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Molecular Analysis of *KCNQ1, KCNH2* and *SCN5A* Genes in Iranian Patients with Long QT Syndrome

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Abstract

Background: Long QT syndrome is a cardiac ion channelopathy characterized by corrected QT interval prolongation on electrocardiograms, leading to syncope and sudden death.

Methods: In this study, the genetic screening of four Iranian LQTS families, including two Romano Ward syndrome families and two families with Jervell and Lange-Nielsen syndrome, was performed by Sanger sequencing and haplotype analysis for three of the most common LQTS genes, *KCNQ1*, *KCNH2* and *SCN5A*.

Results: A *de novo* mutation c.1838C>T in the *KCNH2* gene associated with LQTS2 was identified in a RWS family. A homozygous mutation c.477+5G>A was found in the *KCNQ1* of the two JLNS families, and a novel recessive *KCNQ1* variant c.934A>T (p.T312S) was identified in the *KCNQ1* of another RWS family. The structural, functional and pathogenicity evaluation of the novel *KCNQ1* missense variant by *in silico* predictive programs along with the segregation and population studies revealed that the variant was a likely pathogenic mutation.

Conclusion: To the best of our knowledge, p.T312S is the first mutation identified for an AR-RWS family in the Iranian families. This assay can be used to screen individuals to provide useful information for the identification of the LQTS in the Iranian population. It is yet to be proven that the detection of different types of LQT will result in a more effective therapy.

Keywords: Long QT syndrome; Cardiac repolarization; Genetics; *De novo* mutation; Iran

Introduction

Hereditary long QT syndrome (hLQTS) is one of the most prevalent causes of sudden cardiac death usually in the young people characterized by an abnormality in cardiac repolarization [1]. LQTS can exist either as an autosomal dominant (Romano Ward syndrome, RW, MIM# 192500) or autosomal recessive (Jervel and Lange-Nielsen syndrome, JLNS, MIM# 220400) disorder. Both syndromes lead to recurrent syncope and prolongation of the QT interval in the electrocardiogram (ECG) [2]. In addition to these symptoms JLNS patients suffer from sensorineural deafness [3]. Mutations in sixteen genes encoding cardiac ion channels and associated proteins have so far been identified as responsible for all genotype-positive LQTS [4,5]. *KCNQ1* (also known as KVLQT1) and *KCNH2* (also known as human ether-a-go-go-related gene, *HERG*) are the two most common LQTS genes that mutations in which account for approximately 95% of cases [6]. In this report, four patients with LQTS were analyzed to identify the mutations present in the three most common LQTS genes: *KCNQ1*, *KCNH2* and *SCN5A*.

Materials and Methods

Clinical evaluation

For further clinical assessments, four unrelated LQTS families were referred to the emergency unit at the Rajaei Cardiovascular Medical and Research Center, Tehran, Iran.

LQT patients

Family 1 (RW): The family study was conducted using three members in two generations. The proband was a 3-year-old boy (2:1 in Figure 1A), who was referred to the emergency unit of hospital Rajaei in Iran, due to recurrent syncope, multiple episodes of seizure and convulsion. A 12-lead electrocardiography was done. QTc interval was 560 ms (Figure 2A). The echocardiography showed normal cardiac structure. No auditory phenotype was detected in the proband. A proband's sibling died suddenly at 16 weeks of age (2:2 in Figure 1A). The patient's parents did not show any symptom, although they were also subjected to ECG studies.

Family 2 (RW): The proband (3:1 in Figure 1B) was a 15-years-old boy with a history of repeated syncopal events since the age of 2 years and seizure since the age of 9 years. He also had a history of palpitation around the age of 8 years. His QTc interval was 510 ms (Figure 2B). He showed a normal cardiac structure in the echocardiography and no auditory phenotype was detected in the proband.

Family 3 (JLNS): In this family, there were three siblings (4:5 in Figure 3A) with one deaf who was an 8-year-old boy referred because of recurrent episodes of syncope. He had a history of seizures since the age of 4.5. QTc was markedly prolonged in the index patient, 580

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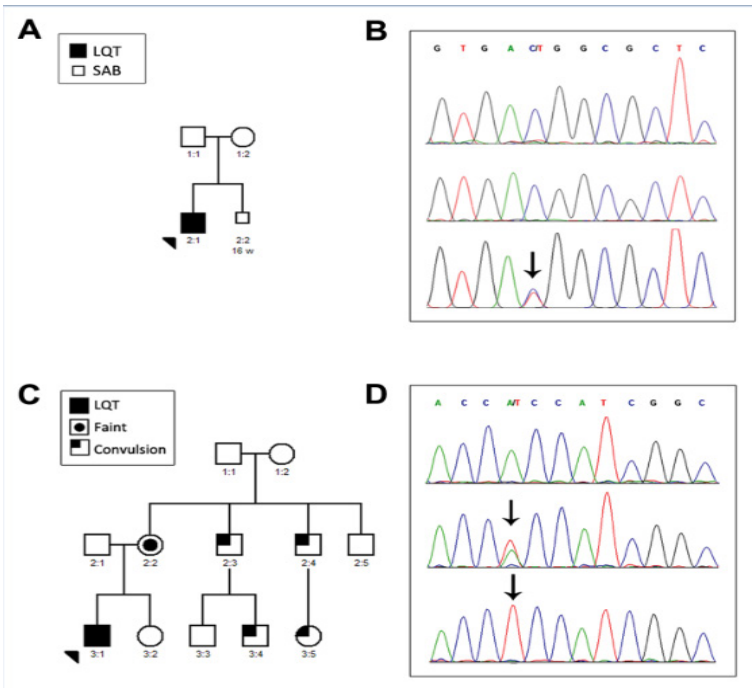

Figure 1: Pedigrees and mutation confirmation. A: Family pedigree for the patient 1. B: DNA Sanger sequencing confirmation for c.1838C >T (p.T613M) mutation in the patient 1 with heterozygote condition (lower) and normal parents (upper and middle). C: Family pedigree for the patient 2. D: DNA Sanger sequencing confirmation for c.934A>T (p.T312S) mutation in the patient 2 with homozygote condition (lower), unaffected heterozygote parents (middle) and normal sequence (upper). SAB: Spontaneously Abortion.

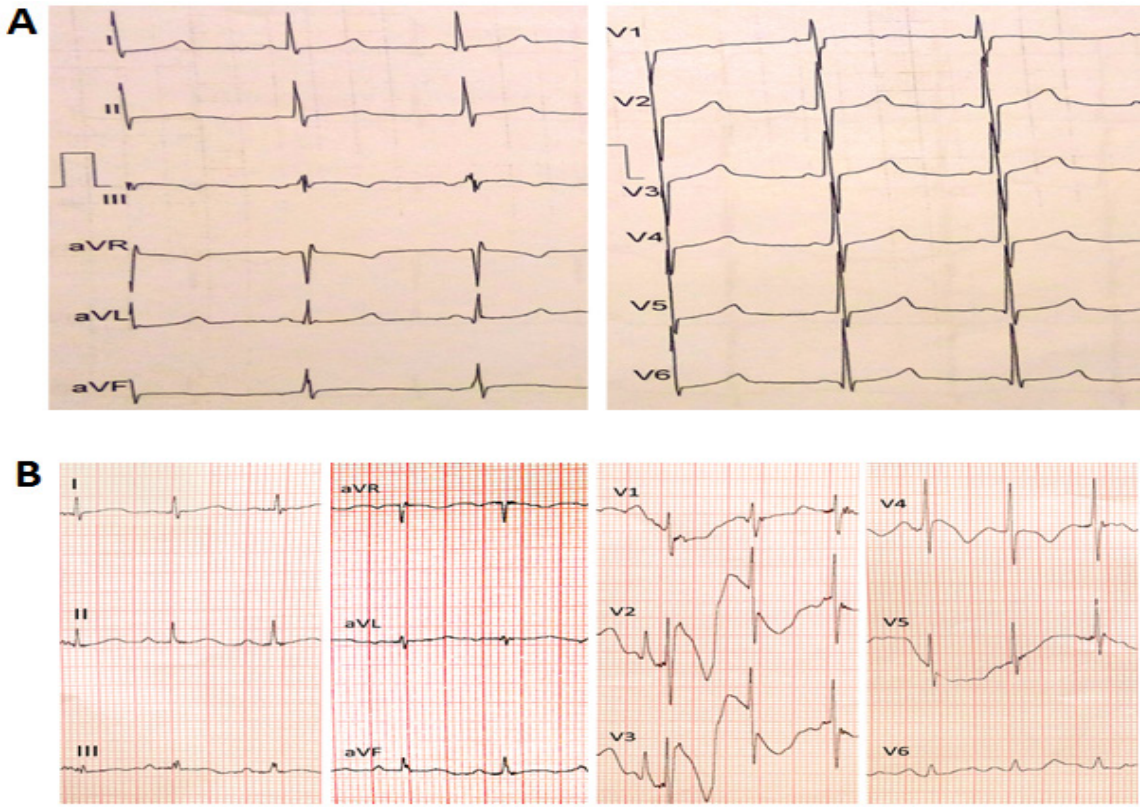

Figure 2: ECG of the patients. **A:** The 12-lead electrocardiogram of the patient A at 3 years of age (QTc 560 ms in lead II). **B:** The 12-lead electrocardiogram of the patient B at 15 years of age (QTc 510 ms in lead II).

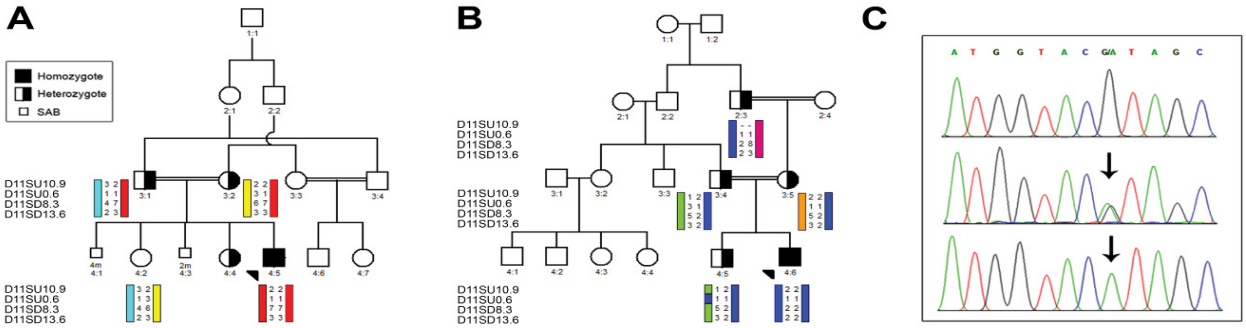

Figure 3: Pedigrees, haplotype analysis and mutation confirmation. **A:** Family pedigree for the patient 3. The results of haplotype analysis with four STR markers encompassing the KCNQ1 gene were displayed below each individual. **B:** Family pedigree for the patient 4 and haplotype analysis results. **C:** DNA Sanger sequencing confirmation for c.477+5G>A mutation in the index cases (lower), unaffected heterozygous parents (middle) and normal sequence (upper). SAB: Spontaneously Abortion

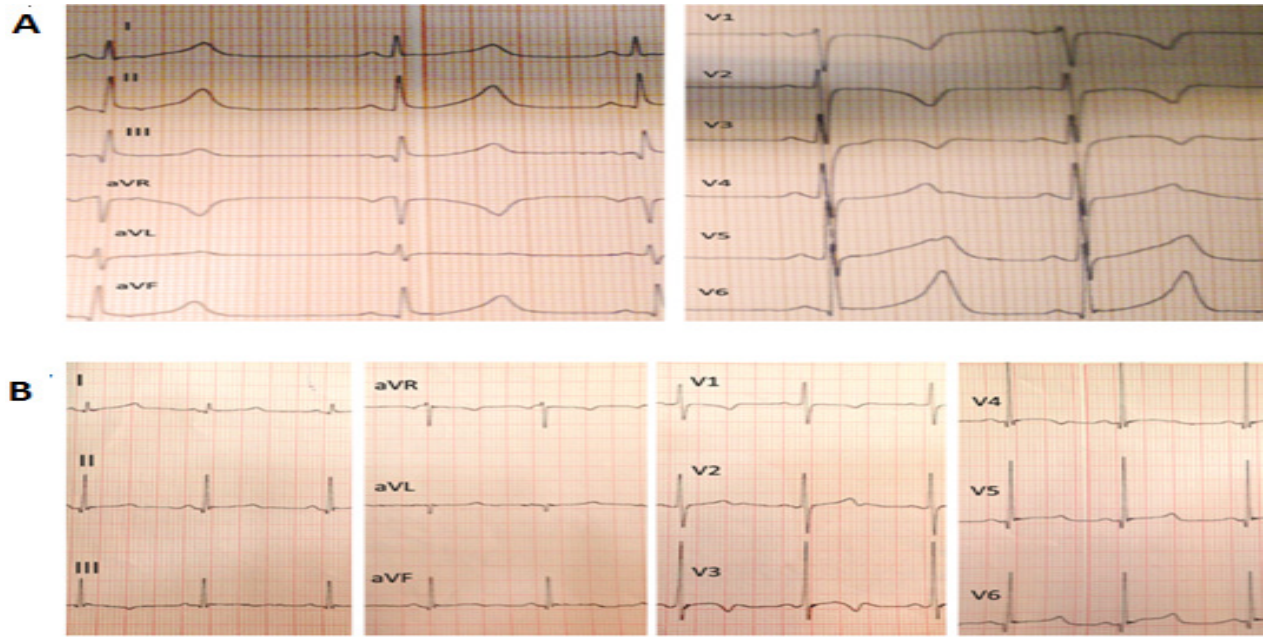

Figure 4: ECG of the patients. **A:** The 12-lead electrocardiogram of the patient 3 at 8 years of age (QTc 580 ms in lead II). **B:** The 12-lead electrocardiogram of the patient 4 at 9 years of age (QTc 560 ms in lead II).

ms (Figure 4A). As a result of the high-risk situation, an endocardial Implantable Cardioverter Defibrillator (ICD) was implanted. Propranolol with a dose of 5 mg/kg/day, divided three times a day, was started for the patient. The Sensorineural deafness was diagnosed at 2.5 years and is managed with hearing aids. Heterozygous carrier parents had no clinical phenotype.

Family 4 (JLNS): The proband was a 9-year-old boy (4:6 in Figure 3B) with a history of recurrent syncope and seizures since the age of 2 years. He was deaf and had cochlear implants at 3 years. After referral to our arrhythmia clinic, an endocardial Implantable Cardioverter Defibrillator (ICD) was implanted. Propranolol was started (5 mg/kg/day, divided three times a day), which suppressed his symptoms. The ECG of the proband showed a QTc of 560 ms (Figure 4B). The parents and his brother were without any cardiac events. Further family history was unavailable.

DNA isolation

After obtaining informed consents and study approval by the ethics committee of the Pasteur Institute of Iran and Rajaie Cardiovascular Medical and Research Centre (adopted from the 1975 Helsinki Declaration), blood samples were collected from patients and their family members in tubes containing EDTA. Genomic DNA was isolated from the peripheral blood according to the standard salting out protocol [6,7].

Haplotype analysis

Haplotype analysis for LQT1–3 (loci) was performed for the detection of related genes in such heterogeneous cardiac diseases, in the families with the utility of a set of 16 polymorphic short tandem repeat (STR) markers which including D11SD8.3, D11SU10.9, D11SU2.2, D11SU0.6, D11SD13.6 (LQT1) as described in detail by Amirian et

S. no	Predictive Software	Prediction	Score
1	SIFT	Deleterious	0
2	Polyphen-2	Probably damaging	0.98
3	Mutation Taster	Protein features (might be) affected Splice site changes	0.98
4	FATHMM	Damaging	-9.35
5	SNPs and GO	Disease	7
6	PhD-SNP	Disease	4
7	HSF	Alteration of an Exonic ESE site Potential alteration of Splicing	-
8	GERP++	Evolutionary constraint	3.93
9	Phylop	Evolutionary conserved	4
10	PhastCons	Evolutionary conserved	1

Table 1: *In silico* analysis results for the variant p.T312S.

al., D7SU7, D7SU4.8, D7SU3, D7SD5, D7SD6, D7SD9 (LQT2); and D3SU11, D3SU10.8, D3SU2.5, D3SI, D3SD5.6 (LQT3) as described in detail by Zafari et al. [8]. All STRs which were unique were selected among penta or tetra-nucleotide repeat markers and were located upstream or downstream of the genes at a distance of less than 1.4 Mb. Size determination of the repeats was performed on ABI 3130XL Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

Mutation analysis

The patients were screened for the pathogenic variant by Sanger sequencing. The primer pairs for all coding exons and exon-intron boundaries and untranslated regions of three common LQTS-causative genes: *KCNQ1* [NM_000218], *KCNH2* (NM_000238) and *SCN5A* (NM_198056.2) were designed by primer 3 online and gene runner software (the sequence of primers are available upon request). Exons of the three genes were amplified by PCR and the purified PCR products were sequenced with both amplification primers, forward and reversed by sanger sequencing chain termination method on ABI 3130XL Genetic Analyzer by Kawsar Biotech Co. (KBC, Tehran, Iran) [9].

In silico variant analysis

The novel recessive variant found in patient was interpreted by a variety of *in silico* predictive programs. For predicting the functional impact of the variant on the protein, MutationTaster, HSF, Mutation Assessor, SIFT, PolyPhen-2 and FATHMM were used. The secondary structure of the protein was predicted by I-TASSER server. GERP++, PhyloP and PhastCons methods were also used to predict the conservation score [10-17].

Family and population study

Genealogy and co-segregation analyses were performed for all members of the family with available DNA samples for the novel missense variant. A total of 100 unrelated healthy individuals with the same ethnicity were collected to detect the genotype by amplification refractory mutation system (ARMS) PCR for the identified variant c.934A>T in the population.

Results

Genetic analysis

Family 1 (RWS): Genetic screening showed the absence of mutation in *SCN5A* and *KCNQ1* genes in either the proband or the parents. However, the sequencing analysis of the *KCNH2* gene in the proband revealed a *de novo* heterozygous single-nucleotide substitution; c.1838C>T in exon 7 of the *KCNH2* gene, which creates a nonsynonymous change (p.T613M) (Figure 1C). *De novo* mutation in LQTS was previously reported for human *HERG* gene [18]. Paternity test based on microsatellite repeat length (VNTR) and RFLP analysis excluded any non-paternity/non-maternity. Additionally, haplotype analysis showed his parents shared the same haplotype (data not shown). This suggests that the C>T change in codon 613 of the *KCNH2* gene in the proband is either a *de novo* mutation in the proband or a germ line mosaic mutation in the parent.

Family 2 (RWS): Bidirectional Sanger sequencing revealed that a novel homozygous missense *KCNQ1* gene variant c.934A>T (ClinVar accession number: SCV000700208) resulted in Threonine to Serine substitution at position 312 (p.T312S) (Figure 1D). The variant was neither reported in 1000 Genome nor Exome Aggregation Consortium (ExAC) and was absent in 200 control alleles in the normal population. The proband shared the same haplotype in the parent (data not shown) and cosegregation analysis confirmed that the variant was associated with LQTS. The p.T312S variant identified in this study has not been reported previously. The predictive software (Phylop, PhastCons and GERP++) determined that the Threonine 312 position on the *KCNQ1* channel is evolutionary conserved (Table 1). The secondary structure for the Threonine 312 in the natural protein was identified as a coil structure by I-TASSER server with an almost high confidence value (Figure 5).

Family 3, 4 (JLNS): Haplotype analysis encompassing the three candidate genes showed homozygosity of the STR markers around the *KCNQ1* gene in two JLNS index cases (Figure 4). This resulted to evaluation of the *KCNQ1* gene in these families. During DNA sequence analysis of the candidate gene, a single, homozygous nucleotide substitution c.477+5G>A was detected in the *KCNQ1* gene of the two JLNS probands (Figure 3C). The mutation was found in heterozygous form in the parents (3:1 and 3:2 in Figure 4A and 3:4 and 3:5 in Figure 3B), and also in the other living sister and brother of patient 3 and patient 4, respectively (4:4 in Figure 3A and 4:5 in Figure 3B). This sequence change that resulted to a splice site alteration in intron 2 of the gene has already been reported as pathogenic in the literature [19]. Likewise splice site prediction tools interpreted this splice variant to be pathogenic due to disruption of probable splicing donor site.

Discussion

In the present study *KCNQ1*, *KCNH2*, and *SCN5A* genes were screened in four Iranian families among a cohort of 31 unrelated LQTS patients. A *de novo* heterozygous missense mutation in exon 7 of the *KCNH2* gene was detected in a RW patient and a novel homozygous missense *KCNQ1* gene variant in another RW patient. JLNS patients in two families had homozygous splice site mutation in the *KCNQ1* gene. In LQTS type2 (*KCNH2*) and type3 (*SCN5A*) with autosomal dominant

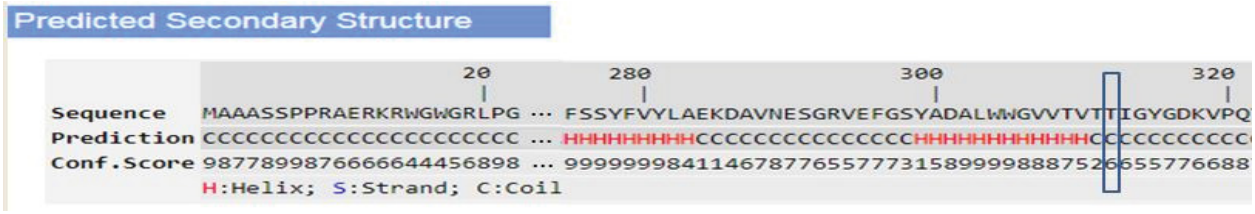

Figure 5: Predicted secondary structure of the KCNQ1 protein. The predicted secondary structure of p.T312S based on threading model by I-TASSER server is indicated as a coil structure at the second line with a confidence score of 6.

inheritance pattern, and catecholaminergic polymorphic ventricular tachycardia (CPVT)(RYR2), *de novo* mutations occur frequently [20-22]. The c.1838C>T substitution has previously been reported in Japan, Netherlands, and USA in association with LQTS patients and in a fetus with prenatal diagnosis of LQTS by fast next generation sequencing [23-25]. This is the first time that the same mutation with a *de novo* pattern was found in an Iranian family. Similar variant (p.T613A) affecting the same residues have been identified in association with Long QT syndrome [18]. Hence, it is possible that the variant detected in this study is more likely pathogenic with a similar effect. Additionally, mutation c.1838 C> T is located in a CpG sequence in the pore helix of the Kv11.1 protein between S5 and S6 potassium channel domains in which common missense mutations such as Y611H, V612L, T613A, and A614V are frequently reported [18,26]. Physiological studies have revealed that p.T613M mutation inhibited normal trafficking of the *HERG* protein to the surface membrane and caused a loss of function as well as a decrease in cell surface protein [24]. The majority of *HERG* mutations, more than 200 reported, have loss of function mechanism; which is, a considerable decrease of the protein product caused by the mutated allele [27]. In concordance with the genetic study result, our patient showed the clinical features of seizure, recurrent episodes of syncope and the family history of serious heart events such as sudden cardiac death in the sibling of the proband (2:2 in Figure 3A) who died at 16 weeks of age.

A new homozygous missense *KCNQ1* gene variant (p.T312S) was identified in the pore region of the human cardiac potassium channel of a RW family. The mutation causes a substitution from threonine to serine, which is well known for its ability to disrupt the secondary structure of the protein. Threonine 312 is located in the extracellular loop of the pore forming within a coil structure which is evolutionary conserved in mammals. The pathogenicity of Threonine substitution at codon 312 with Serine as a novel variant was predicted using all the online predictive tools (Table 1). Additionally, the occurrence of a missense variant in the pore forming alpha subunit of the *KCNQ1* protein is expected to be likely pathogenic with an estimated predicted value (EPV) of 94% [28]. Based on previous reports disruption in the pore region of *KCNQ1* and *KCNH2* in RW families because of full loss-of-function of potassium channels Kv7.1 and Kv11.1could lead to a severe LQTS phenotype [23,29]. Since the recessive mutation did not detect in 200 normal chromosomes, ruled out a typical polymorphism. Overall, according to the American College of Medical Genetics and Genomics guidelines the recessive *KCNQ1* variant is classified as a likely pathogenic variant [30]. The clinical manifestations of the prolonged QT interval of about 510 ms, recurrent episodes of syncope, palpitation and seizure were in concordance with the molecular testing result of the patient. The family history of cardiac events such as fainting in the proband's mother and convulsion episodes in family members has also been presented. This finding indicates that along with clinical evaluations, genetic testing should be done for detection of family members who are at risk.

An intronic homozygous mutation was detected in the splice regulatory site at intron 2 of the *KCNQ1* gene in two children from two unlinked families which co-segregate with the LQT1-JLNS phenotype. It is important to emphasize that as a given LQTS-associated variant, the variant must have involved a conserved amino acid or splice site that change the primary structure of the encoded protein [19]. As described in previous studies from Iran [9,31], although JLNS causing mutations in *KCNQ1* are mostly truncating and result in complete abolishment of IKs channel function [32]. but intronic mutations also besides frameshift mutation lead to full skipping of *KCNQ1,* thereby causing transcriptional deviance. For preservation of hearing, IKs channel is required for K^+ conduction in the inner ear endolymph. Homozygous or compound heterozygous mutations of KvLQTl result to complete loss of IKs function, insufficient endolymph production, decadence of Corti organ, and consequently sensorineural deafness [33]. Functional analysis with the splice mutant *KCNQ1* channel revealed that there was no recognizable IKs current, which is concurrent with the hearing loss [34]. Both homozygous carriers from two unrelated families as a true JLNS phenotype experienced severe cardiac arrhythmias with considerably prolonged QTc and deep congenital neural deafness. Both patients had their first episode of syncope before the age of 2. This splice mutation is associated with a high risk of sudden death if untreated.

Conclusion

Altogether, in our cohort, two LQTS missense mutations and one splice site *KCNQ1* mutation were identified in four index cases in our cardiogenetic clinic in Iran. This indicates that the prevalence of LQTS is indubitably much higher in Iran than what is expected as a result, which exigencies a widespread observation in this country. Further, in the current study a novel recessive mutation in an AR-RWS patient was found for the first time in the Iranian population. Till date, only one report of mutation screening in four AR-RWS patients of Iranian origin has been described and the current study adds to this slight literature [35]. This study helps the development of genetic testing for arrhythmia susceptibility. Finally, mutation identification is of importance for pre-symptomatic diagnosis and treatment, in some cases.

Acknowledgments

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Conflict of Interests

None of the authors have any conflict of interests with regard to this publication.

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