



Congenital long QT syndrome: an update and present perspective in Saudi Arabia

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Primary cardiac arrhythmias are often caused by defects, predominantly in the genes responsible for generation of cardiac electrical potential, i.e., cardiac rhythm generation. Due to the variability in underlying genetic defects, type, and location of the mutations and putative modifiers, clinical phenotypes could be moderate to severe, even absent in many individuals. Clinical presentation and severity could be quite variable, syncope, or sudden cardiac death could also be the first and the only manifestation in a patient who had previously no symptoms at all. Despite usual familial occurrence of such cardiac arrhythmias, disease causal genetic defects could also be *de novo* in significant number of patients. Long QT syndrome (LQTS) is the most eloquently investigated primary cardiac rhythm disorder. A genetic defect can be identified in ~70% of definitive LQTS patients, followed by Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) and Brugada syndrome (BrS), where a genetic defect is found in <40% cases. In addition to these widely investigated hereditary arrhythmia syndromes, there remain many other relatively less common arrhythmia syndromes, where researchers also have unraveled the genetic etiology, e.g., short QT syndrome (SQTs), sick sinus syndrome (SSS), cardiac conduction defect (CCD), idiopathic ventricular fibrillation (IVF), early repolarization syndrome (ERS). There exist also various other ill-defined primary cardiac rhythm disorders with strong genetic and familial predisposition. In the present review we will focus on the genetic basis of LQTS and its clinical management. We will also discuss the presently available genetic insight in this context from Saudi Arabia.

Keywords: arrhythmia, long QT syndrome, genetics, consanguinity

INTRODUCTION

Familial or hereditary cardiac arrhythmias comprise significant percentages of arrhythmias and also causal to sudden cardiac death (SCD) (1, 2). During the last two decades, scientists and clinicians have provided enormous effort to unravel the intricate and complex mechanisms of congenital familial arrhythmias (1–8). To understand the mechanism of arrhythmogenesis, we need to know the basics of cardiac cellular structure and their electrophysiological properties. Cardiac myocytes are the major functioning cells in the heart and they are extensively coupled so that impulses propagate rapidly and uniformly. Cardiomyocytes are separated from each other by a specialized boundary called the intercalated disk; gap junction proteins, cardiac desmosomes, and ion channels are located in the intercalated disk (9). Gap junctions consist of tightly packed connexins which permit intercellular exchange of small molecules and also permit to flow the excitatory currents from one cell to its neighboring cell. Desmosomes along with the adherens junctions are responsible for the mechanical attachments of individual cardiomyocytes. All these components in the intercalated disks are sequentially segregated

and each component exerts its unique function; disruption of the one component affects the function of other components, which predisposes the heart to develop arrhythmias (9–11). Cardiac ion channels are pore-forming protein complexes that provide voltage gated and intricately coordinated inward and outward movement of ionic currents across the cell membranes, essential for cardiac rhythm generation and propagation. Long QT syndrome (LQTS), short QT syndrome (SQTs), sick sinus syndrome (SSS), cardiac conduction defect (CCD), BrS, catecholaminergic polymorphic ventricular tachycardia (CPVT), early repolarization syndrome (ERS), and familial Atrial Fibrillation (AF) are the presently known cardiac channelopathies, which could occur due to a single or multiple defect in the genes linked to cardiac rhythm generation and propagation.

In this review, we will describe exclusively on LQTS linked arrhythmias, its pathophysiology and presently available clinical management. We have pioneered in elucidating genetic pathology in familial cardiac arrhythmias in Saudi Arabia (1, 12–14), we are still conducting cardiogenetic investigations in Saudi Arabia, at the end of this review, we will discuss the presently available knowledge

about the genetic and clinical findings obtained from several Saudi Arabian families with history of syncope and SCD. We will also add the recently published data on LQTS from a team at King Faisal Specialist Hospital and Research Centre, Riyadh (15).

LONG QT SYNDROME

Congenital LQTS is an inherited disorder defined by prolongation of the QT interval on electrocardiogram (ECG). Patients with all forms of LQTS are predisposed to the ventricular tachyarrhythmia, torsades de pointes (TdP) leading to recurrent syncope, or SCD. In many instances, syncope or sudden death could be the first and the only manifestation. LQTS affects an estimated 1 in 2,000 people worldwide (16). The hallmark of the LQTS is prolongation of the QT interval on ECG (corrected for heart rate, i.e., QTc). Normal values of QTc are 440 ms in males and 450 ms in females. In children, age and gender dependent values are relevant. Recent consensus recommendation for LQTS diagnosis are the following (17, 18):

1. LQTS is diagnosed:
 - a. In the presence of an LQTS risk score ≥ 3.5 in the absence of a secondary cause for QT prolongation and/or
 - b. In the presence of an unequivocally pathogenic mutation in one of the LQTS genes or
 - c. In the presence of a QT interval corrected for heart rate using Bazett's formula (QTc) ≥ 500 ms in repeated 12-lead electrocardiogram and in the absence of a secondary cause for QT prolongation.
2. LQTS can be diagnosed in the presence of a QTc between 480 and 499 ms in repeated 12-lead ECGs in a patient with unexplained syncope in the absence of a secondary cause for QT prolongation and in the absence of a pathogenic mutation.

Patients with QTc duration ≥ 500 ms had a significantly higher cumulative probability of experiencing their first syncope as compared to patients with QTc duration < 500 ms from birth through age 20 years (19). But, patients who have experienced 2, 3, and 4 syncope episodes, the risk of a subsequent syncope episode was virtually identical between patients who had narrow or prolonged QTc duration (19). The molecular basis of LQTS is heterogeneous and to date, mutations in 13 different genes have been described causal to LQTS (1–8, 19, 20). A genetic defect is usually found in 70% of the LQTS patients in one of these 13 genes (1–8, 19, 20). Among the presently known 13 different types of LQTS, the most common are LQTS1, LQTS2, and LQTS3, due to defects in cardiac ion channel genes, *KCNQ1*, *KCNH2*, and *SCN5A*, respectively. Ninety percent of all the LQTS causal mutations are found in these three genes (1–8, 19, 20). Mutations in the remaining 10 genes are rare and comprise only $\sim 10\%$ of all the presently known LQTS mutations.

Long QT syndrome is usually an autosomal dominant disease, but, occasionally, multiple mutations in a single gene or in different genes could be found in 5–10% of the patients with LQTS (21, 22). Patients with multiple mutations could exhibit a longer QTc compared with those with a single mutation and such patients are also at ~ 3.5 -fold increased risk for life-threatening cardiac events (21, 22)

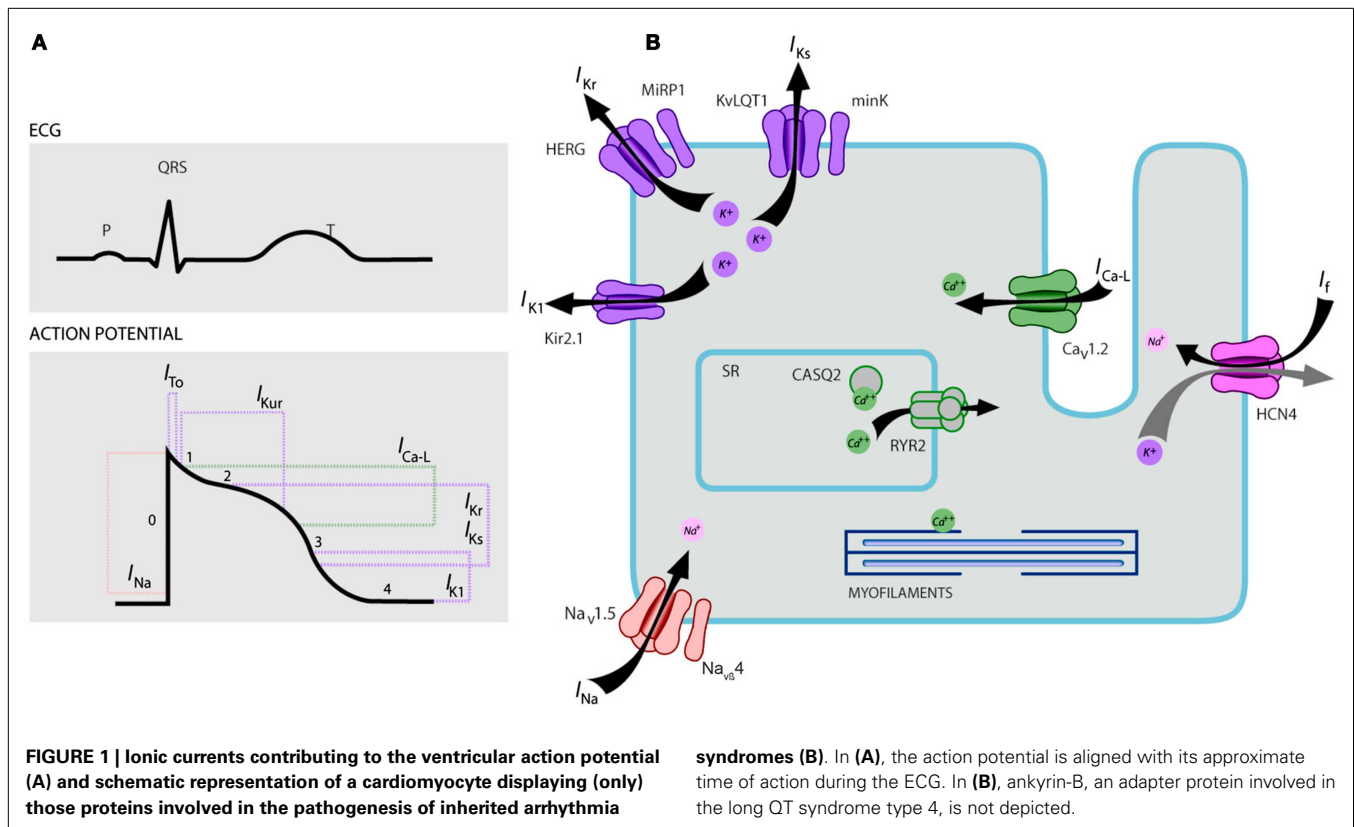
LQTS1

Mutations in the *KCNQ1* gene are the commonest form of all LQTS and referred as LQTS type 1 (LQTS1). Fifty percent of all the LQTS causal mutations are found in the *KCNQ1* gene (20). KvLQT1 (also called Kv7.1) is a protein made by the *KCNQ1* gene and the protein forms tetramers in the endoplasmic reticulum inside the cells, which putatively co-assembles with the protein minK (encoded by *KCNE1*) and are then transported to the plasma membrane of the cardiac myocytes, where they mediate a slowly activating current which accelerates the repolarization of action potential in cardiac tissues, this current is known as IKs (**Figure 1**). LQTS1 causal *KCNQ1* mutations are mostly missense mutations and in rare instances they could be frameshift mutations in the C-terminal region (23). Cardiac arrhythmia in *KCNQ1* mutation carriers are triggered by adrenergic drives, e.g., emotional stress, physical exertion, diving, swimming (24–26). Patients with mutations at the transmembrane domains of KvLQT1 are at higher risk of LQTS-related cardiac events and have greater sensitivity to sympathetic stimulation (26, 27). Patients with missense mutations are at increased risk compared to patients with non-sense or truncating mutations (27, 28). Variation in the 3'-UTR in the *KCNQ1* gene also affects the arrhythmia susceptibility significantly, presumably by impacting on the expression of the gene (29). Patients with arrhythmias due to *KCNQ1* mutations respond quite well to β -blockers, but, some patients could still be less responsive or even resistant to this medication. In a recent article, Barsheshet et al. (30) claimed that the patients with mutations outside the cytoplasmic loop (c-loop) region in the KvLQT1 are less responsive to β -blockers.

Homozygous or compound heterozygous mutations in the *KCNQ1* gene, which could cause the recessive form of the disease, Jervell and Lange-Nielsen syndrome (JLNS), type 1 (31), are quite rare. JLNS patients suffer from severe cardiac arrhythmias and deafness as well (31, 32). Patients with *KCNQ1* mutations causal to JLNS usually do not have any functional IKs (28, 31–33). It is possible that some patients could have no deafness despite having homozygous or compound heterozygous mutations in *KCNQ1*, such cases are referred as autosomal recessive LQTS1 (13, 32). In these patients, small amount of functional IKs current ($< 10\%$ of total IKs) could still be present, which maintains the hearing function, but, their cardiac rhythm defects are equally severe like in JLNS patients (13, 32).

LQTS2

This type of LQTS is equally prevalent as LQTS1, accounting for 35–40% of LQTS patients with a detectable mutation (1, 20, 24, 25). *KCNH2* encodes for the HERG protein (Kv11.1), which is the α -subunit of the rapidly activating delayed rectifier K^+ current (IKr). Pathogenic mutations in this gene that reduces the Kv11.1 channel function prolongs duration of the QT interval (**Figure 1**), and are causal to LQTS2. Twenty-nine percent of the syncopal attacks in LQTS2 occur during rest/sleep and only 13% of the syncopal attacks were reported to occur during exercise (25, 34). Sudden startling noises, e.g., alarm clock rings, doorbells, telephone rings, typically trigger syncopal attacks in these patients (24, 34). Patients with mutations in the pore-forming region of the Kv11.1 (encoded by *KCNH2* gene) are susceptible to high risk



for arrhythmia-related cardiac events compared with patients with non-pore region mutations (35). In neonates, 2:1 Atrioventricular (AV) block is preferentially associated with *KCNH2* mutations (36). Complete AV block complicated by LQTS were also found in 17% of adult patients with a mutation in the *KCNH2* gene (37). Homozygous mutations in *KCNH2* are rare and when present, patients suffer from a severe form of LQTS, with 2:1 AV block and severe ventricular arrhythmias, during intrauterine stages as well as after birth (11, 38–40). In addition to the numerous mutations described in LQTS2 pathology, common polymorphic variants in the *KCNH2* gene could also modulate the disease severity. An intriguing example is K897T polymorphism (SNP) in *KCNH2*, which is present in 33% of the general population (41). K897T was reported to exacerbate the pathogenicity of the *KCNH2* mutations (42, 43).

LQTS3

Nav1.5 is the pore-forming α -subunit of the voltage-dependent cardiac Na^+ channel, it is an integral membrane protein encoded by the *SCN5A* gene and is involved in the initiation and conduction of cardiac action potentials. Cardiac Na^+ channels are composed of a pore-forming α -subunit (encoded by *SCN5A*) and one or more auxiliary β -subunits.

LQTS3 is caused by gain of function mutations that disrupt fast inactivation of the α -subunit (Figure 1) and a mutation in the *SCN5A* gene have been described in <10% of all LQTS patients with a mutation (1, 20, 24). LQTS3 patients experience the majority (39%) of their cardiac events during sleep/rest (25), and about ~13% of the events were reported to occur during exercise (25).

In several instances, a single *SCN5A* mutation was shown to exert two or even three distinct phenotypes of arrhythmias in the same family, e.g., LQTS, BrS, or CCD (44–47). Male patients with a LQTS3 mutation could develop symptoms much earlier than the female patients (48). Both heterozygous and homozygous *SCN5A* mutations have been described in LQTS3 with functional 2:1 AV block (49). We have recently found an Iranian family with the 1507_1509delQKP mutation in multiple family members, where patients had combined LQTS and CCD (data not shown). This mutation has been reported in patients from other countries as well, which suggests that this is a recurrent and hot spot mutation [(49, 50) and our unpublished data]. Mutations with such a loss-and-gain-of-function characteristics during different phases of the action potential were also reported in 1493delK and 1795insD mutations (44, 51).

Occasionally, a SNP could also exert pathogenic effect on its carriers. S1103Y is a common variant in the *SCN5A* gene, present in 13% of the African Americans (52). Carriers with this variant are at increased risk of arrhythmias and sudden infant death syndrome (SIDS) (52).

LQTS4

LQTS4 represents the first non-channel form of LQTS. A mutation in the *ANK2*, an adapter protein, leads to intracellular calcium overload which contributes to the LQTS4 (53, 54). In addition to QT prolongation, patients with this syndrome could have sinus bradycardia, paroxysmal AF, and CPVT (54). Pathogenic effect of the *ANK2* mutations could be moderate to severe and the clinical expressions depend on the severity of the mutation.

LQTS5

Mutations in *KCNE1* are associated with the LQTS5 (Figure 1) (55, 56). Heterozygous *KCNE1* mutations reduce IKs by exerting a dominant negative effect on its accompanying normal allele, and lead to delayed cardiac repolarization (Figure 1), responsible for increased risk of arrhythmias (6). Patients with homozygous *KCNE1* mutations suffer from JLNS (type 2) (57, 58).

D85N is a polymorphism in the *KCNE1* gene, present in 0.7–1% of the general population (41). In a study by Nishio et al. (59), D85N polymorphism was more frequently found in the LQTS patients, making it a risk genotype in LQTS pathology (potentially only in the Asian population). In Europe, D85N was reported in 5% of acquired LQTS (aLQTS) patients (in a cohort of 32 patients), who had experienced TdP (60).

LQTS6

KCNE2 gene encodes for MinK-related peptide 1 (MiRP1), a putative β -subunit of the cardiac potassium channel IKr (Figure 1). Mutations in *KCNE2* gene could also lead to defects in the rapidly activating component of the delayed rectifier potassium current (IKr), pathologic basis of LQTS6 (61). Auditory/acoustic stimulus like alarm clock noise, doorbell etc. could provoke syncopal attacks in *KCNE2* mutation carriers, similar to *KCNH2* mutation (62).

LQTS7

This syndrome is also known as Andersen–Tawil syndrome (ATS). ATS is a rare disorder, manifested by occasional syncope, and cardiac arrest. ECG features include mild QT interval prolongation, abnormal U waves, frequent ventricular ectopy, bidirectional ventricular tachycardia (VT), and polymorphic VT. This syndrome also exhibits extracardiac features, e.g., skeletal muscle periodic paralysis and developmental problems, such as cleft palate, low set ears, short stature, and developmental defects in the limbs (63). Majority of clinically diagnosed ATS patients were reported to have a mutation in *KCNJ2* (63). *KCNJ2* encodes a pore-forming subunit of inwardly rectifying potassium channels (IK1) (Figure 1) (64, 65).

LQTS8

Also known as Timothy syndrome (TS), patients show severe QT prolongation on their ECGs, which is combined with syndactyly, baldness at birth, and small teeth in 100% of cases and less penetrant cardiac structural malformations, mental retardation, autism, and facial dysmorphic features (66). There are two subtypes: TS1 (classical) and TS2 (rare form).

TS2 is cardiologically severer than TS1 (66, 67). TS2 patients also lack syndactyly (67). Mutations in the α -1 subunit of the L-type calcium current (ICa-L) encoding gene *CACNA1C* lead to both forms of TS (LQTS8). There are alternatively spliced, mutually exclusive exon-8 in the *CACNA1C* gene, for clarity, they are named as exon-8 and exon-8A. In heart and brain, where the *CACNA1C* is predominantly expressed, exon-8 is found in ~80% of the mRNA transcripts and exon-8A is present ~20% transcripts (66). G406R mutation in exon-8A is causal to classic form of TS (TS1) and G402S in exon-8 was reported in severer in TS2. A new addition to this list is Ala1473Gly mutation, which has been described in a TS infant with further expanded phenotype (68).

All mutations were either *de novo* or mosaic in the parent, and all result gain of function of the ICa-L channel (66–69).

LQTS9 AND LQTS10

Mutations in *CAV3* or *SCN4B* produce gain of function in late INa, causing an LQTS3-like phenotype (70–74). They are known as LQTS9 (associated with *CAV3* mutation) and LQTS10 (associated with *SCN4B* mutation).

Caveolae are nicely described by Engelman et al. (72) as “little caves” in the plasma membrane. They are small uncoated pits and is considered as the site of important dynamic and regulatory events at the plasma membrane (72, 73). Caveolins are the principal proteins in the caveolae, and caveolin-3 (encoded by gene *CAV3*) is specifically found in cardiomyocytes and skeletal muscle cells. Several cardiac ion channels have been specifically reported to be localized in the caveolae extracted from cardiac myocytes that are enriched in caveolin-3 (72, 73). Additionally, components of the β -adrenergic receptor signaling cascade are also present in caveolae-enriched membranes (72, 73).

SCN4B encodes for Nav β 4, which is an auxiliary β -subunit of the cardiac sodium channel. So far only one mutation (L179F) has been reported in this gene in a Mexican family with multiple affected family members (74). Mutation in this gene was found to result in gain of function of the Nav1.5 current (74).

LQTS11

In the heart, sympathetic regulation of cardiac action potential duration (APD) is mediated by β -adrenergic receptor (β -AR) activation, which requires assembly of AKAP9 (Yotiao) with the α -subunit (KvLQT1) of the IKs channel. Mutation in AKAP9 causes LQTS11 (75). To date only one mutation, S1570L, in AKAP9 has been reported (75).

LQTS12

Mutation in the α -1-Syntrophin (SNTN1) gene are causal to LQTS12. Mutation in this gene leads to gain of function of the cardiac sodium channel (Nav1.5), which is the pathological basis of LQTS12 (76).

LQTS13

G protein-coupled, inwardly rectifying potassium channel subunit (Kir3.4) is encoded by the *KCNJ5* gene. A loss-of-function mutation in this gene could cause LQTS13 (77). So far, only one mutation, G387R, has been described in a Chinese family with nine patients having this mutation. Reduced plasma membrane expression of Kir3.4 was suggested as the pathology of LQTS in the patients.

ACQUIRED LQTS

In addition to the congenital LQTS, another variant of LQTS known as aLQTS also exist, which is caused by factors and substances that decrease potassium flux and impair the ability of the myocardium to repolarize. Well-recognized conditions are female gender, hypokalemia, and drugs that inhibit cardiac potassium channels (78–80). A number of commonly prescribed drugs could also preferentially bind and block the HERG channel (Kv11.1, a protein encoded by *KCNH2* gene) and predisposes to aLQTS

(79, 80). Recently, it was shown that blockade of IKs could also contribute to drug-induced aLQTS, specially when repolarization reserve is compromised (81). Fluoxetine and norfluoxetine were found to suppress the IKs properties, both *in vivo* and *in vitro* and led to marked LQTS (81). Polymorphisms, D85N in minK (gene *KCNE1*), T8A, Q9E in MiRP1 (gene *KCNE2*), which are putative β -sub-units of the IKs and IKr channels, were reported to cause aLQTS (82, 83). Autoimmune LQTS has also been reported in a patient with IgG containing anti-HERG antibodies (84).

ELECTROCARDIOGRAPHIC FEATURES IN THE THREE COMMON FORMS OF LONG QT SYNDROME

Typical ST-T-wave patterns are present in the majority of genotyped LQTS patients and can be used to identify LQTS1, LQTS2, and possibly LQTS3 genotypes (85, 86).

The LQTS1 form of the LQTS is associated with a broad *T*-wave without shortening of the QT interval at exercise (**Figure 2A**). LQTS2 is associated with low-amplitude, often bifid, *T* waves (**Figure 2B**). LQTS3 is associated with a long iso-electric segment and a narrow-based, tall *T* wave (**Figure 2C**). Pause dependence of TdP onset in congenital LQTS is genotype-specific, being predominant in LQTS2 but almost absent in LQTS1 (87).

Although patterns may suggest a specific genotype of the LQTS, exceptions have been frequently found.

GENOTYPE-PHENOTYPE

Long QT syndrome is an autosomal dominant disease. Genotype and phenotype analysis among the heterozygous mutation carriers have been conducted quite extensively in the LQTS1, LQTS2, and LQTS3 patients. During childhood, the risk of cardiac events is significantly higher in LQTS1 males than in LQTS1 females,

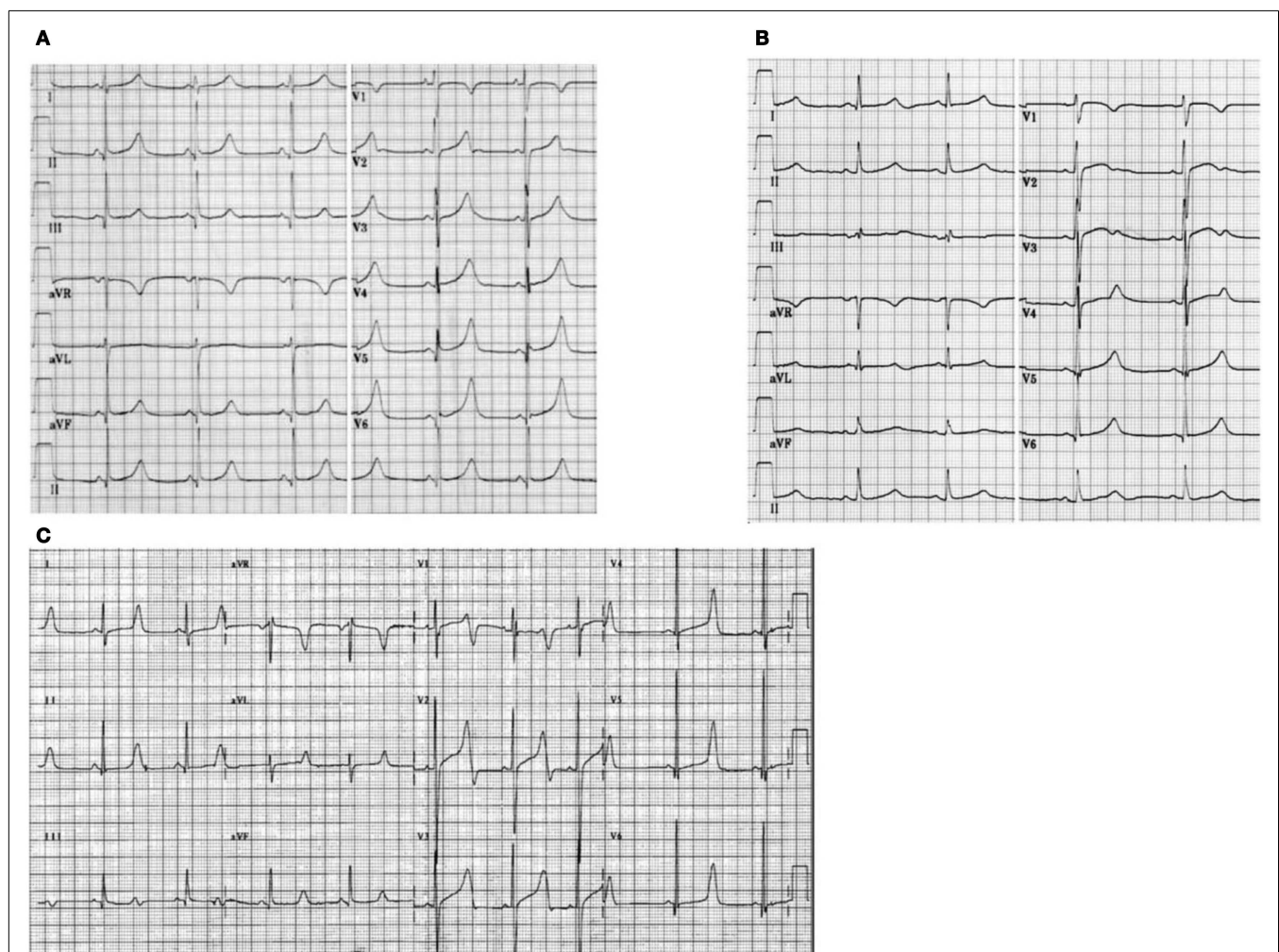


FIGURE 2 | Electrocardiogram recordings from patients with LQTS1, LQTS2, and LQTS3. (A) 12-lead ECG of an 18-year-old male with a *KCNQ1* mutation. The QT interval is prolonged ($QT_c = \pm 500$ ms). The ST segment has a broad base and relatively large amplitude. Conduction interval is normal (standard calibration). **(B)** 12-lead ECG of a 14-year-old girl with a *KCNH2* mutation. The QT interval is prolonged ($QT_c \pm 520$ ms). The ST segment is

notched in lead V3 and has relatively low amplitude in the extremity leads. Conduction interval is normal (standard calibration). **(C)** 12-lead ECG of a 12-year-old boy with a *SCN5A* mutation. The QT interval is prolonged ($QT_c \pm 600$ ms). The ST segment has a long (almost) iso-electric segment with a large, sharp, and narrow *T* wave. Conduction interval is normal (standard calibration).

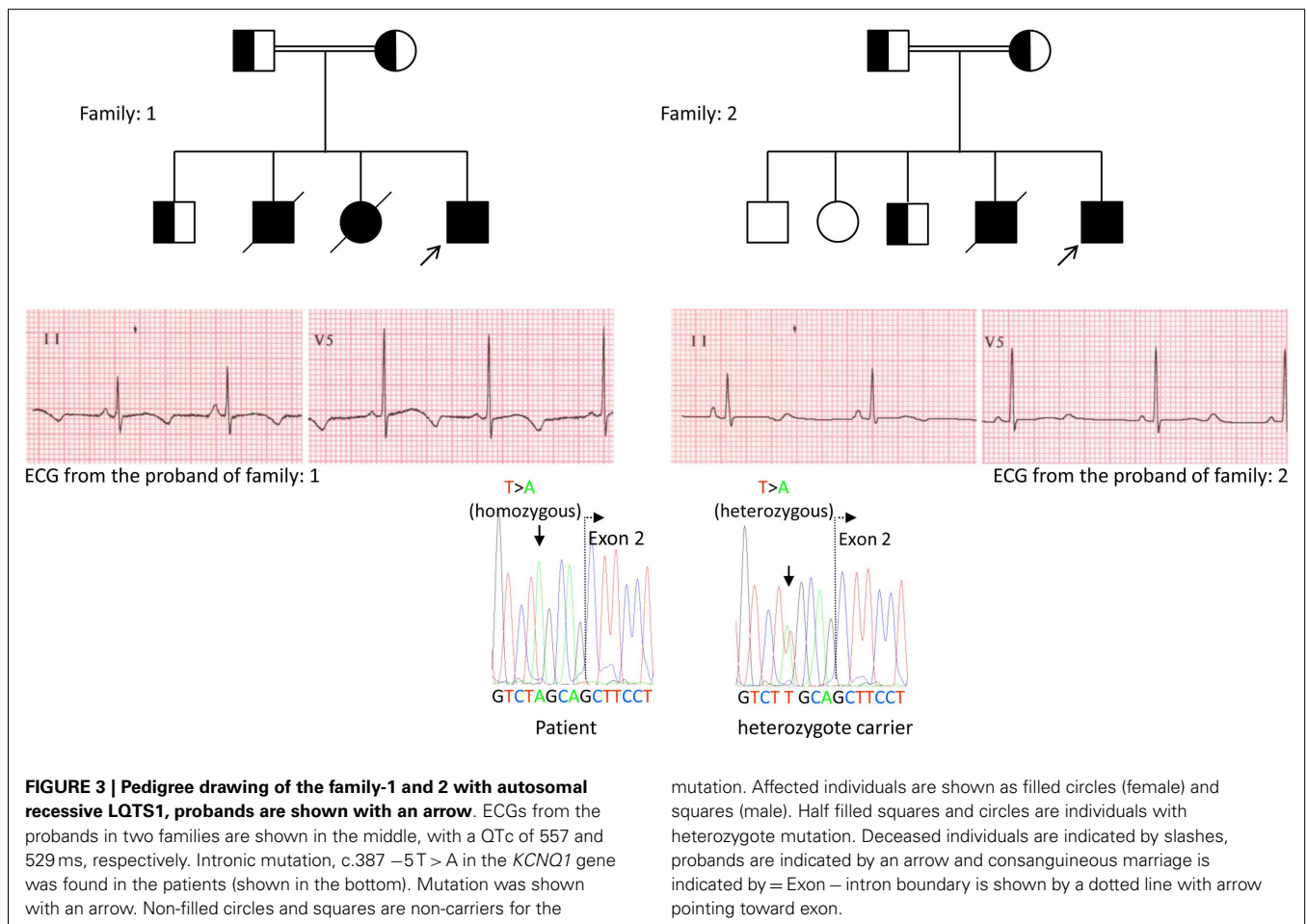
whereas no significant gender-related differences in risk of cardiac events were observed amongst LQTS2 and LQTS3 patients (88–91). During adulthood (also after age 40), LQTS1 and LQTS2 females could have significantly higher risk of cardiac events than respective males (88–91). In general, lethality of cardiac events seems to be predominant in LQTS3 patients than in LQTS1 and LQTS2 patients (91). Women with LQTS have a reduced risk for cardiac events during pregnancy, but the risk quite increases during the 9-month postpartum period, specially in the women with mutation in the *KCNH2* gene (92).

Sudden cardiac death in children could also be caused by mutations in the cardiac ion channel genes (93–96). About 28% of the children with an unexplained SCD (between 1 and 18 years, mean age: 12.3 ± 3.8 years) were carriers of mutations in LQTS causal genes (97). In SIDS, mutations in *SCN5A* seemed predominant (98, 99), but, mutations in *KCNQ1*, *KCNH2*, *KCNE2*, and *CAV3*, *SCN4B*, and *SCN3B* were also found (100, 101). Intrauterine fetal deaths were also reported due to defects in cardiac ion channel genes (12, 102).

CLINICAL MANAGEMENT OF LQTS

Cessation of all drugs that are known to prolong the QT interval and also the correction of electrolyte imbalances and/or precipitating metabolic conditions should be the primary focus while treating (acquired-) LQTS patients. Symptoms in LQTS are often

adrenergically mediated, therefore restriction of patients' participation in athletic activities are generally recommended (24, 25). The mainstay of clinical therapy for the LQTS is β -blockade. Long-acting preparations of propranolol, nadolol, and metoprolol are usually used, and their efficacy in β -blockade is assessed by blunting of the exercise heart rate (e.g., by $>20\%$) (24, 25). Amongst all the β -blockers, propranolol and nadolol are considered superior than metoprolol in symptomatic patients (103). Furthermore, β -blockade can also be used as a prophylactic treatment in silent mutation carriers to reduce SCD (24). In a study by Barsheshet et al. (30), patients with c-loop missense mutations in the *KCNQ1* gene exhibited high risk of life-threatening cardiac events and they had significant benefits from the treatment with β -blockers. As women with LQTS2 have an increased risk during the 9-month postpartum period, β -blockers should be prescribed to reduce any cardiac events during this high-risk period (92). An implantable cardioverter-defibrillators (ICDs) can be considered for patients with recurrent syncope despite β -blocker therapy or in patients with high risk for cardiac arrest (e.g., symptomatic LQTS2 and LQTS3 with a documented QTc prolongation). Left cardiac sympathetic denervation (LCSD) is recommended for high risk LQTS patients in whom an ICD is contraindicated or refused and β -blockers are either not effective, not tolerated, not accepted or contraindicated (18, 104). JLNS patients usually have a QTc >500 ms and are also at high risk, β -blockers have insufficient



efficacy in such patients in whom an early therapy with ICD was recommended (18, 31).

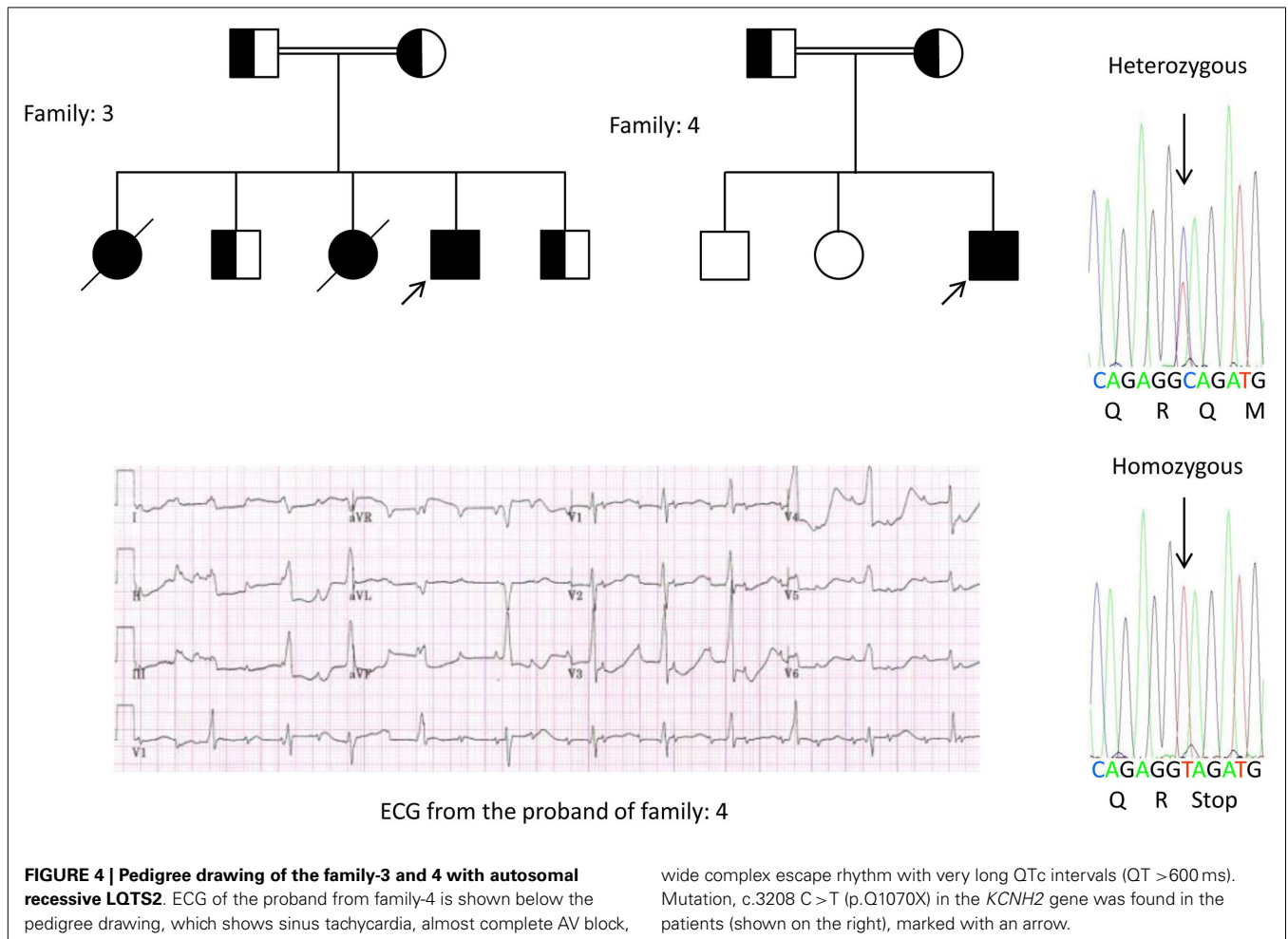
LQTS: SAUDI PERSPECTIVE

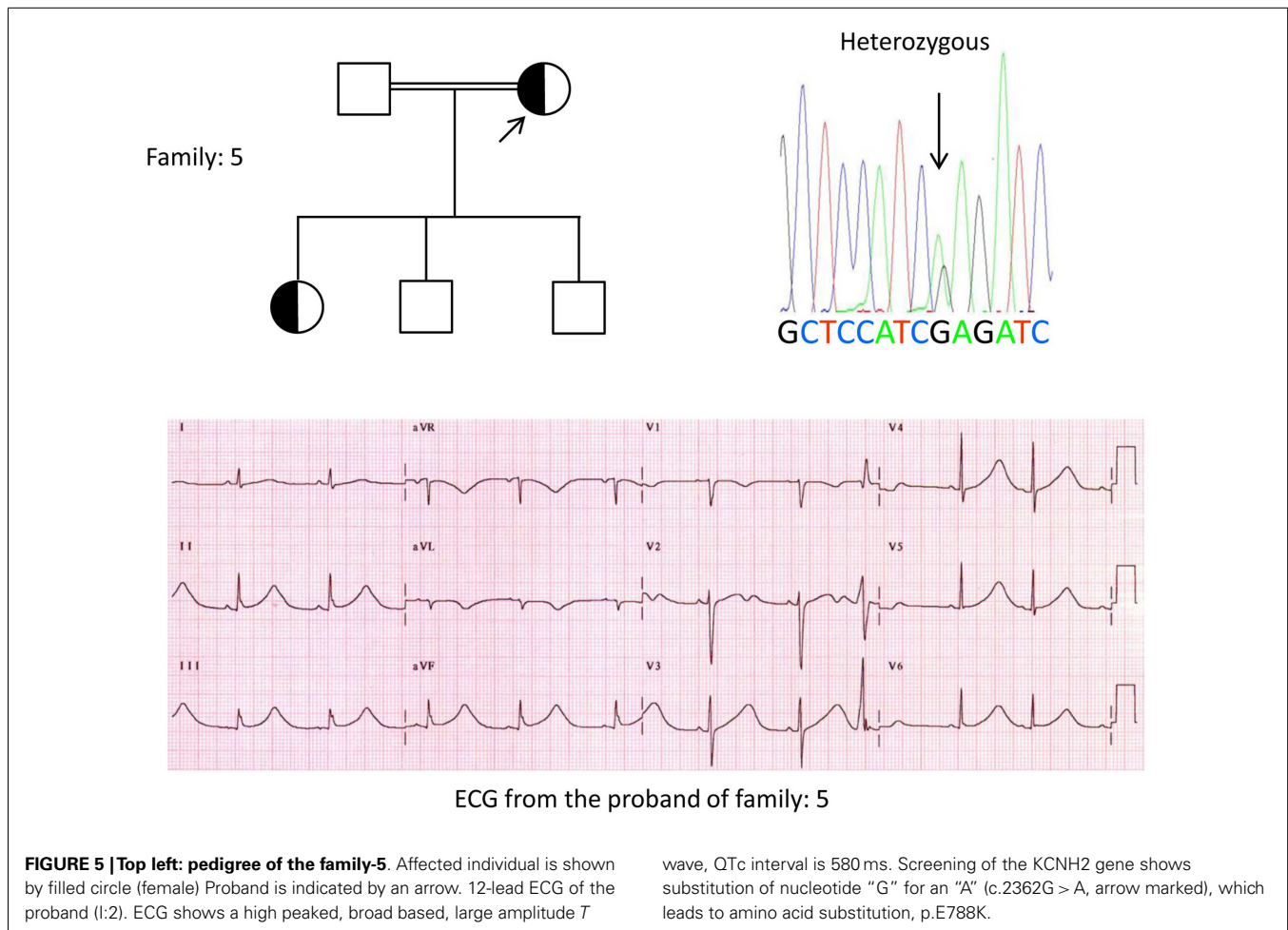
First report on LQTS from Saudi Arabia was published in 1993 from the Riyadh Armed Forces Hospital (105). Four infants and young children between 6 and 48 months with history of recurrent seizures, from a single family, were diagnosed as LQTS (105). Family history revealed that two-other extended family members had similar episodes of sudden loss of consciousness and three-family members died suddenly (105). In all cases, initial diagnosis was epilepsy (105). Several years later, two sporadic case reports with comparatively severer variant of neonatal LQTS combined with 2:1 AV block have been reported (106, 107). All these published clinical reports were without any genetic findings that could explain the pathophysiology of LQTS in them (105–107).

We, for the first time, have reported genetic defects as a pathological basis of LQTS in similar patients from Saudi Arabia. We have investigated six-Saudi families with history of syncope and sudden unexplained deaths of fetus, neonates and children (12–14). Autosomal recessive LQTS1 was diagnosed in children from two families (Figure 3). Autosomal recessive LQTS2 was diagnosed in two families (Figure 4). In one family, a female patient

was diagnosed with autosomal dominant LQTS2 (Figure 5), the patient had syncopal attacks during postpartum recovery period at the hospital, which is very common in *KCNH2* mutation carrier women. In all our patients, identification of pathogenic mutations in the LQTS causal cardiac ion channel genes led to a confirmed clinical diagnosis, which were misdiagnosed as epileptic convulsions before being referred to us (13, 14) Recently, Shinwari et al. (15) from King Faisal Specialist Hospital and Research Centre reported a LQTS1 causal *KCNQ1* mutation, H258P, in a large family with 12 affected individuals. Only two carriers were symptomatic, their QTc were >500 ms, and β -blockers suppressed the clinical symptoms in one patient and the second symptomatic patient required an ICD.

Genetic and clinical findings in our study (12–14) from Saudi Arabia are quite intriguing for several reasons: (1) In total, we have investigated six-families, among them four were homozygous/compound heterozygous for the mutations and the mutations originated from an ancestral source; (2) All the mutations in LQTS were novel, reported only in these Arab families; (3) Due to the homozygosity or compound heterozygosity for the mutations, clinical phenotypes were also severe in our studied families (12–14). We suggested that the genetic and phenotypic observations stemmed from the extreme high rate of consanguineous





marriages in Saudi Arabia (108, 109). Our study provided the first scientific evidence about the role of consanguinity in exerting a pivotal role in unexplained cardiac arrhythmias and SCDs in children and adolescents in Saudi Arabia (12–14). We have also shown that the *KCNQ1* mutation c.387 –5 T > A (NM_000218) (Figure 3) had spread in the Assir province of Saudi Arabia from a common ancestor during several generations due to high incidence of consanguineous marriages [see the map, Figure 6; (12–14)]. So far, this is the most common LQTS1 causal mutation in Saudi Arabian population, which was also observed at King Faisal Specialist Hospital and at Khamis Mashayt Military Hospital (unpublished). A similar result was also obtained for LQTS2 causal mutation, c.3208 C > T (p.Q1070X) (Figure 4) in the *KCNH2* gene (12, 14), which is also a founder mutation in Saudi Arabia and segregated during many generations in the Assir region (see the map, Figure 6). We would predict that there exist a considerable number of individuals with the mentioned ancestral/founder mutations (both in *KCNQ1* and *KCNH2* and other genes) in this region and also in the big cities like Riyadh, Jeddah and Dammam due to urban migration. More founder or ancestral mutations pathogenic to LQTS are very much envisaged in other provinces of Saudi Arabia due to high rate of consanguineous marriages.

As LQTS is an autosomal dominant disease, we expected to observe predominantly heterozygous mutation carrier patients. But in our study, we mainly identified patients with recessive mutations (12–14). Clearly, these patients become first symptomatic and, were predominantly referred to Prince Sultan Cardiac Centre, bringing them under our attention. Nevertheless, findings from our investigations implies to the fact that recessive LQTS could have fatal clinical phenotypes in children, and they are not uncommon in Saudi Arabia (12–14). As the heterozygous mutation carriers are also susceptible to develop arrhythmia and its complications, concerted initiative should be taken to bring the local general physicians, cardiologists, and clinical geneticists in a common platform to identify the individuals at risk. Further, at the moment, we have also no genetic information for other familial arrhythmia disorders, e.g., CPVT, SQTS, BrS, AF, etc. Specialized cardiogenetic centers should take the initiative to search for the genetic defects, mutations, and perform genotype-phenotype studies in all forms of hereditary arrhythmias. It also should be kept in consideration that not all genetic arrhythmias would have a family history, as in many cases arrhythmia causal mutation are *de novo* in origin, i.e., the proband is the first patient in that family with the mutation and he/she is the source to transmit the mutation in downstream generations (110, 111). Due to the very high

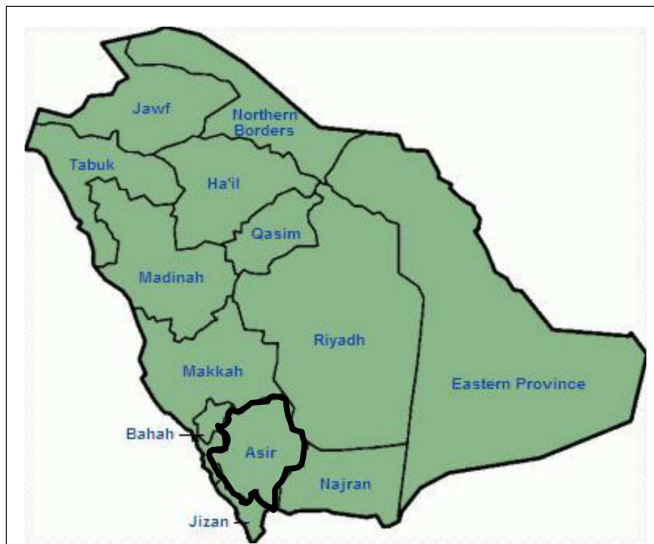


FIGURE 6 | Map of Saudi Arabia (courtesy: Wikipedia). Assir region is marked with thick line, where we have found the founder mutations in *KCNQ1* and *KCNH2* genes, described in family 1–4.

rate of consanguineous marriages in Saudi Arabia, we expect a lot more founder mutations exert a crucial role in congenital arrhythmias in this country. Identifying these founder mutations should be our first and foremost task, which would facilitate us in developing an effective premarital and also pre-symptomatic genetic counseling in this country. Mutations in LQTS causal genes could confer variability in clinical penetrance, in one extreme, some carriers could be presumably completely healthy, but some carriers could have their first manifestation of the disease as syncope or sudden death. Sudden death of a young child or adult poses a great deal of psychological and emotional burden on the family, screening of the carriers are essential as there exist simple medication, e.g., β -blockers (also behavior modification), which could very effectively prevent the carriers from the fatal consequences of arrhythmia and SCDs. Individuals with homozygous mutations in the LQTS causal genes could have severe morbidity and extreme high rate of mortality including fetal brady-tachyarrhythmias, and in many cases miscarriages, spontaneous abortions in the pregnant mothers (12–14).

Not much research has also been conducted in Saudi Arabia about the prevalence of various SNPs in the arrhythmia linked genes and also in the genes that regulate them. Splawski et al. (112) described a common S1103Y variant in the *SCN5A* gene associated with arrhythmia in African-Americans. The variant allele termed Y1103 is responsible for accelerating channel activation, thereby enhancing the probability of cardiac arrhythmias in persons of African descent (52, 112). K393N is a variant in *KCNQ1* gene reported in LQTS1 patients in USA, but, in the Arab population we have detected this variant in 2% of individuals (unpublished data). Whether, K393N variant in *KCNQ1* gene in Arabs is comparable to the S1103Y (*SCN5A*) variant in African-Americans or the D85N (*KCNE1*) variant in the Japanese population could also merit investigation (59).

ACKNOWLEDGMENTS

Our sincere gratitude to Prof. Arthur Wilde, Prof. Connie Bezzina, and the publisher of the journal “Heart” for their permission to use the **Figure 1** in this manuscript from Ref. (113).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 15 October 2013; accepted: 05 November 2013; published online: 20 November 2013.

Citation: Bhuiyan ZA, Al-Shahrani S, Al-Aama J, Wilde AAM and Momenah TS (2013) Congenital long QT syndrome: an update and present perspective in Saudi Arabia. *Front. Pediatr.* 1:39. doi: 10.3389/fped.2013.00039

This article was submitted to *Genetic Disorders*, a section of the journal *Frontiers in Pediatrics*.

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