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Review article

Long QT Syndrome- A Genetic Insight

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ABSTRACT

Long QT syndrome is a rare arrhythmogenic disorder characterized by a prolongation of the QT interval on electrocardiogram (ECG) with a propensity to ventricular tachyarrhythmia, leading to syncope, cardiac arrest or sudden death. It is regarded as the "Rosetta Stone" for studying the genetic basis of ventricular arrhythmogenesis. It is caused mainly due to mutations in sodium and potassium channel genes or in the genes involved in the signal transduction pathway. Molecular, genetic and functional studies revealed the implication of about 13 genes in this disorder. Studies have also revealed the variation in mutations in different ethnic groups, thus necessitating a complete genetic analysis in all the known ethnic groups of the world. This would help to develop personalized medicine, molecular diagnosis, risk stratification, establish a genotype-phenotype correlation, to find the epidemiological variables responsible for the etiology of the disease and identify the possible mode of inheritance.

1. Introduction

The hereditary Long QT syndrome (LQTS) is characterized by a prolongation of the QTc interval (Fig.I) on electrocardiogram (ECG) and a propensity to ventricular tachyarrhythmia, which may lead to syncope, cardiac arrest or sudden death. This rare, life-threatening repolarization disorder has a prevalence of 1 in 10,000 to 15,000 individuals. It is associated with a high mortality rate, which can be as high as 70% in untreated patients in 10 years [1]. LQTS is caused due to mutations in sodium and potassium channel genes leading to a QT prolongation. LQTS is diagnosed in an individual after a cardiac event eg. syncope, cardiac arrest (QTc>440 msec in males and QTc>460 msec in females) in addition

Fig 1. Electrocardiogram of a normal healthy individual and a LQTS patient showing a prolonged QTc..

ECG of a healthy individual

QTc=417ms

ECG of a patient with Long QT syndrome

QTc=564ms
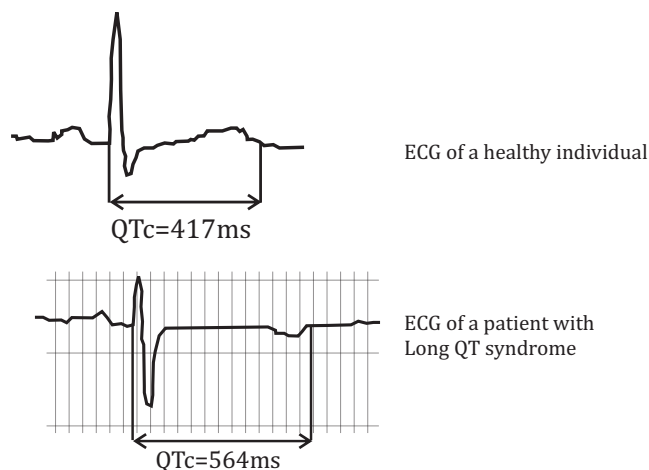
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to a family history of sudden cardiac deaths (SCD). Although sudden cardiac death usually occurs in symptomatic patients, it occurs with the first episode of syncope in about 30 percent of the patients. This occurrence emphasizes the importance of diagnosing LQTS in the presymptomatic period of SCD.

After the first description of LQTS in 1957, efforts have been made to propose diagnostic criteria including ECG and genetic testing [2,3]. Though genetic and molecular biology techniques have offered a realistic potential for the identification of the disease genes and disease-causing mutations, it is still dependent for its success on the availability of well-developed clinical pedigree and family history. This paper attempts to review all the achievements made in identifying the genetic and functional factors responsible for the etiology of Long QT syndrome. A complete review of the genes implicated in LQTS, their mutations and their functional studies, and the additional studies required for a better understanding of this syndrome is being dealt.

2.Classification and epidemiology

Congenital LQTS and Acquired LQTS are the two types identified in LQTS.

2.1. Congenital long QT syndrome (cLQTS), a potentially fatal, heritable cardiac channelopathy characterized by delayed cardiac repolarization, prolonged QT interval (>440 msec), and lethal ventricular arrhythmias, resulting in significant risk of syncope, seizures, and sudden cardiac death [4].

LQTS is the characteristic of certain rare genetic disorders comprising of:

i) Autosomal dominant disorder with normal hearing and characterized by QT prolongation, T-wave abnormalities on the ECG and the ventricular tachycardia torsade de pointes (TdP) called the Romano-Ward syndrome (RW syndrome) with an incidence estimated to be about 1 in 5000 to 10000 [1]. Mutations in the *ANK2, KCNE1, KCNE2, KCNH2, KCNQ1 and SCN5A* genes are reported to cause Romano-Ward syndrome.

ii) The second is the much rarer autosomal recessive syndrome associated with congenital sensorineural deafness with prolonged QTc called the Jervell and Lange-Nielsen (JLN) syndrome [5] with a prevalence of about 1.6 6 per million in children aged 4 to 15 years without an apparent ethnic or geographic predilection [1]. This condition has a higher prevalence in Denmark, affecting 1 in 200,000 live births. JLN type-1 is caused by homozygous mutations in *KCNQ1* while JLN type-2 is due to homozygous mutations in *KCNE1.*

iii) Anderson-Tawil syndrome is also a rare autosomal dominant disorder associated with micrognathia, low-set ears and clinodactyly apart from ventricular arrhythmia and symptoms of long QT syndrome. Two types of Andersen-Tawil syndrome are distinguished based on mutations in the *KCNJ2* gene (type I) and type II being idiopathic [6,7]. The incidence of the disorder is still unknown but, around 100 suspects have been reported worldwide.

iv) Timothy Syndrome, named in honor of Dr. Katherine W. Timothy who has diagnosed the condition, is a rare autosomal dominant disorder that affects the heart, digits (fingers and toes), and the nervous system. It is characterized by a long QT syndrome. The two forms are type 1 (classic) and type 2, a rare form caused by mutations in an isoform of the *CACNA1C* gene. Type 1 of the Timothy syndrome is characterized by cutaneous syndactyly and distinctive facial features such as a flattened nasal

bridge, low-set ears, a small upper jaw, and a thin upper lip. Children with this condition have small, misplaced teeth and frequent cavities (dental caries). Additional signs and symptoms of Timothy syndrome include baldness at birth, frequent infections, episodes of low blood sugar (hypoglycemia), and an abnormally low body temperature (hypothermia). Type 2, or the atypical type, causes a more severe form of long QT syndrome and a greater risk of arrhythmia and sudden death. Unlike the classic type, the atypical type does not appear to cause webbing of the fingers or toes. It is a very rare syndrome as fewer than 20 cases reported worldwide. The classic type appears to be more common than the atypical type, which has been identified in only two individuals [8].

Only 4 cases have been reported so far from India, describing congenital long QT syndrome and JLN syndrome in children indicating a desperate need to spread awareness about the disease in developing countries [9,10,11,12]. In Finland, 1 out of 250 individuals is known to carry a LQTS founder mutation which is the highest documented prevalence of LQTS mutations [13].

Table1. Classification of LQTS based on mutated genes, their loci and the ion-current affected

Type of LQTS	Chromosomal Locus	Mutated Gene	Ion Current Affected
LQT1 (Romanoward syndrome)	11p15.5	*KVLQT1,* or *KCNQ1* (heterozygotes)	Potassium (IKs)
JLN syndrome-1	11p15.5	*KVLQT1,* or *KCNQ1* (homozygotes)	Potassium (IKs)
LQT2 (Romanoward syndrome)	7q35-36	*HERG, KCNH2*	Potassium (IKr)
LQT3 (Romanoward syndrome)	3p21-24	*SCN5A*	Sodium (INa)
LQT4 (Romanoward syndrome)	4q25-27	*ANK2, ANKB*	Sodium, potassium and calcium
LQT5 (Romanoward syndrome)	21q22.1-22.2	*KCNE1* (heterozygotes)	Potassium (IKs)
JLN syndrome-2		*KCNE1* (homozygotes)	Potassium (IKs)
LQT6 (Romanoward syndrome)	21q22.1-22.2	*MiRP1, KCNE2*	Potassium (IKr)
LQT7 (Anderson-Tawil syndrome)	17q23.1-q24.2	*KCNJ2*	Potassium (IK1)
LQT8 (Timothy syndrome)	12q13.3	*CACNA1C*	Calcium (ICa-Lalpha)
LQT9	3p25.3	*CAV3*	Sodium (INa)
LQT10	11q23.3	*SCN4B*	Sodium (INa)
LQT11	7q21-q22	*AKAP9*	Potassium (IKs)
LQT12		*SNTAI*	Sodium (INa)

The classification of LQTS based on their genetic background revealed twelve types of LQTS with two types of Jervel-Lange Neilsen (JLN) syndrome, Timothy syndrome, Anderson Syndrome and Romano-Ward syndrome (Table I).

2.2. Acquired long QT syndrome (aLQTS) describes pathologic QT interval prolongation, generally to greater than 550-600 ms, upon exposure to QT-prolonging antiarrhythmics, antihistamines, gastrointestinal agents, antipsychotics and urologic agents (for example Disopyramide, Dofetilide, Ibutilide, Procainamide, Quinidine, Sotalol, Amiodarone, Arsenic trioxide, Erythromycin, Droperidol, Haloperidol, Thioridazine, Methadone) [14] or to an environmental stressor. When QT intervals are markedly prolonged in this fashion, torsade de pointes can be self-limited or can degenerate to fatal arrhythmias such as ventricular fibrillation. It is the potential for torsade de pointes and sudden cardiac death that has generated much attention to acquired long QT syndrome. It is also observed that on a genetic background, the environment stressors can influence specific clinical phenotypes [14].

3. Relative frequency of LQTS genotypes

About 95% of LQTS cases are due to mutations in the potassium channel genes. The LQT1/LQT5 combination appears to account for about 60%, LQT2/LQT6 about 35%, with mutations in LQT5 and LQT 6 genes alone contributing to 1 %. The sodium channel gene LQT3 accounts for about 4-5% of the cases, Jervell Lange-Nielsen-1 less than 1 % with the LQT4 genotype being the rarest [15].

4. Ethnicity

The genetic epidemiology of LQTS can vary with subpopulation depending on the allele/s. Many polymorphisms, such as HERG (P44BR and A915V) in Asians, and SCN5A (S1102Y) in African Americans, show racial-ethnic specificity. KCNQ1 (P448R) was discovered to be an ethnic-specific polymorphism present in approximately 14% - 20% of the Asian population [5]. *KCNE2* variant, which results in Q9E is a relatively common polymorphism, occurring in 3.2% of Blacks [14]. However, the susceptible alleles in the Indian population are yet to be identified.

5.Diagnosis

Standardized major and minor diagnostic criteria for LQTS have been proposed by Schwartz et al,(1993) [2] encompassing Electrocardiogram, family history and a thorough clinical investigation of the proband with LQTS (Table II) [2]. According to the diagnostic criteria, the presence of either two major criteria or one major and two minor criteria are required to confirm LQTS.

Table 2. Criteria for diagnosing LQTS by Schwartz et al:

Major criteria	Minor criteria
Prolonged QT interval (QTC > 440 msec)	Congenital deafness
Stress-induced syncope	Episodes of T-wave alternans
Family members with LQTS	Low heart-rate (in children) Abnormal ventricular repolarization

5.1.Genotype-specific ECG patterns in long QT syndrome

Different types of the long QT syndrome (LQTS) are associated with distinct ECG manifestations, which relate to the type and magnitude of ion channel dysfunction. The QTc duration does not differentiate LQTS types, therefore other static and dynamic ECG parameters reflecting changes in T wave morphology are used to describe phenotypic expression of different LQTS genotypes. For example, LQTl carriers usually have broad-based T waves, LQT2 carriers show low-amplitude T waves with high incidence of notches, and LQT3 carriers frequently have extended ST segment with relatively narrow peaked T wave [16].

6.Molecular pathogenesis

Genetic investigations demonstrate that all known LQTS susceptibility genes encode cardiac ion channels or for proteins, thought to participate in localization of sodium or calcium channels to the sarcolemma and mutations, results in ion channel dysfunction caused by altered localization [4].

Congenital LQTS is caused by mutations in genes encoding for cardiac ion channel proteins that cause abnormal ion channel kinetics. Loss-of-function of the potassium channel genes in LQT1, LQT2, LQT5, LQT 6, JLN 1, and JLN2 and gain-of-function of a sodium channel gene in LQT3 overcharges a myocardial cell with positive ions [17].

Whilst drug intake is the trigger of acquired LQTS, other factors may also contribute to an increased risk of developing TdP in individual cases, including female gender, electrolyte disturbances, other heart disease, and underlying mutations or functional polymorphisms in one of the cLQTS disease genes [18].

6.1. Role of genetic variants in LQTS

LQTS is caused by mutations in the genes for cardiac potassium, sodium, or calcium ion channels. Genes found to be responsible for LQTS are described below:

KCNQl and KCNE1: The products of these two genes coassemble to form the slowly activating delayed rectifier potassium channel IKs. *KCNQl* encodes for the larger alpha-subunit and *KCNE1* the smaller beta-subunit of the IKs protein.*KCNQl* consists of 16 exons, spanning 400kb, has relatively small amino and carboxy termini, and encodes a protein of 676 amino acids. *KCNE1* has just 3 exons, spanning approximately 40kb and encoding a protein of 129 amino acids [15]. *KCNE1* reportedly encodes the mink protein [19]. It is predicted to have a single transmembrane spanning domain with small intra and extracellular components [15]. IsK, an apparent potassium channel regulatory subunit encoded by the *KCNE1* gene on chromosome 21, has recently been shown to coassemble with both K$_v$LQT1 and HERG. This relationship makes *KCNE1* an attractive candidate gene for LQTS [20].

Since, both *KCNQ1* and *KCNE1* encode for potassium channel proteins, mutations in either gene reduce the IKs current. At least 78, mostly missense mutations, have been reported in *KCNQ1* primarily occurring in the membrane spanning domains and the pore region. Only a few mutations of *KCNE1* have been identified [15]. Both *KCNQ1* and minK proteins assemble to form the slowly activating component of the delayed rectifier potassium current (IKs) present in heart and inner ear, and mutations of either of them may be the underlying molecular pathology in the JLNS when present in a homozygous form [21]. Mutations in *KCNQ1* cause LQT1 and JLN1 while that of *KCNE1* cause LQT5 and JLN2.

KCNH2: The gene products of *KCNH2* and *KCNE2* genes coassemble to form the rapidly activating delayed rectifier potassium channel IKr. *KCNH2* gene encodes the alpha-subunit of the voltage-gated potassium channel. Functional KCNH2 channels are tetrameric proteins formed by a coassembly of 4 alpha-subunits. Each subunit contains 6-transmembrane-spanning domains (S1-S6). The region between S5 and S6 forms the ion-selective pore of the ion-channel whereas, the N-terminus contains an eukaryotic Per-Arnt-Sim(PAS) domain [22]. *KCNH2* consists of 16 exons, spans 55kb, and encodes a protein of 1159 amino acids. It has a predicted topology similar to *KCNQ1*, but has more extensive amino and carboxyl termini. Mutations in this gene reduce the IKr current resulting in LQT2 phenotype. More than 81 mutations of the gene have been thus far identified. Most are in the spanning domains and the pore region, but unlike KCNQ1 many mutations are also reported in the amino and carboxyl termini [15]. The frameshift and nonsense mutations of LQT2 bearing premature termination codons (PTC) can destabilize mRNA transcripts by a mechanism known as nonsense-mediated mRNA decay(NMD) resulting in decreased abundance of mutant mRNA transcripts [23].

KCNE2: As mentioned above, the gene product of *KCNE2* coassembles with the gene products of *KCNH2* to form the rapidly activating delayed rectifier potassium channel IKr. *KCNE2* encodes a protein of 127 amino acids [15], *KCNE2* is a small protein similar in size and function to *KCNE1*, the potassium channel protein. *KCNE2* encodes MiRP1 (Mink-related peptide 1) [24]. It is conceivable that coexpression of *KCNE2* might influence the functional behavior of the *KCNH2* mutant but, the physiological relevance would be uncertain [25]. At least three missense mutations have been identified in this gene [15]. Mutations in *KCNE2* cause LQT6.

HERG: This human ether-a-go-go related gene encodes the pore-forming subunit of the rapidly activating, delayed rectifier current (Ikr), plays an important role in the repolarization of the cardiac action potential. *HERG* gene is localized to chromosome 7q35-36. Mutations in this gene are one of the most common causes for congenital LQT-2. Various mechanisms underlying the dysfunction of the *HERG* channel in these mutants have been suggested, including abnormal channel processing, generation of nonfunctional channels and altered channel gating. From the primary *HERG* structure point of view, there are several sites where mutations have occurred that could result in *HERG* channel dysfunction. Mutations in the N-terminus usually accelerate *HERG* channel deactivation, while mutations in the pore region affect *HERG* channel inactivation or ion selectivity. Mutations in LQT-2 have been mapped to the C-terminus which contains regions essential for Ikr function. Interaction of *HERG* channels with 14-3-3 protein family has been shown to alter the effect of beta-adrenergic signaling. This may provide a mechanism for plasticity in cardiac electrophysiological response to stress. *HERG* associates with 14-3-3 ε and potentiates the cAMP/PKA effect. 14-3-3 accelerates and enhances *HERG* activation, an effect that requires phosphorylation of *HERG* at S283 and S1137. Mutations at any of these two sites can lead to inefficient interaction of *HERG* channel with 14-3-3, which may weaken cAMP/PKA effects on *HERG,* leading to an increased risk for fatal cardiac arrhythmia during stress [26].

SCN5A: The cardiac Na+ channel gene *SCN5A* is the LQT3 gene. *SCN5A* appears to encode a complete sodium ion channel with 28 exons and 2016 amino acids, spanning 80kb. It encodes the alpha subunit of the human cardiac voltage-gated sodium channel hNav1.5 [27], with four homologous domains, DI-DIV, each with six transmembrane spanning domains, a voltage sensor in the S4 domain, and a pore region between the S5 and S6 domains. At least thirteen mutations of this gene have been described, making up approximately 6% of reported LQTS mutations [15]. These LQT3 mutations produce a gain of function, most of them impairing fast inactivation, resulting in the decay of the current slowly or incompletely, thus leading to QT interval prolongation [27]. Mutations in *SCN5A* may also result in a complex phenotype representing combinations of LQTS, Brugada syndrome and conduction system disease. *SCN5A* inheritance is autosomal dominant with incomplete penetrance and a male predominance [23].

ANK2: Ankyrins are a family of adapter proteins that link integral membrane proteins to spectrin-based cytoskeleton, encoded by the *ank2.* Three members of this family of ankyrins have been identified as erythrocyte ankyrin (ankyrin-1 or ankyrin-R), brain ankyrin (ankyrin-2 or ankyrin-B), and general or epithelial ankyrin (ankyrin-3 or ankyrin-G). The ankyrin-B has three major isoforms with molecular weights of 440 kDa, 220 kDa, and 150 kDa, generated by alternative splicing. The major form of ankyrin-B in cardiac cells is 220 kDa. Ankyrins typically contain three functional domains that consist of the membrane binding domain, the spectrin binding domain, and the regulatory domain. Ankyrins bind to several ion channel proteins, such as the anion exchanger (C1-/HC03- exchanger), Na+-K+-ATPase, voltage-sensitive sodium channel (INO), and Na+/Ca2+ exchanger (NCX or INa-Ca), and calcium release channels including those mediated by the receptors for inositol trisphosphate (IP3) or ryanodine. Due to these functions, any mutation in this gene can lead to a dysfunction of the ion channel, leading to LQT4 type [17].

KCNJ2: It is a potassium channel encoding gene located on chromosome 17q23.1-q24.2 with a gene size of about 10kb and 2 exons. *KCNJ2* encodes the inward rectifier Kir2.1, a critical alpha-subunit of cardiac inward potassium rectifier current. Most *KCNJ2* mutations cause loss of function and dominant-negative suppression of the Kir2.1 channel function [28,29]. Mutations in this gene leads to LQT7 (Andersen syndrome).

CACNA1C: It is a voltage-gated calcium channel encoding gene localized to chromosome 12q13.3. Mutations in the *CACNA1C* gene change the structure of CaV1.2 channels, as a result the altered channels stay open for a much longer duration, allowing the calcium ions inflow to the cells abnormally. The resulting overload of calcium ions within cardiac muscle cells changes the rhythm of the heart beats causing arrhythmia leading to LQT8 (Timothy syndrome) [30].

CAV3: Caveolae are 50 to 100nm omega-shaped microdomains of the plasmalemma, particularly abundant in cells of the cardiovascular system, including endothelial cells, smooth muscle cells, macrophages, cardiomyocytes, and fibroblasts. Caveolae are involved in vesicular trafficking and serve as a platform to organize and regulate a variety of signal transducting pathways; apart from maintaining cholesterol homeostasis. 3 isoforms of caveolins, the principal proteins of caveolae, are encoded by separate genes. Although caveolin-1 *(CAV1)* and caveolin-2 *(CAV2)* are coexpressed in most cell types, *CAV3*-encoded caveolin-3 is specifically expressed in cardiomyocytes and skeletal muscle. *CAV3* gene has 2 exons with 456bp coding sequence. Some cardiac ion channels have been specifically localized to caveolae such as the *SCN5A*-encoded voltage-gated Na+ channel (hNavl.5), the voltage-dependent K channel (Kv1.5), the sodium-calcium exchanger, and the L-type Ca^{2}+ channel. In the

other signaling molecules have been found in caveolae, including the beta-2-adrenergic receptor and associated proteins of the G-protein/adenylyl cyclase/protein kinase A pathway. Therefore, caveolae can serve both to compartmentalize and regulate ion channel function and cell signaling factors and any genetic variation can cause an ion-channel dysfunction especially LQT9 [4].

SCN4B: This voltage-gated sodium channel beta subunit gene is located on chromosome 11q23.3 involving about 19.5kb DNA with 5 exons. Since, it codes for the sodium channel subunit, studies show that mutations in this gene lead to LQT10 [31].

AKAP9: This potassium channel-encoding gene is located on chromosome position 7q21-q22 and encodes the *AKAP9.* It is about 170kb in size with 51 exons. *AKAP9* (A-kinase anchoring protein 9) determines the subcellular localization of protein kinase A and the phosphorylation of the potassium channel alpha-subunit KCNQ1 to which it assembles [32]. Yotiao, a splice variant of *AKAP9* gene product is localized to the plasma membrane. Disruption of the KCNQ1 association with Yatiao during signaling cascade leads to LQTS11 [33,34].

SNTA1: This cytoskeletal protein syntrophin-alpha-1 *(SNTA1)*, encoded by *SNTA1,* interacts with the cardiac sodium channel hNav1.5. It is hypothesized that this gene might cause phenotypic LQTS12 in patients with genotypically normal hNav1.5 by secondarily disturbing sodium channel function [32]. It is located on chromosome 20q11.2 region.

7. Functional analysis carried out in LQTS

One of the animal model for the study of torsade de pointes is anesthetized rabbits, in which drugs producing arrhythmia in patients regularly produce torsade de pointes but only if infused after pretreatment with the beta-blocker methoxamine [14]. Another animal model is dogs in which striking action potential ability on drug exposure separates arrhythmia-prone from arrhythmia-resistant animals, suggesting that indices of repolarization beyond simple measurement of the QT interval may be useful in gauging risk [14]. According to a study by Barajas-Martinez et al, 2009 [35] using female dogs, the larger dispersion of INa (sodium current) amplitude within the female cardiac ventricle may contribute to the higher risk of arrhythmias in females. In Zebrafish, genetic mapping and direct sequencing could identify the affected gene in arrhythmia as *KCNH2,* which encodes the channel responsible for the rapidly activating delayed rectifier potassium current (IKr) [36]. Mouse models have also been reported to identify expression and activity of the sodium current potential [37], *KCNE1* [38].

Chinese pedigree with LQT5 related to a *KCNE1* gene mutation and its functional consequence was evaluated in *Xenopus* oocytes [39] wherein gating of IsK channels were expressed in *Xenopus* oocytes [40]. In various studies, dHPLC (denaturing high performance liquid chromatography) analysis has been employed to detect mutations in *KCNQ1, KCNH2, HERG, KCNE1and KCNE2,* genes thus, proving it to be an efficient method for mutation detection in LQTS [41,42]. Functional analysis or expression studies of some genes thought to cause LQTS was carried out using viral vectors and cardiomyocyte cell lines, which helps in dissecting the molecular identity of various native ionic currents [43].

8. Discussion

LQTS indeed represents a paradigm for the understanding of sudden cardiac death in more common cardiac diseases. It is regarded as the "Rosetta Stone" for studying the genetic basis of ventricular arrhythmogenesis [44]. The present review describes various genes implicated in LQTS and the mutations responsible for LQTS. Attempts have been made to identify the implications of drugs in acquired LQTS using functional analyses. Additional new genes and varied genetic mechanisms need to be unraveled; modifier genes that explain the variable ventricular repolarization duration and/or the variable severity of clinical manifestations in individuals with the same mutation are yet to be identified. Gene-specific and mutation-specific therapy is presently in its infancy, and the brain-heart connection with regard to emotional triggers of cardiac events needs more neurophysiologically based investigations.

An important point to be observed is that the genes implicated in congenital LQTS and acquired LQTS are the same and mutations have been reported in these genes in acquired LQTS patients [18]. But, acquired LQTS is caused only when it is triggered by a drug whereas the same gene causes congenital LQTS without a trigger. Studies would be required to find the factors which seem to silence genetic mutation in acquired LQTS patients until it is triggered by specific drugs.

A *KCNQ1* mutation has been reported which occurs in the context of a CpG dinucleotide [45] which are supposed to be the hotspots of epigenetic modifications. This suggests a requirement to carry out studies to find the involvement of epigenetic modifications in the etiology of LQTS. Genetic variants in LQTS genes are responsible for sudden infant death syndrome [46]. Thus, an ECG at birth could identify infants at risk of LQTS. Efforts are required to explore the possibility of using stem cell therapy for the treatment of Long QT Syndrome.

Studies point to the increasingly well-recognized role of ethnicity in polymorphism frequencies and in modulation of important physiologic and drug-response phenotypes [14]. Studies examining the genetic determinants of these endpoints must include a consideration of ethnicity. Thus, estimating the prevalence of LQTS at the population level needs to be attempted.

A detailed genetic analysis can lead to a thorough functional analysis which could include an RNA analysis, microarray and a transgenic mouse model. Such studies may seek to identify the expression pattern of genes responsible for LQTS [47]. Genetic screening can be established with respect to a particular ethnic group which in turn can be used in the Risk Stratification of the unaffected members of the same family [48].

9. Conclusion

In conclusion, the genetic and functional aspects of Long QT Syndrome require a thorough, in depth analysis with respect to each ethnic group and each family in particular. Such information is required for the proper treatment, risk stratification and proper diagnosis of this fatal disorder in addition to focusing on personalized medicine. Efforts can be possibly made to find the epidemiological variables responsible for the etiology of the disease apart from identifying the possible mode of inheritance. Genetic screening has been carried out in populations like Asians,

Blacks and Whites but race specific screening can be carried out in populations like Indian population considering their vast racial and ethnic diversity. Genotype-phenotype correlation can be established with respect to each race and ethnic group as genetic diversity in every population seems to influence the disease phenotype.

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