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The polymorphism of the HERG gene responsible for the autosomal dominant long-QT syndrome

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Introduction

The long-QT syndrome (LQTS) is caused by mutations on several genes, all of which encode cardiac ion channels. The LQTS is a primary electrical disease which is characterised by prolongation of the corrected QT (QTc) interval on the surface electrocardiogram (ECG), sudden death from cardiac arrhythmias, *torsade de pointes*, and ventricular fibrillation. The identification of three of the genes associated with congenital long-QT syndrome (cLQTS) between 1995 and 1996 [1, 2], and the awareness that they all encode cardiac ion channels involved in the control of repolarisation, prompted the concept that cLQTS may represent a distinct model for studying genotype-phenotype correlation in congenital arrhythmogenic diseases. There has been heightened interest in correlation since the mutations identified in these genes cause either loss or gain of function, leading to reduced outward potassium current or excess of late inward sodium current [1, 2].

Up to date, five LQTS genes have been identified, including the potassium channel gene HERG (LQT2) [3], which encodes the α-subunit of the channel that underlies the rapidly activating delayed rectifier potassium current I_{Kr} (fig. 1) and KCNQ1 (LQT1) [4], which encodes the slowly activating delayed rectifier potassium channel I_{Ks}. The majority of the mutations have been identified in the core region, constituted by transmembrane domains and pore of KCNQ1 and HERG. However, mutations in the N- and C-terminal regions have also been reported [5–8]. The summary of the genes associated with LQTS is shown in table 1.

Clinically, the congenital long-QT syndrome exists in two forms, namely Jervell and Lange-Nielsen syndrome and Romano-Ward syndrome. The Jervell and Lange-Nielsen syndrome is a cardioauditory syndrome that is inherited by an autosomal recessive pattern and is associated with congenital deafness [9]. The Romano-Ward syndrome, which is more common, is inherited in an autosomal dominant pattern and is associated with normal hearing [10, 11]. The two syndromes usually manifest in childhood or adolescence [12]. In this review, we will focus on the HERG gene mutations and summarise current information on genotype-phenotype correlation in the LQT2.

The molecular biology of LQT2

The LQT2 *locus* was mapped in affected families to 7q35–36 [13]. The LQT2 pathogenic gene is HERG (human ether-a-go-go related gene), otherwise known as KCNH2, which encodes the rapidly activating potassium delayed rectifier [14]. Curran et al. [3] identified six LQTS associated mutations in HERG and came to the conclusion that HERG is the gene responsible for chromosome 7-linked LQTS (LQT2). LQT2 accounts for approximately 45% of the genotyped LQT families. The HERG is highly expressed in the heart [3], and the encoded protein has six transmembrane domains (S1-S6) (fig. 1).

The S5-P loop of HERG (39 amino acids) is longer than those of most other Kv channels (5–10) amino acids. Several LQT2 associated mutations occurring in the region of S5-P loop allow channel maturation and trafficking to the cell surface, but cause defects in channel function [15]. The HERG (LQT2) and KCNE2 (LQT6) gene products assemble to form a complete I_{Kr} channel protein.

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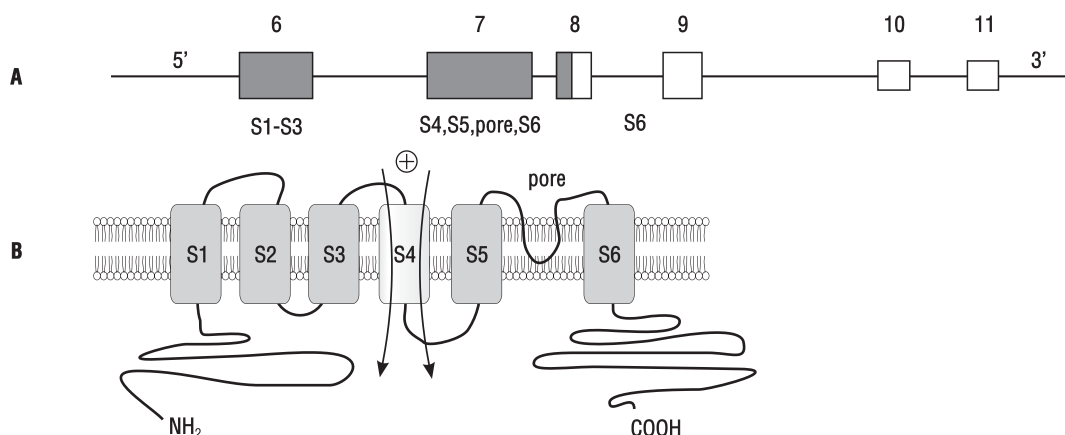

Figure 1. Predicted organisation of HERG; **A**. Genomic structure of HERG; exons are indicated by open boxes; exon coding transmembrane domains are symbolised in grey; **B**. Schematic representation of a voltage-gated K^+ channel α-subunit composed of six membrane-spanning alpha helices (S1-S6); S4 — voltage sensor; P-ion selective pore

Table 1. Summary of genes associated with long-QT syndrome

Locus	Chromosome location	Gene	Channel	Disease
LQT1	11p15.5	KCNQ1	I_{Ks}	RWS & JLNS
LQT2	7q35-36	HERG(KCNH2)	I_{Kr}	RWS
LQT3	3p21-24	SCN5A	I_{Na}	RWS
LQT4	4q25-27	Unidentified	?	RWS
LQT5	21q22.1-22.2	KCNE1	Mink	RWS & JLNS
LQT6	21q22.1-22.2	KCNE2	MiRP1	RWS & JLNS
LQT7	Unknown	Unknown	Unknown	Unknown

RWS — Romano-Ward syndrome, JLNS — Jervell and Lange-Nielsen syndrome

Recently, it has become apparent that not only antiarrhythmic agents but a variety of non-antiarrhythmic drugs may induce QT prolongation and provoke *torsade de pointes*. A number of antiarrhythmic (class IA and III) and noncardiac drugs have been reported to prolong QT interval, including psychiatric, antimicrobal and antimalarial, antihistaminics and others drugs [16].

The principal ion channel affected by the QT--interval prolonging drugs is I_{Kr} (HERG), which coincidentally is the same ion channel that causes congenital LQT2 [17]. This suggests that a physiological relationship may exist between drug induced LQTS and congenital LQT2, which further cements the possibility of a genetic basis for predisposition to the drug induced LQTS. The presence of a forme fruste of a LQTS could play a key role although genetic study of patients with drug-induced *torsade de pointes* revealed that only a minority of the patients had a mutation. However, it cannot be excluded that yet unknown subtle defects may set the stage for abnormal QT prolongation and ventricular arrhythmias [16]. Recent studies indicate that single nucleotide polymorphisms may increase susceptibility to acquired forms of LQTS [18]._The question of drug-induced LQTS may also raise the likelihood of the presence of a LQTS locus in the family and may give an extra caution in the use of QT prolonging drugs among other family members. However, the latter needs further examination.

Mutations in the HERG (KCNH2) gene

LQT2 is caused by mutations in HERG, and the gene product is the a-subunit of a potassium channel that carries the I_{Kr} current. The HERG mutations causes the prolongation of QT interval, leading to the reduction of this current. The identified mutations in HERG [3, 19–21] are chiefly missense mutations resulting in changes in highly conserved amino acids (tab. 2). However, other types of mutations, such as deletions, frame-shi-

Table 2. Summary of mutations associated with the HERG gene

Mutation denotation	Type of mutation	Nucleotide change	Protein domain	Reference
F29L	Missense	c → a	N-terminal	15
N33T	Missense	a → c	N-terminal	15
C44X	Missense	c → a	N-terminal	15
G47V	Missense	g → t	N-terminal	15
G53R	Missense	g → c	N-terminal	15
R56Q	Missense	g → a	N-terminal	15
C66G	Missense	t → g	N-terminal	15
H70R	Missense	a → g	N-terminal	15
P72Q	Missense	c → a	N-terminal	15
R73fs/31	Deletion	31-bp-del	N-terminal	15
A78P	Missense	g → c	N-terminal	15
A83fs/37	Frame-shift	Dupl (1234–1250)	N-terminal	15
Q81X	Missense	c → t	N-terminal	15
L86R	Missense	t → g	N-terminal	15
P141fs/2	Frame-shift	Ins C422–423	N-terminal	15
P151fs/179	Frame-shift	Ins C453–454	N-terminal	15
L200fs/144	Frame-shift	Dupl 558–600	N-terminal	15
P241fs/89	Frame-shift	Ins C724–725	N-terminal	15
V295fs/63	Frame-shift	Del 885	N-terminal	15
R312C	Missense	c → t	N-terminal	15
P347S	Missense	c → t	N-terminal	15
Q376sp	Splice	g → a	N-terminal	15
Q376sp	Splice	a → g	N-terminal	15
Y420fs/12	Frame-shift	Del 1261	S1	3
S428X	Missense	c → a	S1-S2	2
T436M	Missense	c → t	S1-S2	2
N470D	Missense	a → g	S2	3
T474I	Missense	c → t	S2-S3	22
Y493X	Missense	c → g	S2-S3	54
I489	Missense	c → t	S2-S3	3
Del500–508	Deletion	27-bp-del	S3	3
F513	Missense	c → t	S3	55
R531Q	Missense	g → a	S4	15
R534C	Missense	c → t	S4	54
L552S	Missense	t → c	S5	15
T556fs/7	Frame-shift	Del T1671	S5	56
A558P	Missense	g → c	S5	57
A561T	Missense	g → a	S5	15, 58
A561V	Missense	c → t	S5	2, 3, 15
L564	Missense	a → g	S5	3
G572C	Missense	g → t	S5	59
G572R	Missense	g → c	S5-Pore	60
R582C	Missense	c → t	S5-Pore	57
G584S	Missense	g → a	S5-Pore	15
W585C	Missense	g → t	S5-Pore	15
N588D	Missense	a → g	S5-Pore	59
I593R	Missense	t → c	S5-Pore	15
I593G	Missense	t → g	S5-Pore	21
G601S	Missense	g → a	S5-Pore	61

G604S	Missense	g → a	S5-Pore	15, 57
D609N	Missense	g → a	S5-Pore	15
Y611H	Missense	t → c	S5-Pore	22
Y611X	Missense	t → a or g	S5-Pore	56
V612L	Missense	g → t	Pore	62
T613M	Missense	c → t	Pore	15, 57
A614V	Missense	c → t	Pore	2, 22, 62
L615V	Missense	c → g	Pore	15
G626S	Missense	g → a	Pore	15
F627L	Missense	c → g	Pore	15
G628S	Missense	g → a	Pore	3, 15
N629D	Missense	a → g	Pore	62
N629S	Missense	a → g	Pore	62
N629K	Missense	c → a	Pore	63
V630L	Missense	g → c	Pore	22
V630A	Missense	t → c	Pore	59
P632S	Missense	c → t	Pore	15
N633S	Missense	a → g	Pore	62
K638E	Missense	a → g	S6	15
DelK638	Deletion	Del 11913–1915	S6	15
F640L	Missense	c → a	S6	57
M645L	Missense	a → t	S6	15
L650fs/2	Frame-shift	Del 1951–1952	S6	54
M651 del AT	Frame-shift	2-bp-del-at	S6	54
Y652	Missense	t → c	S6	55
Q725X	Missense	c → t	S6	54
E682X	Missense	g → t	S6/cNBD	15
H739fs/63	Frame-shift	Ins T2218–2219	S6/cNBD	15
R752W	Missense	c → t	S6/cNBD	15
V796fs/22	Frame-shift	Dup12356–2386	cNBD	54
I798fs/10	Frame-shift	Del 2395	cNBD	15
L799sp	Splice	G2398 + 1C	cNBD	3, 15
F805S	Missense	t → c	cNBD	15
F805C	Missense	t → g	cNBD	15
S818L	Missense	c → t	cNBD	8
V822M	Missense	g → a	cNBD	8, 64
R823W	Missense	c → t	cNBD	15
Int9-3nt	Missense	g → c	NBD	3
E847/E857del	Frame-shift	31-bp-dup	NBD-ter	54
N861I	Missense	a → t	C-terminal	15
D864sp	Splice	G2592 + 1A	C-terminal	8, 15
K886fs/85	Frame-shift	Del 2660	C-terminal	15
P917L	Missense	c → t	C-terminal	15
R920fs/51	Frame-shift	Del 2762	C-terminal	15
R922W	Missense	c → t	C-terminal	15
G925fs/13	Frame-shift	Ins G2775–2776	C-terminal	15
P968fs//4	Frame-shift	Del 2906	C-terminal	15
P986fs/130	Frame-shift	Del 2959–2960	C-terminal	15
R1014X	Missense	c → t	C-terminal	15
G1031fs/24	Frame-shift	Del 3094	C-terminal	15
G1036fs/82	Frame-shift	Ins G3107–3108	C-terminal	8
P1101fs	Frame-shift	Ins C3303–3304	C-terminal	15

fts and splice-donor errors, have also been reported [19]. In all the four transmembrane regions, point mutations have been identified, and study expressions have indicated that reductions in the major functions of the I_{Kr} current are mainly caused by minimal changes in amino acids. The only "hot spot" area known to be described for HERG seems to be amino acid 561, in which Alanine to Valine substitution has been reported [3, 22, 23]. Sanguinetti et al. [19] have reported that when A561V mutant protein is expressed together with the wild-type protein, a dominant negative effect is produced, causing a remarkable reduction in the channel function.

The reports by Zhou et al. [24] have shown that in some patients, there is a reduction in I_{Kr} current, mainly caused by mutations in the cyclic-nucleotide-binding domain (cNBD), situated on the C-terminus of HERG. The resulting mutations tend to cause abnormal protein trafficking which leads to retention of mutant channels in the endoplasmic reticulum. This suggests that the NBD may play a vital role in the modulation of the HERG channel protein processing and trafficking.

Evaluation of study expressions on the repolarisation of different mutations by Bennett et al. [25] has made it impossible to find a correlation between the severity of clinical manifestations and the spectrum of HERG disorder through in vitro assessment [26]. This shows that there are yet unknown factors which influence the clinical phenotype even when it is of the same genotype. Table 3 shows comparison of types and positions of LQTS gene mutations.

Table 3. Comparison of type and position of long-QT gene mutations

Type	KCNQ1	HERG	SCN5A	KCNE1	KCNE2
Missense	86	71	9	5	3
Nonsense	6	5	0	0	0
Amino acid deletion	13	2	5	0	0
Frameshift	1	22	0	0	0
Splice	7	5	0	0	0
Position					
Extracellular	0	7	1	1	1
Transmembrane	33	13	5	0	2
Pore	22	14	0	NA	NA
Intracellular	33	48	8	4	0

NA — not available

Clinical presentation of LQT2

The clinical features of long-QT syndrome fall into two categories of syncopal attacks and prolongation of repolarisation. However, other features may also contribute in its diagnosis. *Torsade de pointes* is considered to be the arrhythmia causing syncopal episodes, which sometimes degenerates into ventricular fibrillation and may lead to sudden death. In general, an individual case of torsades has a short-life span, usually terminates spontaneously, and may go unnoticed. The initial manifestation of torsade de pointes may be without changes in heart rate and without specific sequences, such as short-long-short interval, even though a pause often precedes its onset [27, 28].

Sympathetic activation, identified by physical or emotional stress, represents the trigger for 88% to above 95% of cardiac events in patients with LQT1 and in Jervell or Lange-Nilsen syndrome, i.e. those with mutations affecting I_{Ks}. In contrast, sympathetic activation occurs in 56% of LQT2 patients and in only 33% of LQT3 patients [29, 30]. In patients with HERG mutations exercise-related, emotional-related and rest-related arrhythmias have all occurred.

The trigger pattern for LQT2 patients is rather intermediate, with only 13% of episodes occurring during exercise and most of the remainder (43%) occurring with emotional stress [31], while that of LQT1 is very distinctive, with most events occurring during exercise and a very small minority (3%) during rest or sleep [31]. Schwartz et al. [31] also showed that 68% of lethal events occurred during exercise for LQT1, whereas this never occurred for LQT2.

Many LQTS patients can be triggered by loud noise, such as mainly alarm clocks, telephone ringing, thunder and explosions. About 80% of patients with events that occurred after auditory stimuli were LQT2 patients, 64% of these events occurred in the course of sleep [31]. Wilde et al. also observed that acoustic stimuli were very characteristic for LQT2 [32].

Swimming, as a trigger, is exceptionally rare among LQT2 patients (0.6%) and virtually absent among LQT3 patients, whereas 33% of LQT1 patients are triggered by swimming [31].

LQTS usually manifests before the age of 40 years, mainly in childhood and adolescence. The genotype of an individual patient determines at which age the disease manifests for the first time. Data from the International Long-QT Syndrome Registry have shown that the median age at which the first cardiac episode occurred was 9, 12, and 16 years for patients

with LQT1, LQT2 and LQT3, respectively [33]. Due to shorter QT intervals, men are less susceptible to cardiac events compared with women, boys and girls, especially in LQT1 and LQT2 patients [34–36].

It has been well established that sex hormones can impact cardiac electrophysiology and, more particularly, cardiac repolarisation [37]. It is therefore conceivable that sex can influence the phenotype through the effects of sex hormones on repolarising potassium currents [38]. However, this hypothesis still need further evaluation.

In the data from the International LQTS Registry, the frequency of cardiac events was higher among subjects with LQT1 (63%) or LQT2 (46%) than among subjects with LQT3 (18%), but the likelihood of dying during a cardiac event was significantly higher among patients with LQT3 [33].

ECG findings

The yardstick for the diagnosis of LQTS has always been associated with the presence of a prolonged QT interval on the ECG. As proposed by Schwartz in 1985 and later in 1993 [39], QT interval prolongation has always been an integral part of the diagnostic criteria in LQTS. The unorthodox hypothesis proposed by Schwartz in 1980 and again in 1985 has shown that LQTS affected patients with normal QT interval must have been in existence. Although this hypothesis was held with caution and scepticism, despite the accruing supportive data, it was given a boost by Priori et al. [40] in their description of low penetrance in LQTS.

The values of QTc interval vary with situation and also with age and gender. On average, normal adult females have higher QTc values than males from the same families. This difference in QTc values is mainly seen in both symptomatic and asymptomatic carriers of KCNQ1 and HERG mutations, but the trend is reversed in families with SCN5A mutations, where affected males have longer QTc values [36].

According to the data from the International Registry of LQTS in 1989, 10% of 503 family members with a QTc < 440 ms had a cardiac arrest [41], while a similar report by Garson et al. [42] on 287 LQTS patients indicated that 6% of them had a normal QTc. These data *per se* demonstrate that it is impossible to exclude the diagnosis of LQTS simply on the basis of a normal QTc.

The different genotypes of LQTS may display specific ECG phenotypes. Zhang et al. [43] identified 4 ST-T wave repolarisation patterns in LQT2. They were characterised by obvious bifid T wave, subtle bifid T wave with second component on top of T wave in limb and left precordial leads, subtle bifid T wave with second component on down slope of T wave in inferior and mid precordial leads, and low-amplitude bifid T wave with second component merged with U wave. However, overlap existed among the repolarisation patterns of different genotypes [43].

Kaufman et al. [44] evaluated 101 genotyped members of a family with LQTS, including 26 carriers of a HERG mutation. In this homogeneous population the phenotype was so variable that clinical and detailed ECG analyses did not permit an accurate diagnosis of gene carrier status.

Lupoglazoff et al. [45] reported that Holter recording analysis was superior to the 12-lead ECG in detecting T wave notches indicative of LQT2.

Subjects with HERG mutations appear to display near-normal QT shortening with exercise while patients with LQT1 mutations present less QT shortening with exercise than do normal subjects.

Management and therapeutic approaches to HERG-related LQTS

Large prospective registries have provided the basis of most of the recommended strategies for LQTS patients management [33]. Unfortunately, no randomised trials are available.

All patients (symptomatic, asymptomatic and silent gene carriers) should reduce physical activity, especially competitive sports, and avoid the use of drugs that prolong repolarisation [46]. It is especially important that their physicians are well aware of those drugs that contain I_{Kr} blockers. The high risk associated with auditory stimuli in LQT2 makes the removal of telephones and alarm clocks from patient bedrooms advisable [31].

Life-long therapy is necessary for patients with symptomatic LQTS to prevent sudden cardiac death. Beta-blockers remain the mainstay of therapy and patients should be informed about compliance to this therapy [47]. Schwartz et al. [31] demonstrated that the success rate of β-blockers therapy was lower among LQT2 than LQT1 patients, the recurrence rate was 41% and 19% ($p < 0.001$) respectively. Similar results were reported by Itoh et al. [48], indicating that LQT2 patients were not as well protected by β-blockers therapy as LQT1 patients.

Left cardiac sympathetic denervation has been used in LQTS patients who were non-responders to β-blockers or who were not compliant with this therapy [49]. Implantation of a permanent pacemaker, in combination with β-blocking therapy, is indicated in LQTS patients with AV block, bradycardia or pau-

se-dependent ventricular tachyarrhythmias. Pacing rate should be adjusted to normalise QT interval. It has been reported that the patients with LQT2 and LQT3 benefit more than patients with LQT1 [31, 50].

Compton et al. [51] reported that an increase in the serum potassium level (potassium chloride, spironolactone) in patients with mutant HERG gene resulted in a shortening of the QTc interval and a decrease in QTc dispersion. Therefore, it was suggested that in LQT2 patients high normal (4.5–5.0 mEq/l) level of serum potassium is preferable to low normal levels. Potassium lowering agents should be avoided in symptomatic and asymptomatic patients.

Potassium channel openers such as nicorandil have been shown to suppress early after depolarisations, abbreviate QT and reduce transmural dispersion of repolarisation in experimental models and LQT1 and LQT2 patients [52, 53]. The long-term effect of potassium channel openers in patients with LQT2 needs to be determined.

For the patients with a history of cardiac arrest, the risk of sudden cardiac death, even on β-blockers, remains unacceptably high. In this group of patients the implantable cardioverter defibrillator, in combination with β-blocking therapy, is recommended in secondary prevention.

The definitive role of the prophylactic use of β-blockers in asymptomatic LQTS patients is not well documented. Some investigators recommend treating patients who are at higher risk of sudden death, especially those with QTc interval > 600 ms, syndactyly and AV block, macroscopic T wave alternans, and in post partum period.

Prolongation of action potential duration by drugs is recognised as a potential risk for *torsade de pointes*. Drug-induced cases of torsade de pointes are particularly difficult to predict clinically because of their idiosyncratic nature. The factors that determine which patients are at the highest risk for drug-induced LQTS and arrhythmia are still not fully understood and so this remains a subject for future investigations.

According to the Task Force on Sudden Cardiac Death of the European Society of Cardiology [46] the steps to be recommended for increasing the awareness of drug-induced *torsade de pointes* include:
— detailed list of all drugs associated with QT prolongation;
— for new drugs, data on block of potassium channels are mandatory;
— avoidance of co-administration of drugs prolonging the QT;
— avoidance of drugs that interfere with metabolism and excretion;
— avoidance of drugs that produce torsade de pointes promoting conditions, such as bradycardia, hypokalemia.

Through this approach, the number of cases of drug-induced LQTS could be minimised and eventually eradicated.

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