hyperpolarizing shift of steady-state inactivation and depolarizing shift of activation. These findings suggest that SCN5A is one of the responsible genes for IVF patients who do not show typical ECG manifestations of the Brugada syndrome.

PMID: 10940383 [PubMed - indexed for MEDLINE]

Baroudi G, Chahine M. Biophysical phenotypes of SCN5A mutations causing long QT and Brugada syndromes. FEBS Lett 2000 Dec 29;487(2):224-8

Laval University, Department of Medicine, Canada.

Long QT and Brugada syndromes are two hereditary cardiac diseases. Brugada syndrome has so far been associated with only one gene, SCN5A, which encodes the cardiac sodium channel. However, in long QT syndrome (LQTS) at least six genes, including the SCN5A, are implicated. The substitution (D1790G) causes LQTS and the insertion (D1795) induces both LQTS and Brugada syndromes in carrier patients. hH1/insD1795 and hH1/D1790G mutant channels were expressed in the tsA201 human cell line and characterized using the patch clamp technique in whole-cell configuration. Our data revealed a persistent inward sodium current of about 6% at -30 mV for both D1790G and insD1795, and a reduction of 62% of channel expression for the insD1795. Moreover, a shift of steady-state inactivation curve in both mutants was also observed. Our findings uphold the idea that LQT3 is related to a persistent sodium current whereas reduction in the expression level of cardiac sodium channels is one of the biophysical characteristics of Brugada syndrome.

PMID: 11150514 [PubMed - indexed for MEDLINE]

2001

Itoh T, Kikuchi K, Odagawa Y, Takata S, Yano K, Okada S, Haneda N, Ogawa S, Nakano O, Kawahara Y, Kasai H, Nakayama T, Fukutomi T, Sakurada H, Shimizu A, Yazaki Y, Nagai R, Nakamura Y, Tanaka T: Correlation of genetic etiology with response to beta-adrenergic blockade among symptomatic patients with familial long-QT syndrome. J Hum Genet 2001;46(1):38-40.

Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Science, University of Tokyo, Japan.

Mutations in any of the five genes KCNQ1, KCNH2, KCNE1, KCNE2, and SCN5A can be responsible for familial long QT syndrome (LQTS), an arrhythmogenic disorder that entails a high risk of sudden death. beta-Adrenergic blocking agents are the first therapeutic choice, and 80% of patients treated with these agents show symptomatic relief; however the remaining 20% do not respond well. We previously performed a nationwide analysis of familial long QT syndrome (LQTS) in Japan and identified 32 mutations in the KCNQ1 and KCNH2 genes. In the present retrospective study, we found that patients carrying mutations in the KCNQ1 gene responded better to beta-adrenergic blocking agents than those with KCNH2 mutations (12 of 13 vs 1 of 5; P = 0.0077, Fisher's exact test). This is a good example of the power of genetic diagnosis to direct the selection of appropriate therapy for patients with diseases of heterogeneous genetic etiology.

Tan HL, Bink-Boelkens MT, Bezzina CR, Viswanathan PC, Beaufort-Krol GC, van Tintelen PJ, van den Berg MP, Wilde AA, Balser JR. A sodium-channel mutation causes isolated cardiac conduction disease. Nature 2001 Feb 22;409(6823):1043-7

The Experimental and Molecular Cardiology Group, Academic Medical Center, University of Amsterdam, The Netherlands.

Cardiac conduction disorders slow the heart rhythm and cause disability in millions of people worldwide. Inherited mutations in SCN5A, the gene encoding the human cardiac sodium (Na+) channel, have been associated with rapid heart rhythms that occur suddenly and are life-threatening; however, a chief function of the Na+ channel is to initiate cardiac impulse conduction. Here we provide the first functional characterization of an SCN5A mutation that causes a sustained, isolated conduction defect with pathological slowing of the cardiac rhythm. By analysing the SCN5A coding region, we have identified a single mutation in five affected family members; this mutation results in the substitution of cysteine 514 for glycine (G514C) in the channel protein. Biophysical characterization of the mutant channel shows that there are abnormalities in voltage-dependent 'gating' behaviour that can be partially corrected by dexamethasone, consistent with the salutary effects of glucocorticoids on the clinical phenotype. Computational analysis predicts that the gating defects of G514C selectively slow myocardial conduction, but do not provoke the rapid cardiac arrhythmias associated previously with SCN5A mutations.

PMID: 11234013 [PubMed - indexed for MEDLINE]

Mutation in the *SCN5A* sodium-channel gene slows heart rate

By Bijal P. Trivedi

February 26, 2001

Scientists have identified a tiny variation in the *SCN5A* sodium-channel protein that can disrupt the heart's electrical activity and lead to a dramatic slowing of heart rate. The protein is basically a donut-shaped molecule through which sodium travels into the cell. The researchers have identified a genetic mutation that underlies the defective sodium channel, and they report that a steroid can be used in combination with a pacemaker to help normalize the heartbeat.

A team of Dutch and American researchers first identified the *SCN5A* mutation in a 3-year-old girl who was hospitalized in The Netherlands after fainting repeatedly during a fever. Doctors found that the girl's heart rate was only about 25 beats per minute (130 beats per minute is normal at that age). The researchers identified four other family members with abnormal rhythms, including a 6-year-old sister whose heart rate was also severely reduced. Testing showed that the problem was not due to a structural heart defect.

Jeffrey R. Balser, of Vanderbilt University School of Medicine in Tennessee, and colleagues suspected that a mutation in the sodium-channel gene might be responsible for the slow heart rate in the Dutch family. A number of mutations in this gene are associated with sudden episodes of rapid heart rhythms.

Balser's team sequenced the *SCN5A* gene in the five affected family members and in 200 healthy individuals. The researchers traced the mutation to a location in the gene where a nucleotide guanine had been changed to thymine. The mutation alters the sodium channel by replacing the amino acid glycine at position 514 of the protein with cysteine. This amino acid change has the potential to dramatically affect the structure of the channel, and the researchers show that the mutant channel fails to open and close normally.

When the channel is open, sodium flows through and generates an electrical current. The mutant channel does not open normally and generates less current. It is the opening and closing of these channels that creates the electrical impulses that make the heart beat.

"These mutant channels are like teenagers in the morning—they need a little encouragement," says Balser. The 'encouragement' comes from a pacemaker that sends electrical impulses that force the channels to open properly. The pacemaker failed to normalize the heartbeats, however, until the sisters received steroid treatments. How the steroid improves the functioning of the mutant sodium channel is not known. The findings appear in the current issue of *Nature*.

While the mutation found in the Dutch family is rare, millions of people have conduction defects that slow the heart rate and require the use of a pacemaker. Balser intends to investigate whether the

Cerrone M, Crotti L, Faggiano G, De Michelis V, Napolitano C, Schwartz PJ, Priori SG. Long QT syndrome and Brugada syndrome: 2 aspects of the same disease?] Ital Heart J 2001 Mar;2(3 Suppl):253-7

[Article in Italian]

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In clinical cardiology, resort has recently been made to molecular genetics in order to explain some mechanisms that underlie sudden cardiac death in young people with structurally normal hearts. It has become evident that genetic mutations regarding cardiac ion channels may disrupt the delicate balance of currents in the action potential, thus inducing malignant ventricular tachyarrhythmias. The cardiac sodium channel gene, SCN5A, is involved in two of such arrhythmogenic diseases, the Brugada syndrome and one form of the long QT syndrome (LQT3). It is believed that these syndromes result from opposite molecular effects: Brugada syndrome mutations cause a reduced sodium current, while LQT3 mutations are associated with a gain of function. The effects of class I antiarrhythmic drugs have been used to differentiate these diseases. Intravenous flecainide is used as a highly specific test to unmask the electrocardiographic phenotype of the Brugada syndrome. On the other hand, on the basis of experimental and clinical studies, the possibility that the same drugs act as a gene-specific therapy in this disorder by contrasting the effect of mutations in LQT3 has been explored. Recent evidence shows that phenotypic overlap may exist between the Brugada syndrome and LQT3. One large family with a SCN5A mutation and a "mixed" electrocardiographic pattern (prolonged QT interval and ST-segment elevation) has been reported. Moreover, our recent data showed that flecainide challenge may elicit ST-segment elevation in some LQT3 patients. The presence of "intermediate" phenotypes highlights a remarkable heterogeneity suggesting that clinical features may depend upon the single mutation. Only deepened understanding of the genotype-phenotype correlation will allow the definition of the individual patient's risk and the development of guidelines for clinical management.

Levy-Nissenbaum E, Eldar M, Wang Q, Lahat H, Belhassen B, Ries L, Friedman E, Pras E. Genetic analysis of Brugada syndrome in Israel: two novel mutations and possible genetic heterogeneity. Genet Test 2001 Winter; 5(4):331-4

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Idiopathic ventricular fibrillation in patients with an electrocardiogram (ECG) pattern of right bundle branch block and ST-segment elevation in leads V1 to V3 (now frequently called Brugada syndrome) is associated with a high incidence of syncopal episodes or sudden death. The disease is inherited as an autosomal dominant trait. Mutations in SCN5A, a cardiac sodium channel gene, have been

recently associated with Brugada syndrome. We have analyzed 7 patients from Israel affected with Brugada syndrome. The families of these patients are characterized by a small number of symptomatic members. Sequencing analysis of SCN5A revealed two novel mutations, G35S and R104Q, in two Brugada patients, and a possible R34C polymorphism in two unrelated controls. No mutations were detected in 5 other patients, suggesting genetic heterogeneity. Low penetrance is probably the cause for the small number of symptomatic members in the two families positive for the SCN5A mutations.

PMID: 11960580 [PubMed - indexed for MEDLINE]

Piippo K, Holmstrom S, Swan H, Viitasalo M, Raatikka M, Toivonen L, Kontula K. Effect of the antimalarial drug halofantrine in the long QT syndrome due to a mutation of the cardiac sodium channel gene SCN5A. Am J Cardiol 2001 Apr 1;87(7):909-11

Department of Medicine, Helsinki University Hospital, Helsinki, Finland.

PMID: 11274952 [PubMed - indexed for MEDLINE]

Wedekind H, Smits JP, Schulze-Bahr E, Arnold R, Veldkamp MW, Bajanowski T, Borggrefe M, Brinkmann B, Warnecke I, Funke H, Bhuiyan ZA, Wilde AA, Breithardt G, Haverkamp W.De novo mutation in the SCN5A gene associated with early onset of sudden infant death. Circulation 2001 Sep 4;104(10): 1158-64

Comment in: Circulation. 2001 Sep 4;104(10):1092-3.

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BACKGROUND: Congenital long QT syndrome (LQTS), a cardiac ion channel disease, is an important cause of sudden cardiac death. Prolongation of the QT interval has recently been associated with sudden infant death syndrome, which is the leading cause of death among infants between 1 week and 1 year of age. Available data suggest that early onset of congenital LQTS may contribute to premature sudden cardiac death in otherwise healthy infants. METHODS AND RESULTS: In an infant who died suddenly at the age of 9 weeks, we performed mutation screening in all known LQTS genes. In the surface ECG soon after birth, a prolonged QTc interval (600 ms(1/2)) and polymorphic ventricular tachyarrhythmias were documented. Mutational analysis identified a missense mutation (Ala1330Pro) in the cardiac sodium channel gene SCN5A, which was

absent in both parents. Subsequent genetic testing confirmed paternity, thus suggesting a de novo origin. Voltage-clamp recordings of recombinant A1330P mutant channel expressed in HEK-293 cells showed a positive shift in voltage dependence of inactivation, a slowing of the time course of inactivation, and a faster recovery from inactivation. CONCLUSIONS: In this study, we report a de novo mutation in the sodium channel gene SCN5A, which is associated with sudden infant death. The altered functional characteristics of the mutant channel was different from previously reported LQTS3 mutants and caused a delay in final repolarization. Even in families without a history of LQTS, de novo mutations in cardiac ion channel genes may lead to sudden cardiac death in very young infants.

Ackerman MJ, Siu BL, Sturner WQ, Tester DJ, Valdivia CR, Makielski JC, Towbin JA. Postmortem molecular analysis of SCN5A defects in sudden infant death syndrome. JAMA 2001 Nov 14;286(18):2264-9

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CONTEXT: Fatal arrhythmias from occult long QT syndrome may be responsible for some cases of sudden infant death syndrome (SIDS). Because patients who have long QT syndrome with sodium channel gene (SCN5A) defects have an increased frequency of cardiac events during sleep, and a recent case is reported of a sporadic SCN5A mutation in an infant with near SIDS, SCN5A has emerged as the leading candidate ion channel gene for SIDS. OBJECTIVE: To determine the prevalence and functional properties of SCN5A mutations in SIDS. DESIGN, SETTING, AND SUBJECTS: Postmortem molecular analysis of 93 cases of SIDS or undetermined infant death identified by the Medical Examiner's Office of the Arkansas State Crime Laboratory between September 1997 and August 1999. Genomic DNA was extracted from frozen myocardium and subjected to SCN5A mutational analyses. Missense mutations were incorporated into the human heart sodium channel alpha subunit by mutagenesis, transiently transfected into human embryonic kidney cells, and characterized electrophysiologically. MAIN OUTCOME MEASURES: Molecular and functional characterization of SCN5A defects. RESULTS: Two of the 93 cases of SIDS possessed SCN5A mutations: a 6-week-old white male with an A997S missense mutation in exon 17 and a 1-month old white male with an R1826H mutation in exon 28. These 2 distinct mutations occurred in highly conserved regions of the sodium channel and were absent in 400 control patients (800 alleles). Functionally, the A997S and R1826H mutant channels expressed a sodium current characterized by slower decay and a 2- to 3-fold increase in late sodium current. CONCLUSION: Approximately 2% of this prospective, population-based cohort of SIDS cases had an identifiable SCN5A channel defect, suggesting that mutations in cardiac ion channels may provide a lethal arrhythmogenic substrate in some infants at risk for SIDS.

Postmortem Molecular Analysis of *SCN5A* Defects in Sudden Infant Death Syndrome

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Context Fatal arrhythmias from occult long QT syndrome may be responsible for some cases of sudden infant death syndrome (SIDS). Because patients who have long QT syndrome with sodium channel gene (*SCN5A*) defects have an increased frequency of cardiac events during sleep, and a recent case is reported of a sporadic *SCN5A* mutation in an infant with near SIDS, *SCN5A* has emerged as the leading candidate ion channel gene for SIDS.

Objective To determine the prevalence and functional properties of *SCN5A* mutations in SIDS.

Design, Setting, and Subjects Postmortem molecular analysis of 93 cases of SIDS or undetermined infant death identified by the Medical Examiner's Office of the Arkansas State Crime Laboratory between September 1997 and August 1999. Genomic DNA was extracted from frozen myocardium and subjected to *SCN5A* mutational analyses. Missense mutations were incorporated into the human heart sodium channel α subunit by mutagenesis, transiently transfected into human embryonic kidney cells, and characterized electrophysiologically.

Main Outcome Measures Molecular and functional characterization of *SCN5A* defects.

Results Two of the 93 cases of SIDS possessed *SCN5A* mutations: a 6-week-old white male with an A997S missense mutation in exon 17 and a 1-month old white male with an R1826H mutation in exon 28. These 2 distinct mutations occurred in highly conserved regions of the sodium channel and were absent in 400 control patients (800 alleles). Functionally, the A997S and R1826H mutant channels expressed a sodium current characterized by slower decay and a 2- to 3-fold increase in late sodium current.

Conclusion Approximately 2% of this prospective, population-based cohort of SIDS cases had an identifiable *SCN5A* channel defect, suggesting that mutations in cardiac ion channels may provide a lethal arrhythmogenic substrate in some infants at risk for SIDS.

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Molecular Pharmacology and Experimental Therapeutics (Dr Ackerman), Mayo Clinic, Rochester, Minn; Departments of Pediatrics and Cardiovascular Sciences (Drs Siu and Towbin) and Human and Molecular Genetics (Dr Towbin), Baylor College of Medicine, Houston, Tex; Medical Examiner's Office of the Arkansas State Crime Laboratory, Little Rock (Dr Sturner); and the Department of Medicine, Section of Cardiovascular Medicine and Department of Physiology, University of Wisconsin, Madison (Drs Valdivia and Makielski).

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Author Contributions: *Study concept and design:* Ackerman, Sturner, Valdivia, Towbin.

Acquisition of data: Ackerman, Siu, Tester, Valdivia, Makielski.

Analysis and interpretation of data: Ackerman, Siu, Sturner, Tester, Valdivia, Makielski, Towbin.

Drafting of the manuscript: Ackerman, Valdivia, Makielski.

Critical revision of the manuscript for important intellectual content: Ackerman, Siu, Sturner, Tester, Makielski, Towbin.

Statistical expertise: Valdivia.

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Study supervision: Ackerman, Valdivia, Makielski, Towbin.

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Aproximadamente 2% das crianças que morrem com a síndrome da morte súbita infantil (SIDS) têm mutação no gene SCN5A dos canais de sódio, relatam

investigadores na recente edição de *The Journal of the American Medical Association.*

O Dr. J. A. Towbin, do Baylor College of Medicine, em Houston, EUA, e colaboradores realizaram uma análise depois da morte em tecido miocárdico de 93 crianças com diagnóstico de SIDS ou possível SIDS. O DNA foi extraído de amostras de miocárdio congelado e analisado para mutações do SCN5A. Foram conduzidos estudos nas células renais para determinar a função dos genes que sofreram mutação.

Os investigadores identificaram dois lactentes que tinham mutação em SCN5A. Um menino branco que tinha mutação de sentido errado em A997S no *exon* 17 e que morreu com 6 semanas de idade; um outro menino branco que tinha mutação R1826H no *exon* 28 e que morreu com 1 mês de idade. As mutações ocorreram em regiões altamente conservadas do canal de sódio e não estavam presentes em amostras de 400 pacientes controles.

A análise funcional revelou que os canais mutantes produziam corrente de sódio com queda mais lenta do que os canais normais. Os canais mutantes também estavam ligados a um aumento de duas a três vezes da corrente tardia de sódio.

Há vários anos, foi publicado um trabalho que sugeria que um certo número de casos de SIDS estivesse associado à síndrome de QT longo, relatou o Dr. Towbin. A síndrome do QT longo sabidamente é causada por mutações nos canais iônicos, mas não há provas definitivas de que estas mutações estejam ligadas à SIDS.

Foram identificadas numerosas mutações de SCN5A claramente causadoras de SIDS. Aproximadamente 2% dos casos de SIDS parecem ser causados por mutações em SCN5A. No entanto, há outras mutações em canais iônicos associadas à síndrome do QT longo para as quais não foram feitos testes; portanto, é provável que muitos casos mais de SIDS sejam causados por estes tipos de mutações.

O Dr. Towbin acredita que os novos achados sejam bom ponto de partida e que estejam justificados mais estudos para identificar outras mutações de canais iônicos ligadas à SIDS.

JAMA 2001;286:2264-2269.

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;104:3081-6.

Laboratoire de Physiopathologie et de Pharmacologie Cellulaires et Moleculaires, INSERM U533, Paris, France.

BACKGROUND: The SCN5A gene encoding the human cardiac sodium channel alpha subunit plays a key role in cardiac electrophysiology. Mutations in SCN5A lead to a large spectrum of phenotypes, including long-QT syndrome, Brugada

syndrome, and isolated progressive cardiac conduction defect (Lenegre disease). METHODS AND RESULTS: In the present study, we report the identification of a novel single SCN5A missense mutation causing either Brugada syndrome or an isolated cardiac conduction defect in the same family. A G-to-T mutation at position 4372 was identified by direct sequencing and was predicted to change a glycine for an arginine (G1406R) between the DIII-S5 and DIII-S6 domain of the sodium channel protein. Among 45 family members, 13 were carrying the G1406R SCN5A mutation. Four individuals from 2 family collateral branches showed typical Brugada phenotypes, including ST-segment elevation in the right precordial leads and right bundle branch block. One symptomatic patient with the Brugada phenotype required implantation of a cardioverter-defibrillator. Seven individuals from 3 other family collateral branches had isolated cardiac conduction defects but no Brugada phenotype. Three flecainide test were negative. One patient with an isolated cardiac conduction defect had an episode of syncope and required pacemaker implantation. An expression study of the G1406R-mutated SCN5A showed no detectable Na(+) current but normal protein trafficking. CONCLUSIONS: We conclude that the same mutation in the SCN5A gene can lead either to Brugada syndrome or to an isolated cardiac conduction defect. Our findings suggest that modifier gene(s) may influence the phenotypic consequences of a SCN5A mutation.

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Brugada R, Roberts R. Brugada Syndrome: Why are there multiple questions to a simple answer? *Circulation*. 2001;104:3017-9.

2002

Wang DW, Viswanathan PC, Balser JR, George AL Jr, Benson DW. Clinical, genetic, and biophysical characterization of SCN5A mutations associated with atrioventricular conduction block. Circulation 2002 Jan 22;105(3):341-6

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BACKGROUND: Three distinct cardiac arrhythmia disorders, the long-QT syndrome, Brugada syndrome, and conduction system disease, have been associated with heterozygous mutations in the cardiac voltage-gated sodium channel alpha-subunit gene (SCN5A). We present clinical, genetic, and biophysical features of 2 new SCN5A mutations that result in atrioventricular (AV) conduction block. Methods and Results- SCN5A was used as a candidate gene in 2 children with AV block. Molecular genetic studies revealed G to A transition mutations that resulted in the substitution of serine for glycine (G298S) in the domain I S5-S6 loop and asparagine for aspartic acid (D1595N) within the S3 segment of domain IV.

The functional consequences of G298S and D1595N were assessed by whole-cell patch clamp recording of recombinant mutant channels coexpressed with the beta1 subunit in a cultured cell line (tsA201). Both mutations impair fast inactivation but do not exhibit sustained non-inactivating currents. The mutations also reduce sodium current density and enhance slower inactivation components. Action potential simulations predict that this combination of biophysical abnormalities will significantly slow myocardial conduction velocity. CONCLUSIONS: A distinct pattern of biophysical abnormalities not previously observed for any other SCN5A mutant have been recognized in association with AV block. These data provide insight into the distinct clinical phenotypes resulting from mutation of a single ion

Weiss R, Barmada MM, Nguyen T, Seibel JS, Cavlovich D, Kornblit CA, Angelilli A, Villanueva F, McNamara DM, London B.
Clinical and molecular heterogeneity in the Brugada syndrome: a novel gene locus on chromosome 3. Circulation 2002 Feb 12;105(6):707-13

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BACKGROUND: Brugada syndrome is a form of idiopathic ventricular fibrillation characterized by a right bundle-branch block pattern and ST elevation (STE) in the right precordial leads of the ECG. Sodium channel blockers increase STE. Mutations of the cardiac sodium channel SCN5A cause the disorder, and an implantable cardioverter-defibrillator is often recommended for affected individuals. Mutations in other genes have not been identified, and it is not known if the efficacy of drug testing or the malignancy of arrhythmias correlates to the gene defect. METHODS AND RESULTS: We performed histories, physical examinations, ECGs, and drug testing on a large multigenerational family with Brugada syndrome. DNA isolated from blood samples, polymorphic genomic markers, and polymorphisms within candidate sodium channels were used for a genome-wide screen, fine mapping, and linkage analysis. We identified 12 affected individuals (right bundle-branch block, > or =1-mm STE) with an autosomal dominant inheritance pattern characterized by incomplete penetrance that appeared to be dependent on age and sex. Four affected individuals had syncope and 2 had documented ventricular arrhythmias, but there was minimal family history of sudden death. Procainamide infusions did not identify additional affected individuals. Linkage was present to an approximately equal 15-cM region on chromosome 3p22-25 (maximum LOD score=4.00). The sodium channel genes SCN5A, SCN10A, and SCN12A on chromosome 3 were excluded as candidates (LOD scores < or =-2). CONCLUSIONS: A Brugada syndrome locus distinct from SCN5A is associated with progressive conduction disease, a low sensitivity to procainamide testing, and a relatively good prognosis in a single large pedigree.

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Priori SG, Napolitano C, Gasparini M, Pappone C, Della Bella P, Giordano U, Bloise R, Giustetto C, De Nardis R, Grillo M, Ronchetti E, Faggiano G, Nastoli J. Natural history of Brugada syndrome: insights for risk stratification and management. Circulation 2002 Mar 19;105(11):1342-7

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BACKGROUND: Treatment of patients with Brugada syndrome is complicated by the incomplete information on the natural history of the disease related to the small number of cases reported. Furthermore, the value of programmed electrical stimulation (PES) for risk stratification is highly debated. The objective of this study was to search for novel parameters to identify patients at risk of sudden death. METHODS AND RESULTS: Clinical data were collected for 200 patients (152 men, 48 women; age, 41+/-18 years) and stored in a dedicated database. Genetic analysis was performed, and mutations on the SCN5A gene were identified in 28 of 130 probands and in 56 of 121 family members. The life-table method of Kaplan-Meier used to define the cardiac arrest-free interval in patients undergoing PES failed to demonstrate an association between PES inducibility and spontaneous occurrence of ventricular fibrillation. Multivariate Cox regression analysis showed that after adjusting for sex, family history of sudden death, and SCN5A mutations, the combined presence of a spontaneous ST-segment elevation in leads V1 through V3 and the history of syncope identifies subjects at risk of cardiac arrest (HR, 6.4; 95% CI, 1.9 to 21; P<0.002). CONCLUSIONS: The information on the natural history of patients obtained in this study allowed elaboration of a risk-stratification scheme to quantify the risk for sudden cardiac death and to target the use of the implantable cardioverter-defibrillator.

Clancy CE, Rudy Y Na(+) channel mutation that causes both Brugada and long-QT syndrome phenotypes: a simulation study of mechanism. *Circulation* 2002 Mar 12;105(10):1208-13

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BACKGROUND: Complex physiological interactions determine the functional consequences of gene abnormalities and make mechanistic interpretation of phenotypes extremely difficult. A recent example is a single mutation in the C terminus of the cardiac Na(+) channel, 1795insD. The mutation causes two distinct clinical syndromes, long QT (LQT) and Brugada, leading to life-threatening cardiac arrhythmias. Coexistence of these syndromes is seemingly paradoxical; LQT is

associated with enhanced Na(+) channel function, and Brugada with reduced function. METHODS AND RESULTS: Using a computational approach, we demonstrate that the 1795insD mutation exerts variable effects depending on the myocardial substrate. We develop Markov models of the wild-type and 1795insD cardiac Na(+) channels. By incorporating the models into a virtual transgenic cell, we elucidate the mechanism by which 1795insD differentially disrupts cellular electrical behavior in epicardial and midmyocardial cell types. We provide a cellular mechanistic basis for the ECG abnormalities observed in patients carrying the 1795insD gene mutation. CONCLUSIONS: We demonstrate that the 1795insD mutation can cause both LQT and Brugada syndromes through interaction with the heterogeneous myocardium in a rate-dependent manner. The results highlight the complexity and multiplicity of genotype-phenotype relationships, and the usefulness of computational approaches in establishing a mechanistic link between genetic defects and functional abnormalities.
MeSH Terms:

Molecular Cardiology

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Sodium channel gene defects have many faces

by Gopi Shah, MD, and Robert Roberts, MD

Special to Today in Cardiology

March 2002

---**Robert Roberts, MD**

The sodium channel gene SCN5A is known to cause long QT syndrome and Brugada syndrome. It is the same gene, but it was assumed the mutations were unique to each syndrome. This was recently challenged by the same mutation in the same family inducing both syndromes.

The same mutation in the SCN5A gene was recently shown to induce Brugada syndrome in some family members and induced isolated cardiac conduction defect (ICCD) syndrome in others. The SCN5A gene encodes for a voltage-gated channel protein predominantly expressed in the heart responsible for rapid depolarization.

Long QT syndrome (LQTS) is associated with an increased incidence of torsade de pointes and sudden death. The mutation in SCN5A causing LQTS leads to gain of function with delayed inactivation of the channel resulting in prolonged action potential.

---**Gopi Shah, MD**

Brugada syndrome is characterized by ECG findings of ST elevation in the right precordial leads accompanied by right bundle branch block and normal QT. Mutations in the SCN5A gene known to cause Brugada syndrome are thought to be loss of function of the Na channel. ECG findings are not always present and may be triggered by sodium channel antagonists. In Southeast Asia, Brugada syndrome due to SCN5A is thought to be the most common cause of sudden death in the young and exhibits a male predominance. LQTS and Brugada syndrome due to the SCN5A gene seem to be electrophysiologic mirror images with LQTS due to gain of function and Brugada syndrome due to loss of function.

In 1999 Bezzina et al published a report on a mutation in the SCN5A in a large Dutch family. Some family members' ECGs showed prolonged QT interval; others exhibited Brugada syndrome. In vitro expression of this mutation showed it disrupts fast inactivation leading to sustained Na current and prolongation of action potential. This mutation also augments slow inactivation of the Na channels, delaying recovery of channels and thereby reducing Na current. Why the latter predominates so that some family members have Brugada and others LQTS remains unknown.

Further complexity was added recently by Kyndt et al who described a G1406R mutation in the SCN5A gene in a large French family causing Brugada syndrome and ICCD. ICCD is diagnosed by isolated prolongation of His-Purkinje conduction system associated with a risk of complete AV block and Stokes-Adam syncope in the absence of ventricular arrhythmia. No ST elevation or QT prolongation is associated with ICCD.

Brugada syndrome was shown in two brothers and their descendants

Vatta M, Dumaine R, Antzelevitch C, Brugada R, Li H, Bowles NE, Nademanee K, Brugada J, Brugada P, Towbin JA. Novel mutations in domain I of SCN5A cause Brugada syndrome. Mol Genet Metab 2002 Apr;75(4):317-24

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Brugada syndrome, an autosomal dominantly inherited form of ventricular fibrillation characterized by ST-segment elevation in leads V1-V3 and right bundle-branch block on surface electrocardiogram, is caused by mutations in the cardiac sodium channel gene SCN5A. Patients with Brugada syndrome were studied using single-strand conformation polymorphism analysis, denaturing high-performance liquid chromatography, and DNA sequencing of SCN5A. Mutations were identified in SCN5A in two families and one sporadic case. In one family, a missense mutation leading to a glycine to valine substitution (G351V) in the pore region between the DIS5 and DIS6 transmembrane segments was detected. Biophysical analysis demonstrated that this mutation caused significant current reduction. In the other family, a 20-bp deletion of the exon 5 splice acceptor site was identified; as exon 5 encodes part of the intracellular loop between DIS2 and DIS3, this portion of the channel is disrupted. In the sporadic patient, a missense mutation resulting in the substitution of lysine by glutamic acid (K126E) in the intracellular loop at the boundary with DIS1 was identified. These three new SCN5A mutations in Brugada syndrome patients are all located within domain I of SCN5A, a region not previously considered important in the development of ventricular arrhythmias.

Papadatos GA, Wallerstein PM, Head CE, Ratcliff R, Brady PA, Benndorf K, Saumarez RC, Trezise AE, Huang CL, Vandenberg JI, Colledge WH, Grace AA. Slowed conduction and ventricular tachycardia after targeted disruption of the cardiac sodium channel gene Scn5a. Proc Natl Acad Sci U S A 2002 Apr 30;99(9):6210-5
Comment in: Proc Natl Acad Sci U S A. 2002 Apr 30;99(9):5755-6.

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Voltage-gated sodium channels drive the initial depolarization phase of the cardiac action potential and therefore critically determine conduction of excitation through the heart. In patients, deletions or loss-of-function mutations of the cardiac sodium channel gene, SCN5A, have been associated with a wide range of arrhythmias including bradycardia (heart rate slowing), atrioventricular conduction delay, and ventricular fibrillation. The pathophysiological basis of these clinical conditions is unresolved. Here we show that disruption of the mouse cardiac sodium channel gene, Scn5a, causes intrauterine lethality in homozygotes with severe defects in ventricular morphogenesis whereas heterozygotes show normal survival. Whole-cell patch clamp analyses of isolated ventricular myocytes from adult Scn5a(+/-) mice demonstrate a approximately 50% reduction in sodium conductance. Scn5a(+/-) hearts have several defects including impaired atrioventricular conduction, delayed intramyocardial conduction, increased ventricular refractoriness, and ventricular tachycardia with characteristics of reentrant excitation. These findings reconcile reduced activity of the cardiac sodium channel leading to slowed conduction with several apparently diverse clinical phenotypes, providing a model for the detailed analysis of the pathophysiology of arrhythmias.

Clinical Investigation and Reports

Ping Yang, PhD; Hideaki Kanki, MD; Benoit Drolet, PhD; Tao Yang, PhD; Jian Wei, MD PhD; Prakash C. Viswanathan, PhD; Stefan H. Hohnloser, MD; Wataru Shimizu, MD; Peter J. Schwartz, MD; Marshall Stanton, MD; Katherine T. Murray, MD; Kris Norris, RN; Alfred L. George, Jr, MD; Dan M. Roden, MD
Allelic Variants in Long-QT Disease Genes in Patients With Drug-Associated Torsades de Pointes *Circulation.* 2002;105:1943.

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Correspondence to Dan M. Roden, MD, Professor of Medicine and Pharmacology, Director, Division of Clinical Pharmacology, 532 Medical Research Bldg I, Vanderbilt University School of Medicine, Nashville, TN 37232. E-mail dan.roden@mcmail.vanderbilt.edu

***Background*—** DNA variants appearing to predispose to drug-associated "acquired" long-QT syndrome (aLQTS) have been reported in congenital long-QT disease genes. However, the incidence of these genetic risk factors has not been

systematically evaluated in a large set of patients with aLQTS. We have previously identified functionally important DNA variants in genes encoding K^+ channel ancillary subunits in 11% of an aLQTS cohort.

Methods and Results— The coding regions of the genes encoding the pore-forming channel proteins KvLQT1, HERG, and SCN5A were screened in (1) the same aLQTS cohort (n=92) and (2) controls, drawn from patients tolerating QT-prolonging drugs (n=67) and cross sections of the Middle Tennessee (n=71) and US populations (n=90). The frequency of three common nonsynonymous coding region polymorphisms was no different between aLQTS and control subjects, as follows: 24% versus 19% for H558R (SCN5A), 3% versus 3% for R34C (SCN5A), and 14% versus 14% for K897T (HERG). Missense mutations (absent in controls) were identified in 5 of 92 patients. KvLQT1 and HERG mutations (one each) reduced K^+ currents in vitro, consistent with the idea that they augment risk for aLQTS. However, three SCN5A variants did not alter I_{Na}, which argues that they played no role in the aLQTS phenotype.
Conclusions— DNA variants in the coding regions of congenital long-QT disease genes predisposing to aLQTS can be identified in ≈10% to 15% of affected subjects, predominantly in genes encoding ancillary subunits.

Key Words: arrhythmia • genetics • drugs • long-QT syndrome

Lupoglazoff JM, Denjoy I, Cheav T, Berthet M, Extramiana F, Cauchemez B, Villain E, Leenhardt A, Guicheney P.[Homozygotous mutation of the SCN5A gene responsible for congenital long QT syndrome with 2/1 atrioventricular block] Arch Mal Coeur Vaiss 2002 May;95(5):440-6

[Article in French]
Hopital Robert-Debre, 48, bd Serurier, 75019 Paris. jean-marc.lupoglazof@rdb.ap-hop-paris.fr

Long QT syndrome is characterized by a prolongation of the QT interval on the surface ECG. This clinically and genetically heterogeneous cardiac disease is potentially lethal due to ventricular polymorphic tachyarrhythmias leading to syncope or sudden death. It is transmitted according to different mendelian modes due to mutations in several genes coding for cardiac ion channels. Heterozygous mutations in KCNQ1, HERG, SCN5A, KCNE1 and KCNE2 genes are responsible for the dominant form without deafness whereas homozygous mutations in KCNQ1 and KCNE1 are responsible for the recessive form (Jervell and Lange-Nielsen syndrome) associated with congenital deafness. We report the case of a 5 year-old boy referred for syncope with a prolongation of the QTc interval (526 ms) and a 2/1

Atrio-Ventricular (AVB) block on the surface ECG. Under beta-blocking therapy, the sinus rate decreased and the 2/1 AVB disappeared. Electrophysiological study evidenced an infra-hisian block and a unipolar ventricular endocardial pacemaker was implanted. A V1777M missense mutation was identified in the C-terminal part of SCN5A, cardiac sodium channel gene, at the homozygous state in the proband and at the heterozygous state in both parents and 2 sibblings. Only the proband had a severe phenotype with syncope and AV conduction anomalies. All other genetically affected subjects were asymptomatic. This study provides evidence for the involvement of homozygous LQT3 forms in "functional" AVB.

PMID: 12085742 [PubMed - indexed for MEDLINE]

Sangwatanaroj S, Yanatasneejit P, Sunsaneewitayakul B, Sitthisook S. Linkage analyses and SCN5A mutations screening in five sudden unexplained death syndrome (Lai-tai) families. Med Assoc Thai 2002 Jun;85 Suppl 1:S54-61

Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

Sudden Unexplained Death Syndrome (SUDS) (or in Thai Lai-tai) share the same ECG pattern as Brugada Syndrome: RSR' and ST segment elevation in V1 to V3. Brugada Syndrome is a genetic disorder with the inheritance pattern of autosomal dominant (using the ECG pattern and unexplained sudden death as phenotype) and the cardiac sodium channel gene (SCN5A) mutations caused this syndrome. To determine whether SUDS was associated with the same mutations as Brugada Syndrome, the authors performed a linkage studies on 5 SUDS families with the Brugada Syndrome ECG pattern and found one family could not be excluded from linkage to SCN5A. However, the direct sequencing in 8 reported mutations on exon 5, 12, 17, 18 and 28 in this family failed to demonstrate the mutations. It was concluded that SUDS mutations maybe a novel mutation different from previously reported mutations, further genetic studies in SCN5A and other candidate genes might elucidate the molecular basis of SUDS.

Roden DM.The problem, challenge and opportunity of genetic heterogeneity in monogenic diseases predisposing to sudden death. J Am Coll Cardiol 2002 Jul 17;40(2):357-9

Comment on: J Am Coll Cardiol. 2002 Jul 17;40(2):350-6.

Smits JP, Eckardt L, Probst V, Bezzina CR, Schott JJ, Remme CA, Haverkamp W, Breithardt G, Escande D, Schulze-Bahr E, LeMarec H, Wilde AA. Genotype-phenotype relationship in Brugada syndrome: electrocardiographic features differentiate SCN5A-related patients from non-SCN5A-related patients. J Am Coll Cardiol 2002 Jul 17;40(2):350-6

Comment in:
J Am Coll Cardiol. 2002 Jul 17;40(2):357-9.

Experimental and Molecular Cardiology Group, Academic Medical Center, University of Amsterdam, 1100 DE Amsterdam, The Netherlands.

OBJECTIVES: We have tested whether a genotype-phenotype relationship exists in Brugada syndrome (BS) by trying to distinguish BS patients with (carriers) and those without (non-carriers) a mutation in the gene encoding the cardiac sodium channel (SCN5A) using clinical parameters. BACKGROUND: Brugada syndrome is an inherited cardiac disease characterized by a varying degree of ST-segment elevation in the right precordial leads and (non)specific conduction disorders. In a minority of patients, SCN5A mutations can be found. Genetic heterogeneity has been demonstrated, but other causally related genes await identification. If a genotype-phenotype relationship exists, this might facilitate screening. METHODS: In a multi-center study, we have collected data on demographics, clinical history, family history, electrocardiogram (ECG) parameters, His to ventricle interval (HV), and ECG parameters after pharmacologic challenge with I(Na) blocking drugs for BS patients with (n = 23), or those without (n = 54), an identified SCN5A mutation. RESULTS: No differences were found in demographics, clinical history, or family history. Carriers had a significantly longer PQ interval on the baseline ECG and a significantly longer HV time. A PQ interval of > or =210 ms and an HV interval > or =60 ms seem to be predictive for the presence of an SCN5A mutation. After I(Na) blocking drugs, carriers had significantly longer PQ and QRS intervals and more increase in QRS duration. CONCLUSIONS: We observed significantly longer conduction intervals on baseline ECG in patients with established SCN5A mutations (PQ and HV interval and, upon class I drugs, more QRS increase). These results concur with the observed loss of function of mutated BS-related sodium channels. Brugada syndrome patients with, and those without, an SCN5A mutation can be differentiated by phenotypical differences.

Liu H, Tateyama M, Clancy CE, Abriel H, Kass RS. Channel Openings Are Necessary but not Sufficient for Use-dependent Block of Cardiac Na(+) Channels by Flecainide: Evidence from the Analysis of Disease-linked Mutations. J Gen Physiol 2002 Jul;120(1):39-51

Department of Pharmacology, College of Physicians and Surgeons of Columbia University, New York, NY 10032.

Na(+) channel blockers such as flecainide have found renewed usefulness in the diagnosis and treatment of two clinical syndromes arising from inherited mutations in SCN5A, the gene encoding the alpha subunit of the cardiac voltage-gated Na(+) channel. The Brugada syndrome (BrS) and the LQT-3 variant of the Long QT syndrome are caused by disease-linked SCN5A mutations that act to change functional and pharmacological properties of the channel. Here we have explored a set of SCN5A mutations linked both to BrS and LQT-3 to determine what disease-modified channel properties underlie distinct responses to the Na(+) channel blocker flecainide. We focused on flecainide block that develops with repetitive channel activity, so-called use-dependent block (UDB). Our results indicate that mutation-induced changes in the voltage-dependence of channel availability (inactivation) may act as determinants of flecainide block. The data further indicate that UDB by flecainide requires channel opening, but is not likely due to open channel block. Rather, flecainide appears to interact with inactivation states that follow depolarization-induced channel opening, and mutation-induced changes in channel inactivation will alter flecainide block independent of the disease to which the mutation is linked. Analysis of flecainide block of mutant channels linked to these rare disorders has provided novel insight into the molecular determinants of drug action.

Makita N, Horie M, Nakamura T et al.:**Drug-induced long-QT syndrome associated with a subclinical SCN5A mutation. Circulation 2002; 106(10), 1269-1274**

BACKGROUND: Subclinical mutations in genes associated with the congenital long-QT syndromes (LQTS) have been suggested as a risk factor for drug-induced LQTS and accompanying life-threatening arrhythmias. Recent studies have identified genetic variants of the cardiac K+ channel genes predisposing affected individuals to acquired LQTS. We have identified a novel Na+ channel mutation in an individual who exhibited drug-induced LQTS. METHODS AND RESULTS: An elderly Japanese woman with documented QT prolongation and torsade de pointes during treatment with the prokinetic drug cisapride underwent mutational analysis of LQTS-related genes. A novel missense mutation (L1825P) was identified within the C-terminus region of the cardiac Na+ channel (SCN5A). The L1825P channel heterologously expressed in tsA-201 cells showed Na+ current with slow decay and a prominent tetrodotoxin-sensitive noninactivating component, similar to the gain-of-function phenotype most commonly observed for SCN5A-associated congenital LQTS (LQT3). In addition, L1825P exhibited loss of function Na+ channel features characteristic of Brugada syndrome. Peak Na+ current density observed in cells expressing L1825P was significantly diminished, and the voltage dependence of activation and inactivation was shifted toward more positive and negative potentials, respectively. CONCLUSIONS: This study demonstrates that

subclinical mutations in the LQTS-related gene SCN5A may predispose certain individuals to drug-induced cardiac arrhythmias.

Comments from Steven L Roberds, Pharmacia Corp., USA: "Drug-induced QTc prolongation is a life-threatening side effect that can lead to torsade de pointes and sudden death. The development of drug-induced QTc prolongation is relatively rare, but it is presently impossible to predict which individuals are likely most susceptible and, therefore, who should be closely monitored or avoid drugs with this potential. Polymorphisms associated with susceptibility to drug-induced QTc prolongation have now been identified in the cardiac sodium channel gene (SCN5A) and the MiRP1 potassium channel subunit gene. These polymorphisms apparently do not affect cardiac function until an agent that blocks the HERG potassium channel is brought on board. This paper, coupled with the previous MiRP1 findings, forms the basis for developing methods to identify individuals at risk of drug-induced QTc prolongation. This application of pharmacogenomics will benefit not only patients at risk, but will also facilitate the more wide-spread use of important drugs whose use would otherwise would be limited by concern for the risk of serious, but rare and unpredictable, arrhythmias."

Splawski I, Timothy KW, Tateyama M, Clancy CE, Malhotra A, Beggs AH, Cappuccio FP, Sagnella GA, Kass RS, Keating MT. Variant of SCN5A sodium channel implicated in risk of cardiac arrhythmia. Science 2002 Aug 23;297(5585):1333-6
Comment in: Science. 2002 Aug 23;297(5585):1252.

Department of Cardiology, Children's Hospital, Harvard Medical School and Howard Hughes Medical Institute, Boston, MA 02115, USA.

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Every year, approximately 450,000 individuals in the United States die suddenly of cardiac arrhythmia. We identified a variant of the cardiac sodium channel gene SCN5A that is associated with arrhythmia in African Americans (P = 0.000028) and linked with arrhythmia risk in an African-American family (P = 0.005). In transfected cells, the variant allele (Y1102) accelerated channel activation, increasing the likelihood of abnormal cardiac repolarization and arrhythmia. About 13.2% of African Americans carry the Y1102 allele. Because Y1102 has a subtle effect on risk, most carriers will never have an arrhythmia. However, Y1102 may be a useful molecular marker for the prediction of arrhythmia susceptibility in the context of additional acquired risk factors such as the use of certain medications.

Variant of SCN5A sodium channel implicated in risk of cardiac arrhythmia.
Splawski I, Timothy KW, Tateyama M et al.: Science 297(5585), 1333-1336 (2002).
Every year, approximately 450,000 individuals in the United States die suddenly of cardiac arrhythmia. We identified a variant of the cardiac sodium channel gene

SCN5A that is associated with arrhythmia in African Americans (P = 0.000028) and linked with arrhythmia risk in an African-American family (P = 0.005). In transfected cells, the variant allele (Y1102) accelerated channel activation, increasing the likelihood of abnormal cardiac repolarization and arrhythmia. About 13.2% of African Americans carry the Y1102 allele. Because Y1102 has a subtle effect on risk, most carriers will never have an arrhythmia. However, Y1102 may be a useful molecular marker for the prediction of arrhythmia susceptibility in the context of additional acquired risk factors such as the use of certain medications.
Comments from Joel Bader, Curagen, USA: "This good paper illustrates several important points:

(i) The SCN5A gene is responsible for rare, familial forms of heart disease. This paper shows that a common variant in the same gene can contribute to increased risk for heart disease. It validates the concept of looking for disease-risk SNPs in known disease-related genes.

(ii) Race and ethnicity have been raised as major issues in human genetics studies. The functional SNP in this study has 7% allele frequency in African-Americans but less than 0.1% allele frequency in Caucasians or Asians.
(iii) Carriers of one copy of the variant allele have a 9x greater odds of cardiac arrhythmia. Common medications (erythromycin, Prozac, Paxil, serevent) might provide triggers for arrhythmia in the 13% of African-Americans who carry this allele. Carriers could benefit from knowledge of their status."
Comments from David A Campbell, GlaxoSmithKline, UK: "Drug induced Cardiac Arrhythmias are a significant cause of morbidity and mortality and represent a major burden on Healthcare World wide. Although much is know about the genetic predisposition to syndromes such as long QT syndrome most of the known mutations are rare. Splawski et ai present data on a common polymorphism, occurring in approximately 19% of the African-American test population, in the LQT3 gene SCN5A. Mutations in this gene have previously been linked to rare, familial forms of LQT. Although the authors demonstrate a functional role for the Y1102 allele, they clearly state that it is unlikely that this allele imparts a significant risk to most carriers. However, the identification of a common, functional polymorphism may move us one step closer to prospective identification of individuals at risk of drug induced cardiac arrhythmias"

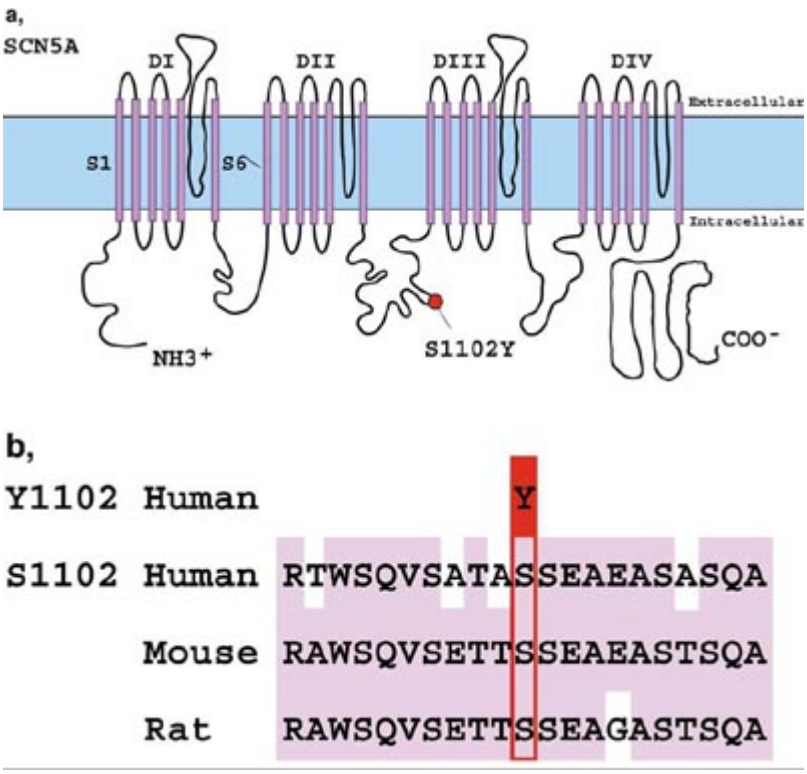
Gene variant linked to arrhythmia in African Americans

By Edward R. Winstead

August 30, 2002

Heart Disease

Scientists have identified a gene variant that slightly increases the risk for developing an irregular heartbeat, known as arrhythmia. The variant is primarily found in African Americans and persons of African descent. Most individuals with the variant will not develop arrhythmia, but the researchers say the gene warrants further study in a larger group of individuals.



Splawski *et al* identified a variant of the cardiac sodium channel gene *SCN5A* that is associated with arrhythmia in people of African descent. In certain cells, the variant (the "Y" version shown above) accelerated this channel's activation, increasing the likelihood of abnormal cardiac arrhythmia.

Close Window

Detail from diagram of *SCN5A* gene. View full

Forms of cardiac arrhythmias are a relatively common cause of death, and risk factors include structural heart problems and medication such as diuretics, which are taken to reduce blood

Variação genética aumenta em 8 vezes risco de arritmia cardíaca

Por Merritt McKinney

NOVA YORK (Reuters Health) - Uma variação genética encontrada em mais de um em cada dez afro-americanos aumenta o risco de anormalidades potencialmente fatais no ritmo dos batimentos do coração, as chamadas arritmias cardíacas, sugeriu uma pesquisa.

Mas o risco de sofrer de arritmia continua muito baixo entre os portadores da tal variação genética, informou um dos autores do estudo, Mark T. Keating, da Escola Médica Harvard, em Boston (Massachusetts).

Anualmente, cerca de 450 mil norte-americanos morrem em consequência de arritmia cardíaca. Vários fatores de risco podem influenciar o surgimento de anormalidades no ritmo do coração, entre os quais estão o enfarte, a redução do fluxo sanguíneo para o coração e o uso de determinados medicamentos. No entanto, nem todo mundo que apresenta probabilidade elevada de ter a doença acaba por desenvolver arritmia. Uma das possibilidades é que fatores genéticos influenciem o risco individual de apresentar a enfermidade.

Keating explicou à Reuters Health que qualquer pessoa é portadora de variações genéticas -- ou polimorfismos -- que aumentam, de forma sutil, o risco de doenças. Para identificar as variantes que poderiam aumentar a probabilidade de se sofrer alteração do ritmo do coração, a equipe avaliou amostras de DNA de pessoas que apresentavam arritmia cardíaca. Os pesquisadores encontraram a Y1102, variante do gene SCN5A. Exames complementares de DNA mostraram que, entre os portadores da variante Y1102, o risco de desenvolver o distúrbio foi oito vezes maior que o normal.

Os especialistas estimam que a variação ocorra em cerca de 13 por cento dos afro-americanos. Nenhum integrante de um grupo de várias centenas de brancos e de asiáticos apresentou a variante do gene, presente em uma pessoa em cada grupo de mais de 100 hispânicos, informou o artigo publicado na edição de 23 de agosto da revista Science.

Apesar do aumento do risco associado à presença da variante, "é importante observar que a maioria dos portadores da variação do gene nunca terá arritmia," explicou o pesquisador. A informação será mais útil para as pessoas que já apresentam probabilidade maior de ter arritmia, como as afetadas por cardiomiopatia ou aquelas que consomem determinados medicamentos, como os diuréticos, usados no tratamento da hipertensão.

"O Y1102 será mais uma ferramenta na maleta dos médicos, quando esse e outros testes genéticos estiverem disponíveis", disse Keating. "Os médicos poderão usar as informações genéticas para prever o risco de doenças e para as evitar."

Como a probabilidade de desenvolver arritmia permanece muito baixa entre as pessoas portadoras da variante do gene, "não há urgência de se obter um teste.

Ele terá utilidade maior para as pessoas que já apresentam risco de ter arritmia provocado por outros motivos", explicou Keating.

Caso uma pessoa apresente probabilidade elevada de ter arritmia, há diversas formas de prevenir a ocorrência de anormalidades no ritmo cardíaco. Evitar determinados medicamentos que aumentam o risco, como os diuréticos, manter níveis adequados de potássio no sangue, e tratar-se com betabloqueadores, tudo isso pode minimizar o risco de arritmias.

Fonte: Science 2002;297:1333-1336.

Gene Variant Increases Risk of Cardiac Arrhythmia for African-Americans

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"It is worth knowing if you have the variant because there are simple things you can do to prevent arrhythmias," said HHMI investigator Mark T. Keating.

August 23, 2002— A variant form of a gene found in the heart muscle of some African-Americans may increase the chances of developing a potential deadly heart condition called cardiac arrhythmia, say researchers from the Howard Hughes Medical Institute at Children's Hospital in Boston.

The researchers estimate that 4.6 million African-Americans carry this gene variant. The finding could benefit African-Americans by making it possible to detect who is at increased risk for developing arrhythmia and allowing those affected to take preventive measures. The study is one of the first in which researchers have

been able to discern how genetics influences arrhythmia risk across a range of populations of people who originated from different geographic regions.

In an article published in the August 23, 2002, issue of the journal *Science*, the research team led by HHMI investigator Mark T. Keating reported that 13.2 percent of African-Americans in the study carried an altered form of the gene *SCN5A*. This gene codes for a protein called a sodium channel, a molecular pore that initiates heartbeats by allowing sodium to flow across the membrane of the cardiac muscle cell.

The variant form of the gene creates sodium channels in heart muscle cells that remain open longer than normal sodium channels, prolonging contraction of the heart and contributing to arrhythmia. Keating authored the paper with colleagues at Harvard Medical School, the University of Utah, Columbia University and St. George's Hospital Medical School in London.

Keating emphasized that although arrhythmias are serious disorders, the effect of the gene variant is subtle. "People who have this gene variant are not likely to have an arrhythmia," he said. "All of us harbor gene variants that we may not know about. Fortunately, our hearts are remarkably well buffered against such problems, and arrhythmias are rare. What's often required for a dangerous arrhythmia is that several things go wrong at the same time."

Keating does not believe that routine testing is warranted. The test is fairly simple and inexpensive, so many people may elect to have it, if and when it becomes commercially available, he said. Those most likely to seek testing are people whose medical condition or medications might make them vulnerable to arrhythmias. Currently the test is available only as part of a research study.

"It is worth knowing if you have the variant because there are simple things you can do to prevent arrhythmias," he said. According to Keating, these steps include avoiding any of a broad range of drugs, including antibiotics such as erythromycin and antihistamines such as Seldane, which affect heart rhythm. People with a risk of arrhythmia should monitor their potassium levels to ensure that they remain in the normal range and take beta-blockers to stabilize the heartbeat.

In beginning their search for polymorphisms (gene variants) that might contribute to arrhythmia, Keating and his colleagues started with the gene *SCN5A* because mutations in that gene were known to play a role in rare inherited arrhythmia disorder, called long QT syndrome, that can cause sudden death.

"Almost nothing was known about the effects of polymorphisms on cardiac arrhythmias, but we were among those predicting that variants would be discovered that were reasonably common and would have a subtle effect on arrhythmia risk," said Keating. He pointed out that the effort to understand the genetic and environmental origins of arrhythmias is spurred by the seriousness of the disorder, which kills about 450,000 people in the United States each year.

In their initial studies, the scientists found the same polymorphism, which they named Y1102, in several patients with arrhythmias that did not appear to run in

their families. Their studies showed that changing one nucleotide in the *SCN5A* gene resulted in a sodium channel that carried an alteration in a single amino acid.

A broader survey of several population groups revealed that the Y1102 polymorphism occurred in 19.2 percent of people of West Africans and Caribbean descent, and in 13.2 percent of African-Americans studied. However, the gene variant was not found in Caucasians or Asians, and in only one of 123 Hispanics.

Keating and his colleagues also found that the Y1102 polymorphism occurred disproportionately in African-American patients with arrhythmia and in all phenotypically affected members of one African-American family.

"It would appear that this variant originated in Africa long ago, and been in that population for some time," said Keating. "And the people who migrated out of Africa to found other populations still carry it."

The scientists also conducted cell culture studies that revealed how the Y1102 variant affected the sodium channel by subtly altering its "gating," causing it to remain open slightly longer, which prolongs action potential duration and increases the excitability of cardiac muscle cells. This effect could cause transient conduction abnormalities between heart cells, contributing to arrhythmia risk. Finally, the scientists compared a computer simulation of the effects of Y1102 with actual clinical findings of drug effects on arrhythmia, discovering that the polymorphism did produce the predicted sensitivity.

While the researchers hope their findings will benefit people who have the Y1102 variant, they also emphasize the broader implications of their discovery. "We believe this finding is especially significant because it constitutes a proof of principle that points the way to identifying more of these variants in different population groups," said Keating.

"This is among the first pieces of a big puzzle of genetic affects on arrhythmia," he said. "We need to have many more pieces before we can begin large-scale genetic testing of people for such variants. And although testing for the variant we have discovered may prove useful, it is only one of many risk factors. So, I would hope that such testing will be done in a research setting, where these findings can be confirmed and extended, and put into a larger clinical context," said Keating.

The research was partially funded by the National Heart, Lung, and Blood Institute

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;110:1201-9

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S, Chung MK, Martin D, Rozich R, Tchou PJ, Wang Q. SNP S1103Y in the cardiac sodium channel gene SCN5A is associated with cardiac arrhythmias and sudden death in a white family. J Med Genet 2002 Dec;39(12):913-5

Center for Molecular Genetics, Department of Molecular Cardiology, Lerner Research Institute, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA.

Cardiac arrhythmias cause 400 000 sudden deaths annually in the United States alone. Mutations in the cardiac sodium channel gene SCN5A on chromosome 3p21 cause cardiac arrhythmias and sudden death. In this study, we define an SCN5A mutation, S1103Y, in a white family associated with syncope, ventricular fibrillation, and sudden death. A very recent study reported the same mutation in 13.2% of African Americans, but not in the white population. Our study shows that mutation S1103Y does exist in the white population, and it is associated with a considerable risk of syncope, ventricular arrhythmia, ventricular fibrillation, and sudden death in this population.

Liu W, Yang J, Hu D, Kang C, Li C, Zhang S, Li P, Chen Z, Qin X, Ying K, Li Y, Li Y, Li Z, Cheng X, Li L, Qi Y, Chen S, Wang Q. KCNQ1 and KCNH2 mutations associated with long QT syndrome in a Chinese population. Hum Mutat 2002 Dec;20(6):475-6

Cardiology Division, the People's Hospital of Peking University, Beijing, P. R. China.

The long QT syndrome (LQTS) is a cardiac disorder characterized by prolongation of the QT interval on electrocardiograms (ECGs), syncope and sudden death caused by a specific ventricular tachyarrhythmia known as torsade de pointes. LQTS is caused by mutations in ion channel genes including the cardiac sodium channel gene SCN5A, and potassium channel subunit genes KCNQ1, KCNH2, KCNE1, and KCNE2. Little information is available about LQTS mutations in the Chinese population. In this study, we characterized 42 Chinese LQTS families for mutations in the two most common LQTS genes, KCNQ1 and KCNH2. We report here the identification of four novel KCNQ1 mutations and three novel KCNH2 mutations. The KCNQ1 mutations include L191P in the S2-S3 cytoplasmic loop, F275S and S277L in the S5 transmembrane domain, and G306V in the channel pore. The KCNH2 mutations include L413P in transmembrane domain S1, E444D in the extracellular loop between S1 and S2, and L559H in domain S5. The location and character of these mutations expand the spectrum of KCNQ1 and KCNH2 mutations causing LQTS. Excitement, exercises, and stress appear to be the triggers for developing cardiac events (syncope, sudden death) for LQTS patients with KCNQ1 mutations F275S, S277L, and G306V, and all three KCNH2 mutations L413P, E444D and L559H. In contrast, cardiac events for an LQTS patient with KCNQ1 mutation L191P occurred during sleep or awakening from sleep. KCNH2 mutations L413P and L559H are associated with the bifid T waves on ECGs. Inderal or propanolol (a beta blocker) appears to be effective in preventing arrhythmias and syncope for an LQTS patient with the KCNQ1 L191P mutation.

HGMD®
The Human Gene Mutation Database
Cardiff

Sodium channel, voltage gated, type V, alpha polypeptide

Gene symbol : SCN5A

Location : 3p

In association with CELERA

Mutations in this gene were first reported in 1995

Wang (1995) *Hum Mol Genet* **4**, 1603

Wang (1995) *Cell* **80**, 805

Number of entries by mutation type

Click on the respective mutation type to view detailed information about the mutations as logged in HGMD.

Mutation type	Total number of mutations
Nucleotide substitutions (missense / nonsense)	21
Nucleotide substitutions (splicing)	4
Nucleotide substitutions (regulatory)	0
Small deletions	4
Small insertions	1
Small indels	0
Gross deletions	0
Gross insertions & duplications	0
Complex rearrangements (including inversions)	0
Repeat variations	0
TOTAL	30

Number of entries by phenotype

Phenotype	Nucleotide substitutions	Micro-lesions	Gross lesions
Cardiac conduction disease	1	0	0

Long QT syndrome	14	3	0
Ventricular fibrillation, idiopathic ?	1	0	0
Brugada syndrome	5	0	0
Ventricular fibrillation, idiopathic	2	1	0
Romano-Ward syndrome	1	0	0
Lenegre-Lev disease	1	1	0

Clicking on the respective phenotype will start a search for that item at the OMIM web site. As HGMD only records the first literature report of a mutation, the possibility that reported mutations may be responsible for more than one disease state cannot be ruled out.

Associated data -	HGMD options -	External sites -
Mutation map	HGMD search	OMIM entry for SCN5A
cDNA sequence	HGMD help	GDB entry for SCN5A
	HGMD home	GenAtlas entry for SCN5A
		Nomenclature entry for SCN5A
		GeneCards entry for SCN5A
		LocusLink entry for SCN5A
		Long QT syndrome

Aliases and Additional Descriptions (According to GDB, HUGO, and/or SWISS-PROT)	• HB1 • IVF • LQT3 • sodium channel, voltage-gated, type V, alpha polypeptide (long (electrocardiographic) QT syndrome 3) • Sodium channel protein, cardiac muscle alpha-subunit (HH1).

Chromosomal Location (According to LocusLink and/or UDB and/or HUGO, Genomic Views According to UCSC and Ensembl)	*Chromosome:* **3** *LocusLink cytogenetic band:* **3p21** *Unified DataBase coordinate (from pter):* 38,361 mega bases *Genomic View:* UCSC Golden Path

Proteins (According to SWISS-PROT and/or MIPS)	CIN5_HUMAN · **Size**: 2016 amino acids; 227160 Da · **Function**: THIS PROTEIN MEDIATES THE VOLTAGE-DEPENDENT SODIUM ION PERMEABILITY OF EXCITABLE MEMBRANES. ASSUMING OPENED OR CLOSED CONFORMATIONS IN RESPONSE TO THE VOLTAGE DIFFERENCE ACROSS THE MEMBRANE, THE PROTEIN FORMS A SODIUM-SELECTIVE CHANNEL THROUGH WHICH NA+ IONS MAY PASS IN ACCORDANCE WITH THEIR ELECTROCHEMICAL GRADIENT. IT IS A TETRODOTOXIN-RESISTANT NA+ CHANNEL ISOFORM. THIS CHANNEL IS RESPONSIBLE FOR THE INITIAL UPSTROKE OF THE ACTION POTENTIAL IN THE ELECTROCARDIOGRAM. · **Subcellular location**: Integral membrane protein. · **Tissue specificity**: EXPRESSED IN HUMAN ATRIAL AND VENTRICULAR CARDIAC MUSCLE BUT NOT IN ADULT SKELETAL MUSCLE, BRAIN, MYOMETRIUM, LIVER, OR SPLEEN. · **Domain**: THE SEQUENCE CONTAINS 4 INTERNAL REPEATS, EACH WITH 5 HYDROPHOBIC SEGMENTS (S1,S2,S3,S5,S6) AND ONE POSITIVELY CHARGED SEGMENT (S4). SEGMENTS S4 ARE PROBABLY THE VOLTAGE-SENSORS AND ARE CHARACTERIZED BY A SERIES OF POSITIVELY CHARGED AMINO ACIDS AT EVERY THIRD

Protein Domains/Families (According to BLOCKS and/or InterPro)	**Blocks protein family:** PR00170 Sodium channel signature **InterPro Domains and Families:** IPR001682; Ca/Na_pore IPR000636; M+channel_nlg IPR002111; Cat_channel_TrpL IPR001696; Na_channel IPR000048; IQ_region Graphical View of Domain Structure for SP Entry Q14524
(GenBank/EMBL/DDBJ Accessions According to Unigene or GenBank, RefSeq According to LocusLink, Assembly According to MIPS and/or DOTS)	**REFSEQ mRNAs:** NM_000335.1 **Additional Gene/cDNA sequence:** AY038064 M77235 M77235.1 **MIPS assembly:**H30731S1 **DOTS assembly:** DT.104220 DT.75174024 **Unigene Cluster for SCN5A:** (Build 151 Homo sapiens; May 27 2002) sodium channel, voltage-gated, type V, alpha polypeptide (long (electrocardiographic) QT syndrome 3) Hs.169331 [show with all **ESTs**] **Unigene Representative Sequence:** NM_000335

Disorders & Mutations (in which this Gene is Involved, According to OMIM, SWISS-PROT, Genatlas, GeneClinics, HGMD, BCGD, and/or TGDB.)

OMIM ID: 600163
search databases for MIM named disorders:

- Long QT syndrome-3
- Brugada syndrome
- Heart

SWISS-PROT: CIN5_HUMAN

- **Disease**: DEFECTS IN SCN5A ARE THE CAUSE OF LONG QT SYNDROME TYPE 3 (LQT3), AN AUTOSOMAL DOMINANT CARDIAC DISEASE CHARACTERIZED BY RECURRENT SYNCOPE AND SUDDEN CARDIAC DEATH.

Human Gene Mutation Database entry for SCN5A

Research Articles (in PubMed)	• Primary structure and functional expression of the human cardiac tetrodotoxin-insensitive voltage-dependent sodium channel. • Two long QT syndrome loci map to chromosomes 3 and 7 with evidence for further heterogeneity Search PubMed for SCN5A to find abstracts of **research articles** containing this gene name
SCN5A in Other Genome Wide Resources: (According to GDB, LocusLink, euGenes, Ensembl and/or GeneLynx)	GDB: 132152 LocusLink: 6331 euGenes: HUgn6331 Ensembl GeneLynx: 8071

SCN5A in Specialized Databases (According to ATLAS, GENATLAS, HORDE, IMGT, MTDB and/or SWISS-PROT)	*name description* **Genatlas** biochemistry entry for SCN5A: sodium voltage-gated channel,type V,alpha polypeptide,tetradotoxin-resistant,heart Links to **sequences**, linkage data, **maps**, and **papers** · LQTSdb -SCN5A mutations page. Databases mined from Swiss-Prot

Genes and proteins involved in Long QT Syndrome

1. SCN5A

Description

The SCN5A gene (LQT3) (GeneCard) (OMIM 600163) encodes the cardiac muscle alpha subunit sodium channel protein. The SCN5A gene is located on the Human 3p21 chromosome. Its protein, Sodium Channel Protein, consists of 2016 amino acods. This protein mediates the voltage-dependent sodium ion permeability of excitable membranes. assuming opened or closed conformations in response to the voltage difference across the membrane, the protein forms a sodium-selective channel through which Na^+ ions may pass in accordance with their electrochemical gradient. it is a tetrodotoxin-resistant Na^+ channel isoform. This channel is responsible for the initial upstroke of the action potential in the electrocardiogram.

The sequence contains 4 internal repeats, each with 5 hydrophobic segments (s1,s2,s3,s5,s6) and a positively charged segment (s4). Segments s4 are probably the voltage-sensors and are characterized by a series of positively charged amino acids at every third position.

SCN5A was identified in Human (Q14524)

Gene and Protein

cDNA Acc. N°: M77235 hyperlinked to mutation table
Protein Acc. N°: Q14524 hyperlinked to mutation table

Sequence Analysis

No Homology Model
Multiple sequence alignment (pbil)
Blast (pairwise alignment output, multiple sequence alignment output)
Feature Table of Q14524

Predicted Transmembrane Topology of *SCN5A* Encoded Protein

back to: LQT3 mutation table - BS mutations table - CCD mutation table