GENE MESSENGER

☆ **Topic: Long QT Syndrome**

☆ **Summary: Some researchers claim that babies should be routinely tested for long QT syndrome (LQTS) by electrocardiogram (ECG) at around three weeks of age because it would be cost-effective and save lives.**

☆ **Bottom line: The ECG is neither sensitive nor specific for hereditary LQTS, and can be hard to interpret in newborns. Routine ECG screening of newborns remains controversial, but any individual with clinical features (e.g. syncope with exercise in a young person), typical ECG, or a family history of LQTS or young sudden death should be referred to a heart rhythm specialist and a genetics clinic, for assessment of self, at-risk relatives and genetic testing where indicated.**

✓ The Disease: LQTS

- A disorder involving the cardiac ion channels that affects approximately 1 in 5,000 people
- Results in prolongation of the ventricular action potential during cardiac repolarization (i.e. prolonged QT interval on ECG)
- In women and children, a QTc of > 460ms is considered abnormal; in men, QTc > 450ms is abnormal. There is a considerable borderline range between normal and abnormal QTc. (QTc: heart rate corrected QT interval)
- Predisposes to syncope and/or sudden cardiac death
- Cardiac events may be triggered by exercise, auditory stimuli (e.g. alarms) or emotional stress. These cardiac events may appear seizure-like and may be mislabeled as epilepsy.
- LQTS is treatable with beta-blockers, implantable cardioverter defibrillators, and avoidance of triggers & QT-prolonging drugs.
- Hereditary forms of LQTS are usually autosomal dominant.
- LQTS is one of numerous causes of SIDS.
- LQTS can also be acquired, for example by drug use (see www.qtdrugs.org) or anorexia nervosa.

✓ The Genes

- At least 8 genes have been implicated in LQTS. The 3 most common are:
  LQT1 (KCNQ1) on chromosome 11, encodes potassium channel subunits
  LQT2 (HERG, KCNH2) on chromosome 7, encodes potassium channel subunits
  LQT3 (SCN5A) on chromosome 3, encodes sodium channel subunits
- Some genotype-phenotype correlations may be drawn.

✓ Consequences of having a faulty gene

- A man or woman with LQTS has a 50% chance of passing the tendency to arrhythmia to each child.
- Females are more likely than males to experience clinical symptoms of LQTS.
- LQTS demonstrates reduced penetrance and variable expressivity.
- First events often occur in the teen years.
- Individuals with 2 abnormal copies of the LQT1 and LQT5 genes develop Jervell and Lange-Nielsen syndrome (JNLS) which is characterized by bilateral sensorineural hearing loss in addition to significantly prolonged QT interval.

✓ Who should be offered referral for genetic counseling/testing?

- Individuals with clinical symptoms of LQTS or a suggestive ECG **should be referred to a cardiac arrhythmia specialist**. If the cardiologist suspects LQTS, then a referral for genetic counseling/testing is indicated.
- Family members of individuals diagnosed with LQTS, or with a history of young sudden death.
- Family members of an infant who has died of SIDS; referral to genetics for detailed family history and consideration of postmortem genetic testing.

✓ Testing - for the faulty genes

- Testing of LQTS genes is not currently performed on a clinical basis in Ontario, although some testing is offered on a research basis. A genetics service can arrange testing for eligible patients in an out-of-province clinical genetics laboratory.

✓ Benefits of genetic testing

- Clarification of LQTS risk status among individuals with borderline clinical investigations
- Assistance with life planning (e.g. decisions about careers, participation in competitive sports)
- For those who test negative for a known family mutation, relief from worry that they will develop the disease in the future and knowledge that their children are not at risk of inheriting the disease

✓ Harms/limitations of genetic testing

- Adverse psychological reaction, family issues/distress
- Uncertainty due to a genetic variant of unknown significance
- Insurance/job discrimination, confidentiality issues
- Survivor guilt for family members who did not inherit the gene mutation.

☆ Web Resources: **National Institutes of Health GeneTests website: www.genetests.org**
Center for Education and Research on Therapeutics: www.qtdrugs.org

☆ Review Articles:

1. Quaglini S, Rognoni C, Spazzolini C, Priori SG, Mannarino S, Schwartz PJ. Cost-effectiveness of neonatal ECG screening for the long QT syndrome. *Eur Heart J* 2006;27(15):1824-32. Epub 2006 Jul 13.
2. Modell SM, Lehmann MH. The long QT syndrome family of cardiac ion channelopathies: a HuGE review. *Genet Med* 2006;8(3):143-55.

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GenetiKit KNOWLEDGE IN TRANSLATION

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In alphabetical order, other members of the GenetiKit Team are as follows: **Dr Allanson** is Chief of the Department of Genetics at the Children's Hospital of Eastern Ontario (CHEO) in Ottawa, Ont, and Full Professor in the Department of Pediatrics at the University of Ottawa. **Dr Blaine** is an Assistant Professor in the Department of Family and Community Medicine at the University of Toronto in Ontario and Lead Physician of

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