Genotype-phenotype analysis of three Chinese families with Jervell and Lange-Nielsen syndrome

Yuanfeng Gao, Cuilan Li, Wenling Liu, Robby Wu¹, Xiaoliang Qiu, Ruijuan Liang, Lei Li, Li Zhang², Dayi Hu

Heart Center, Peking University People’s Hospital, Beijing – 100 044, P. R. China, ¹Philadelphia College of Osteopathic Medicine, ²Lankenau Medical Center, Lankenau Institute for Medical Research, Jefferson Medical College, Philadelphia, U.S.A.

Address for correspondence: Dr. Cuilan Li, Heart Center, Peking University People’s Hospital, Beijing – 100 044, P. R. China. E-mail: licuilan@gmail.com

ABSTRACT

Background: Long QT syndrome (LQTS) is characterized by QT prolongation, syncope and sudden death. This study aims to explore the causes, clinical manifestations and therapeutic outcomes of Jervell and Lange-Nielsen syndrome (JLNS), a rare form of LQTS with congenital sensorineural deafness, in Chinese individuals. Materials and Methods: Three JLNS kindreds from the Chinese National LQTS Registry were investigated. Mutational screening of KCNQ1 and KCNE1 genes was performed by polymerase chain reaction and direct DNA sequence analysis. LQTS phenotype and therapeutic outcomes were evaluated for all probands and family members. Results: We identified 7 KCNQ1 mutations. c.1032_1117dup (p.Ser373TrpfsX10) and c.1319delT (p.Val440AlafsX26) were novel, causing JLNS in a 16-year-old boy with a QTc (QT interval corrected for heart rate) of 620 ms and recurrent syncope. c.605-2A>G and c.815G>A (p.Gly272Asp) caused JLNS in a 12-year-old girl and her 5-year-old brother, showing QTc of 590 to 600 ms and recurrent syncope. The fourth JLNS case, a 46-year-old man carrying c.1032G>A (p.Ala344Alasp) and c.569G>A (p.Arg190Gln) and with QTc of 460 ms, has been syncope-free since age 30. His 16-year-old daughter carries novel missense mutation c.574C>T (p.Arg192Cys) and c.1032G>A (p.Ala344Alasp) and displayed a severe phenotype of Romano-Ward syndrome (RWS) characterized by a QTc of 530 ms and recurrent syncope with normal hearing. Both the father and daughter also carried c.253G>A (p.Asp85Asn; rs1805128), a rare single nucleotide polymorphism (SNP) on KCNE1. Bizarre T waves were seen in 3/4 JLNS patients. Symptoms were improved and T wave abnormalities became less abnormal after appropriate treatment. Conclusion: This study broadens the mutation and phenotype spectrums of JLNS. Compound heterozygous KCNQ1 mutations can result in both JLNS and severe forms of RWS in Chinese individuals.

Key words: Compound heterozygous mutation, frameshift mutation, Jervell and Lange-Nielsen syndrome, KCNQ1, KCNE1, long QT syndrome, Romano-Ward syndrome, single nucleotide polymorphism

INTRODUCTION

Long QT syndrome (LQTS) is an inherited cardiac disorder characterized by QT interval prolongation, ventricular arrhythmias, syncope and sudden death (SD). Two forms of LQTS have been classified: Autosomal dominant Romano-Ward syndrome (RWS), which presents without hearing deficiency, and the more rarely occurring autosomal recessive Jervell and Lange-Nielsen syndrome (JLNS), which presents with congenital sensorineural deafness.

Physiologically, the slowly activating delayed rectifier K⁺ current (Iₖₛ) is crucial in maintaining the cardiac responses that generate a normal T wave and QT interval. Proteins encoded by the KCNQ1 and KCNE1 genes co-assemble to form Iₖₛ, potassium channel.²⁻³ Homozygous
or compound heterozygous mutations of either KCNQ1 or KCNE1 can result in JLNS. Single heterozygous mutations found in ≥13 genes, on the other hand, cause RWS and account for the vast majority of LQTS.

Severe phenotypes are often seen in patients carrying more than one LQTS-causing mutations. Such a “cumulative effect,” occurring as either homozygous or compound heterozygous mutations, can severely impair or even completely obliterate functional expression of I\(_{\text{Ks}}\), resulting in severe variants of LQTS. Patients with JLNS often present with early onset of cardiac events, bizarre T waves and marked QTc (QT interval corrected for heart rate) prolongation. Beta-blockers, the first line therapy of LQTS, generally provide limited protection to JLNS patients. Malfunction, or complete loss of function of I\(_{\text{Ks}}\) in the inner ear is the underlying cause of the auditory impairment or sensorineural deafness in JLNS.

Among reported mutations associated with JLNS, three of 31 cases were found in Chinese individuals and include homozygous mutation T322M and a compound heterozygous mutation T2C/1149insT in KCNQ1. In this study, we report seven additional compound heterozygous mutations in KCNQ1 and one rare SNP on KCNE1, identified in three Chinese JLNS kindreds.

**MATERIALS AND METHODS**

**Study subjects**

Three JLNS kindreds, two of Han and one of Miao descent, selected from 160 LQTS families in the Chinese Channelopathy Registry, were enrolled into this study.

Written consents, approved by the Ethics Committee of Peking University People’s Hospital, were obtained from participants. Individuals were diagnosed with JLNS based on QT prolongation in the presence of profound sensorineural deafness. Phenotype characteristics were determined by the presence or absence of syncope and precipitating factors, age at first cardiac event, and changes in T wave morphology before and after therapies.

**Mutation analysis**

Genomic DNA from patients and family members was extracted from whole blood. All samples underwent polymerase chain reaction (PCR) amplification and direct sequencing in accordance to standard protocols (94°C for 3 minutes, followed by 30 cycles of 94°C for 10 seconds, 58°C for 20 seconds, and 72°C for 20 seconds, and a 5 minute extension at 72°C). The sequence of PCR primer pairs was based on reference or re-designed using Primer 3 online (KCNQ1: NM_000218.2; KCNE1: NM_000219.3) to flank all exons and intron-exon junctions (suppl.1). PCR amplification was carried out using standard protocols for all samples with the exception of exon 1c, which was amplified with the GC RICH PCR system (Roche, Rotkreuz, Zug, Switzerland) due to its high GC content. PCR products were purified by vacuum pump Axygen PCR (Microplate, Winooski, USA). Direct sequencing was carried out with BigDye Terminator (Applied Biosystems, Foster City, California, U.S.A) DNA sequencing kit (version 3.1) and 3730XL DNA Analyzer (Applied Biosystems, Foster City, California, U.S.A). DNA samples from 50 healthy Han Chinese volunteers were used as controls. The mutation data were recorded onto a publicly available database LOVD and the accession numbers are: KCNQ1_00582, 00583, 00584, 00585, 00586, 00587, 0589.

**Nomenclature of new mutations**

LQTS-causing mutations and other variants were denoted using known and accepted nomenclature. The numbering for all mutations started at the ATG initiation codon of the full-length isoform 1 of KCNQ1. The exon numbering was labeled according to Splawski et al. Frameshift mutations resulting from nucleotide insertions or deletions were annotated using the p.Ser6ProfsX2 format. Here, p.Ser6ProfsX2 denotes a frameshift change with Serine 6 as the first affected amino acid, changing into a Proline and the new reading frame ending with stop codon X at position 2 in the shifted reading frame. A substitution of either the first or the last two nucleotides of a particular exon has the capacity to alter proper mRNA splicing, regardless of whether the nucleotide substitution codes for a different amino acid (missense mutation), produces a stop codon (nonsense mutation) or does not alter the open reading frame at all (i.e., a synonymous or silent single nucleotide substitution).

**Electrocardiogram (ECG) parameters**

The paper speed for all ECGs was 25 mm/s. Each QT interval was defined as the interval between the onset of the Q wave and the end of the T wave, and was based upon the mean of 2–3 consecutive heart beats on leads II, V5 or on any of the 12 leads where the QT interval appeared to be the longest. Heart rate-corrected QT (QTc) was calculated using Bazett’s formula (QT/√RR), and a diagnosis of LQTS was considered when QTc was ≥0.47 s for males and ≥0.48 s for females. A QTc in the range of 0.44–0.47 s was considered borderline. Bifid T waves were included and U waves were excluded in the QT measurements.
RESULTS

*KCNQ1* gene screening in three Chinese JLNS kindreds revealed six disease-causing mutations responsible for JLNS and one novel mutation resulting in RWS. Four mutations previously reported in RWS caused JLNS in our patients when formed as compound mutations [Table 1].

Clinical characteristics and mutation findings in Family L148

Family L148 consisted of two asymptomatic parents and their two profoundly deaf children, a 12-year-old girl and a 5-year-old boy.

The young siblings presented with recurrent syncope starting at age 2, and markedly prolonged QTc intervals (590 ms and 600 ms, respectively) [Figure 1] at time of JLNS diagnosis. No consanguineous marriage was identified in the family and both parents had normal QT intervals. Prior to LQTS therapy, both deaf children experienced approximately 5–6 syncopal episodes per year, mostly triggered by emotional stress or physical exercise, including one reported incidence from the girl during 2008’s Wenchuan Earthquake. Considering the severity of their LQTS phenotype, both children were treated with beta-blockers (Propranolol, 2.1–2.5 mg/kg/day) and left cardiac sympathetic denervation (LCSD) in 2009. The girl reported one episode and the boy reported three episodes of syncope at the 2-year follow-up. Due to financial constraints and the possibility of unwarranted side effects, their parents refused installation of an implantable cardioverter defibrillator (ICD).

Compound heterozygous mutations, c.605-2A>G a splicing mutation and c.815G>A (p.Gly272Asp), a missense mutation of *KCNQ1*, were identified in these two siblings. Family genotyping revealed that the father carried

| ID | Sex | Deafness | SD | First event age | Syncope frequency (time/year) | QTc (ms) | Mutations | Mutation type |
|----|-----|----------|----|-----------------|-------------------------------|---------|-----------|--------------|
| Kindred L148 | | | | | | | |
| I:1 | M | N | N | N | 0 | 432 | c.605-2A>G | FS/splice |
| I:2 | F | N | N | N | 0 | 418 | none | N |
| I:3 | M | N | N | N | 0 | 411 | c.815G>A | Missense |
| I:4 | F | N | N | N | 0 | 448 | none | N |
| II:1 | F | N | N | N | 0 | 437 | none | N |
| II:2 | F | N | N | N | 0 | 448 | c.605-2A>G | FS/splice |
| II:3 | M | N | N | N | 0 | 410 | c.815G>A | Missense |
| II:4 | M | N | N | N | 0 | 387 | none | N |
| II:5 | F | N | N | N | 0 | 453 | c.815G>A | Missense |
| III:1# | F | Y | N | 2 | 5-6 | 590 | c.815G>A; c.605-2A>G | FS/splice; missense |
| III:2# | M | Y | N | 2 | 5-6 | 600 | c.815G>A; c.605-2A>G | FS/splice; missense |
| Kindred L151 | | | | | | | |
| I:1 | M | N | N | N | 0 | 506 | c.1032G>A | FS/splice |
| I:2 | F | N | N | N | 0 | 506 | c.569G>A; D85N-KCNE1 | Missense; rare SNP |
| II:1# | M | Y* | N | 2 | 1-2¶ | 465 | c.1032G>A; c.569G>A; D85N-KCNE1 | FS/splice; missense; rare SNP |
| II:2 | F | N | N | N | 0 | 411 | c.574C>T; D85N-KCNE1 | Missense |
| II:3 | F | N | N | N | 0 | 388 | ND | ND |
| II:4 | F | Y | Y | N | 0 | ND | ND | ND |
| III:1 | F | N | N | 2 | 1-2 | 480 | c.1032G>A; c.574C>T; D85N-KCNE1 | FS/splice; missense; rare SNP |
| Kindred L155 | | | | | | | |
| I:1 | M | N | N | N | 0 | 406 | c.1319delT | FS/del |
| I:2 | F | N | N | N | 0 | 444 | c.1032_1117dup | FS/dup |
| II:1* | M | Y* | N | 6 | ND | 514 | c.1319delT; c.1032_1117dup | FS/del; FS/dup |

*#Proband; *#hearing impairment; *The patient had syncope once or twice a year as a child but no syncope after 30-y-o; “F” stands for female, “M” stands for male; “N” stands for no deafness or no SCD; “ND” stands for no data; FS: Frame shift; del: Deletion; ins: Insertion; SNP: Single nucleotide polymorphism*
a heterozygous p.Gly272Asp and the mother carried a heterozygous c.605-2A>G [Figure 2]. These two mutations were absent in 100 control alleles.

Clinical characteristics and mutation finding in Family L151

The proband of Miao descent family L151 was a 46-year-old man with congenital deafness, a history of recurrent syncope and borderline QTc prolongation (460 ms). Starting at the age of 2, he experienced syncope 1–2 times per year until the age of 30 and none thereafter without any etiotropic treatment. His 17-year-old daughter, although with normal hearing, was very symptomatic. At age 2, she was diagnosed with epilepsy and treated with Phenobarbital (30–60 mg/day). While on Phenobarbital, she experienced five more seizure-like attacks, triggered by physical or mental stress. At age 12, she was diagnosed with LQTS and treated with Metoprolol 25 mg/day (the equivalent of 0.725 mg/kg of Propranolol). Her QTc on serial ECGs ranged from 480 to 530 ms [Figure 3]. During the third year of beta-blocker treatment, she experienced another syncopal episode, evoked by exercise. Metoprolol dosage was therefore adjusted to 50 mg/day (the equivalent of 1.45 mg/kg of Propranolol) and she has remained event-free for the last 2 years. Family screening revealed that one of her aunts was congenitally deaf and died suddenly at age 33. Both paternal grandparents had QTc of 506 ms, although they had never experienced any cardiac events. There was no consanguineous marriage in the family.

Compound heterozygous mutations c.1032G>A (p.Ala344Alasp) and c.569G>A (p.Arg190Gln) were identified in the proband. His daughter, who displayed a RWS phenotype, inherited c.1032G>A (p.Ala344Alasp) from him and novel missense mutation c.574C>T (p.Arg192Cys) from her mother who was a silent mutation carrier. A rare single nucleotide polymorphism (SNP), c.253G>A (p.Asp85Asn) in KCNE1, was found in the proband, his mother, sister and daughter [Figure 4]. c.253G>A (p.Asp85Asn; rs1805128) and the three pathogenic mutations identified in kindred L151 were absent in 100 control alleles.

Clinical characteristics and mutation finding in Family L155

The proband for L155 was a 16-year-old boy with significant hearing loss and required the use of a hearing aid. Between the ages of 6 and 16, he experienced four exercise-induced syncopal episodes. His ECG showed marked sinus bradycardia and a prolonged QTc of 620
Since being diagnosed with JLNS, he has been treated with Propranolol (2.0 mg/kg) and a pacemaker, and has remained event-free. His parents had normal QT intervals and their marriage was not consanguineous.

Two novel complex mutations were found in the proband of kindred L155: c.1032_1117dup (p.Ser373TrpfsX10), a frameshift mutation causing a truncated protein containing a total of 381 amino acids, and c.1319delT (p.Val440AlafsX26), another frameshift mutation resulting in a truncated protein, containing a total of 464 amino acids. His father carries a heterozygous p.Ser373TrpfsX10 only, while the mother carries a heterozygous p.Val440AlafsX26 [Figure 6]. These two mutations were absent in 100 control alleles.

**The bizarre T waves in Chinese patients with JLNS**

Marked QT prolongation associated with bizarre T waves (broad, bifid, notched or biphasic) was seen on 3/4 JLNS patients [Figures 1 and 5]. These ECG abnormalities were more prominent when patients were symptomatic, and improved after treatment. One individual who did not demonstrate such T wave anomalies was the proband of L151, a 46-year-old male with borderline QTc prolongation (460 ms) who has been event-free for the past 16 years.

**DISCUSSION**

There have been four reports regarding JLNS-causing mutations in Asian patients thus far,[11-13,18] all found in
that two KCNQ1 mutations can result in a severe variant of RWS in Chinese.

Furthermore, we found that the degree of ECG abnormalities seen in our JLNS patients was associated with the severity of their clinical manifestations. After effective treatments such as beta-blockers, left cardiac sympathetic denervation, or pacemakers, improvement was gauged by reduced syncopal episodes and less abnormal T wave morphologies on ECG readings.

Of the 31 JLNS-causing mutations previously reported [Table 2 and Figure 7], three were splicing, three nonsense, 14 missense, and 11 were frameshift (insertion/deletion) mutations. In the present study, we have identified two additional splice mutations, c.605-2A>G and c.1032G>A combined with c.815G>A and c.569G>A, respectively, in two Chinese families with JLNS. Kapplinger et al.,[20] reported in 2009 that c.605-2A>G was an LQTS-causing mutation, while the c.1032G>A transition was described by Murray et al.,[21] and by six other groups[22-27] as a cause of LQTS. However, each of these previous studies identified single mutations as causes of RWS. Our study on the other hand, demonstrates that when seen as compound mutations, they can also cause JLNS.

The two novel complex mutations identified in this study, c.1032_1117dup and c.1319delT, expanded the total number of JLNS-causing frameshift mutations in KCNQ1 to 13.

A diverse genotype/phenotype presentation was found in kindred L151 [Figures 3 and 4]. Inherited from each parent, the proband carried compound KCNQ1 mutations and showed a JLNS phenotype. Unlike most JLNS cases, he showed a mild QT interval prolongation (460 ms) and has been event-free for the last 16 years. This finding may imply that with increasing age, cardiac event rates may decrease over time in patients with JLNS, a trend
Table 2: JLNS-related mutations

| Nucleotide change | Amino acid change* | Mutation type | Region | Phenotype | Reference |
|-------------------|--------------------|---------------|--------|-----------|-----------|
| T2C               |                    | Frameshift/deletion | S1     | JLNS      | Wang RR *al*, 2011 |
| 451-452delCT      | L151fs+283X        | Frameshift/deletion | S2     | JLNS      | Chen *al*, 1999 |
| 477+1G>A          | M159               | Splice error    | S2     | JLNS+RWS  | Donger *al*, 1997 |
| G502A             | G168R              | Missense        | S2     | RWS+JLNS  | Donger *al*, 1997 |
| C513G             | Y171X              | Nonsense        | S2-S3  | JLNS      | Pippot *al*, 2001 |
| insG567           | G189               | Frameshift/insertion | S2-S3  | RWS+JLNS  | Splawski *al*, 1997 |
| G569R             | R190L              | Missense        | S2-S3  | RWS+JLNS  | Kanovsky J, 2009 |
| c.569G>A (L151)   | p.Arg190Gln        | Missense        | S2-S3  | RWS+JLNS  | Wang Q, 1996; this study |
| 572-576del        | L191fs281X         | Frameshift/deletion | S2-S3  | JLNS+RWS  | Tyson J, 2000 |
| 585delG           | R195fs+40X         | Frameshift/deletion | S2-S3  | JLNS      | Wang Z *al*, 2002 |
| G604A             | D202N              | Missense        | S3     | JLNS      | Wang Z *al*, 2002 |
| c.605-2A>G(L148)  | D202sp             | Splice error    | S3     | JLNS      | This study |
| G728A             | R243H              | Missense        | S4-S5  | RWS+JLNS  | Tyson J, 2000 |
| G743T>G44C        | W248F              | Missense        | S4-S6  | JLNS      | Ohno *al*, 2008 |
| G783C             | E261D              | Missense        | S4-S5  | JLNS      | Tyson J, 2000 |
| G806A             | G269D              | Missense        | S5     | JLNS      | Wang Z *al*, 2002 |
| c.815G>A (L148)   | p.Gly272Asp        | Missense        | S5     | JLNS      | Tyson J, 2000 |
| 828-830delCTC     | S277del            | Missense        | S5     | JLNS      | Baek JS *al*, 2010 |
| G914C             | W305S              | Missense        | Pore   | JLNS      | Neyroud *al*, 1998 |
| G917T             | G306V              | Missense        | Pore   | RWS+JLNS  | Liu W *al*, 2002 |
| 921G>A            | V308sp             | Splice error    | Pore   | JLNS      | Baek JS *al*, 2010 |
| C965T             | T322M              | Missense        | Pore-S6| JLNS      | Zhang S, 2008 |
| 1008delC          | A337fs+16          | Frameshift/deletion | S6     | JLNS      | Tyson J, 2000 |
| c.1032_1117dup(L155) | p.Ser373TrfpsX10 | Frameshift/duplication | C-term | JLNS      | This study |
| c.1032G>A (L151)  | p.Ala344Alasp      | Splice error    | S6     | JLNS      | This study |
| 1149insT          | A384fs/79          | Frameshift/deletion | C-term | JLNS      | Wang RR *al*, 2011 |
| 1188delC          | I936fsX418         | Frameshift/deletion | C-term | JLNS      | Wei *al*, 2000 |
| 1244, -7 +8       | Q415fs+107X        | Frameshift/deletion | C-term | JLNS      | Neyroud N *al*, 1997 |
| c.1319delT (L155) | p.Val440AlafsX26  | Frameshift/deletion | C-term | JLNS      | This study |
| C1552T            | R518X (2)          | Nonsense        | C-term | JLNS      | Tyson J, 2000 |
| C1588T            | Q530X (2)          | Nonsense        | C-term | JLNS      | Tyson J, 2000 |
| 1630del/ins7      | E543fsX650         | Frameshift      | C-term | JLNS      | Neyroud *al*, 1997 |
| G1686-1A          | R562fs+30X         | Splice site     | C-term | JLNS      | Tyson J, 2000 |
| C1760T            | T587M              | Missense        | C-term | RWS+JLNS  | Neyroud *al*, 1999 |
| G1766A            | G589D              | Missense        | C-term | RWS+JLNS  | Pippot *al*, 2001 |
| 1781G>A           | R594Q              | Missense        | C-term | JLNS      | Tyson J, 2000 |
| 1829del20         | P831fsX844         | Frameshift/deletion | C-term | JLNS      | Neyroud *al*, 1999 |

*Notes: The aminoacid changes for frameshift mutations shown here may not comply with the same mutation nomenclature as mentioned in the methods section. They are quoted here as they appeared in their original reports.

Generally seen in most patients with RWS. The proband’s parents were silent single-gene mutation carriers and both only presented with markedly prolonged QT intervals. His daughter carried a slightly different set of KCNQ1 compound mutations and presented with a severe RWS phenotype: A significantly prolonged QT interval (530 ms), and recurrent syncope, but without hearing impairment. This observation is consistent with other findings that may exacerbate a patient’s phenotype.

The allele frequencies of KCNE1-D85N i.e. c.253G>A (p.Asp85Asn), according to Ackerman *al*, 1998 are 0.7% in Blacks, 0.7% in Asians, 1.1% in Caucasians, and 0.0%
in Hispanics. Additional data from 95 unrelated Han Chinese individuals (50 in the present study and 45 from the International HapMap project\cite{33}) indicates that the allele frequency is 0.0% in the Chinese population. A number of studies have demonstrated that D85N can cause loss of function to both I_{kr} (the rapidly activating delayed rectifier K\(^+\) channel) and I_{Ks}, suggesting that it might function as a disease-causing variant.\cite{34,36} In the present study, both the proband of L151 and his daughter carried a couple of compound mutations on KCNQ1 accompanied by a SNP of D85N on KCNE1, but the daughter maintained normal hearing. It is our hope that the more severe LQTS phenotype seen in the father can help support Lahtinen et al.\cite{37} proposition that the KCNE1-D85N mutation might preferentially affect males.

The identification of mutations and the investigation of genotype-phenotype relationships of channelopathies have become focal points in the field of genetics and cardiology.\cite{38} Although the molecular genetic mechanisms underlying JLNS remain elusive, important progress has been made. With this study, we have expanded the mutation and phenotype spectrum of JLNS and we have substantiated the important role that compound heterozygous mutations play in the disease. Furthermore, we have documented clinical outcomes and salient ECG irregularities from our patients that with further research may potentially prove to be useful in evaluating the clinical severity of JLNS.

REFERENCES

1. Barhanin J, Lesage F, Guillemare E, Fink M, Lazdunski M, Romey G: KvLQT1 and InK (minK) proteins associate to form the IKs cardiac potassium current. Nature 1996;384:78-80.
2. Sanguinetti MC, Curran ME, Zou A, Shen J, Spector PS, Atkinson DL, et al. Assembly of the KCNQ1 channel. Nature 1997;384:40-83-380.
3. Neyroud N, Tessson F, Denjoy I, Leibovici M, Donger C, Barhanin J, et al. A novel mutation in the potassium channel gene KVLQT1 causes the Jervell and Lange-Nielsen cardioauditory syndrome. Nat Genet 1997;15:186-9.
4. Splawski I, Timothy KW, Vincent GM, Atkinson DL, Keating ME. Molecular basis of the long-QT syndrome associated with deafness. N Engl J Med 1997;336:1562-7.
5. Schulze-Bahr E, Wang Q, Wedekind H, Haverkamp W, Chen Q, Sun Y, et al. Jervell and Lange-Nielsen syndrome: Novel Compound Heterozygous Mutations in the KCNQ1 in a Korean Family. J Korean Med Sci 2010;25:1522-5.
6. Ogiño S, Guilley ML, den Dunnen JT, Wilson RB. Association for Molecular Pathology Training and Education Committee: Standard mutation nomenclature in molecular diagnostics: Practical and educational challenges. J Mol Diagn 2007;9:1-6.
7. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome. An update. Circulation 1993;88:782-4.
8. Back JS, Bae EJ, Lee SY, Park SS, Kim SY, Jung KN, et al. Jervell and Lange-Nielsen Syndrome: Novel Compound Heterozygous Mutations in the KCNQ1 in a Korean Family. J Korean Med Sci 2010;25:1522-5.
9. Inoh H, Shimizu W, Hayashi K, Yamagata K, Sakaguchi T, Ohno S, et al. Long QT syndrome with compound mutations is associated with a more severe phenotype: A Japanese multicenter study. Heart Rhythm 2010;7:1411-8.
10. Kapplinger JD, Tester DJ, Salisbury BA, Carr JL, Harris-Kerr C, Pollevick GD, et al. Spectrum and prevalence of mutations from the first 2,500 consecutive unrelated patients referred for the FAMILION long QT syndrome genetic test. Heart Rhythm 2009;6:1297-303.
11. Murray A, Donger C, Fenske C, Spillman I, Richard P, Dong YB, et al. Splicing mutations in KCNQ1: A mutation hot spot at codon 344 that produces in frame transcripts. Circulation 1999;100:1077-84.
12. Li H, Chen Q, Moss AJ, Robinson J, Goytia V, Perry JC, et al. New mutations in the KVLQT1 potassium channel that cause long-QT syndrome. Circulation 1998;97:1264-9.
13. Kanter JS, Larsen LA, Ortholm M, Agner E, Anderssen PS, Vuust J, et al. Novel donor splice site mutation in the KVLQT1 gene is associated with long QT syndrome. J Cardiovasc Electrophysiol 1998;9:620-4.
14. Inoh T, Tanaka T, Nagai R, Kikuchi K, Ogawa S, Okada S, et al. Genomic organization and mutational analysis of KVLQT1, a gene responsible for familial long QT syndrome. Hum Genet 1998;103:290-4.
15. Splawski I, Shen J, Timothy KW, Lehmann MH, Priori S, Robinson JL, et al. Spectrum of mutations in long QT syndrome genes. KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. Circulation 2006;114:2522-5.
16. Choi G, Kopplin LJ, Tester DJ, Will ML, Haglund CM, Ackerman MJ. Spectrum and frequency of cardiac channel defects in swimming-triggered arrhythmias syndrome. Circulation 2004;110:2119-24.
17. Stuurt J, Kanters JK, Andersen MP, Hardahl T, Graff C, Christiansen M, et al. Classification of the long QT syndrome based on discriminant analysis of T-wave morphology. Med Biol Eng Comput 2006;44:543-9.
18. Bhuiyan ZA, Momenah TS, Amin AS, Al-Khadra AS, Alders M, Wilde AA, et al. Identification of a Kir3.4 mutation in congenital long QT syndrome. Am J Hum Genet 2010;86:872-80.
19. Schwartz PJ, Spazzolini C, Crotti L, Bathen J, Amlie JP, Timothy K, et al. The Jervell and Lange-Nielsen syndrome: Natural history, molecular basis, and clinical outcome. Circulation 2006;113:783-90.
32. Ackerman MJ, Tester DJ, Jones GS, Will ML, Burrow CR, Curran ME. Ethnic differences in cardiac potassium channel variants: Implications for genetic susceptibility to sudden cardiac death and genetic testing for congenital long QT syndrome. Mayo Clin Proc 2003;78:1479-87.
33. International HapMap Project. Available from: http://www.hapmap.org/citinghapmap.html.en [Last accessed on 2011 Dec 25].
34. Gousas I, Nicaud V, Berthet M, Forhan A, Tirez L, Balkau B, et al. D.E.S.I.R. Study Group: Association of KCNQ1, KCNE1, KCNH2 and SCN5A polymorphisms with QTc interval length in a healthy population. Eur J Hum Genet 2005;13:1213-22.
35. Westenskow P, Splawski I, Timothy KW, Keating MT, Sanguinetti MC. Compound mutations: A common cause of severe long-QT syndrome. Circulation 2004;109:1834-41.
36. Nishio Y, Makiyama T, Itoh H, Sakaguchi T, Ohno S, Gong YZ, et al. D85N, a KCNE1 Polymorphism, Is a Disease-Causing Gene Variant in Long QT Syndrome. J Am Coll Cardiol 2009;54:812-9.
37. Lahtinen AM, Marjamaa A, Swan H, Kontula K. KCNE1 D85N polymorphism—a sex-specific modifier in type 1 long QT syndrome? BMC Med Genet 2011;12:11.
38. Zhou P, Wang J. Genetic testing for channelopathies, more than ten years progress and remaining challenges. J Cardiovasc Dis Res 2010;1:47-9.

How to cite this article: Gao Y, Li C, Liu W, Wu R, Qiu X, Liang R, Li L, Zhang L, Hu D. Genotype-phenotype analysis of three Chinese families with Jervell and Lange-Nielsen syndrome. J Cardiovasc Dis Res 2012;3:67-75.

Source of Support: Nil, Conflict of Interest: None declared.

Announcement

Android App

A free application to browse and search the journal’s content is now available for Android based mobiles and devices. The application provides “Table of Contents” of the latest issues, which are stored on the device for future offline browsing. Internet connection is required to access the back issues and search facility. The application is compatible with all the versions of Android. The application can be downloaded from https://market.android.com/details?id=comm.app.medknow.
For suggestions and comments do write back to us.