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Original Article

The Role of Genetic Testing In Paediatric Syndromes of Sudden Death: State Of The Art and Future Considerations

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THE UNEXPECTED DEATH OF AN INFANT, CHILD OR young adult, is not only a tragic event for the family and community, but it often leaves unanswered the three most basic questions:

- Why did this happen?
- Could it have been prevented?
- Can it happen again in this family?

The last decade has seen significant progress in unravelling the mystery of unexplained sudden death. The spectrum of these events is broad, affecting infants with the so called "Sudden Infant Death Syndrome" or "SIDS", as well as adults. Sudden death can occur during mild, moderate or extreme physical activity but it can also occur while asleep.

Differential Diagnosis of Sudden Death in the Young

The early, pioneering work by Barry Maron established the most common causes of "Sudden Death" in the United States of America.[1] It is important to note that this landmark study only reported on aetiologies of sudden death which could be diagnosed in a careful anatomical or histological post mortem examination. While fundamental to our understanding of the differential diagnosis of sudden death in the young, the study does not address the autopsy negative aetiologies of sudden death, some of which may be uncovered by a "genetic autopsy", as will be discussed in this review.

Many of the aetiologies of sudden death that have been described have a negative post mortem examination. Furthermore, reported causes of sudden death vary widely among different countries, as illustrated on Table 1.[2,3,4,5,6]

The differences between the countries cannot be explained solely by difference in the genetic makeup of each country, but rather, awareness or interest in the different potential diagnoses of sudden death. Furthermore, variability in protocols of post mortem examination can also explain the international differences. For example, in the case of "arrhythmogenic right ventricular dysplasia /cardiomyopathy" (ARVD/C) the diagnosis lies primarily in the histology of the right ventricle, and may be missed if that is not included as part of the protocol of the post mortem examination.

If genetic evaluation of victims of sudden death with negative autopsies increases in popularity, the causes of sudden death such as channelopathies will likely increase in prevalence as more of these "undiagnosed" cases will finally have a diagnosis. This knowledge is of the utmost importance as we try to not only answer the question as to why a seemingly healthy individual dies, but also, can we detect the same condition in other asymptomatic members of the family, who may be at risk for sudden death as well. Therefore, genetic testing in these families will ultimately save lives.

Prevalence

Sudden cardiac death claims between 1000 and 7000 children annually in the United States of

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Table 1. Reported causes of sudden death vary greatly between different countries.[2,3,4,5,6]

Country	France[2]	Italy[3]	Spain[4]	India[5]	USA[6]
IHSS	29%	2%	6.5%	47%	36%
ARVD	25.9%	12.5%	16.3%		3%
CONG. CORONARY AN	14.8%	8.5%	3.2%	27%	24%
AO. STENOSIS	7.4%				4%
ASD	3.7%				
ACQ. CORONARY DIS	3.7%	23%	40.9%		2%
LVH			4.9%		
MYOCARDITISM/CM		12.5%	3.2%		
MVP		10%	1.6%		2%
AO. RUPTURE					5%
AS		2%			

America, representing 5 to 7% of all paediatric deaths and resulting in an incidence of 8 to 62 per 1,000,000.[7] It accounts for 19% of the causes of sudden death in children between 1 and 13 years and 30% of sudden death that occurs between 14 and 21 years of age.[8] "Sudden Infant Death Syndrome" also claims an equal number of lives. In this review, we will discuss the causes of sudden death in the young, focusing on those conditions in which a genetic aetiology may exist, as well as the "state of the art" evaluation for these conditions.

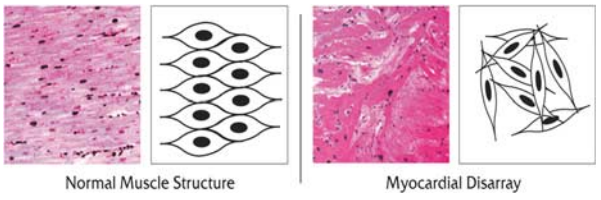

Figure 1.
Histologic differences between normal and hypertrophic cardiomyopathy. Hypertrophic cardiomyopathy is characterized by hypertrophied myocytes arranged in a disorganized fashion.
(Courtesy of PGx Health)

Hypertrophic Cardiomyopathy

Studies generally agree that hypertrophic cardiomyopathy (HCM) is a leading cause of sudden death in the young. It is estimated that about 1/500 individuals are carriers of the disease[9,10] but phenotypic expression is highly variable.[11] The hallmark finding of hypertrophic cardiomyopathy is myocellular disarray (Fig. 1). Such a finding not only may be confirmatory in mild cases, it also correlates with increased risk of sudden death.

Hypertrophic cardiomyopathy is a heterogeneous condition affecting the sarcomere. The first molecular genetic cause of hypertrophic cardiomyopathy was reported in 1990, as a mutation in the gene encoding the Beta Myosin heavy chain.[12] A number of additional new mutations were soon reported.[13] Currently, there are numerous mutations that have been identified, and are usually inherited in an autosomal dominant fashion. Table 2 presents the most commonly identified mutations and their relative frequency. As the table indicates, only about 60% of the cases of hypertrophic cardiomyopathy will have an identifiable mutation when tested by the current commercially available tests. No doubt, this number will increase as new mutations are discovered and added to these panels.

The mutations associated with hypertrophic cardiomyopathy affect different portions of the sarcomere, including the thick filament, the thin filament, and myosin binding protein (Fig. 2).

Table 2. Most common mutations in hypertrophic cardiomyopathy.[9,14,15]

Gene	Protein	Estimated Percentage of HCM Patients[1,2,3]
MYH7	β-Myosin heavy chain	20–30%
MYPBC3	Myosin-binding protein C	20–30%
TNNT2	Troponin T	3–5%
TNNI3	Troponin I	<5%
TNNC1	Troponin C	Rare
TPM1	Tropomyosin-1α	<5%
MYL2	Regulatory myosin light chain 2	<5%
MYL3	Essential myosin light chain 3	Rare
ACTC	α-Cardiac actin 1	Rare

(Courtesy of PGx Health)

There are several morphologic anatomical subtypes of hypertrophic cardiomyopathy as illustrated on Figure 3. While the most common type is the so called sigmoid curvature of the interventricular septum, mutations are only identified in 8% of this subset. A clinical finding of this subset was hypertension in 20% and obstruction of the left ventricular outflow tract in 87%. In the absence of familial history, it is possible that sigmoid septal

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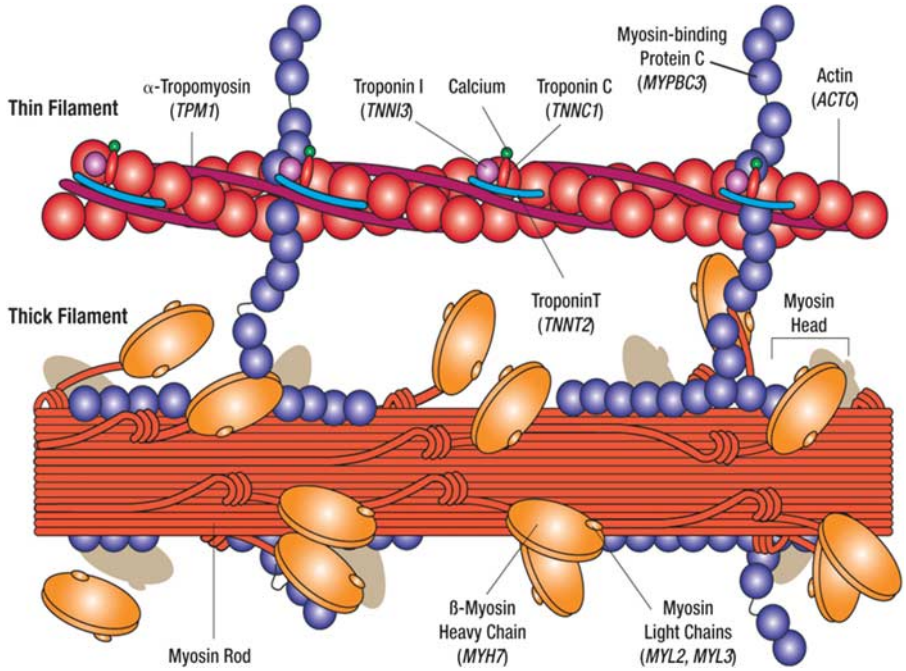

Figure 2.
Hypertrophic cardiomyopathy is a disease of the sarcomere. Shown are the most common mutations affecting components of the thick filament, thin filament and myosin binding protein.[16]
(Courtesy of PGx Health)

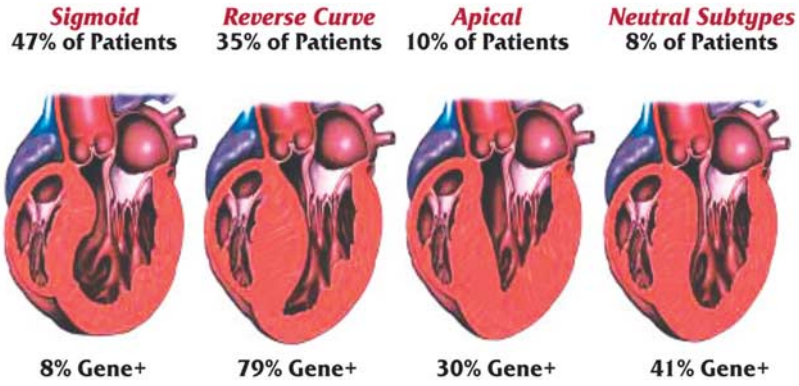

Figure 3.
Relative frequency of the different forms of septal curvature and likelihood of finding a mutation utilizing the currently available panels.[18]
(Courtesy of PGx Health)

hypertrophic cardiomyopathy may not be an inheritable but rather an acquired cardiomyopathy. The second most common morphology is the reverse curve type, in which septal thickness is greatest in the mid portion of the septum. This subtype has the greatest likelihood of having a known mutation and is more often found in younger patients. This septal contour is associated with mutations involving the MYH7 – encoded Beta myosin heavy chain.[17,18]

Identification of the morphological as well as the genetic subtype may prove useful in selecting therapies for the prevention of sudden death. For example, some myosin mutations are thought to be benign whereas others are associated with a high likelihood of premature sudden death. Given the concern of the use of chronic therapy with amiodarone or the use of implantable cardioverter defibrillators (ICDs) in children, aggressive therapies may be reserved for the carriers of the more lethal mutations. This data should be used to complement clinical data such as obstruction of the left ventricular outflow, arrhythmias, etc.

In 2007, a task force composed of members from the American College of Cardiology, the American

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Heart Association and the European Society of Cardiology published the following conclusions:

> *"Genetic analysis is useful in families with hypertrophic cardiomyopathy because whenever a pathogenic mutation is identified, it becomes possible to establish a pre symptomatic diagnosis of the disease among family members and to provide them with genetic counseling to assess the risk of disease development and transmission of the disease to offspring. Genetic analysis may contribute to risk stratification in selected circumstances."*[19]

When a mutation is identified in the "index case", first degree relatives must also be tested. This strategy is called "family specific testing". The testing facility, instead of testing for the entire panel of common mutations, will focus only in trying to identify whether the mutation present in the index case is also present in the member of the family in question. The accuracy of such testing, that is, the positive and negative predictive value, is believed to be quite high. Thus, non carriers may be reassured and carriers can be offered careful evaluation and preventive therapy. Furthermore, by performing "family specific testing" on first degree relatives, whether or not they exhibit signs of hypertrophic cardiomyopathy, studies may be undertaken to determine whether early initiation of treatment, either with beta blockers, calcium channel blockers, or other strategies, may indeed alter the course of the disease, reduce the severity of the hypertrophy, and hopefully reduce the need for more aggressive therapies such as implantable cardioverter defibrillators.

Arrhythmogenic Right Ventricular Dysplasia/ Cardiomyopathy

This condition was originally thought of as a developmental anomaly resulting in fibrofatty replacement of right ventricular myocardium, in other words, dysplasia, as shown in Figure 4.

The myocardial disruption results in an increased risk of ventricular tachyarrhythmias and sudden death. As its familial occurrence was described,[20] the condition was reclassified as a cardiomyopathy. Thus, the names of arrhythmogenic right ventricular dysplasia (ARVD) and arrhythmogenic right ventricular cardiomyopathy (ARVC) are used interchangeably.[21]

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is a disease of the desmosome, which are specialized intercellular junctions anchoring filaments to the cytoplasmic membrane of adjoining cells. Defects in components of desmosomes may impair their function and result in detachment of adjoining myocytes, and predisposition of these myocytes to premature cellular death. Because the regenerative capacity of the myocardium is limited,

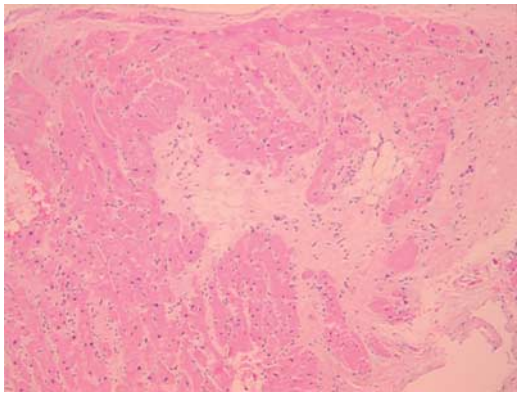

Figure 4.
Histologic findings in arrhythmogenic right ventricular dysplasia/ cardiomyopathy. Notice the presence of fat cell and fibrosis deep inside the myocardium.

repair is by way of fibrofatty replacement of these cells. Numerous mutations encoding for desmosomal function have been implicated in cases of arrhythmogenic right ventricular dysplasia/cardiomyopathy.[22] The three most common genes associated with arrhythmogenic right ventricular dysplasia/cardiomyopathy are desmoplakin, plakophilin and desmoglein-2. Screening for mutation of these three genes yields successful genotyping in 40% of the probands.[23] At this point, data to predict the severity of phenotypic expression, or a clinical prognosis, based solely on a genetic finding is scarce. Rather, the true value of genetic testing for arrhythmogenic right ventricular dysplasia/ cardiomyopathy in this era is twofold. First, it will help the clinician confirm an otherwise difficult diagnosis to establish. Second, genetic screening of asymptomatic members of the family will allow the clinician to closely monitor otherwise seemingly "normal" patients, and anticipate and hopefully prevent unexpected life-threatening cardiac events.

Congenital Long QT Syndrome

Long QT syndrome (LQT) is a familial disease characterized by abnormally prolonged ventricular repolarisation and a high incidence of ventricular tachyarrhythmia, occurring commonly, but not exclusively, during physical or emotional stress.[24] In 1856, Meisner reported the case of a deaf girl who collapsed and died suddenly while being admonished at school. The girl had two brothers who also died suddenly, one after a violent fright, the other during rage. These patients are probably the first reported cases of Long QT syndrome. There were several case reports of similar cases, but it was not until 1953, when Moller reported the electrocardiographic findings of a deaf boy with frequent syncope. In 1957, Jervell and Lange-Nielsen

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provided the first complete description of Long QT syndrome; thus, the disease was named the "Jervell and Lange-Nielsen Syndrome".[25] In 1963, Romano and Ward reported, independently, on patients with cardiac disorders similar to the patients with Jervel and Lange-Nielsen syndrome, but without the deafness. An autosomal dominant inheritance pattern was proposed.[26,27]

The Long QT syndromes are characterized by prolongation of the QT interval, corrected for heart rate, clinical findings such as syncope, and familial history of syncope or sudden death. QTc is the observed QT interval corrected for the heart rate. The most commonly utilized formula was proposed by Bazett in 1920[28] and is as follows:

$$QTc = \frac{QT}{\sqrt{RR}}$$

Both observed QT and R-R are measured in milliseconds.

QTc values up to 460 milliseconds may still be normal in females while values over 440 milliseconds are considered prolonged in males. Significant variability exists in QTc measurements, even in the same affected individual over time, as well as in carriers of the same mutation. However, it is well recognized that normal individuals may have somewhat prolonged QTc intervals at times while Long QT syndrome patients may also demonstrate normal measurements of QTc,[29] as illustrated by Figure 5.

An abnormally prolonged QTc does not, by itself, establish the diagnosis of Long QT syndrome. In 1993, Schwartz proposed a system of "scoring" in order to establish a diagnosis.[30] (Table 3) Results of genetic testing were obviously not included in the score. In the current era, this system remains clinically useful. However, genetic confirmation of a Long QT syndrome case supersedes the Long QT syndrome score, and confirms a diagnosis.

In order to understand the disease better, a prospective registry was created in 1979 and continues today. The collaboration between the registry and the molecular biologists performing the search for mutations has been paramount in the great advances achieved in the last decade.[31] There has been a phenomenal gain in knowledge resulting from the genetic and molecular findings that began in the early 1990s when Keating and his group identified three separate genes related to Long QT syndrome.[32,33,34]

By 1996, it was clear that genetic testing could potentially identify patients with the disease. Since then, numerous additional mutations responsible for Long QT syndrome have been reported. The mutations responsible for Long QT syndrome are in genes which encode for several different transmembranous ion channels, responsible for the action potential, as illustrated in Figure 6.

Thus, the conglomerate of mutations that result in any one of the 12 known types of Long QT

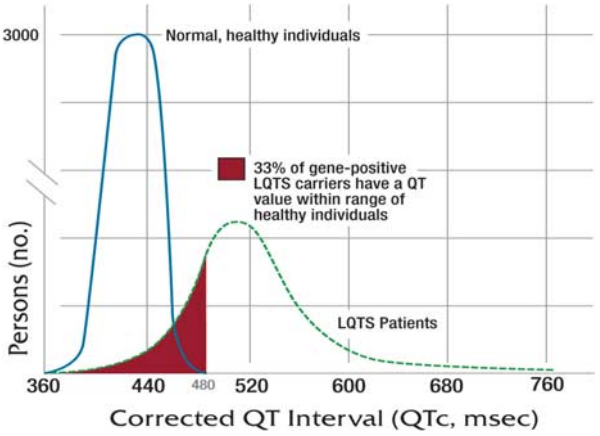

Figure 5.
Relative frequency of QTc measurements in the normal population as compared with patients with Long QT syndrome. Notice that there is a significant overlap between both groups.
(Courtesy of PGx Health)

Table 3. Criteria used to establish the diagnosis of Prolonged QT syndrome, established in 1993.

	Points
ECG findings*	
A. QT_c†	
⩾480 msec$^{1/2}$	3
460–470 msec$^{1/2}$	2
450 msec$^{1/2}$ (in males)	1
B. Torsade de pointest‡	2
C. T-Wave alternans	1
D. Notched T wave in three leads	1
E. Low heart rate for age§	0.5
Clinical history	
A. Syncope‡	
With stress	2
Without stress	1
B. Congenital deafness	0.5
Family history‖	
A. Family members with definite LQTS#	1
B. Unexplained sudden cardiac death below age 30 among immediate family members	0.5

LQTS, long QT syndrome.
*In the absence of medications or disorders known to affect these electrocardiographic features.
†QT_c calculated by Bazett's formula, where $QT_c = QT/\sqrt{RR}$.
‡Mutually exclusive.
§Resting heart rate below the second percentile for age,[25]
‖The same family member cannot be counted in A and B.
#Definite LQTS is defined by an LQTS score ⩾4.
Scoring: ⩽1 point, low probability of LQTS; 2 to 3 points, intermediate probability of LQTS; ⩾4 points, high probability of LQTS.

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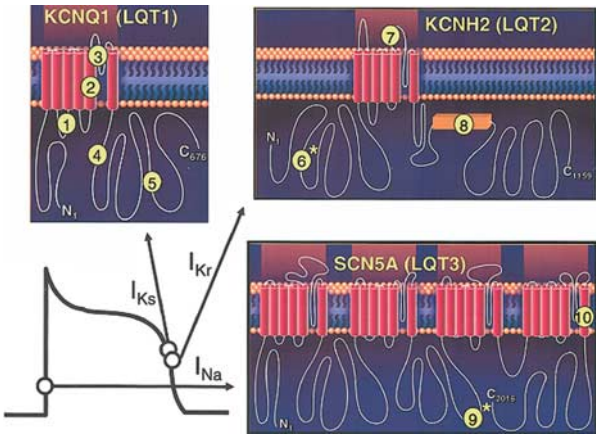

Figure 6.
The three most common channelopathies causative of Long QT syndrome. Defects associated with gain or loss of function in cardiac ionic channels result in abnormalities of the action potential, and thus, Long QT syndrome or Brugada syndrome. Cardiac ionic channels have a transmembranous component and an intracytoplasmic component. Mutations that occur in the transmembranous portion of the channel generally result in greater ionic channel dysfunction, and thus, are potentially more lethal than those involving the intracytoplasmic portion of the ion channel. (Reproduced with permission from Dr. Michael Ackerman and Journal of the American College of Cardiology.)

syndromes are also known as channelopathies and summarized in Table 4.

In 1999, Priori and colleagues demonstrated that for each gene carrier showing symptoms and QT prolongation, asymptomatic carriers may exist in those families and carriers may also have normal electrocardiograms.[35] Therefore, the phenotypic expression of the mutations can vary greatly, even within the same family. To date, there are no clear explanations for this variability and this topic will likely become the focus of future research.

While some have suggested that type specific changes in the morphology of the T wave are associated with the most common subtypes, as suggested by Figure 7 below,[36] others have questioned the reliability of employing the morphology of the T wave to determine the subtype.

A dilemma often faced by paediatric cardiologists is the differentiation of benign syncope, such as neurocardiogenic syncope, orthostatic syncope, and vasovagal syncope, from malignant syncope that may be an episode of aborted sudden death. Unfortunately, syncope associated with Long QT syndrome is often associated with physical exertion, it can also occur during emotional stress, startling, sleeping, and in the "post partum syndrome". Each subtype of Long QT syndrome has "typical" events associated with it, although any subtype of Long QT syndrome can have any type of syncope (Fig. 8). As an example, Long QT syndrome Type 1 is most commonly associated with syncope during physical exertion or swimming, Long QT syndrome Type 2 is associated with sudden frights, startling noises such as alarm clocks, and also carries an increased risk of events in the postpartum period. Events associated with Long QT syndrome Type 3 are usually during bradycardia and can cause death while asleep.

Establishing the diagnosis of Long QT syndrome can often be difficult. The social implications of carrying this diagnosis are substantial. Patients with this diagnosis may be discriminated against, may be denied certain jobs, and may be denied health or life insurance. In fact, the diagnosis itself often results in significant emotional issues. On the other hand, not arriving at a diagnosis in a carrier of Long QT syndrome can carry obvious potentially lethal implications not only for the patient but also for members of their family. Since phenotypic expression of Long QT syndrome is often variable, even within the same family, it is conceivable that an asymptomatic carrier may have a severely symptomatic offspring or sibling.

Finally, not all subtypes of Long QT syndrome are treated the same and subtypes can only be reliably determined by identifying the genetic mutation responsible for Long QT syndrome.

Long QT syndrome Type 1 is treated primarily with beta blockers, preferably long acting beta blockers such as nadolol or metoprolol, in order to avoid wide fluctuations in protection. Patients with Long QT syndrome Type 1 are discouraged from competitive sports, and in particular, water sports. If these patients are compliant with medications and lifestyle modifications, additional therapy such as a placement of an implantable cardioverter defibrillator, is rarely needed.

Long QT syndrome Type 2 is generally more malignant than Type 1. It is also treated with beta blockers. Since the trigger can be startling due to noises such as alarms and doorbells, avoidance of these triggers cannot always be accomplished. It is also particularly dangerous during the post partum period. For these reasons, many clinicians tend to recommend placement of implantable cardioverter defibrillators as a back up to beta blockers.

Long QT syndrome Type 3 is a sodium channelopathy. Symptoms often occur during bradycardia and thus, beta blockers are of limited use, if any. Instead, this type is treated with mexiletene. The QT interval often shortens as a response to therapy. Long QT syndrome Type 3 tends to be highly lethal, with patients often dying after the first event. Therefore, many clinicians recommend insertion of an implantable cardioverter defibrillator as a back up to medical therapy.[37]

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Table 4. There are currently 12 described subtypes of autosomal dominant Long QT syndrome and two types of Jervell and Lange-Nielsen Syndrome. Last Update: of this data was August 2008 by Professor Dr Hugues Abriel of The University of Lausanne.[29]

Type	Gene	Protein	Chromosomal Locus	Comment	Frequency, %
Romano-Ward (autosomal dominant)					
LQT1	*KCNQ1*	KvLQT1 (Kv7.1)	11p15.5	Trigger: Stress	30–35
LQT2	*KCNH2*	HERG (Kv11.1)	7q35-q36	Trigger: Noise	25–30
LQT3	*SCN5A*	Nav1.5	3p24-p21	Trigger: Sleep, rest. Beta blockertherapy seems to be the less effective.	5–10
LQT4	*ANK2*	Ankyrin-B	4q25-q27	LQT4 has been associated to the production of a defective accessory protein called Ankyrin-B.	less than 1
LQT5	*KCNE1*	Mink	21q22.1	Associated to the Jervell, Lange-Nielsen syndrome (congenital deafness).	less than 1
LQT6	*KCNE2*	MiRP1	21q22.1	Triggers: certain drugs, exerceise.	less than 1
LQT7	*KCNJ2*	Kir2.1	17q23	Associated to the Andersen-Tawil syndrome	less than 1
LQT8	*CACNA1C*	Cav1.2	12p13.3	Associated to the Tirnothy syndrome	less than 1
LQT9	*CAV3*	Caveolin-3	3p25	Mutation of *CAV3* also associated to muscle disease	less than 1
LQT10	*SCN4B*	Navβ4	11q23.3	So far, only found in one single family	less than 1
LQT11	*AKAP9*	AKAP9/yotiao	7q21-q22		less than 1
LQT12	*SNTA1*	α1-syntrophin	20q11.2		less than 1
Jervel, Lange-Nielsen (autosomal recessive)					
JLN1	*KCNQ1*	KvLQT1	11p15.5		more than 90.5
JLN2	*KCNE1*	Mink	21q22.1		less than 0.5

Last Update: August 2008/ Prof. Dr. Hugues Abriel. University of Lausanne.
Source: Clinical and Genetic characteristics of Long QT Syndrome: Rev Esp Cardiol. 2007;60(7):739–52.
(Courtesy of PGx Health)

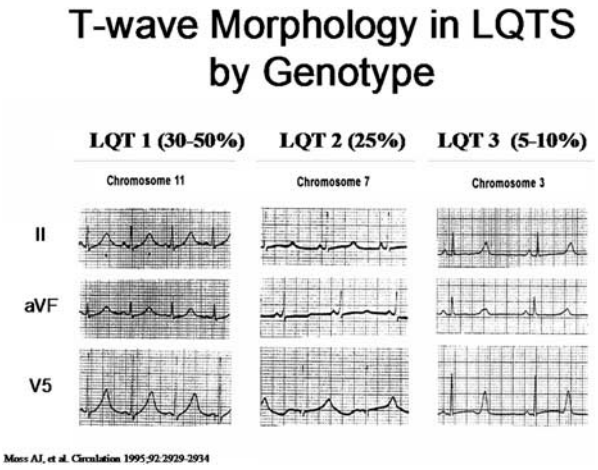

Figure 7.
Long QT syndrome may have distinctive abnormalities of the T wave morphology.

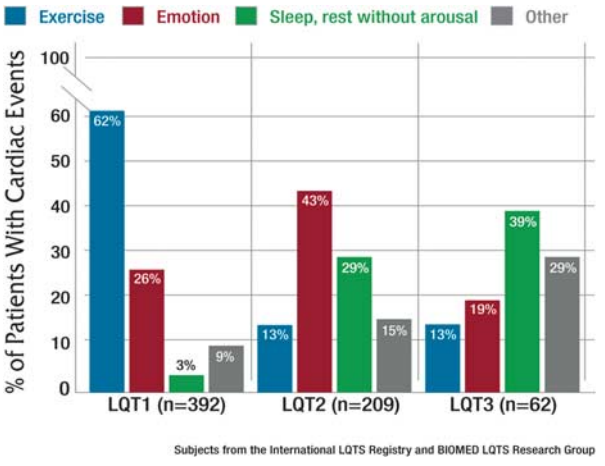

Figure 8.
Activities associated with cardiac events for the most common Long QT syndrome types. Although there is significant overlap between the groups, each type has typical precipitating events.
(Courtesy of PGx Health)

As illustrated in Figure 6, channel mutations can occur in the transmembranous portion of the channel, or in the intracytoplasmic portion. The latter can be further subdivided into mutations involving the N terminal and the C terminal. It is becoming increasingly evident that not all mutations are alike. For example, in Long QT syndrome Type 1, a mutation in the transmembranous portion may have greater phenotypic expression and be more malignant than a mutation located in the intracytoplasmic portion. While both cases would

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still be labelled as Long QT syndrome Type 1, the clinical implications may vary. At this point, however, it would be misguided to use the location of the mutation to label these patients as having "benign" or "malignant" mutations. Future research may help clarify this issue.

Because Long QT syndrome is inherited in an autosomal dominant fashion and because the phenotypic expression of the disease can be quite variable within families, it is imperative that "family specific testing" is performed once a mutation is identified in the proband. Electrocardiographic interpretation on newborns can often be difficult due to the transitional electrocardiographic changes occurring. Therefore, if a mutation has been identified in a mother, testing on fetal cells can be performed via amniocentesis, in the hope to have the diagnosis available by the time the child is born.[38] Alternatively, the physicians, together with the expectant mother and her support, can coordinate to collect blood from the umbilical cord for submission for testing. This way, the result should be available within a few weeks. "Family specific genetic testing" is a cost effective method to identify individuals at risk, and thus, save lives.[39]

In summary, genetic testing for suspected cases of Long QT syndrome will identify the subtype and therefore guide therapy and allow appropriate lifestyle modification. It can also help detect asymptomatic carriers who may either become symptomatic in the future, or who may pass on the gene to an offspring who may become symptomatic. The consequence of not knowing the subtype is possibly mismanaging the patient, such as selection of beta blockers versus Mexiletene, and could result in sudden death that may otherwise have been preventable.

Brugada Syndrome

In 1992, Pedro and Joseph Brugada presented data on eight patients with recurrent episodes of aborted sudden death, and whose hearts were otherwise unremarkable. Their electrocardiograms showed the following features:

- normal QT intervals
- the presence of incomplete right bundle branch block, and
- persistent ST elevation in V_1, V_2 and occasionally V_3.

This report was the first description of Brugada syndrome.[40] An autosomal pattern of inheritance was described by Corrado and colleagues in 1996,[41] and in 1998, Chen and co-workers linked Brugada syndrome to the α subunit of the sodium channel SC5NA.[42]

Mutations causative of Brugada syndrome result in a loss of function of SC5NA sodium channel. That is, the channel is less permeable to sodium than normal. Thus, drugs that block the sodium channel, such as ajmaline, flecainide, procainamide and pilsicainide, have been utilized to "unmask" the Brugada syndrome. Attempts have been made to perform stratification of risk in this condition. In adults, Brugada syndrome in patients with history of syncope or cardiac arrest carries a poor prognosis.[43] Other risk factors are male sex, positive electrophysiological study (EPS) and spontaneous ST elevation.[44] Limited pharmacological options exist to treat these patients; only quinidine and tedisamil have been proposed as agents of possible efficacy. Insertion of implantable cardioverter defibrillators remains the preferred option to protect high risk patients from sudden death.[45]

Little is known about the prevalence, diagnostic criteria, and natural history of this disease in the paediatric population. In a longitudinal follow-up study of a large family with known mutation of SC5NA, it was noted that the pattern of Brugada appeared significantly later in childhood.[46] Probst and co-workers[47] reported the first large scale multicentric analysis of children, less than 16 years of age, with electrocardiographic appearance consistent with Brugada syndrome during evaluation for syncope or screening of the family. Provocative pharmacological challenge, with ajmaline, flecainide, procainamide or pilsicainide, was effective in exacerbating the pattern of Brugada in these patients, helping establish or confirm the diagnosis. Response to these tests does not imply worse clinical outcome. By contrast, electrophysiological study was positive in patients who had syncope, suggesting that electrophysiological study can predict negative events. Fever has been noted to exacerbate events in children in this study and others.[48] Treatment with hydroquinidine was believed to be a good alternative to insertion of an implantable cardioverter defibrillator, although the number of patients receiving this drug was small.

The diagnosis of Brugada syndrome in children can be difficult. Electrocardiographical patterns suggestive of Brugada may not be present in a small child, and may become evident later in life. Thus, normal electrocardiograms in children do not exclude the possibility of Brugada. The relatively low yield of positive mutations in suspected probands makes "family specific testing" a difficult task. When evaluating the child of an adult with a negative genotype and a positive phenotype, it is important to insist on periodic re-evaluations of that child, and to consider testing with provocative pharmacological challenge and electrophysiological study as a way to assist in establishing a diagnosis. On the other hand, first degree family members

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of an individual with a positive genotype should undergo genetic testing even if they are asymptomatic and their electrocardiogram is normal. A negative family specific test will be highly reassuring. If the family specific test is positive, the clinician should consider performing an electrophysiological study for stratification of risk.

Catecholaminergic Polymorphic Ventricular Tachycardia

Also referred to as "Normal QT Long QT syndrome", catecholaminergic polymorphic ventricular tachycardia (CPVT) is a highly malignant disease affecting the sacroplasmic reticulum. The end result is an uncontrolled calcium release during electrical diastole. Two genetic variants exist. The autosomal dominant RyR2 mutation is far more common. The autosomal recessive mutation, CASQ2, is rare,[49] and can be detected in about 55 to 60 percent of affected individuals.[50] The pathognomonic arrhythmia is bidirectional ventricular tachycardia that generally occurs during stimulation with cathecholamines (Fig. 9).

Often, premature ventricular contractions induced by stress can be seen during sinus tachycardia. Electrophysiological studies, on the other hand, have been generally found to be of little value in assessing risk in this condition.

Left untreated, catecholaminergic polymorphic ventricular tachycardia is highly malignant, and it is estimated that, by age 40, 80 percent of patients will have had a symptom (Fig. 10).

Conflicting data exists regarding the efficacy of beta blockers as the only treatment for catecholaminergic polymorphic ventricular tachycardia, as breakthrough events have been reported by some investigators.[51,52] Therefore, insertion of implantable cardioverter defibrillators should be considered as soon as the diagnosis is confirmed. As with all cardiac channelopathies, "family specific genetic testing" is of paramount importance in detecting asymptomatic members of the family. In these cases, treatment should be considered.

Sudden Infant Death Syndrome

The World Health Organization (WHO) has defined sudden infant death syndrome as the sudden death of an infant which remains unexplained after a thorough case investigation, including the performance of a complete autopsy, examination of the death scene, and a review of the clinical history. In the year 2000, 12 out of 100,000 babies became victims of sudden infant death syndrome in the Netherlands, as compared to 41 out of 100,000 in England and 62 out of 100,000 in the United States

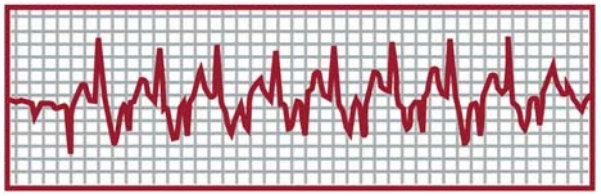

Figure 9.
Bidirectional ventricular tachycardia during exercise or sinus tachycardia is pathognomonic of catecholaminergic polymorphic ventricular tachycardia.
(Courtesy of PGx Health)

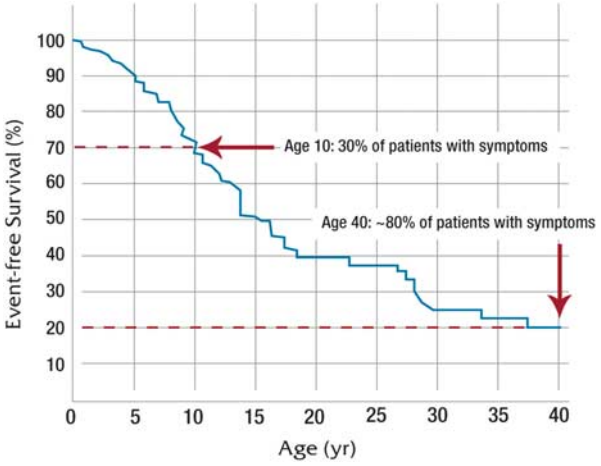

Figure 10.
Presence of cardiac events in patients with catecholaminergic polymorphic ventricular tachycardia by age.
(Courtesy of PGx Health)

of America. Despite its relative high incidence, perhaps no greater mystery exists in paediatrics than the aetiology of sudden infant death syndrome. Progress is being made. The incidence of sudden infant death syndrome has significantly reduced since sleeping in the supine position was noted to decrease its incidence.[53] The difference in incidence in the countries mentioned may be in part due to the different success of this campaign in each country, as well as exposure to additional risk factors such as passive smoking, low birth-weight, and others.[54]

In 1976, Maron and co-workers first proposed that one of the many causes of sudden infant death syndrome could be Long QT syndrome.[55] Proving that theory, however, remained elusive. In 1998, Schwartz reported the results of a prospective evaluation over a period of 19 years involving more than 34,000 infants who had an electrocardiogram in the third or fourth day of life.[56] They reported that 50 percent of the infants who died of sudden infant death syndrome had a prolonged QTc and that a prolonged QTc greater than 440 milliseconds

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in the first week of life increased the risk by a factor of 41. In 2000, the same group reported a case study of a patient with a "near miss sudden infant death" in whom they found a spontaneous mutation in SC5NA, one of the genes associated with Long QT syndrome. Another case of "near miss sudden infant death" was linked to the Brugada syndrome.[57] Several studies have since evaluated tissue from post mortem examinations of infants with sudden infant death syndrome, searching for known mutations associated with Long QT syndrome in that population. Ackerman and colleagues reported that 2% of tissue from post mortem examinations of infants with sudden infant death syndrome carried SC5NA mutations. Arnestad and colleagues found that up to 9.5% of tissue from post mortem examinations of infants with sudden infant death syndrome carried mutations associated with Long QT syndrome Type 1 through Long QT syndrome Type 6.[58] More recently, a mutation involving caveolin 3, another gene associated with Long QT syndrome was found in 3 of 135 babies with sudden infant death-syndrome,[59] and RyR2, the gene related to catecholaminergic polymorphic ventricular tachycardia, was found in 2 of 135.[60]

General agreement exists that the aetiologies of sudden infant death are numerous and that a "common theme" is yet to be found. However, evidence exists that the genetic mutations associated with Long QT syndrome are found in some cases of sudden infant death; and therefore, careful screening of surviving members of the family of babies with sudden infant death is imperative. Furthermore, a case can be made for performing a "genetic autopsy" on these babies. If a Long QT syndrome mutation is found, "family specific testing" should proceed at once in order to identify potential "at risk" asymptomatic individuals.

Future Considerations

The past decade has seen phenomenal advances in the understanding of the syndromes of sudden death. These advances are in a large part secondary to the collaboration between clinicians contributing data to clinical registries, and molecular biologists discovering a myriad of mutations causing the subcellular malfunctions which are responsible for the often lethal events discussed in this review. While these efforts should no doubt continue, we must educate medical professionals as well as the lay public, that we now have new tools to help unravel the mystery of sudden death in the young.

Ackerman and colleagues have proposed the concept that a "genetic autopsy" can and should be performed in selected cases with a negative conventional autopsy.[61] They found a mutation of the types commonly associated with sudden death in 35% of the decedents. These mutations were as follows:

- catecholaminergic polymorphic ventricular tachycardia (RyR2) = 14%,
- Long QT syndrome Type 1 (KCNQ1) = 10%,
- Long QT syndrome Type 2 (KCNH2) = 6%, and
- Long QT Syndrome Type 3 (SC5NA) = 4%.

After a tragic, sudden and unexpected death occurs in a young person, electrocardiographic information is rarely available. Absent pathologic findings at autopsy following these tragic deaths, searching for these mutations may be the only way to answer the three most important questions asked by the surviving loved ones of a young victim of sudden death:

- Why did this happen?
- Could it have been prevented?
- Can it happen again in this family?

Only by answering these questions in the face of a tragedy will the loved ones of a young victim of sudden death begin the healing process and also identify and protect other members of the family who may be at risk.

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