Pregnancy and Channelopathies

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Julia Wynn, MS, CGC
Planning a Pregnancy?

Consider meeting with:

• Geneticist
  • Risk of channelopathy
  • Reproductive options

• Maternal Fetal Medicine physician

• Cardiologist
  • Your cardiologist (Often already engaged)
  • Fetal/pediatric cardiologist
Referral to Genetics: What to Expect
Genetic Considerations

Many of these syndromes will be Autosomal Dominant but some are Autosomal Recessive

What does that mean?

AD- children of affected parents (or sibling) will have a 50% chance to have it
AR-children who have an affected sibling will have a 25% chance to have it (with same parents)

Long QT Syndromes: mainly autosomal dominant (AD)
Romano-Ward: autosomal dominant (AD)
Jervell syndrome and Lange-Nielsen: Autosomal recessive (AR)
Non-invasive fMCG*

*More later!
Example Maternal Test Results

<table>
<thead>
<tr>
<th>Test(s) Requested:</th>
<th>Long QT Syndrome (LQTS) Sequencing and Deletion/Duplication Panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes Evaluated:</td>
<td>KCNQ1 (LQT1 and Jervell and Lange-Nielsen syndrome), KCNH2 (LQT2), SCN5A (LQT3), ANK2 (LQT4), KCNE1 (LQT5 and Jervell and Lange-Nielsen syndrome), KCNE2 (LQT6), KCNJ2 (LQT7 and Andersen-Tawil syndrome), CACNA1C (LQT8 and Timothy syndrome), CAV3 (LQT9), SCN4B (LQT10), AKAP9 (LQT11), SNTA1 (LQT12)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Result:</th>
<th>POSITIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene</td>
<td>cDNA</td>
</tr>
<tr>
<td>KCNH2 (aka HERG)</td>
<td>c.3027 C&gt;G</td>
</tr>
</tbody>
</table>

No other disease-causing mutations associated with Long QT syndrome were detected by sequence analysis of the 12 genes of the LQTS panel in this individual. No deletion or duplication involving any of these 12 genes was found by concurrent targeted arrayCGH analysis with exon-level resolution (ExonArrayDx).

| Interpretation:          | This individual is heterozygous for a novel nonsense mutation in the KCNH2 gene, consistent with a genetic form of LQTS. |

Familial Long QT syndrome is primarily an autosomal dominant disease caused by mutation(s) in cardiac ion channel genes. Mutations in these genes tend to prolong the duration of the ventricular action potential, thus lengthening the QT interval seen on an ECG (Goldenberg I et al., 2008; Priori S et al., 2004). LQTS is associated with increased risk for syncope, ventricular arrhythmia and sudden cardiac death in young adults with normal heart structure (Vincent G, 1998). Mutations in the KCNH2 gene have been reported in approximately 25-35% of patients with autosomal dominant long QT syndrome, and are associated with increased risk of cardiac events triggered by exercise and auditory stimulation, especially during sleep.
Referral to MFM/Preconception: What to Expect

- Optimizing health prior to pregnancy
  - Beta blockers?
  - Pacemaker?
  - Trigger avoidance

- Planning for the pregnancy/postpartum
  - Medications to avoid
  - Evaluation of fetus
  - Engage with Cardiologists (Adult and Fetal)
  - Recommendations to prenatal team
  - Postpartum
Beta Blocker Therapy-SAFETY

β-adrenergic blockers strongly recommended: smallest reduction in risk is 50%

Beta Blockers most protective post-partum
- w/o. BB: 3.7 events/year w. BB: 0.8 events/year
- Reduced risk from 1 in 50 to 1 in 2500 pregnancies

Propranolol
- best transplacental transfer
- infrequently associated with
  - neonatal bradycardia
  - respiratory depression
  - hypoglycemia
  - intrauterine growth retardation

Nadolol:
- Recommended by Heart Rhythm as most protective for LQTS mothers
- Similar safety profile

Seth R et al JACC 2007 49(10):1092-1098
Referral to Fetal Cardiology: What to Expect
Risk Factors, Signs and Symptoms of LQTS Differ by Age

**Pediatric LQTS**
- Family history of LQTS
- Symptoms of LQTS
  - Sudden unexplained death or cardiac arrest
  - Syncope/Seizures
  - Near drowning
  - SIDs
- ECG Findings
  - QTc > 450 msec

**Fetal LQTS**
- Family history LQTS
- Symptoms and signs of LQTS
  - 75-95% sinus bradycardia
  - 5-25% VT and/or 2° AVB
  - Unexplained heart failure
  - Fetal demise
- Echo findings
  - Structurally normal heart w. LQTS rhythm
What to Discuss

Question

1. In utero diagnosis: why should we?

2. What is safest and most definitive prenatal test?

3. If I am asymptomatic will the baby be asymptomatic?

Answer

- Change in care and monitoring of pregnancy
- Risk of cardiac event for fetus/infant
- Non-invasive fMCG at 24-28 wks
- Invasive prenatal diagnosis at 12 wks (CVS)
- Variable phenotype with same genotype
“...This report (of the first confirmed case of Romano Ward syndrome diagnosed prenatally) confirms that moderate fetal bradycardia (110-120 bpm) does not indicate fetal distress, but indicates that fetuses should be studied for fetal cardiac conduction defects in the newborn period”

Mother, maternal grandmother and infant had prolonged QTc on ECG

Vigliani M. J Reprod Med 1995
Sinus Rates of Fetal LQTS Subjects

OB definition of bradycardia

Mitchell J et al
Circulation
2012
More on FHR and LQTS

Winbo A et al. Circ Arrhythm Electrophysiol 2015; 8:805-814

- Retrospective study 3rd trimester (29-41 weeks)
- FHR from 184 fetuses with parental LQT1
- 110 mutation carriers
- FHR varied with number of mutations and disease severity
- Some double mutation carriers had FHR>110 bpm

“...the current OB standard for fetal bradycardia is not useful with regards to LQTS...but what FHR should signal the need for what type of follow-up is not yet known.”

![Graph showing FHR and KCNQ1 genotype](image-url)
Preliminary Results: FHR by GA

**KCNQ1**

**KCNH2**

**SCN5A**

**No LQTS mutation**
Maybe it's more than the FHR/Rhythm?
Other features of fetal LQTS
Mechanical Dysfunction in Extreme QT Prolongation

Himeshkumar Vyas, MD, Patrick W. O’Leary, MD, Michael G. Earing, MD, Frank Cetta, MD, and Michael J. Ackerman, MD, PhD, Rochester, Minnesota; and Milwaukee, Wisconsin

Conclusions: This infantile presentation of QT extremis and cardiac dysfunction provides support for the hypothesis of mechanical perturbations stemming from abnormal repolarization. Future studies are needed to investigate whether or not the typical patient with congenital LQTS exhibits any evidence for mechanical dysfunction.
IRT during sinus rhythm

Normal: IRT 40 ms

CALM 2 mutation: IRT 100 ms

KCNH2 mutation IRT 70 ms
### Fetal Magnetocardiography (fMCG):
A Non-invasive Measurement of Fetal Cardiac Electromagnetic Activity

<table>
<thead>
<tr>
<th>Recorded without direct contact with source (mother)</th>
</tr>
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<tbody>
<tr>
<td>Superconducting quantum Interference device (SQUID)</td>
</tr>
<tr>
<td>Unaffected by amniotic fluid or vernix</td>
</tr>
<tr>
<td>Excellent signal to noise ratio</td>
</tr>
<tr>
<td>Limited maternal (signal) interference</td>
</tr>
<tr>
<td>Can be recorded from 18-40 weeks</td>
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</tbody>
</table>
The Role of fMCG in LQTS Ascertainment

Direct measurement of QTc interval

Prolonged MCG QTc = LQTS in 30/31 subjects
Confirming Clinical Suspicion of LQTS
Complete Rhythm Ascertainment

34 wk fetus
Maternal KCNH2
• 5 Echoes with SB
• TdP 6 hrs after birth

28 Wk fetus
Negative FH
• 10 Echoes with SB
• 2° AVB, TdP, VF arrest after birth
fMCG and LQTS

Can fMCG to diagnose LQTS before birth? YES
- 39 fetuses evaluated 19-38 (29.5 ± 5.2) weeks
  - 27 family history
  - 12 LQTS rhythms (sinus brady, VT, SSA negative 2°AVB)
- No significant difference between fetal/neonatal HR or QTc
- QTc of 490 ms (> 95%) identified LQTS with 89% sensitivity/specificty

Can fMCG risk stratify LQTS before birth? YES
- 2°AV block (KCNH2) (± family history)
  - QTc <600 ms: postnatal SR or transient 2° AV block
  - QTc > 600 ms: postnatal TdP and aborted sudden cardiac death
- Sinus brady (KCNQ1) (usually +family history)
  - QTc ≤ 550 ms: postnatal sinus brady
- TdP (KCNH2, SCN5A R1623Q) (rarely +family history)
  - QTc >600: postnatal TdP
  - Prenatal TdP = postnatal TdP

Circulation. 2013;128:2183-2191
Fetal surveillance w. + FH

- Treat maternal Mg and/or 25,OH Vit D deficiency
- No QT prolonging meds
- Continue maternal BB if mother LQTS +
- fMCG at 24-28 wks

LQT1
- Monthly FHR
- After 32 weeks every other week FHR

LQT2
- Monthly FHR
- Between 20-24 weeks:
  - Fetal echo
- After 30 weeks
  - Follow-up fMCG
  - q week non-stress testing
  - qo week fetal echo

LQT3
- Monthly FHR
- After 32 weeks every other week FHR

- Postnatal ECG and Genetic testing
Pregnancy and ICDs

SAFETY (Natale A et al. Circulation 1997)

Multicenter retrospective study of 44 pregnant women (13 with LQTS)

1. 82% uneventful pregnancy
2. 18% had medical or device problem
3. 37 delivered by NSVD
4. 2/13 babies had LQTS
5. 11 patients had 1-5 shocks with no fetal demise
6. Expected number of shocks for population
Triggers of cardiac events in KCNH2 (LQT2)

Big Brother wants attention

Teach the care Team!!!

Time to wake up

LQT1: Stress, swimming
LQT2: Sleep

I am hungry (wet, poopy, etc)
Medications to Avoid

- Antihistamines (Benadryl)
- **Antibiotics (Erythromycin, Bactrim)**
- Ondansetron
- Antifungals
- Psychotropic (Haldol, Risperdol, TCAs, Compazine)
- To use with caution: **Pitocin**
- And others, always look! (Crediblemeds.com)
Multidisciplinary Example
A New Pregnancy!

32 year old woman with Long QT2 in her first pregnancy

Preconception done

- On beta blocker
- Declined embryo/fetal testing
- Fetal Cardiologist appointment!
What about delivery?

- No indication for elective cesarean
- Watch for fetal bradycardia
  - Heradien et al. JACC 2006
    - 100% of NRNST were carriers
    - P value <0.001 for affected if NRNST
  - Tanaka et al. JMFNM 2015
    - Increased NRNST in LQT2
    - Increased cesarean rate
What about delivery?

- Avoid triggers: sudden noises, intense exertion, emotional stress
- Telemetry in labor/postpartum
- Avoid QT prolonging medications (a word on Pitocin)
- Maintain normal electrolyte balance (especially potassium, Mg, Vitamin D)
- Keep on adrenergic blockers and ICD if in place
What about postpartum?

“9-month after birth associated with a 4.1-fold increased risk of experiencing a life-threatening event when compared with the preconception time period”

Seth R et al JACC 2007 49(10):1092-1098
Percentage of 111 LQTS probands with:

Multiple cardiac events

New-onset cardiac events

- Multiple cardiac events and new-onset cardiac events: significantly more common during postpartum interval compared to pregnancy and pre-pregnancy intervals.
- A history of cardiac events before the first pregnancy was associated with a 9-fold increase in risk for subsequent cardiac events ($P=.01$).
- Treatment with beta blockers reduced the risk OR 0.023, $p=0.01$

Rashba EJ et al *Circulation* 1998;97:451-456
What about postpartum?

- Consider serial EKG q 1-2 weeks for 9 months
- Continue beta blockers
- Minimize stress/sleep deprivation
- Watch for/treat depression
- Limited data on OCPs suggests no harm or protective effect*

Rest of slides in case of detailed questions, not planning to present
Long QT Syndrome Overview

- Incidence of 1 in 2,000 (last year 1 in 2,500)
- 500 + LQTS mutations in 13 genes
- 85-90% LQT1 (KCNQ1) or LQT2 (KCNH2)
- Mostly inherited in Autosomal Dominant fashion
- Can lead to syncope, cardiac arrest and death
- Diagnosis suspected based on event or family history
- Very limited research in pregnancy, all retrospective
Long QT Molecular Mechanism

Ion channels (Na, Ca or K) on the surface of the heart cells allow flow in and out of the electrically charged molecules. This leads to the electrical signal to the heart to contract.

Diagram from Crotti et al JAMA 2013
Long QT on EKG

Normal value is less than 450 ms
Prolonged over 460-480 ms
This means that the cells in the ventricles are responding slowly to the electrical signals which can lead to arrhythmias specifically Torsades de Pontes (>500 ms)
Arrhythmia Genetic Testing

- Next-generation DNA sequencing
  - Rapid analysis of large panels of disease-specific genes
- Arrhythmia Panels (~30 genes)
  - LQT (13 genes)
- Pan Cardio Panels (>80 genes)
- Whole genome sequencing

Many options covered by insurance are now available

Familial Variants common
Influence of pregnancy on risk for cardiac events in patients with hereditary Long QT

- Seth et al JACC 2007
- Subjects: 391 women with live births from 1980-2003 from the International LTQS Registry
- Genotype data: LQT1, 2, 3 reported
- Outcome Times: 9 months of pregnancy and 9 months after
- Outcome Events: LTQS related death, aborted cardiac arrest and syncope
Aborted cardiac arrest and LQTS-related death account for 17% of the annualized events in the postpartum period. The risk for aborted cardiac arrest or LQTS-related death was increased in the postpartum period (p = 0.001), but the pregnancy and post-postpartum time periods were not.
Annualized cardiac event rates by genotype

LQT2 highest risk

Post-partum

Seth R et al JACC 2007 49(10):1092-1098
Annualized cardiac event rates by beta-blocker use in the pregnancy, postpartum, and post-postpartum time periods

Postpartum Hazard Ratio: 0.34 (0.14-0.84)

Seth R et al JACC 2007 49(10):1092-1098
Maternal cardiac physiology as it pertains to Long QT

Pregnancy:
- Increased blood volume and cardiac output about 30-50% at term
- Increased heart rate 10-20 bpm

Postpartum:
- Rapid hemodynamic alterations
- Slow complete resolution with cardiac output still elevated at 24 weeks postpartum
Maternal endocrine physiology as it pertains to Long QT

Hypothesis: lack of estrogen increases adrenergic activity and cardiac myocyte excitability resulting in a higher probability of adverse cardiac events
Why is there an increased risk of cardiac events after pregnancy

Increased maternal HR protective in bradycardia associated prolonged QTc interval

  Post partum: decreased heart rate and increased QT interval

Decreased estrogen and progesterone levels

  Effecting the adrenergic responses/number or function of the mutant ion channels

More pronounced QTc interval prolongation in women during REM sleep: New baby = disturbed sleep

Role of estrogen?

Estrogen down regulates the protein expression of cardiac beta-1–adrenergic receptors in ovariectomized animals.

Estrogen has weak antiarrhythmic effects?
reduce the risk of TdP

Hypothesis: lack of estrogen increases adrenergic activity and cardiac myocyte excitability resulting in a higher probability of adverse cardiac events.
What happens to fetal umbilical artery flow after defibrillation?

Pregnant woman with SVT

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>DC energy (J)</th>
<th>Umbilical blood flow (S/D ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before DC</td>
<td>After DC</td>
</tr>
<tr>
<td>16 1/7</td>
<td>None (IV adenosine)</td>
<td>2.7</td>
</tr>
<tr>
<td>23 5/7</td>
<td>50, 100, 200, 200</td>
<td>2.4</td>
</tr>
<tr>
<td>29</td>
<td>200</td>
<td>2.8</td>
</tr>
<tr>
<td>32</td>
<td>200</td>
<td>2.4</td>
</tr>
</tbody>
</table>


1. Uterus is NOT in the field
2. Fetal heart is very small
3. Fetal heart has high fibrillation threshold
Case

- 32 yr old G1P0 8wk pregnant
- Medical History:
  - 13 year old history of seizure like episode
  - Fainting episodes triggered by alarms or phone ringing
  - Self regulations of these triggers
  - Very active child and young adult
Case: Medical History

- Age 20 syncope when getting out of bed
  - Dx with vasovagal, positive tilt table test
- Age 25 syncopated in waiting room of cardiologist
  - EKG 500ms
  - Admitted to ED
  - ICD recommended and declined
- Second opinion
  - Dx with LQT syndrome and started on beta blocker
  - Presyncope while on beta blocker
  - Self discontinued
Genetics continued

- Suspicious for LQT2
- Questionable if de novo or reduced penetrance
- Consented to LQT panel
Referral to Electrophysiologist

- ECG QTC 480-500, diffuse T wave abnormalities
- ECHO normal
- Loop recorder placed
- Beta blocker recommended
- Pregnancy uncomplicated
- Normal fetal heart rhythm
Case continued

- Full term pregnancy
- Pt concerned that pain/fatigue could be trigger
- Private room because of noise trigger
- Vaginal delivery with epidural
- Neonatal ECG
  - 500-528
  - Likely diagnosis of LQT discharged on propranolol
Neonatal Test Results

Test(s) Requested:
KCNH2 (HERG) Gene / Evaluate for Y1009X Mutation / Long QT Syndrome (LQTS) Type II

Relevant History:
Parent (GeneDx# 1476989) is heterozygous for the Y1009X mutation in the KCNH2 gene.

Result:

<table>
<thead>
<tr>
<th>Result</th>
<th>Gene</th>
<th>Zygosity</th>
<th>cDNA</th>
<th>Variant</th>
<th>Ref. Seq.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRESENT</td>
<td>KCNH2</td>
<td>Heterozygous</td>
<td>c.3027 C&gt;G</td>
<td>p.Tyr1009Ter (Y1009X)</td>
<td>NM_00238.2</td>
</tr>
</tbody>
</table>

Interpretation:
This result indicates that this individual harbors the Y1009X mutation previously identified in a relative. Mutations elsewhere in the evaluated gene or in other genes associated with the disorder in this family would not be identified by this targeted analysis.

The Y1009X mutation in the KCNH2 gene has not been reported as a disease-causing mutation or as a benign polymorphism to our knowledge. Y1009X is predicted to cause loss of normal protein function either by protein truncation or nonsense-mediated mRNA decay. Other nonsense mutations in the KCNH2 gene have been reported in HGMD in association with LQTS (Stenson P et al., 2014). The Y1009X mutation was not observed in approximately 6,100 individuals of European and African American ancestry in the NHLBI Exome Sequencing Project, indicating it is not a common benign variant in these populations.

Therefore, the presence of this mutation indicates that this individual is at increased risk to develop LQTS. However, other genetic and environmental factors influence disease expression and severity, and some mutation carriers may never become symptomatic.
Risk for Stillbirth/NRNST

Crotti et al  JAMA 2013
- Evaluation of 91 unexplained IUFD
- 8.8% genetic variants in LongQT associated ion channels

- Evaluation of 25 pregnancies with known Maternal LQTS
- 20% cesarean for NRNST
Conclusion

“Fetal LQTS is diagnosed by an fMCG QTc >490ms with an 89% sensitivity and specificity. TdP are seen with uncharacterized, KCNH2 or SCN5A R1623q mutations. Fetal TdP occurs when QTc ≥620ms. Identifying fetal LQTS and defining its rhythms by fMCG risk stratifies postnatal management.”