Genes in Long QT Syndromes

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Introduction

The congenital long QT syndrome (LQTS) is a rare disorder (incidence 1:10 000 – 1:15 000) characterized by prolongation of the QT interval on the surface ECG, recurrent syncope and sudden death. There are two major clinical variants, the Romano-Ward syndrome, which shows autosomal dominant inheritance, and the Jervell and Lange-Nielson syndrome that is characterized by autosomal recessive inheritance and congenital deafness. The latter is extraordinarily rare.

The Sticky Door

Most patients with LQTS have inherited a genetic mutation that causes formation of an abnormal potassium channel in the heart, leading to a prolonged QT interval. This problem can be illustrated in the analogy of the "sticky door". With each heartbeat, the heart is activated by an electrical signal. This can be thought of as an electric door that requires 1/10th of a second to open, and 3/10ths of a second to close. This door has 3 hinges; 2 potassium channels and 1 sodium channel. If one of these hinges is "sticky", the door takes too long to close, leaving the door "open" to abnormal electrical impulses that may lead to fast heart beating. Patients with LQTS are born with a defective or sticky hinge, leaving them prone to abnormal electric door behavior. This is often a problem

when the door is challenged by a sudden increase in opening rate, such as when the heart speeds up with exercise, emotion or when the phone or alarm clock rings. The sticky hinge has more trouble keeping up when the heart suddenly speeds up. Treatment of LQTS is primarily focused on preventing stress on the defective hinge by preventing sudden heart acceleration (beta blockers). Current research is focusing on developing therapies directed at "greasing up" specific hinges. This is the case with use of Mexilitine in the uncommon form of LQTS caused by a sodium channel abnormality (LQT3). The following is a more detailed description of the genetics of mutations that cause abnormal cardiac ion channels (hinges).

Genetics

DNA is a 4 letter alphabet that is a blueprint for manufacturing cells in the body. A mutation is an abnormal letter or group of letters that is present in the gene that can lead to abnormal cell or protein production. Many of these are some form of "typo". In most cases of LQTS, a normal gene is inherited from 1 parent, and an abnormal gene with the "typo" is inherited from the other parent. Genetic testing is analogous to "spellcheck" of the genes that are known to code for the cardiac ion channels that have been associated with LQTS. This process will be negative in one-third to one-half of patients with LQTS, which suggests that there may be many more undiscovered mutations. Alternatively, unexplained cases may represent genetic heterogeneity involving mutations in other genes encoding different repolarizing ion channels, receptors or proteins important for intracellular calcium transport or involved in cardiac sympathetic activity. Put another way, there may be many more hinges and problems with hinges than are currently known.

Genetic linkage studies have identified five gene regions associated with LQTS located on chromosomes 3, 4, 7, 11, and 21 (Table). At least 300 mutations have been identified in LQTS patients, 87% of which involve *KVLQT1* (LQT1) or *HERG* (LQT2). The vast majority are of the first 3 types. Jervell and Lange-Neilson syndrome is a distinctly uncommon form of LQTS because it requires inheritance of a mutant *KVLQT1* or *mink* gene from both parents, hence the affected person must inherit 2 mutations. Deafness results from the loss of functional KVLQT1 channels in the inner ear. Of interest, several recent studies have suggested that LQTS may be an uncommon cause of sudden infant death syndrome (SIDS), also called crib death. In a recent study, 2% of SIDS cases that underwent autopsy had a mutation described in the gene on Chromosome 3 that codes for the sodium channel (LQT3). This estimate may actually be low, with some experts believing that up to 10% of SIDS is QT related.

Surface ECG screening of families with a single affected member suggests that up to 45% of asymptomtic family members with normal ECGs may carry the abnormal gene (incomplete penetrance). Although the frequency of incomplete penetrance is uncertain, the traditional bedside concept of autosomal dominant transmission with apparently "isolated" cases being attributed to sporadic mutations is called into question. This also raises uncertainty when advising apparently unaffected family members with respect to

risk and genetic transmission. Further testing is needed to help identify those patients with LQTS that is “under the surface”. This is why genetic testing is so important.

Simply checking for the gene is not possible in Long QT Syndrome, like most other genetic causes of arrhythmia. Most new patients will have a new genetic abnormality if it can be detected (called a private mutation), so the process is expensive and time consuming since a gene sequencer has to read every letter of the DNA in the region of the gene to look for the typo. As with other conditions, genetic screening raises issues regarding branding (you feel well but your genes tell us you have a disease), life insurance, and the usual range of human responses to family health issues (anger, denial, hypervigilance etc). Nonetheless, there are plenty of situations where the diagnosis is not clear from clinical testing, so that genetic testing is extremely helpful.

At present, genetic testing is available in research laboratories or by arrangement with specialized genetic testing laboratories. Recent Ontario funding has become available on a case-by-case basis to permit clinical testing for Long QT mutations, at a cost of $4500 USD per patient. We are unaware of any health care systems that provide genetic testing on an unrestricted basis at no charge. Select research centers such as University of Western Ontario are performing genetic testing on patients with LQTS that undergo clinical assessment as part of a research assessment. The future of genetic testing in this area is somewhat uncertain, as gene chip technology promises to provide a more efficient means to test for mutations, tempered by the frequent limitation that new patients will have previously unrecognized mutations. Lets hope is gets cheaper and easier so that we can get useful answers when necessary to help make a diagnosis and make peoples lives better.

Table 1: *Classification of LQTS.*

	Locus	Gene	Percent of Mutations*
LQT1	11p15.5	*KCNQ1 (KVLQT1)*	42%
LQT2	7q35-q36	*KCNH2 (HERG)*	45%
LQT3	3p21-p23	*SCN5A*	8%
LQT4	4q25-q27	ANK2	Rare
LQT5	21q22.1-p22	*KCNE1 (MinK)*	Rare
LQT6	21q22.1	*KCNE2 (MiRP1)*	Rare
LQT7	17	*KCNJ2*	Rare
LQT*	11p15	*KCNQ1*	Rare
LQT*	21q22	*KCNQ2*	Rare

* Recessive with deafness (Jervell and Lange-Nielsen)