LQTS Gene LOVD Database

Tao Zhang1,2,*, Arthur Moss3,*, Peikuan Cong2,*, Min Pan 2,*, Bingxi Chang4, Liangrong Zheng5, Quan Fang4, Wojciech Zareba3, Jennifer Robinson3, Changsong Lin2, Zhongxiang Li6, Junfang Wei7, Qiang Zeng8, Long QT International Registry Investigators, HVP-China Investigators, and Ming Qi1,2,9**

1James D. Watson Institute of Genome Sciences, College of Life Sciences, Zhejiang University, Hangzhou, Zhejiang, China; 2Center for Genetic and Genomic Medicine, Zhejiang University School of Medicine First Affiliated Hospital, Hangzhou, Zhejiang, China; 3Department of Medicine(Cardiology), University of Rochester, Rochester, New York, USA; 4Peking Union Medical College Hospital, Beijing, China; 5Department of Cardiology, Zhejiang University School of Medicine First Affiliated Hospital, Hangzhou, Zhejiang, China; 6Zhejiang Academy of Medical Sciences, Hangzhou, Zhejiang, China; 7Division of Sport Medicine, College of Education, Zhejiang University, Hangzhou, Zhejiang, China; 8General Hospital of PLA, Beijing, China; 9Department of Pathology and Laboratory Medicine, University of Rochester, Rochester, New York, USA

*These authors contributed equally to this manuscript.

**Correspondence to Ming Qi, PhD, FACMG, Center for Genetic and Genomic Medicine, Zhejiang University School of Medicine First Affiliated Hospital, 79 Qingchun Road, Hangzhou, Zhejiang, China, 310003, Telephone: +86-571-88208274, Fax: +86-571-88208274, E-mail: ming_qi@urmc.rochester.edu

Communicated by Alastair F. Brown

ABSTRACT: The Long QT Syndrome (LQTS) is a group of genetically heterogeneous disorders that predispose young individuals to ventricular arrhythmias and sudden death. LQTS is mainly caused by mutations in genes encoding subunits of cardiac ion channels (KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2). Many other genes involved in LQTS have been described recently (KCNJ2, AKAP9, ANK2, CACNA1C, SCN4B, SNTA1, and CAV3). We created an online database (http://www.genomed.org/LOVD/introduction.html) that provides information on variants in LQTS-associated genes. As of February 2010, the database contains 1738 unique variants in 12 genes. A total of 950 variants are considered pathogenic, 265 are possible pathogenic, 131 are unknown/unclassified, and 292 have no known pathogenicity. In addition to these mutations collected from published literature, we also submitted information on gene variants, including one possible novel pathogenic mutation in the KCNH2 splice site found in ten Chinese families with documented arrhythmias. The remote user is able to search the data and is encouraged to submit new mutations into the database. The LQTS database will become a powerful tool for both researchers and clinicians. ©2010 Wiley-Liss, Inc.

KEY WORDS: Long QT Syndrome, Arrhythmia, LOVD, Mutation database

INTRODUCTION

Long QT Syndrome (LQTS) is a familial disorder characterized by prolongation of the QT-interval and a high
incidence of sudden cardiac death mostly at a young age. Two phenotypic variants have been described: i) the more common autosomal dominant Romano-Ward syndrome (Romano, et al., 1963; Ward, 1964), and ii) the less common autosomal recessive Jervell and Lange-Nielsen syndrome, which is associated with sensorineural deafness (Jervell and Lange-Nielsen, 1957). The hereditary LQTS is a genetic channelopathy with variable penetrance that is associated with increased propensity for polymorphic ventricular tachyarrhythmias, particularly torsades de pointes, leading to syncope, seizures and sudden death in young patients with normal cardiac morphology. The disease is relatively infrequent, with variable prevalence estimated from 1:2000 to 1:5000 (Goldenberg, et al., 2008; Schwartz, et al., 2009).

QT prolongation is the hallmark of LQTS, and it may form via one of two pathways: reduction in the outward potassium current during phase 3 of the action potential (“loss of function”) or an augmented late entry of sodium or calcium ions into the cardiac myocytes (“gain of function”) (Goldenberg, et al., 2008; Moss and Kass, 2005). In 1995, Curran et al. first found LQTS caused by KCNH2 gene mutations (Curran, et al., 1995). The rapidly activating potassium repolarization channel mutation (KCNH2; LQT2) results in a reduction in IKr current. Wang et al. reported SCN5A mutations associated with congenital cardiac arrhythmia and LQTS (Wang, et al., 1995). This sodium channel mutation (SCN5A; LQT3) results in an increase in late INa current. In 1996, the KCNQ1 gene was identified as a cause of LQTS (Wang, et al., 1996). The slowly activating potassium repolarization channel mutation (KCNQ1; LQT1) results in a reduction in IKs currents. LQTS has also been identified infrequently in patients with mutations involving the auxiliary β-subunits of KCNQ1 (mink, KCNE1; LQT5) (Splawski, et al., 1997) and of KCNH2 (MiRP1, KCNE2; LQT6 (Abbott, et al., 1999), respectively. Mutations in five genes (KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2) account for approximately 72% of clinically definite LQTS (Napolitano, et al., 2005). Mutations in three other ion-channel genes have been identified in some LQTS families: i) mutation of the KCNJ2 gene results in a reduction in Kir2.1 current, long QT interval and skeletal abnormalities (Andersen-Tawil’s syndrome) (LQT7; Plaster, et al., 2001); ii) mutation in the CACNA1C gene results in an increase in Cav1.2 current, QT prolongation, and multiorgan dysfunction, including webbing of fingers and toes, congenital heart disease, immune deficiency, intermittent hypoglycemia, cognitive abnormalities, and autism (Timothy syndrome) (LQT8; Splawski, et al., 2004); iii) mutation in the SCN4B gene causes an increase in late sodium current (LQT10; Medeiros-Domingo, et al., 2007). A summary of LQT1-12 genotypes, their affected ion-channel currents, and their variant distribution found in our database is presented in Table 1.

| Phenotype | LQT1  | LQT2  | LQT3  | LQT4  | LQT5  | LQT6  | LQT7  | LQT8  | LQT9  | LQT10 | LQT11 | LQT12 |
|-----------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Gene      | KCNQ1 | KCNH2 | SCN5A | ANK-2 | KCNE1 | KCNE2 | KCNE2 | KCNQ1 | KCNE1 | KCNE2 | KCNE2 | KCNE2 |
| Chromosome| 11p15.5 | 7q35-  | 3p21  | 4q25-  | 21q22 | 21q22 | 17q23.1| 12p13.3| 3p25  | 11q23.3| 7q21-  | 20q11.2|
| OMIM #    | 607542 | 152427| 600163| 106410 | 176261| 603796| 600681| 114205| 601253| 608256| 604001| 601017|
| Pathogenicity | 75 | 61 | 84 | 14 | 15 | 9 | 5 | 2 | 8 | 2 | 13 | 4 |
| Possible pathogenicity | 56 | 67 | 105 | 9 | 19 | 6 | 2 | 0 | 0 | 0 | 1 | 0 |
| Pathogenicity | 333 | 433 | 189 | 7 | 16 | 13 | 45 | 5 | 6 | 1 | 1 | 1 |
| Total unique mutations | 471 | 590 | 402 | 60 | 51 | 28 | 53 | 7 | 14 | 6 | 47 | 9 |

Advances in molecular genetics have helped reveal a number of genes that may give rise to LQTS. In addition to these eight ion channel genes described above, mutations in non-ion channel genes can also affect ion-channel currents through direct or indirect interaction with the ion channel complexes. Thus far, four non-ion channel LQTS-susceptibility genes have been discovered: (1) the ankyrin-B gene, which encodes a protein that functions as a cytoskeletal membrane adapter and is involved with the sodium pump, the sodium/calcium exchanger, and the inositol-1,4,5-triphosphate receptors, and can cause LQT4 when mutated (Mohler, et al., 2003); (2) caveolin-3,
which alters gating kinetics in the cardiac sodium channel, and if mutated may result in an increase in sustained late sodium current (Nav1.5; LQT9)(Cronk, et al., 2007; Vatta, et al., 2006); (3) AKAP9 (LQT11), mutation of which reduces the interaction between KCNQ1 and AKAP9 (Yotiao), reduces the cAMP-induced phosphorylation of the channel, eliminates the functional response of the IKs channel to cAMP, and prolongs the QT interval (Chen, et al., 2007); (4) SNTA1 (LQT12), which when mutated increases direct nitrosylation of SCN5A and results in augmentation of late sodium current (Ueda, et al., 2008). Despite this progress in uncovering the genes responsible for LQTS, roughly 25% of patients with clinical LQTS are negative for mutations in the twelve LQTS-associated genes, indicating that more genetic abnormalities remain to be identified.

The variants that have been found in the identified LQTS-associated genes are of different types. To date, hundreds of nonsynonymous (amino-acid-altering, missense, nonsense, and frameshift) mutations and splice-site altering mutations have been found in these twelve LQTS-susceptibility genes. Out of 1738 published or reported unique variants, mutations in KCNQ1, KCN1H2 and SCN5A genes account for almost 85% of total LQTS-associated mutations collected in our database (See Table 1). However, discerning the clinical relevance and pathogenicity of individual mutations is still a challenge. Classification of LQTS-associated gene mutations is generally based on the following several criteria: 1) the electrophysiological abnormality of the ion-channel caused by the mutation; 2) the structure of the protein formed by frameshift, splice-site or nonsense mutations; 3) amino acid changes in the conserved domains of a gene due to missense mutation; 4) failure of protein trafficking due to mutation; 5) the relative frequency of the mutation in healthy individuals.

Two earlier LQTS-variant databases have been set up, one of which collected 232 mutations and 27 polymorphisms through 2003 (including KCNQ1, KCN1H2, SCN5A, KCNE1 and KCNE2) (http://www.ssi.dk/graphics/html/lqtsdb/lqtsdb.htm); the other database collected over 798 mutations and 122 polymorphisms through 2007 (including LQT1-LQT9) (http://www.fsm.it/cardmoc/). Both databases have their own unique features, though neither has been updated. Clinicians and researchers need more comprehensive and timely information about genes associated with LQTS. Thus, we here established this LQTS-variant database (http://www.genomed.org/LOVD/LQTs/home.php) to allow researchers and physicians access to comprehensive and current mutation information.

**DATABASE STRUCTURE**

**Data Collection and Submission**

The bulk of the data on gene variants is derived from published papers and the NCBI SNP database; we also included our own data on the mutations found in ten Chinese families with arrhythmias. For the compiled mutations extracted from the literature, we searched Entrez PubMed (www.ncbi.nlm.nih.gov/sites/entrez) using “Long QT syndrome”, “Sudden unexplained cardiac death”, and the names and abbreviations of genes published as related to LQTS (KCNQ1, KCN1H2, SCN5A, KCNE1, KCNE2, KCNJ2, AKAP9, ANK2, CACNA1C, SCNA4B, SNTA1, and CAV3) as key words. English and Chinese papers matching these search results were collected, as well as papers in other languages that had English abstracts. From the selected papers and abstracts, we compiled the mutations, including the details of DNA and amino acid changes, and judged the classification of pathogenicity reported by the authors. In general, silent mutations and mutations reported in healthy controls were designated as “not known pathogenicity” (Ackerman, et al., 2003; Gouas, et al., 2005; Jongbloed, et al., 2002). Missense mutations found as a result of large screenings of patients with LQTS or Sudden Infant Death Syndrome, and which lack sufficient data to support their pathogenicity, were categorized as “possible pathogenicity” (Jongbloed, et al., 2002; Kapplinger, et al., 2009; Napolitano, et al., 2005; Splawski, et al., 2000; Tester, et al., 2005). The mutation names comply with the accepted guidelines proposed by the Human Genome Variation Society(HGVS)(www.hgvs.org/mutnomen ) (den Dunnen and Antonarakis, 2000). We also searched the NCBI SNP database (www.ncbi.nlm.nih.gov/SNP) and included these SNPs in our database. However, we uniformly classified the pathogenicity of these SNPs as “unknown”, except for those SNPs already described in other published papers.
Because of the large volume of LQTS-related articles, we organized a Human Virome Project (HVP) student club to recruit volunteers interested in genetic and genomic medicine at Zhejiang University. After being trained, these volunteers were divided into several groups to upload the data in the Leiden Open Variation Database (LOVD) format (Fokkema, et al., 2005). Once submitted, the uploaded data were checked by curators before being released for access by the public.

We have also screened 10 Chinese families with various clinical arrhythmias, including 3 with LQTS, 2 with Brugada syndrome, 3 with sudden death syndrome, and 2 with Sick Sinus syndrome for mutations in KCNQ1, KCNH2, SCN5A, KCNE1 and KCNE2. Several common polymorphisms were identified, including p.Ser38Gly in KCNE1 and p.Arg1193Gln in SCN5A. Interestingly, a novel splice mutation c.2690A>C in SCN5A was discovered in a Sick Sinus syndrome patient with compound mutations c.1141-3C>A (homozygous) and p.His558Arg in SCN5A. This novel mutation has not been previously reported and we categorized the mutation as “possible pathogenicity”; a functional analysis is still ongoing. Two pathogenic mutations were found in two families: p.81_82delIleAlaGln in KCNH2 and p.Asp1275Asn in SCN5A, which have both been previously described. All this data have been included in the database.

Database Structure

The database is based on the Leiden Open Variation Database system, which is a web-based database format designed to collect and display DNA variants in specific genes (Fokkema, et al., 2005).

Our database website is http://www.genomed.org/LOVD/introduction.html. On the homepage is a simple table, with the left row showing the 12 total LQTS-associated genes. Each gene links to its own home database (see Figure 1). For example, the web page for the KCNQ1 variant database consists of four sections: general information, sequence variant tables, database search, and links to other resources. Each section provides useful information through a user-friendly interface. At the top of the web page are function buttons designated “Home”, “Variants”, “Submitters”, “Submit” and “Document”. The remote user is able to search the data and is encouraged to submit new mutations into the database after registering as a submitter.

Database Content

In the KCNQ1 variant home database, there are 943 total variants reported (see Figure 1), which are separated into 471 unique DNA variants. Each entry contains two categories of information: patient data and variant data (see Figure 2). The patient data contains the following items: disease, reference, template, technique, remarks, mutation origin, gender, occurrence, de novo origin, geographic origin, ethnic origin and population. The section for variant data is likewise separated into subcategories as follows: allele, reported pathogenicity, concluded pathogenicity, exon, DNA change, DNA published, RNA change, protein, restriction site, frequency, patients, control, DB-ID, type, location and variant remarks.

The data for each gene is based on the published literature, but many published articles do not provide all the details that are available for input in the database, as described above. For example, many papers only describe the amino acid changes that result from DNA mutations. Thus, it is left to the database inputter to check the wildtype DNA sequence, fill in the “DNA change” item as appropriate for that amino acid mutation, and then to mark the “DNA published” item as “No”. For complicated amino acid changes, such as frameshifts, we have opted to add “c.” in the “DNA change” category if the DNA sequence is not already published (Makita, et al., 2007; Mank-Seymour, et al., 2006; Meregalli, et al., 2009; Moss, et al., 2002; Struijk, et al., 2006; Westenskow, et al., 2004).

One gene in particular, ANK-2, does not have a consensus DNA sequence. For this gene, which is associated with LQT4 syndrome, we have downloaded a reference sequence from NCBI (NM00127493.1). Some published articles, however, use a reference sequence different from our selected reference sequence; in these cases, we respect the authors’ choice by submitting the DNA change as described in those papers (Mank-Seymour, et al., 2006; Mohler, et al., 2007; Mohler, et al., 2004; Sherman, et al., 2005).
DISCUSSION

We have set up a publicly accessible online database for variants in genes associated with LQTS. The database contains the most comprehensive variant data available from the published literature, including the entire corpus of Chinese literature on the subject. The database will not only assist clinical geneticists in counseling families found to have a variant of these genes, but will also aid genetic scientists investigating the function of the mutations, which should reduce the time spent searching the literature and help to predict the possible pathogenetic nature of the variant.

Figure 1. Homepage of the KCNQ1 database. The main function menu, shown on the left side, contains the four options provided for the users, which is available at the website http://www.genomed.org/LOVD/LQTs/home.php?select_db=KCNQ1.

The 12 genes contained in the database appear not only to be associated with LQTS, but also with other syndromes. Mutations in the SCN5A gene, for instance, are also found in patients with Brugada syndrome, cardiac
conduction defects, sudden infant death syndrome, arrhythmogenic right ventricular cardiomyopathy, and sick sinus syndrome (Makita, et al., 2005; Miyoshi, et al., 2005; Priori, et al., 2002; Priori, et al., 2000). Even within a single family, the same variant may present different phenotypes in different family members (Bezzina, et al., 1999; Smits, et al., 2005). Our database includes this valuable data by listing the other associated diseases in the patient data section. Moreover, patients carrying two or three mutations in these 12 genes (especially in the KCNQ1, KCNH2, SCN5A, KCNE1 and KCNE2 genes) may have severe clinical symptoms (Shim, et al., 2005; Westenskow, et al., 2004; Ning, et al., 2003b). We also present this information in our database under the rubric for "Remarks" (Figure 2).

**Figure 2.** Details of mutation KCNH2: p.Lys525Asn. In addition to the p.Lys525Asn mutation, the patient carries another mutation KCNH2: p.Arg528Pro. The page also contains the articles reporting the two variants, with a link to their corresponding Pubmed entries. This page is available at http://www.genomed.org/LOVD/LQTs/variants.php?select_db=KCNH2&action=view&view=0001836%2C0000205%2C0

The distribution of mutations is not always random. Marjamaa et al revealed four founder mutations which constitute up to 70% of the known genetic spectrum of LQTS in 6,334 Finnish subjects (Marjamaa, et al., 2009). The four founder mutations are KCNQ1 p.Gly589Asp, KCNQ1 c.1033-2A>G (IVS7-2A>G), KCNH2 p.Leu552Ser and KCNH2 p.Arg176Trp, which have a prevalence estimate of 0.4% (95% CI 0.3%–0.6%) in the Finnish population (Marjamaa, et al., 2009). A comprehensive mutational analysis involving 744 apparently healthy individuals from four race/ethnicity groups (black, white, Asian and Hispanic) revealed that even the common polymorphisms were not equally distributed; p.Lys897Thr-KCNH2 was more common in whites, while
p.Pro448Arg-KCNQ1 was almost absent in whites and more often in Asians (Ackerman, et al., 2003). The proportion of the different types of mutations from the five major LQTS-associated genes (KCNQ1, KCNH2, SCN5A, KCNE1 and KCNE2) is represented in a pie chart demonstrating that missense and frameshift mutations account for 79% (Figure 3).

**Figure 3.** Pie chart showing the proportion of KCNQ1, KCNH2, SCN5A, KCNE1 and KCNE2 mutation types. “Others” includes mutations in introns, the 5’UTR and 3’ UTR, and silent mutations.

The 12 LQTS susceptible genes have been shown to account for about 36% to 72% of identified variants in LQTS patients (Berge, et al., 2008; Kapplinger, et al., 2009; Napolitano, et al., 2005; Splawski, et al., 2000; Tester, et al., 2005; Ning, et al., 2003a). There remain 30% or more LQTS patients without a documented pathogenic variation in these genes. There may be other genes involved in these patients, or the mutations may be in the introns or other so-called junk sequences of the 12 known genes, which can affect their expression or translation process. Crotti et al identified a c.2399-28A>G (IVS9-28A/G) mutation in KCNH2 that disrupted the acceptor splice site definition by affecting the branch point (BP) sequence and thereby promoting intron retention (Crotti, et al., 2009). In other LQTS patients, a large segment duplication or deletion has been identified, which were not easily screened for by current polymerase chain reaction-based exon-scanning methods (Eddy, et al., 2008; Koopmann, et al., 2006).

Our database provides the most complete and universal format published variants for LQTS, although further investigation will likely yield more data. As new variant are identified, we will update the database with the help of remote users and scholars, who may submit their own variants.

**ACKNOWLEDGMENTS**

We are grateful to the patients and their family members who participated in this study. We thank Shouzhang Yang from Zhejiang University, Karolyn Morris from Cornell University and Chinese volunteer club of the International Human Variome Project for their assistance in data input for the database. In addition, we are grateful to D. Owen Young from University of Rochester Medical Center for his assistance in the editing of the manuscript. We also thank Xindong Tao from Hangzhou for his advice in the construction of the database.

Contract grant number: This project was partially supported by 985 Project Grant from the Ministry of Education of China (Dr. Ming Qi), and the “Qiangjiang Research Talent” grant (2006R10018) from the Science and Technology Department of Zhejiang Province.
REFERENCES

Abbott GW, Sesti F, Splawski I, Buck ME, Lehmann MH, Timothy KW, Keating MT, Goldstein SA. 1999. MiRP1 forms IKr potassium channels with HERG and is associated with cardiac arrhythmia. Cell 97(2):175-87.

Ackerman MJ, Tester DJ, Jones GS, Will ML, Burrow CR, Curran ME. 2003. Ethnic differences in cardiac potassium channel variants: implications for genetic susceptibility to sudden cardiac death and genetic testing for congenital long QT syndrome. Mayo Clin Proc 78(12):1479-87.

Berge KE, Haugaa KH, Frueh A, Anfinsen OG, Gjesdal K, Siem G, Oyen N, Greve G, Carlsson A, Rognum TO and others. 2008. Molecular genetic analysis of long QT syndrome in Norway indicating a high prevalence of heterozygous mutation carriers. Scand J Clin Lab Invest 68(5):362-8.

Bezzina C, Veldkamp MW, van Den Berg MP, Postma AV, Rook MB, Viersma JW, van Langen IM, Tan-Sinduhunata G, Bink-Boelkens MT, van Der Hout AH and others. 1999. A single Na(+) channel mutation causing both long-QT and Brugada syndromes. Circ Res 85(12):1206-13.

Chen L, Marquardt ML, Tester DJ, Sampson KJ, Ackerman MJ, Kass RS. 2007. Mutation of an A-kinase-anchoring protein causes long-QT syndrome. Proc Natl Acad Sci U S A 104(52):20990-5.

Cronk LB, Ye B, Kaku T, Tester DJ, Vatta M, Makielski JC, Ackerman MJ. 2007. Novel mechanism for sudden infant death syndrome: persistent late sodium current secondary to mutations in caveolin-3. Heart Rhythm 4(2):161-6.

Crotti L, Lewandowska MA, Schwartz PJ, Insolia R, Pedrazzini M, Bussani E, Dagirdi F, George AL, Jr., Pagani F. 2009. A KCNH2 branch point mutation causing aberrant splicing contributes to an explanation of genotype-negative long QT syndrome. Heart Rhythm 6(2):212-8.

Curran ME, Splawski I, Timothy KW, Vincent GM, Green ED, Keating MT. 1995. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. Cell 80(5):795-803.

den Dunnen JT, Antonarakis SE. 2000. Mutation nomenclature extensions and suggestions to describe complex mutations: a discussion. Hum Mutat 15(1):7-12.

Eddy CA, MacCormick JM, Chung SK, Crawford JR, Love DR, Rees MI, Skinner JR, Shelling AN. 2008. Identification of large gene deletions and duplications in KCNQ1 and KCNH2 in patients with long QT syndrome. Heart Rhythm 5(9):1275-81.

Fokkema IF, den Dunnen JT, Taschner PE. 2005. LOVD: easy creation of a locus-specific sequence variation database using an "LSDB-in-a-box" approach. Hum Mutat 26(2):63-8.

Goldenberg I, Zareba W, Moss AJ. 2008. Long QT Syndrome. Curr Probl Cardiol 33(11):629-94.

Gouas L, Nicaud V, Berthet M, Forhan A, Tietet L, Balkau B, Guicheney P. 2005. Association of KCNQ1, KCNE1, KCNH2 and SCN5A polymorphisms with QTc interval length in a healthy population. Eur J Hum Genet 13(11):1213-22.

Jervell A, Lange-Nielsen F. 1957. Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval and sudden death. Am Heart J 54(1):59-68.

Jongbloed R, Marcelis C, Velter C, Doevendans P, Geraedts J, Smeets H. 2002. DHPLC analysis of potassium ion channel genes in congenital long QT syndrome. Hum Mutat 20(5):382-91.

Kapplinger JD, Tester DJ, Salisbury BA, Carr JL, Harris-Kerr C, Pollevick GD, Wilde AA, Ackerman MJ. 2009. Spectrum and prevalence of mutations from the first 2,500 consecutive unrelated patients referred for the FAMILION long QT syndrome genetic test. Heart Rhythm 6(9):1297-303.

Koopmann TT, Alders M, Jongbloed RJ, Guerrero S, Mannens MM, Wilde AA, Bezzina CR. 2006. Long QT syndrome caused by a large duplication in the KCNH2 (HERG) gene undetectable by current polymerase chain reaction-based exon-scanning methodologies. Heart Rhythm 3(1):52-5.

Makita N, Sasaki K, Groenewegen WA, Yokota T, Yokoshiki H, Murakami T, Tsutsui H. 2005. Congenital atrial standstill associated with coinheritance of a novel SCN5A mutation and connexin 40 polymorphisms. Heart Rhythm 2(10):1128-34.

Makita N, Sumitomo N, Watanabe I, Tsutsui H. 2007. Novel SCN5A mutation (Q55X) associated with age-dependent expression of Brugada syndrome presenting as neurally mediated syncope. Heart Rhythm 4(4):516-9.
Mank-Seymour AR, Richmond JL, Wood LS, Reynolds JM, Fan YT, Warnes GR, Milos PM, Thompson JF. 2006. Association of torsades de pointes with novel and known single nucleotide polymorphisms in long QT syndrome genes. Am Heart J 152(6):1116-22.

Marjamaa A, Salomaa V, Newton-Cheh C, Porthan K, Reunanen A, Karanko H, Jula A, Lahermo P, Vaananen H, Toivonen L and others. 2009. High prevalence of four long QT syndrome founder mutations in the Finnish population. Ann Med:1-8.

Medeiros-Domingo A, Kaku T, Tester DJ, Iturralde-Torres P, Itty A, Ye B, Valdivia C, Ueda K, Canizales-Quinteros S, Tusie-Luna MT and others. 2007. SCN4B-encoded sodium channel beta4 subunit in congenital long-QT syndrome. Circulation 116(2):134-42.

Meregalli PG, Tan HL, Probst V, Koopmann TT, Tanck MW, Bhuiyan ZA, Sacher F, Kyndt F, Schott JJ, Albuissone J and others. 2009. Type of SCN5A mutation determines clinical severity and degree of conduction slowing in loss-of-function sodium channelopathies. Heart Rhythm 6(3):341-8.

Miyoshi S, Mitamura H, Fukuda Y, Tanimoto K, Hagiwara Y, Kanki H, Takatsuki S, Murata M, Miyazaki T, Ogawa S. 2005. Link between SCN5A mutation and the Brugada syndrome ECG phenotype: simulation study. Circ J 69(5):567-75.

Mohler PJ, Le Scouarnec S, Denjoy I, Lowe JS, Guicheney P, Caron L, Driskell IM, Schott JJ, Norris K, Leenhardt A and others. 2007. Defining the cellular phenotype of "ankyrin-B syndrome" variants: human ANK2 variants associated with clinical phenotypes display a spectrum of activities in cardiomyocytes. Circulation 115(4):432-41.

Mohler PJ, Schott JJ, Gramolini AO, Dilly KW, Guatimosim S, duBell WH, Song LS, Haurogne K, Kyndt F, Ali ME and others. 2003. Ankyrin-B mutation causes type 4 long-QT cardiac arrhythmia and sudden cardiac death. Nature 421(6923):634-9.

Mohler PJ, Sadowski I, Napolitano C, Bottelli G, Sharpe L, Timothy K, Priori SG, Keating MT, Bennett V. 2004. A cardiac arrhythmia syndrome caused by loss of ankyrin-B function. Proc Natl Acad Sci U S A 101(24):9137-42.

Moss AJ, Kass RS. 2005. Long QT syndrome: from channels to cardiac arrhythmias. J Clin Invest 115(8):2018-24.

Moss AJ, Zareba W, Kaufman ES, Gartman E, Peterson DR, Benhorin J, Towbin JA, Keating MT, Priori SG, Schwartz PJ and others. 2002. Increased risk of arrhythmic events in long-QT syndrome with mutations in the pore region of the human ether-a-go-go-related gene potassium channel. Circulation 105(7):794-9.

Napolitano C, Priori SG, Schwartz PJ, Bloise R, Nastoli J, Bottelli G, Cerrone M, Leonardi S. 2005. Genetic testing in the long QT syndrome: development and validation of an efficient approach to genotyping in clinical practice. JAMA 294(23):2975-80.

Ning L, Moss AJ, Zareba W, Robinson J, Rosero S, Ryan D, Qi M. 2003b. Novel compound heterozygous mutations in the KCNQ1 gene associated with autosomal recessive long QT syndrome (Jervell and Lange-Nielsen syndrome). Ann Noninvasive Electrocardiol 8(3):246-50.

Ning L, Moss A, Zareba W, Robinson J, Rosero S, Ryan D, Qi M. 2003a. Denaturing high-performance liquid chromatography quickly and reliably detects cardiac ion channel mutations in long QT syndrome. Genet Test 7(3):249-53.

Plaster NM, Tawil R, Tristani-Firouzi M, Canun S, Bendahhou S, Tsunoda A, Donaldson MR, Iammacone ST, Brunt E, Barohn R and others. 2001. Mutations in Kir2.1 cause the developmental and episodic electrical phenotypes of Andersen's syndrome. Cell 105(4):511-9.

Priori SG, Napolitano C, Gasparini M, Pappone C, Della Bella P, Giordano U, Giustetto C, De Nardis R, Grillo M and others. 2002. Natural history of Brugada syndrome: insights for risk stratification and management. Circulation 105(11):1342-7.

Priori SG, Napolitano C, Schwartz PJ, Bloise R, Crotti L, Ronchetti E. 2000. The elusive link between LQT3 and Brugada syndrome: the role of flecainide challenge. Circulation 102(9):945-7.

Romano C, Gemme G, Pongiglione R. 1963. [Rare Cardiac Arrhythmias of the Pediatric Age. II. Syncope Attacks Due to Paroxysmal Ventricular Fibrillation. (Presentation of 1st Case in Italian Pediatric Literature)]. Clin Pediatr (Bologna) 45:656-83.

Schwartz PJ, Stramba-Badiale M, Crotti L, Pedrazzini M, Besana A, Bosi G, Gabbarini F, Goullone K, Insolia R, Mannarino S and others. 2009. Prevalence of the Congenital Long-QT Syndrome. Circulation.
Sherman J, Tester DJ, Ackerman MJ. 2005. Targeted mutational analysis of ankyrin-B in 541 consecutive, unrelated patients referred for long QT syndrome genetic testing and 200 healthy subjects. Heart Rhythm 2(11):1218-23.

Shim SH, Ito M, Maher T, Milunsky A. 2005. Gene sequencing in neonates and infants with the long QT syndrome. Genet Test 9(4):281-4.

Smits JP, Koopmann TT, Wilders R, Veldkamp MW, Opthof T, Bhuiyan ZA, Mannens MM, Balser JR, Tan HL, Bezzina CR and others. 2005. A mutation in the human cardiac sodium channel (E161K) contributes to sick sinus syndrome, conduction disease and Brugada syndrome in two families. J Mol Cell Cardiol 38(6):969-81.

Splawski I, Shen J, Timothy KW, Lehmann MH, Priori S, Robinson JL, Moss AJ, Schwartz PJ, Towbin JA, Vincent GM and others. 2000. Spectrum of mutations in long-QT syndrome genes. KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. Circulation 102(10):1178-85.

Splawski I, Timothy KW, Sharpe LM, Decher N, Kumar P, Bloise R, Napolitano C, Schwartz PJ, Joseph RM, Condouris K and others. 2004. Ca(V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. Cell 119(1):19-31.

Splawski I, Tristani-Firouzi M, Lehmann MH, Sanguinetti MC, Keating MT. 1997. Mutations in the hminK gene cause long QT syndrome and suppress IKs function. Nat Genet 17(3):338-40.

Struijk JJ, Kanters JK, Andersen MP, Hardahl T, Graff C, Christiansen M, Toft E. 2006. Classification of the long-QT syndrome based on discriminant analysis of T-wave morphology. Med Biol Eng Comput 44(7):543-9.

Tester DJ, Will ML, Heglund CM, Ackerman MJ. 2005. Compendium of cardiac channel mutations in 541 consecutive unrelated patients referred for long QT syndrome genetic testing. Heart Rhythm 2(5):507-17.

Ueda K, Valdivia C, Medeiros-Domingo A, Tester DJ, Vatta M, Farrugia G, Ackerman MJ, Makielski JC. 2008. Syntrophin mutation associated with long QT syndrome through activation of the nNOS-SCN5A macromolecular complex. Proc Natl Acad Sci U S A 105(27):9355-60.

Vatta M, Ackerman MJ, Ye B, Makielski JC, Ughanze EE, Taylor EW, Tester DJ, Balijepalli RC, Foell JD, Li Z and others. 2006. Mutant caveolin-3 induces persistent late sodium current and is associated with long-QT syndrome. Circulation 114(20):2104-12.

Wang Q, Curran ME, Splawski I, Burn TC, Millholland JM, VanRaay TJ, Shen J, Timothy KW, Vincent GM, de Jager T and others. 1996. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. Nat Genet 12(1):17-23.

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

Ward OC. 1964. A New Familial Cardiac Syndrome in Children. J Ir Med Assoc 54:103-6.

Westenskow P, Splawski I, Timothy KW, Keating MT, Sanguinetti MC. 2004. Compound mutations: a common cause of severe long-QT syndrome. Circulation 109(15):1834-41.