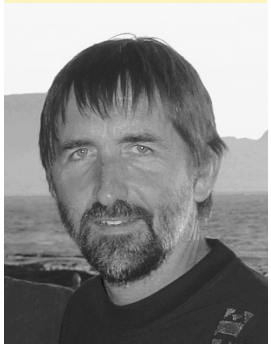
GENOMICS FROM THE HEART: COT DEATH AND THE LONG QT SYNDROME

Cot death or sudden infant death syndrome (SIDS) is a devastating problem and one of the leading causes of infant death between the ages of 1 month and 1 year.



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To varying degrees, children worldwide are at a risk of SIDS of 1 - 2 per 1 000. The terrible impact of an unexpected infant death is compounded when no obvious cause can be determined after a thorough postmortem examination. The parents are left with guilt and many unanswered questions, including the risk of recurrence in a next child. A single cause for SIDS remains obscure and the medical literature is characterised by diverse theories and speculation.

In the last decade, however, a large Italian study has shed light on a possible link between SIDS and the long QT syndrome (LQTS), a genetic disorder which predisposes to cardiac arrhythmias, or sudden cardiac death. This remarkable story serves as a striking example of the power of genomics. It illustrates how a clear understanding of the exact genetic mechanisms of disease may lead to accurate genotype-phenotype correlations and effective therapeutic options. It has also served as a paradigm for how other inherited disorders may be studied to reveal new, more effective therapeutic possibilities.

This review will briefly outline the history of the increasing genomic understanding of the LQTS, its link to cot death and the improvement in individualised treatment based on new understandings of its genotype-phenotype correlations.

THE LONG QT SYNDROME

The first case report of probable LQTS was by Meissner in 1856,[1] who described the sudden death of a child at a school for the deaf, after being admonished by her teacher. Her parents reported that two older brothers had suffered similar cataclysmic outcomes after emotional stress.

Classically, LQTS has been divided into 2 syndromes:
- the Romano-Ward syndrome, an autosomal dominant form of LQTS only
- the Jervell-Lange-Nielsen syndrome, an autosomal recessive form of LQTS associated with deafness.

Diagnosis was made by a scoring system which combined an ECG finding of a prolonged corrected QT interval (QTc) with suggestive features in the clinical and/or family history. Often a suggestive history is unavailable and a definitive diagnosis cannot be made on the basis of prolonged QTc only (Fig. 1).

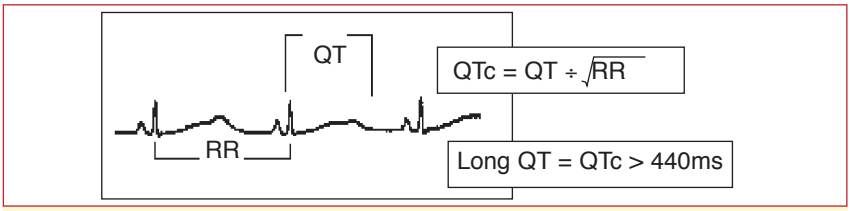

Fig. 1. The QT and RR intervals on an ECG.

A prolonged QTc interval predisposes one to unstable arrhythmias, most commonly Torsades de Pointes (Fig. 2), a chaotic ventricular tachycardia. In itself the rhythm is not lethal and may revert spontaneously to sinus rhythm, but it commonly degenerates to ventricular fibrillation, followed soon after by cardiac death. If the patient dies before a diagnosis has been made (at first presentation, or previous events misdiagnosed as syncope or epilepsy), a postmortem examination will be unable to establish a cause of death. Such a scenario is compatible with a natural history of cot death.

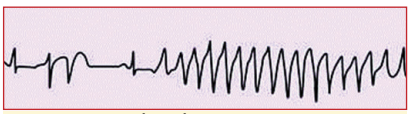

Fig. 2. Torsades de Pointes.

GENOTYPE-PHENOTYPE CORRELATIONS

Genetic investigations have led to the finding of seven distinct chromosomal loci (Table I), of which 6 genes have been identified. The gene for LQT4, located on chromosome 4, remains unrevealed as yet. Mutations in the gene for LQT1 (*KVLQT1* gene) is the commonest cause for LQTS, followed by LQT2 (*HERG* gene) and LQT3 (*SCN5A* gene). LQT4, 5 and 6 are very rare. LQTS7 has only recently been described, and is associated with the rare Andersen syndrome of skeletal dysplasia and cardiac arrhythmias.

Soon after the different LQT genes were identified, it became clear that each gene, if mutated, predisposes its host to different triggers for cardiac events (Fig. 3).

Although there is some degree of phenotypic overlap, LQT1 patients usually suffer their cardiac events during exercise, LQT2 patients during sleep or emotional upheaval, and LQT3 patients predominantly during sleep. The clearest genotype-phenotype correlations occur in LQT1 and LQT3 phenotypes.

Table I. **The LQT genotypes**

Phenotype	Chromosome	Gene
LQT1	11	KVLQT1
LQT2	7	HERG
LQT3	3	SCN5A
LQT4	4q25-27	unknown
LQT5	21	KCNE1
LQT6	21	MiRP1
LQT7	17	KCNJ2

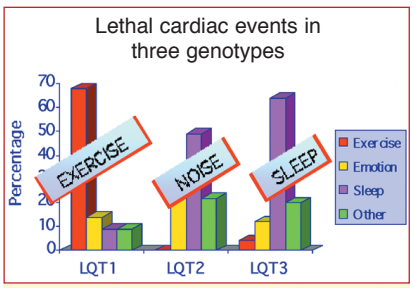

Fig. 3. Phenotype-genotype correlations in the LQTS. (Adapted from Schwartz et al. Circulation *2001;* ***103:*** *89-95).*

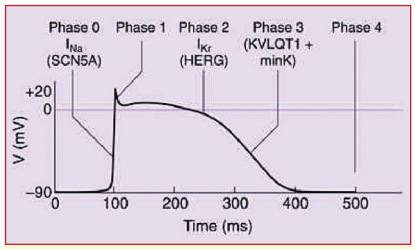

Fig. 4. Genes active during different phases of the cardiac action potential. (Adapted from Schwartz et al. Circulation *2001;* ***103:*** *89-95.)*

All the LQT genes code for channels controlling potassium flux through heart muscle cell membranes, except *SCN5A* (LQT3) which is the gene for a sodium channel. *SCN5A*, *HERG* and *KVLQT1* have been linked to specific phases of the cardiac action potential (Fig. 4).

For example: *SCN5A*, the transmembrane sodium channel, is critical during the initiation of the action potential by controlling influx of sodium ions to alter the intracellular charge from negative to positive. In return, the *HERG* and *KVLQT1* transmembrane channels reduce the charge by allowing controlled efflux of potassium ions. Mutations in any of these 3 genes alter the characteristics and duration of the action potential in very specific ways which may all prolong the QT interval.

Three differing functional consequences are illustrated by the mutations in these 3 genes:

- mutations of the *KVLQT1* gene causes loss of function of its protein product
- *HERG* mutations behave in a dominant-negative fashion: the product of the mutated gene interferes with the normal function of the unaltered *HERG* gene
- mutations of the *SCN5A* gene cause gain of function of the abnormal channel, with the result that the channel remains 'open' too long, causing a prolonged QT interval.

THE ITALIAN COT DEATH STUDY

What has all this to do with cot death? As long ago as 1972, Maron *et al.*[2] suggested a link between cot death and the LQTS by showing that of 42 parents who had lost children due to SIDS, 11 (26%) had prolonged QTc, while 39% of their surviving children had prolonged QT intervals. They also presented an infant with 'near-miss' SIDS with a markedly prolonged QT interval. The study was too small to allow firm conclusions to be drawn and they commented that 'definitive confirmation...will require large prospective investigations'.

This challenge was taken up by a very large Italian multicentre trial that recruited 34 442 infants over a 19-year period (1976 - 1994). Schwartz and co-workers[3] performed ECGs on day 3 of life on all these infants and followed up 33 034 one year later.

Of this large cohort, 34 children had died — 24 of SIDS, and 10 of other causes. Of the 24 SIDS cases, 12 (50%) had had documented prolonged QTc intervals on day 3.

This study, as with many cot death investigations, unleashed a storm of controversy in the paediatric medical literature. Some pertinent criticisms were the absence of any evidence of lethal arrhythmias preceding cot death and the lack of clear significant benefit of any treatment for children at risk. In addition, the 99% false-positive rate of the prolonged QT intervals on day 3 meant that 100 infants would require preventive treatment to potentially save only 2.

Schwartz went on to postulate that new (spontaneous or *de novo*) mutations in one of the LQT genes could account for cot death in babies of parents without LQTS. Alternatively, inherited mutations could have variable penetrance, with lethal expression in SIDS infants, but reduced effect in their parents.

FOUR CASE REPORTS: PROOF OF CONCEPT?

Several case reports soon vindicated the controversial postulates of Prof. Peter Schwartz, and supported the findings of the Italian cot death study. In the first,[4] a 6-week-old Italian baby was discovered by his parents to be cyanosed, apnoeic and pulseless. On admission to the local medical casualty, his ECG revealed Torsades de Pointes. After defibrillation and resuscitation, a very prolonged QTc of 648 ms — far above the normal of 440 ms — was measured. Genetic sequencing studies revealed a new (*de novo*) mutation in the *SCN5A* (LQT3) gene, not present in his parents.

In 2001, two case reports of post-mortem DNA sequencing of the LQT1 (*KVLQT1*)[5] and LQT3 (*SCN5A*)[6] genes detected *de novo* mutations in 2 cot death babies.
A fourth[7] reports a hydropic newborn baby exhibiting multiple antenatal and postnatal runs of Torsades and atrio-ventricular block, unresponsive to intravenous propranolol. A mutation in the *SCN5A* gene was detected and the baby was successfully treated with mexiletine, a sodium channel blocker which specifically corrects the gain of function mutation in the abnormal LQT3 cardiac channel. The baby improved dramatically and was discharged from hospital without recurring arrhythmias or AV block, remaining asymptomatic to date.

MANAGEMENT OPTIONS AND GENOMIC CORRELATIONS

Knowledge of the genotype-phenotype correlations of the different LQT genes allows cardiologists to advise avoidance of certain triggers in patients at risk. Precise molecular testing is therefore important for both diagnostic confirmation and planning of effective management strategies. This may include avoidance of triggers, individualised drug therapy, and/or an implantable cardiac pacemaker or defibrillator.

Painstaking research has established the LQTS syndrome as the first (but probably not the only) confirmed cause for cot death. Detailed genomic investigations have not only shed some light on the aetiology of SIDS, but have also widened our knowledge of this rare channelopathy enormously.

In conclusion, the LQTS examples vividly illustrate the power of detailed genetic knowledge, steadily gained over several decades, in assisting the planning of individualised and precisely targeted therapy. It is an eloquent (and poignant) paradigm for many other complex disorders which will similarly be dissected to allow the introduction of effective therapeutics designed to address the specific deficits of abnormal physiology and metabolism. The Human Genome Project will be of immeasurable value in this regard by accelerating the detection of disease-causing mutations.

References available on request.

IN A NUTSHELL

The LQTS syndrome, a genetic disorder characterised by cardiac arrhythmias which may be lethal, has been epidemiologically linked to cot death.

Previously it was classified as a disorder with only two forms, autosomal dominant and autosomal recessive, by a possible family history and the association with deafness.

It has now been mapped to at least 7 chromosomal loci (LQT 1-7); of these, 6 genes are known, of which all but one (LQT 3) are genes for transmembrane myocardial potassium channels.

The commoner forms (LQT 1-3) can be differentiated from one another by specific genotype-phenotype correlations, based on triggers for cardiac events.

Genetic studies of infants have confirmed molecular (DNA) links to the LQTS, and have defined effective drug treatment based on genotype.

Genetic testing now can establish the diagnosis, test individuals at familial risk and assist with accurate drug or other therapeutic options.