Keeping Pace: The Genetics of Heritable Arrhythmia Syndromes

Christina Miyake MD MS
Associate Professor, Pediatric Electrophysiology
Associate Professor, Molecular Physiology and Biophysics
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Goals

1. Provide a broad overview of different heritable cardiac arrhythmia diseases – both with and without extracardiac signs/symptoms

2. Example of clinical scenarios

3. Discuss genetic mutations and how alterations result in arrhythmia development

4. Review basics of genetic testing and how to begin to interpret genetic reports (panel testing)
Types of Genetic Changes

- Trisomy 21 (Karyotype/CMA)
- 22q11 deletion
- 3 million (CMA)
- Duchenne muscular Dystrophy (3000 bp)
- Long QT syndrome

Gene Panels
Why Genetics is Important

• Arrhythmia disorders contribute to sudden death but can be preventable if recognized

• Among medical fields, genetics has perhaps made one of the largest impacts on the cardiac arrhythmia disorders

• Genetic Testing results in specific disease can help determine appropriate medications, counseling, risk/prognosis AND it can help identify other at-risk family members (CASCADE SCREENING)
Genetic Testing Results

- PATHOGENIC
- BENIGN
- VARIANT OF UNKNOWN SIGNIFICANCE (VUS)

** The frequency of VUS is increasing

Recognizing phenotype associated with mutations among specific genes will help distinguish benign variants from potentially pathogenic ones.
Review Paper

HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies

This document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA)

Michael J. Ackerman, MD, PhD¹, Silvia G. Priori, MD, PhD², Stephan Willems, MD, PhD³, Charles Berul, MD, FHR, CCDS⁴, Ramon Brugada, MD, PhD⁵, Hugh Calkins, MD, FHR, CCDS⁶, A. John Camm, MD, FHR⁷, Patrick T. Ellinor, MD, PhD⁸, Michael Gollob, MD⁹, Robert Hamilton, MD, CCDS¹⁰, Ray E. Hershberger, MD¹¹, Daniel P. Judge, MD,¹², Hervè Le Marec, MD¹³, William J. McKenna, MD¹⁴, Eric Schulze-Bahr, MD, PhD¹⁵, Chris Semsaesian, MBBS, PhD¹⁶, Jeffrey A. Towbin, MD¹⁷, Hugh Watkins, MD, PhD¹⁸, Arthur Wilde, MD, PhD¹⁹, Christian Wolpert, MD²⁰, and Douglas P. Zipes, MD, FHR²¹

¹From Mayo Clinic, Rochester, Minnesota; ²Fondazione Salvatore Maugeri University of Pavia, Pavia, Italy and New York University, New York, New York; ³University Hospital Hamburg-Eppendorf, Hamburg, Germany; ⁴Children’s National Medical Center and George Washington School of Medicine, Washington, District of Columbia; ⁵Girona Institute of Biomedical Research and University of Girona School of Medicine, Girona, Spain; ⁶Johns Hopkins University, Baltimore, Maryland; ⁷St. George’s University of London, London, United Kingdom; ⁸Massachusetts General Hospital, Cardiac Arrhythmia Service, Boston, Massachusetts; ⁹University of Ottawa Heart Institute, Ottawa, Canada; ¹⁰Hospital for Sick Children, Toronto, Canada; ¹¹University of Miami Miller School of Medicine, Miami, Florida; ¹²Université Paris Descartes, Paris, France; ¹³Institut du thorax, Nantes Cedex, Nantes, France; ¹⁴Institute of Cardiovascular Science, University College London, London, United Kingdom; ¹⁵University Hospital Meinsberg, Meinsberg, Germany; ¹⁶University of Sydney, Sydney, Australia; ¹⁷Cincinnati Children’s Hospital, Cincinnati, Ohio; ¹⁸University of Oxford John Radcliffe Hospital, Oxford, United Kingdom; ¹⁹University of Amsterdam, Academic Medical Center, Amsterdam, The Netherlands; ²⁰Ludwigshurg Clinic, Ludwigshurg, Germany; and ²¹Krahnert Institute of Cardiology, Indiana University School of Medicine, Indianapolis, Indiana.
Syndrome 1

- 2 year old female is status post surgical repair of a large atrial septal defect
- Baseline ECG prior to surgery with first degree AV block, suspected to be due to atrial enlargement from ASD.
- In the CVICU she is noted to have a change in her rhythm
AH Hands
Holt Oram Syndrome

• 1:100,000
• AD, TBX5– T-Box transcription factor
• Abnormalities of the upper limbs (carpal bones)
• 75% with cardiac defect, most commonly atrial septal defect
• Conduction disease, AV block

**NKX2.5 – cardiac specific homeobox protein
Atrial septal defects with or without AV block
Genetic Testing

Summary

Variants of Uncertain Significance identified in PLN and RBM20.

Clinical Summary

- A Variant of Uncertain Significance, c.34A>G (p.Ile12Val), was identified in PLN.
  - The PLN gene is associated with autosomal dominant dilated cardiomyopathy (DCM) (MedGen UID: 322782), hypertrophic cardiomyopathy (HCM) (MedGen UID: 462615), and arrhythmogenic right ventricular cardiomyopathy (ARVC) (PMID: 22820313).
  - The clinical significance of this variant is uncertain at this time. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
  - This variant is not eligible for complimentary family studies as part of our VUS Resolution Program because the results are unlikely to assist Invitae in reclassifying this particular variant. However, if desired, testing for this variant in other family members can be ordered at a reduced cost through the Family Variant Testing Program. Details on our VUS Resolution and Family Variant Testing Programs can be found at www.invitae.com.

- A Variant of Uncertain Significance, c.530C>G (p.Thr177Arg), was identified in RBM20.
  - The RBM20 gene is associated with autosomal dominant dilated cardiomyopathy (DCM) (MedGen UID: 416441).
  - The clinical significance of this variant is uncertain at this time. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
  - This variant is not eligible for complimentary family studies as part of our VUS Resolution Program because the results are unlikely to assist Invitae in reclassifying this particular variant. However, if desired, testing for this variant in other family members can be ordered at a reduced cost through the Family Variant Testing Program. Details on our VUS Resolution and Family Variant Testing Programs can be found at www.invitae.com.

- These results should be interpreted within the context of additional laboratory results, family history, and clinical findings. Genetic counseling is recommended to discuss the implications of this result. For access to a network of genetic providers, please contact Invitae at clientservices@invitae.com, or visit www.nsgc.org or tagc.med.sc.edu/professional_organizations.asp.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>Zyosity</th>
<th>Variant Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLN</td>
<td>c.34A&gt;G (p.Ile12Val)</td>
<td>heterozygous</td>
<td>Uncertain Significance</td>
</tr>
<tr>
<td>RBM20</td>
<td>c.530C&gt;G (p.Thr177Arg)</td>
<td>heterozygous</td>
<td>Uncertain Significance</td>
</tr>
</tbody>
</table>

The following genes were evaluated for sequence changes and exonic deletions/duplications:

ABCC9, ACTC1, ACTN2, AGL, ANK2, BAG3, CACNA1C, CACNB2, CALM1, CALM2, CALM3, CASQ2, CAV3, CRYAB, CSRP3, DES, DMD, DOLK, DSC2, DSG2, DSP, EMD, EYA4, FH1L, FKR, FTKN, FLNC, GAA, GLA, GPD1L, HCN4, JUP, KCN1, KCN8, KCNE1, KCNE2, KCNH2, KCNJ2, KCNO1, LAMP2, LMNA, MYBPC3, MYH7, MYL2, MYL3, MYL4, NKK2-5, PKP2, PLN, PRKAG2, RAP1, RBM20, RYR2, SCN5A, SGCD, SLC22A5, TAZ, TCAP, TGFB3, TMEM43, TNRC1, TNN13, TNNT2, TPM1, TRDN, TTN, TTR, VCL

Results are negative unless otherwise indicated.

**Variant Details**

**PLN, Exon 2, c.34A>G (p.Ile12Val), heterozygous, Uncertain Significance**

- This sequence change replaces isoleucine with valine at codon 12 of the PLN protein (p.Ile12Val). The isoleucine residue is highly conserved and there is a small physicochemical difference between isoleucine and valine.
- This variant is present in population databases (rs749571694, ExAC 0.02%).
- This variant has not been reported in the literature in individuals with PLN-related disease. ClinVar contains an entry for this variant (Variation ID: 234806).
- Algorithms developed to predict the effect of missense changes on protein structure and function (SIFT, PolyPhen-2, Align-GVGD) all suggest that this variant is likely to be tolerated, but these predictions have not been confirmed by published functional studies and their clinical significance is uncertain.
- Algorithms developed to predict the effect of sequence changes on RNA splicing suggest that this variant may create or strengthen a splice site, but this prediction has not been confirmed by published transcriptional studies.
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

**RBM20, Exon 2, c.530C>G (p.Thr177Arg), heterozygous, Uncertain Significance**

- This sequence change replaces threonine with arginine at codon 177 of the RBM20 protein (p.Thr177Arg). The threonine residue is weakly conserved and there is a moderate physicochemical difference between threonine and arginine.
- While this variant is not present in population databases (rs183130427), the frequency information is unreliable, as metrics indicate poor data quality at this position in the ExAC database. This variant has not been reported in the literature in individuals with a RBM20-related disease. ClinVar contains an entry for this variant (Variation ID: 44033).
- Algorithms developed to predict the effect of missense changes on protein structure and function do not agree on the potential impact of this missense change (SIFT: "Not Scored"; PolyPhen-2: "Possibly Damaging"; Align-GVGD: "Class C0").
- In summary, this variant is a rare missense change with uncertain impact on protein function. It has been classified as a Variant of Uncertain Significance.
RE-REQUEST REPORT: This report supersedes RQ184769 (07.27.2017) and includes additional analyses. All genes analyzed to date are listed in the table below.

Summary
Positive result. Pathogenic variant identified in TBX5. Variants of Uncertain Significance identified in PLN and RBM20.

Clinical Summary
- A pathogenic variant, c.587C>A (p.Ser196*), was identified in TBX5.
  - The TBX5 gene is associated with autosomal dominant Holt-Oram syndrome (MedGen UID: 120524).
  - This result is consistent with a predisposition to, or diagnosis of, TBX5-related conditions.
  - Holt-Oram syndrome (HOS) is characterized by radial ray defects in the upper limb and congenital heart disease. The upper limb malformations specifically involve the radial, thenar, or carpal bones, and the congenital heart disease can include structural malformations, such as atrial or ventricular septal defects, and/or conduction disease. While some degree of upper limb malformations are expected with HOS, there is clinical variability and some individuals have very mild features (PMID: 16183809).
Painting by John Waterhouse 1872
Ondine’s Curse

• Ondine was a Greek heroine who tells her love Hans on the day that they meet: “I shall be the shoes of your feet… I shall be the breath of your lungs”

• Hans and Ondine marry. She makes a pact with her uncle, King of Ondines that if Hans ever deceives her, he will die.

• Hans ultimately returns to his first love, Bertha and Ondine leaves him.

• When Hans and Ondine meet again on his wedding day to Bertha, he tells her “all the things my body once did by itself, it now does only by special order, a single moment of inattention and I forget to breath”. They kiss and he dies
Syndrome 2:
Congenital Central Hypoventilation Syndrome
"Ondine’s Curse"

PHOX2B
Congenital Central Hypoventilation Syndrome

- Autosomal dominant disorder
- Typically denovo mutations (neither parent is affected)
- Two CCHS types (2 polyalanine repeat regions in exon 3):
  - Polyalanine repeat expansion mutations (PARMs)
    - Genotype 20/25, 20/26, 20/33
  - Non polyalanine expansion repeat (NPARMs)

Pediatrics
Congenital Central Hypoventilation Syndrome

- Diagnosis in newborn, although later onset occurs
- Hypoventilation (awake or asleep)
- Autonomic dysregulation
- Can have neural crest altered development (ex: Hirschprungs) or tumors (neuroblastoma, ganglioneuroma, ganglioneuroblastoma)
- ***Severe sinus pause is associated with PARMs – larger number of repeats increases risk of SCD
Management

• Evaluation every 6 months until age 3 then yearly

• Echocardiogram yearly for RVH and pulmonary hypertension - evidence of cor pulmonale

• Holter to identify pauses >3 seconds. Pacemaker if needed
Syndrome 3: Rhett Syndrome

MECP2
Rhett Syndrome

• Primarily females. Normal development until age 6-18 months followed by stagnation

• Progressive neurodevelopmental delay with rapid regression of language and motor skills followed by long term stability

• Repetitive stereotypic hand movement, screaming fits, crying, bruxism, seizures, gait ataxia, apraxia

•***Prolonged QT with associated risk of sudden death***
Management

• Yearly ECG with QTc

• If QT is prolonged, yearly Holter

• Treatment with beta blocker if QTc >500msec
Syndrome 4
Kearns-Sayre Syndrome

- Mitochondrial disorder
- Onset <20 years
- Muscle weakness/ataxia
- Progressive external opthalmoplegia (bilateral ptosis) and retinopathy
- Progressive conduction disease
Naxos Syndrome

- Autosomal recessive form first described families from the Greek Island of Naxos (incidence of 1:1000)
- Cardiomyopathy, palmoplantar keratoderma, wholly hair
- Caused by mutations in Plakoglobin
- Plakoglobin encodes a component of desmosomes: specialized adhesive junctions that enable cardiac and epithelial tissue to withstand mechanical stress

McKoy Lancet 2000
# Cardiomyopathies

<table>
<thead>
<tr>
<th>Hypertrophic Cardiomyopathy</th>
<th>Left ventricular noncompaction</th>
<th>Arrhythmogenic Cardiomyopathy</th>
<th>Dilated Cardiomyopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:500</td>
<td>1:1000</td>
<td>1:2000-5000</td>
<td>1:50,00 (?)</td>
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<tr>
<td>VT/SCD</td>
<td>SVT/VT, SCD</td>
<td>VT, SCD</td>
<td>VT/SCD</td>
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<tr>
<td>Strokes</td>
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<table>
<thead>
<tr>
<th>Gene Test: 50%</th>
<th>Gene Test: 40-50%</th>
<th>Gene Test: 50%</th>
<th>Gene Test: 25-50%</th>
</tr>
</thead>
</table>

### Hypertrophic Cardiomyopathy

- VT/SCD
- SVT/VT, SCD
- Strokes
- Gene Test: 50%

### Left Ventricular Noncompaction

- VT/SCD
- SVT/VT, SCD
- Strokes
- Gene Test: 40-50%

### Arrhythmogenic Cardiomyopathy

- VT, SCD
- Strokes
- Gene Test: 50%

### Dilated Cardiomyopathy

- VT/SCD
- Strokes
- Gene Test: 25-50%
Genetic Overlap of Cardiomyopathies

Wilde et al. Nature Reviews 2013

Pediatrics

Texas Children's Hospital
Syndrome 5: Patient JC

• 16 yo previously healthy male presents with new onset left sided weakness, slurred speech, left facial droop

• Also reports fatigue for past 3 weeks and has been taking several naps

• Echocardiogram reveals severely depressed function
Patient JC - ECG

Atrial tachycardia/atrial fibrillation

In sinus rhythm baseline conduction delay and intermittent high grade AV block
LMNA related dilated Cardiomyopathy

- Dilated cardiomyopathy
- Arrhythmias
- Conduction defects
- LV thrombus
JC Genetic Testing & Interpretation

**Clinical Team**
- Corey Gates
- Hari Tunuguntla

**Report Date**
08.01.2018

**Sample Type**
Blood

**Sample**
07.12.2018

**Reason for Testing**
Diagnostic test for a personal history of disease

**Test Performed**
Sequence analysis and deletion/duplication testing of the 67 genes listed in the results section below.
- Invitae Arrhythmia and Cardiomyopathy Comprehensive Panel

**Summary**
Variant of Uncertain Significance identified in LMNA.

**Complete Results**

<table>
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<th>Zygosity</th>
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<td>heterozygous</td>
<td>Uncertain Significance</td>
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Results are negative unless otherwise indicated

**Variant Details**
LMNA, Exon 5, c.857_859delGGG (p.Gly286del), heterozygous, Uncertain Significance
- This variant, c.857_859delGGG, results in the deletion of 1 amino acid of the LMNA protein (p.Gly286del), but otherwise preserves the integrity of the reading frame.
- This variant is not present in population databases (ExAC no frequency).
- This variant has not been reported in the literature in individuals with LMNA-related disease.
- Experimental studies and prediction algorithms are not available for this variant, and the functional significance of the deleted amino acids is currently unknown.
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.
Variant Interpretation - Gnomad

146,000 Samples

<table>
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<th>Gene</th>
<th>Variant</th>
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<tbody>
<tr>
<td>LMNA</td>
<td>c.857_859delGGG (p.Gly286del)</td>
</tr>
</tbody>
</table>

Amino Acid position/change

Chromosome position

Pediatrics
# JC Parental Genetic Testing

## MOTHER

<table>
<thead>
<tr>
<th>Test Performed</th>
<th>Type</th>
<th>Report Date</th>
<th>Sample Type</th>
<th>Sample Collection Date</th>
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<tbody>
<tr>
<td>Sequence analysis and deletion/duplication testing of the gene listed in the results section below.</td>
<td>Saliva</td>
<td>08.17.2018</td>
<td>08.23.2018</td>
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**Reason for Testing:**
- Family history
- Family variant testing

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## FATHER

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<tr>
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<th>Sample Type</th>
<th>Sample Collection Date</th>
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<td>Saliva</td>
<td>09.11.2018</td>
<td>08.19.2018</td>
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**Reason for Testing:**
- Family history
- Family variant testing

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**AMENDED REPORT:** This report supersedes RQ461772 (08.30.2018) and updates the interpretation of the below variant(s).
- The LMNA variant was reclassified from Variant of Uncertain Significance to Likely Pathogenic. The change in variant classification was made as a result of re-review of the evidence in light of new variant interpretation guidelines and/or new information.

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**Pediatrics**

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**Texas Children’s Hospital**
Costello Syndrome

HRAS
Costello Syndrome

- Diagnosis in infancy
- Growth retardation, developmental delay, coarse facial features (full lips, large mouth, full nasal tip), curly or sparse hair, loose skin folds with deep palmar and plantar creases, tight Achilles tendon
- Risk of malignant tumors
  - HCM, valvar pulmonary stenosis
- ***ATRIAL ARRHYTHMIAS IN 30%*****
PRIMARY ARRHYTHMIA DISORDERS
Syndrome 1

- 13 yr old female with a history of febrile seizures since age 5 yrs
- Followed by neurology at TCH, on antiepileptic meds
- Had a seizure at school and fell out of chair, taken to ER
- Bradycardic in ER, admitted to general pediatrics service for observation
The following morning

The pediatrics resident went in to do his physical exam
Long QT Syndrome

QTc = QT/sqrtRR, normal <450msec

QTc = 565 msec
Long QT Syndrome

- Most common channelopathy (1:2500)
- At least 15 genes have been identified, 14-15 distinct LQTS
- Characterized by QT prolongation, structurally normal heart, life threatening ventricular arrhythmias: torsade de pointes +/- extracardiac manifestations
- Although QT prolongation is the hallmark, 10-40% of patients may have nondiagnostic QTc at baseline
LQTS – Diagnosis

- ECG
- Clinical history
- Family History and screening
- Provocative testing
  - Treadmill stress test, Drug challenge
- Schwartz score
- Genetic testing (positive in 75% clinically affected)

### TABLE 2. Schwartz Score for the Diagnosis of Long QT Syndrome (1993)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiogram</td>
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<tr>
<td>QTc ms*</td>
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<tr>
<td>≥480</td>
<td>3</td>
</tr>
<tr>
<td>460-470</td>
<td>2</td>
</tr>
<tr>
<td>450 (males)</td>
<td>1</td>
</tr>
<tr>
<td>Torsade de pointes</td>
<td>2</td>
</tr>
<tr>
<td>T wave alternans</td>
<td>1</td>
</tr>
<tr>
<td>T wave notches in 3 leads</td>
<td>1</td>
</tr>
<tr>
<td>Bradycardia†</td>
<td>0.5</td>
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<tr>
<td>Clinical history</td>
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<tr>
<td>Syncope</td>
<td></td>
</tr>
<tr>
<td>With stress</td>
<td>2</td>
</tr>
<tr>
<td>Without stress</td>
<td>1</td>
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<tr>
<td>Congenital deafness</td>
<td>0.5</td>
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<tr>
<td>Family history‡</td>
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<tr>
<td>Family members with confirmed LQTS§</td>
<td>1</td>
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<tr>
<td>Unexplained sudden death in first-order family members &lt;30 years</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*QTc calculated with the formula of Bazett (QTc = QT/ RR).
†Resting heart rate below the second percentile for age.
‡The same family member cannot be considered twice.
§Schwartz score ≥4: <1 point: low probability; 2-3 points: intermediate probability; ≥4 points: high probability. Rev Esp Cardiol. 2007;60:739
<table>
<thead>
<tr>
<th>Type</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Protein</th>
<th>Dysfunction</th>
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<tr>
<td>LQT – 1</td>
<td>KCNQ1</td>
<td>11p15.5</td>
<td>Kv7.1</td>
<td>$I_{Ks}$ α-subunit, loss fxn</td>
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<tr>
<td>LQT - 2</td>
<td>KCNH2</td>
<td>7q35-q36</td>
<td>Kv11.1</td>
<td>$I_{Kr}$ α-subunit, loss fxn</td>
</tr>
<tr>
<td>LQT - 3</td>
<td>SCN5A</td>
<td>3p21</td>
<td>Nav1.5</td>
<td>$I_{Na}$ α-subunit, gain fxn</td>
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<tr>
<td>LQT - 4</td>
<td>ANK2</td>
<td>4q25-q27</td>
<td>Ankyrin B</td>
<td>Anchor, loss of fxn</td>
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<tr>
<td>LQT - 5</td>
<td>KCNE1</td>
<td>21q22</td>
<td>MinK</td>
<td>$I_{ks}$ β-subunit, loss fxn</td>
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<tr>
<td>LQT - 6</td>
<td>KCNE2</td>
<td>21q22</td>
<td>MiRP1</td>
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<tr>
<td>LQT - 7</td>
<td>KCNJ2</td>
<td>17q24.3</td>
<td>Kir2.1</td>
<td>$I_{K1}$ α-subunit, loss fxn</td>
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<tr>
<td>LQT - 8</td>
<td>CACNA1C</td>
<td>12p13.3</td>
<td>Cav1.2</td>
<td>$I_{LTCC}$ α-subunit gain fxn</td>
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<tr>
<td>LQT - 9</td>
<td>CAV3</td>
<td>3p25</td>
<td>Caveolin 3</td>
<td>Gain fxn (Nav1.5)</td>
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<tr>
<td>LQT - 10</td>
<td>SCN4B</td>
<td>11q23</td>
<td>Navb4</td>
<td>$I_{Na}$ β-subunit, gain fxn</td>
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<td>LQT - 11</td>
<td>AKAP9</td>
<td>7q21-q22</td>
<td>Yotiao</td>
<td>Loss fxn, Kv11.1</td>
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<td>LQT - 12</td>
<td>SNTA1</td>
<td>20q11.2</td>
<td>α-1syntropin</td>
<td>Gain fxn (Nav1.5)</td>
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<tr>
<td>LQT - 13</td>
<td>KCNJ5</td>
<td>11q24.3</td>
<td>Kir3.4/Girk4</td>
<td>$I_{K,Ach}$ α-subunit loss fxn</td>
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<td>LQT - 14</td>
<td>CALM1</td>
<td>14q32.11</td>
<td>Calmodulin 1</td>
<td>Decreased binding</td>
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<tr>
<td>? LQT - 15</td>
<td>CALM2</td>
<td>2p21</td>
<td>Calmodulin 2</td>
<td>Decreased binding</td>
</tr>
</tbody>
</table>
LQTS - mechanism

Cardiac K channel
Who to test?

**STATE OF GENETIC TESTING FOR LONG QT SYNDROME (LQTS)**

**Class I (is recommended)**
Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing is recommended for any patient in whom a cardiologist has established a strong clinical index of suspicion for LQTS based on examination of the patient’s clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative stress testing with exercise or catecholamine infusion) phenotype.

Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing is **recommended** for any asymptomatic patient with QT prolongation in the absence of other clinical conditions that might prolong the QT interval (such as electrolyte abnormalities, hypertrophy, bundle branch block, etc., i.e., otherwise idiopathic) on serial 12-lead ECGs defined as QTc >480 ms (prepuberty) or >500 ms (adults).

Mutation-specific genetic testing **is recommended** for family members and other appropriate relatives subsequently following the identification of the LQTS-causative mutation in an index case.

**Class IIb (may be considered)**
Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing may be considered for any asymptomatic patient with otherwise idiopathic QTc values >460 ms (prepuberty) or >480 ms (adults) on serial 12-lead ECGs.

---

**Definitely test (Class I)**
1. Strong suspicion based on patients history, family history or ECG
2. Asymptomatic with serial QTc >480 (pre-pubertal) or >500 adult
3. Confirmatory testing if appropriate relative with LQTS-causing mutation

**Consider testing (Class IIb)**
1. Asymptomatic with serial QTc >460 (pre-pubertal) or >480 adult
Long QT Syndrome (AR Form)

• Jervell and Lange-Nielsen Syndrome:
  - Severe QTc prolongation >550msec, high rate of sudden cardiac death
  - Associated with congenital ear deafness (loss of endolymph)
Family Pedigree

*KCNH2 Ala614Val
Long QT 2

13 yrs
10 yrs
7 yrs
4 yrs

QTc 565
QTc 418
QTc 540
QTc 560

52 yrs died in sleep
70 yrs
Died of “old age”
The Role of Genetics in LQTS

<table>
<thead>
<tr>
<th>Disease</th>
<th>Diagnostic</th>
<th>Prognostic</th>
<th>Therapeutic</th>
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<tbody>
<tr>
<td>LQTS</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>CPVT</td>
<td>+++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Brugada</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
The type of LQTS affects prognosis.
Specific mutations are more lethal
Arrhythmia “triggers” differ by genotype

- Long QT 1 → Swimming/Exercise
- Long QT 2 → Emotion/Fear, Alarm Clocks, Peripartum
- Long QT 3 → Sleep

![Genotype and Triggers for Life-Threatening events (cardiac arrest or SCD) in 110 LQTS patients]

- LQT1 (n=52): 75% Exercise, 15% Emotion, 10% Sleep
- LQT2 (n=38): 37% Exercise, 63% Emotion, 5% Sleep
- LQT3 (n=20): 80% Exercise, 15% Emotion, 15% Sleep

Pediatrics
LQTS – Therapy/Management

1. First line is beta blocker
   - Most effective in LQT1
   - LQT2 Nadolol is most effective
   - LQT3 consider Na channel blocker (Mexilitine)

2. Life style modifications
   - Avoidance of QT prolonging drugs
   - LQT1: Swimming, +/-exercise restriction
   - LQT2: Minimize sudden startle (alarm clocks, bells), peripartum
   - LQT3: Early dx and treatment

3. ICD if symptoms occur despite medications

4. Left cervical stellate ganglionectomy
# Extracardiac manifestations in LQT

<table>
<thead>
<tr>
<th>Type</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Protein</th>
<th>Dysfunction</th>
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<tbody>
<tr>
<td>LQT – 1</td>
<td>KCNQ1</td>
<td>11p15.5</td>
<td>Kv7.1</td>
<td>(I_{Ks}) α-subunit, loss fxn</td>
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<tr>
<td>LQT - 2</td>
<td>KCNH2</td>
<td>7q35-q36</td>
<td>Kv11.1</td>
<td>(I_{Kr}) α-subunit, loss fxn</td>
</tr>
<tr>
<td>LQT - 3</td>
<td>SCN5A</td>
<td>3p21</td>
<td>Nav1.5</td>
<td>(I_{Na}) α-subunit, gain fxn</td>
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<tr>
<td>LQT - 4</td>
<td>ANK2</td>
<td>4q25-q27</td>
<td>Ankyrin B</td>
<td>Anchor, loss of fxn</td>
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<tr>
<td>LQT - 5</td>
<td>KCNE1</td>
<td>21q22</td>
<td>MinK</td>
<td>(I_{ks}) β-subunit, loss fxn</td>
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<tr>
<td>LQT - 6</td>
<td>KCNE2</td>
<td>21q22</td>
<td>MiRP1</td>
<td>(I_{Kr}) β-subunit, loss fxn</td>
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<tr>
<td>LQT - 7</td>
<td>KCNJ2</td>
<td>17q24.3</td>
<td>Kir2.1</td>
<td>(I_{K1}) α-subunit, loss fxn</td>
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<tr>
<td>LQT - 8</td>
<td>CACNA1C</td>
<td>12p13.3</td>
<td>Cav1.2</td>
<td>(I_{LTCC}) α-subunit gain fxn</td>
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<td>LQT - 9</td>
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<td>3p25</td>
<td>Caveolin 3</td>
<td>Gain fxn (Nav1.5)</td>
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<tr>
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<td>7q21-q22</td>
<td>Yotiao</td>
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<tr>
<td>LQT - 12</td>
<td>SNTA1</td>
<td>20q11.2</td>
<td>α- 1syntropin</td>
<td>Gain fxn (Nav1.5)</td>
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<tr>
<td>LQT - 13</td>
<td>KCNJ5</td>
<td>11q24.3</td>
<td>Kir3.4/Girk4</td>
<td>(I_{K, Ach}) α-subunit loss fxn</td>
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<td>LQT - 14</td>
<td>CALM1</td>
<td>14q32.11</td>
<td>Calmodulin 1</td>
<td>Decreased binding</td>
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<tr>
<td>? LQT - 15</td>
<td>CALM2</td>
<td>2p21</td>
<td>Calmodulin 2</td>
<td>Decreased binding</td>
</tr>
</tbody>
</table>
Andersen Tawil Syndrome (LQT 7)

- AD, prevalence of 1:1,000,000.
- KCNJ2 mutation
- Dysmorphic: micrognathia, hypertelorism, low set ears, broad forehead, digit clinodyactyl, 2-3 toe syndactyl, abnormal or absence of lateral incisors, microcephaly and small hands/feet
- PVC’s, Bidirectional VT, arrhythmias rarely life-threatening
- Periodic paralysis

Am J Hum Genet
Timothy Syndrome (LQT 8)

- AD, CACNA1c, L-type Ca Channel
- High rate of sudden death in first decade, treatment is ICD
- Variable extracardiac manifestations (can be non-syndromic)
- Dysmorphic facies: round face, flat nasal bridge, small upper jaw, low set ears, syndactyl, bald at birth, small or misplaced teeth (100%)
- Developmental delays (language, motor, cognitive), autism
- Congenital heart malformations: PDA, VSD, TOF

QTC > 500msec

**Fukuyama et al Europace 2014**

*Pediatrics*
Syndrome 2

• This syndrome is the reason why young southeast asian males may go to bed dressed as a female.

• It is also the premise behind the movie "Nightmare on Elm Street".
Brugada Syndrome - mechanism

SCN5A = Na ion channel Nav1.5

Gain of Fxn = LQT 3
Loss of Fxn = Brugada

Triggers for lethal arrhythmia: Fever, sleep, large meals, alcohol, drugs (anesthetics, antiarrhythmics)
Brugada Syndrome

- Estimated prevalence 1-5:10,000 in Europe and 12:10,000 in Southeast Asia (sudden unexpected nocturnal death syndrome)
- Lethal VT/VF, bradycardia, sinus pauses
- 20% of sudden death in normal hearts
- Male predominance, accounts for 80% of affected
- Most events occur in 3\textsuperscript{rd} - 4\textsuperscript{th} decade of life during sleep or after large meals
- In children presents most commonly with arrhythmias during fever and has been associated with SIDS

Brugada JACC 1992
ECG in Brugada Syndrome

1. Brugada ECG changes come and go. A normal ECG doesn’t rule out
2. ECG changes are brought out by: Fever, Na channel blockers, and large meals * modifying ECG leads (high V1, V2)
3. Patients with Type I changes at baseline are at higher risk
Brugada – Diagnosis

• ECG (modified leads, during fever)
• Provocative testing
  - Procainamide challenge (Na channel blocker)
• Screening of family members
• Genetic testing is negative in 70-75%
Who to test?

STATE OF GENETIC TESTING FOR BRUGADA SYNDROME (BrS)

Class I (is recommended)
Mutation-specific genetic testing is **recommended** for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case.

Class IIa (can be useful)
Comprehensive or BrS1 (SCN5A) targeted BrS genetic testing can be useful for any patient in whom a cardiologist has established a clinical index of suspicion for BrS based on examination of the patient’s clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype.

Class III (is not indicated/recommended)
Genetic testing is **not indicated** in the setting of an isolated type 2 or type 3 Brugada ECG pattern.

**Definitely test (Class I)**
1. Confirmatory testing if appropriate relative with Brugada-causing mutation

**Consider testing (Class IIa)**
1. Targeted testing if established clinical suspicion for BrS based on clinical history, family hx, or ECG phenotype

**Do Not Test (Class III)**
1. Type 2 or 3 Brugada Pattern
Brugada – Therapy/Management

• Aggressive treatment and admissions for fever
• No effective antiarrhythmic although quinidine is a drug that has been used
• Only current definitive effective therapy is an ICD, recommended only if documented VT or cardiac events (syncope/arrest), +/-EP study (controversial)
• EP study with epicardial ablation is a new therapy that may be curative
Case Example - TB

• TB is a 10 year old male referred to clinic by his pediatrician due to bradycardia

• Heart rate 40bpm. He is asymptomatic

• Grandfather died in his sleep at age 40

• His father died in a single car accident after driving home from lunch. He had a history of needing to get his “heart shocked” when he went to the ER with a fever.
Genetic Report

Pediatrics

Circulation Arrhythm Electrophysiol 2015

Original Article

Loss-of-Function SCN5A Mutations Associated With Sinus Node Dysfunction, Atrial Arrhythmias, and Poor Pacemaker Capture

David Y. Chiang, PhD; Jeffrey J. Kim, MD; Santiago O. Valdes, MD; Caridad de la Uz, MD; Yuxin Fan, MD, PhD; Jeffrey Occeri, MD; Melissa Domino, RN; Melissa Smith, RN; Xander H.T. Welrens, MD, PhD; Christina Y. Miyai, MD, MS
TB’s Rhythm Monitor during admission

5.5 seconds  11 bpm
Case 1 – TB Defibrillator (ICD) Device Implant

- 10 minutes after device implant:
Device Implant 9-21-16

• His body temperature was 39.2

• Bair hugger had been on “high” and his temperature was 39.2

• With cooling the VT improved although he had another storm that evening in the PICU when his temperature rose to 99 degrees which lead to a code event
Syndrome 3

- DR is a 12 yo male found unresponsive and seizing outside the bathroom at 3AM
- Known history of seizures but had not been taking antiepileptics prescribed by his neurologist
- EMS performed CPR

- He is intubated in the CVICU
- Echo EF 14%
ECG in CVICU

HR 130bpm, QTc = 489msec
ECG from ER in April 2014

HR 75bpm, QTc = 436msec
April – December 2014

- Evaluated in TCH ER due to history of multiple seizure events that have been occurred since age 8 yrs while playing or running around
- ECG normal. Referred to neurology for EEG
- EEG normal. Neurology prescribed antiepileptics
- ECG normal, Echo normal
### EST Report

**Original Document:**

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>STANDING</td>
<td>109</td>
<td>142/10</td>
</tr>
<tr>
<td>SUPINE</td>
<td>109</td>
<td>133/10</td>
</tr>
</tbody>
</table>

**EKG Response:**

- Normal
- No PVC's seen

**Interpretation:**

1. The patient achieved **10.1** METS and exercised for **9:12** minutes on **Bruce** protocol to a maximum heart rate of **175** (84% of his/her maximum predicted heart rate).
2. The patient achieved a rate pressure product of **224 x 10**.
3. Test terminated due to **dizzy**.
4. **Normal** response to exercise.
5. Occasional PVCs producing **rigidity and couplets**.
6. **Significant**

**Duke Score:**

- Risk: Low: __________ Medium: __________ High: __________

**Impression:**

- **Negative**
- **Unconditioning** exercise capacity.
- Few PVCs. No supraventricular arrhythmias.
- Long-QRS. Vocal cords dysfunction is likely.
DR arrested on September 12\textsuperscript{th}, 2016

He died on September 14\textsuperscript{th}, 2016
Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

- Most malignant inheritable arrhythmia
  - Sudden death up to 50% by 30yrs
- Mean age of onset 8-12 yrs
- Triggers – adrenergic response or acute emotion
- Genetics first discovered in 2001*
  - RyR2 = 50-60% of mutations
  - CasQ2 = 3-5%
  - Triadin, KCNJ2, ANK2

*Reid et al, Br Heart J 1975    Swan JACC 1999
CPVT - Mechanism

- KCNJ2 (w/o Anderson Tawil phenotypes and Ankyrin B)
- RyR2
- CASQ2
- LTCC
- Ca\textsuperscript{2+}
- Sarcoplasmic Reticulum

[Diagram showing the mechanism of CPVT with labeled pathways and calcium ions.]
CPVT – Diagnosis

- ECG and echocardiogram will be normal
- Exercise Testing
- Drug infusion (epi or isoproterenol)
- Genetic testing 65% of individuals with a clear phenotype will be positive
CPVT Therapy and Management

• Beta blockers attenuate the adrenergic response and is proven to be protective although ~30% of patients experience at least 1 arrhythmic event

• Flecainide as second dual therapy agent

• ICD therapy can be considered with caution

• Left cervical stellate ganglionectomy
Who to test?

Definitely test (Class I)

1. Targeted testing if clinical suspicion for CPVT based on history, family hx, and ECG phenotype
2. Confirmatory testing if appropriate relative with CPVT-causing mutation

STATE OF GENETIC TESTING FOR CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT)

Class I (is recommended)

Comprehensive or CPVT1 and CPVT2 (Ryr2 and Casq2) targeted CPVT genetic testing is recommended for any patient in whom a cardiologist has established a clinical index of suspicion for CPVT based on examination of the patient’s clinical history, family history, and expressed electrocardiographic phenotype during provocative stress testing with cycle, treadmill, or catecholamine infusion.

Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the CPVT-causative mutation in an index case.
CPVT Family

- 34 yrs
- 21 yrs
- 32 yrs ICD
- 30 yrs ACA, ICD

LQT panel negative
Novel mutation in RyR2 Asn4634del
Pearls

• The most important thing you can do is recognize those patients in whom there may be an inheritable arrhythmia syndrome.

• A thorough and detailed clinical history including a family history is critical.
Screening Questions

• Hx of syncope, seizures (w/o post-ictal state), sudden death or unusual accidents

• Circumstances surrounding event:
  - fever, febrile seizures, large meal, alcohol – Brugada syndrome
  - exercise – LQT1
  - emotion/fear – LQT2, CPVT
  - loud noise, post-partum – LQT2
  - Sleep – LQT3, Brugada syndrome

• History of drowning, near drowning, congenital deafness

• Fhx: syncope, seizures, drownings, accidents, sudden death, early MI, pacemakers/defibrillators, CM/heart failure

• Review Autopsy report
Genetic Testing is not always Right

- 13 yo cardiac arrest
- Hx of syncope
- Dx: Myocarditis
- ECG QTc 580-600msec

Mother's Results, ECG QTc 460msec, syncope as teenager, neg FHx

Father's Results ECG QTc 460msec, neg FHx

### Panel V: Pan Arrhythmia Panel — Sequencing Analysis

<table>
<thead>
<tr>
<th>Gene</th>
<th>DNA Change</th>
<th>Amino Acid Change</th>
<th>Zygosity</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>DES</td>
<td>c.1375G&gt;A</td>
<td>p.Val459Ile</td>
<td>Heterozygous</td>
<td>Uncertain significance</td>
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<tr>
<td>DSC2</td>
<td>c.1552G&gt;C</td>
<td>p.Val518Leu</td>
<td>Heterozygous</td>
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</tr>
<tr>
<td>KCNH2</td>
<td>c.253G&gt;A</td>
<td>p.Ala85Thr</td>
<td>Heterozygous</td>
<td>Uncertain significance</td>
</tr>
<tr>
<td>RYR1</td>
<td>c.487C&gt;T</td>
<td>p.Thr161Met</td>
<td>Heterozygous</td>
<td>Uncertain significance</td>
</tr>
<tr>
<td>SCN5A</td>
<td>c.80G&gt;A</td>
<td>p.Arg27His</td>
<td>Heterozygous</td>
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</tbody>
</table>

**Summary**

Variant of Uncertain Significance identified in KCNH2. Familial SCN5A variant present in this individual. Familial KCNH2 c.253G>A (p.Ala85Thr), RYR1, DES and DSC2 variants not present in this individual.

**Clinical Summary**

- A Variant of Uncertain Significance, c.3279...3303del (p.Leu1094Profs*153), was identified in KCNH2.
  - The KCNH2 gene is associated with autosomal dominant long QT syndrome (LQTS), type 2 (MedGen UID: 462939), short QT syndrome (SQT1) (MedGen UID: 355891) and Brugada syndrome (BrS) (MedGen UID: 22975).
  - The clinical significance of this variant is uncertain at this time. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
  - In the absence of a personal history of KCNH2-related conditions, this variant is not currently eligible for complimentary family studies as a part of our VUS Resolution Program. However, if desired, testing for this variant in other family members can be ordered at a reduced cost through the Family Variant Testing Program. Details on our VUS Resolution and Family Variant Testing Programs can be found at www.invitae.com.

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Pediatrics

Texas Children's Hospital

Baylor College of Medicine
Genetic Testing is not always Right

Summary

Variants of Uncertain Significance identified in KCNH2.

Clinical Summary

- Two Variants of Uncertain Significance, c.253G>A (p.Ala85Thr) and c.3279_3303del (p.Leu1094Profs*153), were identified in KCNH2. These variants are on opposite chromosomes.
  - The KCNH2 gene is associated with autosomal dominant long QT syndrome (LOTS), type 2 (MedGen UID: 462293) and short QT syndrome (SQTS) (MedGen UID: 355891). Additionally, the KCNH2 gene has preliminary evidence supporting a correlation with autosomal dominant Brugada syndrome (PMID: 24400717). For information about the location of a KCNH2 variant, please visit www.invitae.com/KCNH2-topology.
  - The clinical significance of these variants is uncertain at this time. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
  - These variants may qualify for complimentary family studies as part of our VUS Resolution Program. Details on our VUS Resolution and Family Variant Testing Programs can be found at www.invitae.com. Please contact Invitae Client Services to discuss eligibility.
  - These results should be interpreted within the context of additional laboratory results, family history, and clinical findings. Genetic counseling is recommended to discuss the implications of this result. For access to a network of genetic providers, please contact Invitae at clientservices@invitae.com, or visit www.nsgc.org or tagc.medic.edu/professional_organization.sasp.

Complete Results

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>Zygosity</th>
<th>Variant Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCNH2</td>
<td>c.253G&gt;A (p.Ala85Thr)</td>
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<tr>
<td>KCNH2</td>
<td>c.3279_3303del (p.Leu1094Profs*153)</td>
<td>heterozygous</td>
<td>Uncertain Significance</td>
</tr>
</tbody>
</table>

The following genes were evaluated for sequence changes and exonic deletions/duplications:

ABC9, ACTN2, AKAP9, ANK2, ANKRD11, CACNA1C, CACNA2D1, CACNB2, CALM1, CALM2, CALM3, CASQ2, CAV3, CTNNA3, DES, DSC2, DSG2, DSP, EM, FLNC, GATA6, GJA5, GPD1, HCN4, JUP, KCN2A, KCN3, KCN4, KCN6, KCN8, KCN12, KCN15, KCN16, KCN17, KCNQ1, LDLB3, LMNA, MLH4, NKO2-5, NPPA, PDLIM3, PKP2, PLN, PRKAG2, RANGRF, RBM20, RYR2, S100A6, SCN1B, SCN2B, SCN3B, SCN4B, SCN5A, SLMAP, SNTA1, TGBF3, TMEM43, TNBS, TNNT2, TRDN, TRPM4, TTN

Results are negative unless otherwise indicated.
Final Words

- Genetic testing must not be viewed as a simple blood test.
- Yield of genetic testing is disease dependent and a negative test can never rule out disease.
- The ordering physician should be knowledgeable in interpreting genetic findings.
- Prognostic and therapeutic contributions of genetic testing are disease dependent and should be based on comprehensive clinical evaluation.
Thank You