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ORIGINAL ARTICLE

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Identification of a novel pathogenic variant in *KCNH2* in an Iranian family with long QT syndrome 2 by whole-exome sequencing

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Abstract

Background: Long QT syndrome (LQTS) is a lethal cardiac condition. However, the clinical implementation of genetic testing has now made LQTS eminently treatable. Next-generation sequencing has remarkable potential for both clinical diagnostics and research of LQTS. Here, we investigated the genetic etiology in an LQTS-suspected Iranian pedigree by whole-exome sequencing and collected all *KCNH2* variants with consensus based on publications.

Methods: WES was performed on the proband of this pedigree to reveal the underlying cause of sudden cardiac death (SCD). The variant found was validated and segregated by polymerase chain reaction and Sanger sequencing. Based on the literature review, *KCNH2* variants were retrospectively analyzed to identify pathogenic variants, likely pathogenic variants, and variants of uncertain significance by using different prediction tools.

Results: WES identified an autosomal dominant nonsense variant, c.1425C>A: p.Tyr475Ter, in the *KCNH2* gene, which appeared to be the most likely cause of LQTS in this pedigree. Moreover, our comprehensive literature review yielded 511 *KCNH2* variants in association with the LQTS phenotype, with c.3002G>A (CADD Phred=49) being the most pathogenic variant.

Conclusions: Variants in the *KCNH2* gene are considered a major cause of LQTS worldwide. The detected c.1425C>A is a novel variant to be reported from Iran for the first time. This result indicates the importance of *KCNH2* screening in a pedigree with SCD cases.

KEYWORDS
KCNH2 gene, long QT syndrome, variant, whole-exome sequencing

1 | INTRODUCTION

Long QT syndrome (LQTS), as an arrhythmic inherited disorder, is determined by the QT interval prolongation in the electrocardiogram (ECG), syncope, and sudden cardiac death (SCD) owing to ventricular tachyarrhythmia.[1,2] LQTS is caused by a late potassium ion input or an increase in the sodium/calcium membrane channel, followed by a repolarizing power reduction. The

most common cause of LQTS is a genetic mutation. *KCNQ1* (potassium channel), *HERG/KCNH2* (potassium channel), and *SCN5A* (sodium channel) are the main genes leading to LQT1, LQT2, and LQT3, respectively.[3] Approximately, 45% of LQTS cases result from potassium channel changes (i.e., *KCNQ1* and *KCNH2*). *KCNE1*, *KCNE2*, *KCNJ2*, and *CACNA1c*, which encode cardiac ion channel subunits, are also correlated with LQTS.[4] *KCNH2* maps to chromosome 7q36.1 and has 19 exons. This gene encodes a voltage-gated potassium ion channel protein, Kv11.1, which leads to cardiomyocyte repolarization.[1] Thus far, *KCNH2* variants have been reported in LQTS, sudden death, and arrhythmia phenotypes.[5–7] The loss-of-function variant of *KCNH2*, as the second cause of LQT2 (MIM: #613688), makes the Kv11.1 protein dysfunction, which is followed by the loss of plasma membrane trafficking and, then, a reduction in cell-surface functional channels.[8]

The emergence of new genetic diagnostic tools such as next-generation sequencing (NGS) has augmented the detection of disease etiology and the understanding of genotype/phenotype relationships. In the present study, using whole-exome sequencing, we identified a novel pathogenic nonsense c.1425C>A: p.Tyr475Ter variant in *KCNH2*, which was the most likely cause of LQT2 in an Iranian family. In addition, we conducted a comprehensive review on all reported *KCNH2* variants in patients with LQTS. To our knowledge, the current study is the first report of this heterozygous variant in the *KCNH2* gene the world over.

2 | METHODS

2.1 | Clinical presentation and ethics

The current investigation recruited a 3-generation Iranian pedigree (Figure 1A) with 2 SCDs and 2 suspected individuals with a history of several fainting episodes. The suspected proband, a 52-year-old woman (II-5; Figure 1A), was referred to our center, Cardiogenetics Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran, for genetic testing. According to the proband, her mother (I-2; Figure 1A) and sister (II-3; Figure 1A) had SCD aged 25 and 39 years, respectively. The proband had experienced fainting at 28 years of age during pregnancy, after which time she suffered another 3 episodes of fainting. The proband's daughter (III-4; Figure 1A) had a similar experience to her mother (II-5; Figure 1A) in that she became pregnant at age 30. The echocardiographic examinations of the mother and the daughter were normal (Figure 1C); nonetheless, the Holter monitoring test showed non-sustained ventricular tachycardias.

The study was conducted based on the ethical standards of the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran (IR.RHC.REC.1400.113). Written informed consent was obtained from all the available members of the pedigree.

2.2 | Electrocardiography

Electrophysiological examination was performed by a 2-electrode voltage-clamp amplifier (TEC10CD, NPI Electronics) featuring KCl-filled electrodes of about 0.8 MU resistance.[9] The currents were measured at room temperature by applying bath solutions, including 105 mM of NaCl, 10 mM of KCl, 1.8 mM of $CaCl_2$, and 10 mM of HEPES (pH 7.2). The QT interval was measured manually via the Bazett formula.

2.3 | DNA extraction and WES

The genomic DNAs of the proband (II-5; Figure 1A) and all the available family members were extracted from peripheral blood by using the DNSol Midi kit (Roche: Product No. 50072012). WES was done on the affected proband (II-5; Figure 1A). Exome was enriched with the aid of an Agilent SureSelect All Exon V6 kit, and the library was sequenced on an Illumina HiSeq 4000 with a 100 average coverage depth. An in-house setup pipeline, comprising read alignments to the human reference genome (GRCh37/hg19) (BWA: http://bio-bwa.sourceforge.net/), the variant calling of single-nucleotide variants and insertions/deletions (GATK: http://www.broadinstitute.org/gatk/), annotation (ANNOVAR: http://annovar.openbioinformatics.org/), propitiation, and filtering, was applied. All variants with minor allele frequencies of less than 1% in the 1000 Genomes Project (http://www.1000genomes.org/), the Exome Aggregation Consortium (ExAC: http://exac.broadinstitute.org/), the Genome Aggregation Database (gnomAD: http://gnomad.broadinstitute.org/), and the Exome Sequencing Project (ESP: http://evs.gs.washington.edu/EVS/) were considered.

Our results yielded only one novel pathogenic variant, c.C1425A, in the *KCNH2* gene (NM_000238.4).

2.4 | Bioinformatics and segregation analysis

The consequence prediction of c.1425C>A: p.Tyr475Ter was obtained from online tools, namely CADD (http://cadd.gs.washington.edu/home) and MutationTaster (http://www.mutationtaster.org/). Additionally, ClustalW (http://www.genome.jp/tools-bin/clustalw) was used to check the conservation in the variant region, and the American College of Medical Genetics standards were applied to interpret the sequence variants.[10] Segregation analysis was conducted on the available members of the pedigree. To that end, primers were designed surrounding the identified variant by using the Primer3 version 0.4.0 server (http://bioinfo.ut.ee/primer3-0.4.0/). Polymerase chain reaction (PCR) was performed with the aid of a SimpliAmp Thermal Cycler (Thermo Fisher Scientific) with 10 pmol/L primers (forward primer: TGCTGCTGGTCATCTACACG and reverse primer: CAGAGCGAGCATCAGAGGT), 100 ng of DNA, 200 mmol/L of dNTP, 1.5 mmol/L of $MgCl_2$, and 1 U of Taq DNA polymerase (Amplicon). The PCR schedule was incubation at 95°C for 5 min, and then 35 cycles (40 s at 95°C, 30 s at 59°C, and 30 s at 72°C). Subsequently, the PCR products were sequenced on an

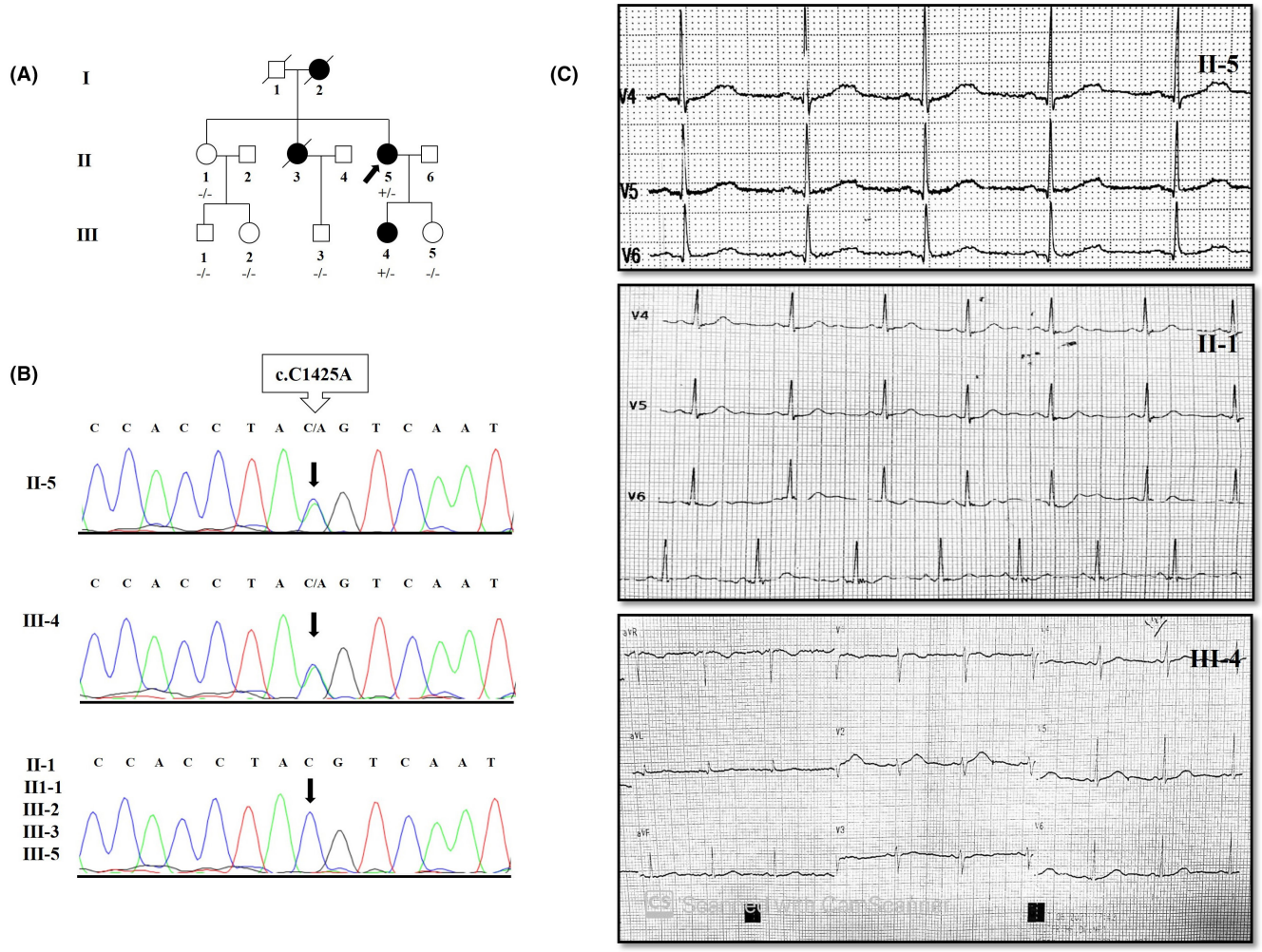

FIGURE 1 The image presents the pedigree, the chromatogram, and the electrocardiogram. (A) The LQTS family pedigree is presented herein. The black symbols indicate the affected members, and white symbols denote the normal members. The arrow represents the proband. (B) The image illustrates the chromatograms of a novel pathogenic variant, c.C1425A, in the *KCNH2* gene detected in the affected members of the pedigree. (C) The image demonstrates the electrocardiogram of the proband (II-5), as well as the suspected (III-4) and normal (II-1) individuals. The QTs in II-5 and III-4 were 480 ms and 476 ms, respectively, and 425 ms in II-1. A bifid T wave was also observed in II-5.

ABI Sequencer 3500XL PE (Applied Biosystems) and Codon Code Aligner version 7.1.2 (CodonCode Corp).

2.5 | Structural modeling and variant effects on splicing

For the evaluation of variant effects, structural modeling (3D) of the KCNH2 protein was applied by using the SWISS-MODEL server (http://swissmodel.expasy.org/). The FASTA (canonical) sequence of the KCNH2 protein was obtained from the UniProt online database (UniProt ID: Q12809) (http://www.uniprot.org/) and entered as an input. The SWISS-MODEL makes structures of target proteins and includes conserved ligands by drawing upon HHblits and BLAST. It displays an estimated model quality per residue based on a Qualitative Model Energy ANalysis (QMEAN) score, and CAMEO checks the SWISS-MODEL accuracy. Additionally, the Berkeley Drosophila Genome Project (BDGP) (http://www.fruitfly.org/seq_tools/splice.html) and the Human Splicing Finder online server (HSF) V.3.1 (http://umd.be/Redirect.html) were applied to analyze variant consequences on splicing.

2.6 | Search strategy and data extraction

Variants reported in ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/) and the Human Gene Mutation Database (HGMD) (http://www.hgmd.cf.ac.uk/ac/index.php) were surveyed up to September 2022. In addition, a combination of the keywords "*KCNH2*" and "long QT syndrome" and "*KCNH2* mutations" and "*KCNH2*" [title/abstract] was applied by searching PubMed and Google Scholar. The variants consisted of pathogenic variants, likely pathogenic variants, and variants of unknown significance. All the collected variants were analyzed with different bioinformatics tools such as CADD, SIFT, PolyPhen-2, PROVEAN, and MutationTaster (Table 1). The inclusion

TABLE 1 Bioinformatics analysis of pathogenic, likely pathogenic, unknown significance reported variants in *KCNH2* gene related to long QT.

No.	HGVS DNA	HGVS protein	Chromosome 7 position (hg19)	dbSNP	CADD	SIFT	Polyphen-2	PROVEAN	MutationTaster	ClinVar	Protein region
1	c.3365C>G	p.P1122R	150642568	rs531460655	12.7	D	PD	N	PO	VUS	TR4
2	c.3394C>G	p.P1132A	150642539	rs786205422	16.24	D	PD	N	DC	VUS	TR4
3	c.2956_2960dupCCCCT	p.S988PfsX71	150947611	N/A	N/A	D	N/A	N/A	DC	N/A	LC
4	c.1859G>A	p.S620N	150648622	N/A	24.8	D	PD	D	DC	VUS	LC
5	c.442C>T	p.R148W	150656690	rs139544114	24.2	D	PD	D	DC	VUS	PAC
6	c.2108delA	p.H703PfsX11	150950958	N/A	22	D	PD	D	DC	N/A	LC
7	c.140G>A	p.G47D	150671966	N/A	25.8	D	PD	D	DC	N/A	PAS
8	c.2810G>A	p.S937N	150644849	rs199473540	22.6	T	PD	N	PO	VUS	TR2
9	c.212G>A	p.G71E	150671894	N/A	23.1	D	PD	D	DC	LP	LC
10	c.2759G>A	p.R920Q	150644900	rs199473670	21.4	T	B	N	PO	VUS	TR2
11	c.1421C>T	p.T474I	150649649	N/A	26.4	T	PD	D	PO	P	LC
12	c.2467C>T	p.R823W	150646069	rs199473538	25.5	D	PD	D	DC	LP	LC
13	c.1849T>C	p.F617L	150648632	rs796052195	24.7	D	PD	D	DC	VUS	LC
14	c.1831T>G	p.Y611D	150648650	rs199472942	24.7	D	PD	D	DC	LP	LC
15	c.307+2T>A	N/A	150974709	rs796052196	5.63	N/A	N/A	N/A	PO	LP	N/A
16	c.77G>T	p.S26I	150974941	rs199472827	2.98	D	B	D	PO	N/A	LC
17	c.87C>A	p.F29L	150672019	rs199472830	24.1	D	B	D	DC	P	LC
18	c.92T>G	p.I31S*	150672014	rs199472833	32	D	PD	D	DC	N/A	LC
19	c.157G>C	p.G53R	150671949	rs199472842	29.5	D	PD	D	DC	LP	PAS
20	c.164C>T	p.S55L*	150671942	rs199472844	28.7	D	PD	D	DC	P/VUS	PAS
21	c.193A>C	p.T65P	150671913	rs121912511	25.5	D	PD	D	DC	P	PAS
22	c.209A>G	p.H70R	150671897	rs199473419	22.5	D	PD	D	DC	LP	PAS
23	c.232G>C	p.A78P	150671874	rs199472848	21.4	T	B	D	DC	N/A	PAS
24	c.254C>T	p.A85V	150671852	rs199473494	28.4	D	PD	D	DC	N/A	LC
25	c.299G>A	p.R100Q*	150671807	rs199472855	24.3	D	N/A	N	PO	P/VUS	PAC
26	c.395–456del GGTGGGGGGGC CCCGGTGGTTGGTGTCAT GAGCCGGGGACCCCACCA TGTCCTTCTCCATCA	p. V132Efs*179	150656676_150656737	N/A	N/A	N/A	N/A	N/A	DC	N/A	PAC
27	c.453–454nsCC	P.T152Pfs*15	150656678_150656679	N/A	20	N/A	N/A	N/A	DC	N/A	LC
28	c. 453–454 insC	P.T152Hfs*180	150656678_150656679	N/A	24	N/A	N/A	N/A	DC	N/A	LC
29	c.insGGTGCGGT544–545	P.S182Wfs*22	150655518_150655519	N/A	36	N/A	N/A	N/A	DC	N/A	LC
30	c.545C>A	p.S182X*	150655518	rs1057517742	33	N/A	N/A	N/A	DC	P	LC

(Continues)

TABLE 1 (Continued)

No.	HGVS DNA	HGVS protein	Chromosome 7 position (hg19)	dbSNP	CADD	SIFT	Polyphen-2	PROVEAN	MutationTaster	ClinVar	Protein region
31	c.685G>T	p.E229X*	150655378	rs730880116	35	N/A	N/A	N/A	DC	P	LC
32	c.712G>A	p.G238S*	150655351	rs199473501	11.1	T	N/A	N	PO	N/A	TR1
33	c.916G>T	p.G306W*	150655147	rs199472884	35	D	N/A	D	DC	LP	TR1
34	c.959C>T	p.S320L*	150654548	rs199472886	24.9	D	N/A	D	DC	N/A	LC
35	c.del981–991	P.Y327*	150654516_150654526	N/A	N/A	N/A	N/A	N/A	DC	N/A	LC
36	c.982C>T	p.R328C*	150654525	rs199473505	29.9	D	N/A	D	DC	B/LP/VUS	LC
37	c.1096C>T	p.R366*	150654411	rs794728364	38	N/A	N/A	N/A	DC	P	LC
38	c.1128G>A	p.Q376sp	150654379	rs770047651	33	D	N/A	N/A	DC	P/LP/VUS	LC
39	c.1259A>G	p.Y420C*	150649811	rs199473507	28	D	N/A	D	DC	N/A	LC
40	c.1262C>T	p.T421M*	150649808	rs199472894	26.8	D	N/A	D	DC	LP/US	LC
41	c.1264G>A	p.A422T*	150649806	rs199472895	27.6	D	N/A	D	DC	P	LC
42	c.1280A>C	p.Y427S*	150649790	rs199472897	27.2	D	N/A	D	DC	LP	LC
43	c.1366G>T	p.D456Y*	150649704	rs199473510	28.0	D	N/A	D	DC	N/A	LC
44	c. 1423–1425 delTAC	p.Y475del*	150649645_150649647	N/A	10	D	N/A	D	DC	N/A	LC
45	c.1600C>T	p.R534C	150648881	rs199472916	25.0	D	PD	D	DC	P	LC
46	c.1655T>C	p.L552S	150648826	rs199472918	24.5	D	PD	D	DC	P	LC
47	c.1681G>A	p.A561T	150648800	rs199472921	25.4	D	PD	D	DC	P	LC
48	c.1682C>T	p.A561V	150648799	rs121912504	25.5	T	PD	D	DC	LP	LC
49	c.1685A>C	p.H562P*	150648796	rs199472922	24.4	D	N/A	D	DC	N/A	LC
50	c.1711A>C	p.I571L*	150648770	rs199472928	24.9	T	N/A	N	DC	N/A	LC
51	c.1714G>A	p.G572S*	50648767	rs9333649	5.32	T	N/A	D	DC	P	LC
52	c.1744C>T	p.R582C	150648737	rs121912508	24.5	D	PD	D	DC	P	LC
53	c.1750G>A	p.G584S	150648731	rs199473428	23.9	T	PD	D	DC	LP	LC
54	c.1762A>G	p.N588D	150648719	rs199473431	22.7	T	PD	D	DC	N/A	LC
55	c.1787C>G	p.P596R*	150648694	rs199472933	14.83	T	PD	D	DC	N/A	LC
56	c.1810G>A	p.G604S	150648671	rs199473522	25.6	T	PD	D	DC	P	LC
57	c.1838C>T	p.T613M	150648643	rs199473524	24.3	T	PD	D	DC	P/LP	LC
58	c.1841C>T	p.A614V	150648640	rs199472944	25.0	D	PD	D	DC	P	LC
59	c.1864C>T	p.L622F*	150648617	rs199473525	25.1	D	N/A	D	DC	US	LC
60	c.1868C>T	p.T623I*	150648613	rs199472950	24.7	D	N/A	D	DC	N/A	LC
61	c.1882G>A	p.G628S	150951511	rs121912507	3.10	D	PD	D	DC	P	LC

TABLE 1 (Continued)

No.	HGVS DNA	HGVS protein	Chromosome 7 position (hg19)	dbSNP	CADD	SIFT	Polyphen-2	PROVEAN	MutationTaster	ClinVar	Protein region
62	c.1883G>T	p.G628V*	150648599	rs121912507	24.6	D	PD	D	DC	N/A	LC
63	c.1889T>C	p.V630A	150648592	rs199473526	24.4	T	PD	D	DC	N/A	LC
64	c.1898A>G	p.N633S	150648583	rs199472961	24.0	T	PD	D	DC	LP	LC
65	c.1904A>T	p.N6351*	150648577	rs199472964	25.3	N/A	N/A	N/A	DC	VUS	LC
66	c.1918T>G	p.F640V*	150648563	rs199473529	25.4	N/A	N/A	D	DC	N/A	LC
67	c.1922C>T	p.S641F*	150648559	rs199472971	26.7	N/A	N/A	D	DC	P	LC
68	c.2011–2025del TGTGGTAGCGGGC	p.671–675del*	150648131_150648143	N/A	20	N/A	N/A	D	DC	N/A	LC
69	c.2145G>A	p.A715=	150648009	rs794728384	20.6	N/A	N/A	N	DC	US	LC
70	c.2162C>T	p.P721L*	150647492	rs199472986	30	N/A	N/A	D	DC	LP	LC
71	c.2320G>T	p.D774Y*	150647334	rs199472995	29.9	N/A	N/A	D	DC	LP	LC
72	c.2350C>T	p.R784W	150647304	rs12720441	28.6	D	PD	D	DC	LP/VUS	LC
73	c.2364G>C	p.E788D*	150647290	rs199473535	25.	D	PD	D	DC	N/A	LC
74	c.2398+5G>T	N/A	150647251	rs1554425149	20.5	N/A	N/A	N/A	DC	LP	N/A
75	c. 2395 delC	P.L799Wfs*1	150647259_150647259	N/A	16	N/A	N/A	N/A	DC	N/A	LC
76	c.2398+1G>C	N/A	150647255	rs794728391	33	N/A	N/A	N/A	DC	p	N/A
77	c.2414T>G	p.F805C	150646122	rs199472999	31	T	PD	D	DC	LP	LC
78	c.2458G>A	p.G820R*	150646078	rs199473001	29.5	T	N/A	N	DC	US	LC
79	c.2464G>A	p.V822M	150646072	rs121912506	25.6	D	PD	D	DC	p	LC
80	c.2510A>G	p.D837G*	150646026	rs199473004	28.5	D	N/A	D	DC	LP	LC
81	c.2587C>T	p.R863X*	150645949	rs773724817	41	N/A	N/A	N/A	DC	p	LC
82	c.2592+3G>A	p.D864/sp*	150645941	rs906562788	14.96	N/A	N/A	N/A	DC	LB/VUS	LC
83	c.2626G>T	p.E876X*	150645598	rs1554424688	42	N/A	N/A	N/A	DC	p	TR2
84	c.2660G>A	p.R887H*	150645564	rs199473432	24.5	N/A	N/A	N/A	DC	LP/VUS	TR2
85	c. 2705 delC	p.Q901fs/71*	150644954_150644954	N/A	26	N/A	N/A	N/A	DC	N/A	TR2
86	c. 2728–2762 del CCCCGGCT ACTCGGCCCTGCCCCCGC CCGGCCCGG	p.P910fs/16*	150644897_150644931	N/A	N/A	N/A	N/A	N/A	DC	N/A	TR2
87	c.2738C>T	p.A913V*	150644921	rs77331749	19.85	N/A	N/A	N	PO	LB/LP/VUS	TR2
88	c. 2762 delG	p.R920fs/51	150644897_150644897	N/A	28	N/A	N/A	N/A	DC	N/A	TR2
89	c. 2766 delG	p.R922fs/50*	150644893_150644893	N/A	32	N/A	N/A	N/A	DC	N/A	TR2
90	c.2773G>A	p.G925R*	150644886	Rs199473010	22.0	N/A	N/A	N	PO	N/A	TR2

(Continues)

TABLE 1 (Continued)

No.	HGVS DNA	HGVS protein	Chromosome 7 position (hg19)	dbSNP	CADD	SIFT	Polyphen-2	PROVEAN	MutationTaster	ClinVar	Protein region
91	c.2785–2786 insG	p.G928fs/10*	150644873_150644874	N/A	31	N/A	N/A	N/A	DC	N/A	TR2
92	c.2948C>T	p.T983I*	150644711	rs149955375	24.0	N/A	N/A	N	DC	LB/VUS	LC
93	c.2987A>T	p.N996I*	150644581	rs199473018	27.9	N/A	N/A	D	DC	p	LC
94	c. 3014 del G	p.R1005fs/50*	150644554_150644554	N/A	16	N/A	N/A	N/A	DC	N/A	LC
95	c.3040C>T	p.R1014X	150644528	rs794728403	46	N/A	N/A	N/A	DC	p	LC
96	c. 3098–3099 insCG	p.R1033fs/23*	150644469_150644470	N/A	15	N/A	N/A	N/A	DC	N/A	TR3
97	c.del3101–3108	p.R1033fs/81*	150644460_150644467	N/A	24	N/A	N/A	N/A	PO	N/A	TR3
98	c.3103del C	p.P1034fs/21*	150644465_150644465	N/A	28	N/A	N/A	N/A	DC	N/A	TR3
99	c.3107G>A	p.G1036D*	150644461	rs199473022	22.6	N/A	N/A	D	DC	VUS	TR3
100	c.3157G>T	p.E1053*	150644138	N/A	47	N/A	N/A	N/A	DC	N/A	LC
101	c. 3168 insT	p.L1056fs/61*	150644126_150644127	N/A	25.8	N/A	N/A	N/A	DC	N/A	LC
102	c. 3173 insG	p.S1057fs/60*	150644121_150644122	N/A	29.5	N/A	N/A	N/A	DC	N/A	LC
103	c.128A>G	p.Y43C	150671978	rs199472836	24.1	D	B	D	DC	LP	PAS
104	c.146G>A	p.C49Y	150671960	rs199472840	29.3	D	B	D	DC	N/A	PAS
105	c.173A>C	p.E58A	150671933	rs199472847	24.2	D	B	N	DC	P	PAS
106	c.173A>G	p.E58G	150671933	rs199472847	25.	D	B	D	DC	P	PAS
107	c.174G>C	p.E58D	150671932	rs199473492	21.4	T	PD	D	DC	N/A	PAS
108	c.202T>C	p.F68L	150671904	rs199473417	26.7	D	PD	D	DC	LP	PAS
109	c.211G>C	p.G71R	150671895	rs199473420	26.0	D	PD	D	DC	P	LC
110	c.221C>T	p.T74M	150671885	rs199473422	25.0	D	PD	D	DC	LP/VUS	LC
111	c.244-252del	p.IAQ82-84del	150671854_150671862	N/A	23.8	N/A	N/A	N/A	DC	N/A	LC
112	c.308-310insATG	S104*	150656823	N/A	22.6	N/A	N/A	N/A	DC	N/A	PAC
113	c.337-339del	p.V113=	150656793_150656795	N/A	31	N/A	N/A	D	DC	N/A	PAC
114	c.558_565delinsTTCGC	p.A185fs+143X	150655498_150655505	N/A	N/A	N/A	N/A	N/A	PO	N/A	LC
115	c.576delG	p.G192fs+7X	150655487_150655487	N/A	24	N/A	N/A	N/A	DC	N/A	LC
116	c.578-582del CCGTG	p.G192fs+135X	150655481_150655485	N/A	23.5	N/A	N/A	N/A	DC	N/A	LC
117	c.735-736InsCC	p.P245fs+114X	150655327_150655328i	N/A	22.1	N/A	N/A	N/A	DC	N/A	LC
118	c.1171C>T	p.Q391X	150649899	N/A	39	N/A	N/A	N/A	DC	P	LC
119	c.1229G>C	p.W410S	150649841	rs199472892	30	D	PD	D	DC	N/A	LC
120	c.2255G>A	p. R752Q	150950311	rs121912512	31	D	N/A	N/A	DC	LP	LC
121	c.1277C>A	p.P426H	150649793	rs199472896	27.4	D	PD	D	DC	N/A	LC

TABLE 1 (Continued)

No.	HGVS DNA	HGVS protein	Chromosome 7 position (hg19)	dbSNP	CADD	SIFT	Polyphen-2	PROVEAN	MutationTaster	ClinVar	Protein region
122	c.1279 T>C	p.Y427H	150649791	rs199472898	27.6	D	PD	D	DC	N/A	LC
123	c.1283C>T	p.S428L	150649787	rs199472899	24.7	T	PD	D	DC	VUS	LC
124	c.1378G>T	p.D460Y	150649692	rs199472903	28.6	D	PD	D	DC	N/A	LC
125	c.1501G>C	p.D501H	150649569	rs199472912	27.1	D	PD	D	DC	N/A	LC
126	c.1601G>T	p.R534L	150648880	rs199473516	26.6	D	PD	D	DC	VUS	LC
127	c.1613-1619del AGCTGGA	p.R537fs+24X	150648862_150648868	N/A	30	D	N/A	N/A	DC	N/A	LC
128	c.1697G>C	p.C566S	150648784	rs199472925	25.5	T	PD	D	DC	N/A	LC
129	c.1701delC	P.W568Gfs*26	150648780_150648780	N/A	25.5	D	N/A	N/A	DC	N/A	LC
130	c.1702 T>C	p.W568R	150648779	rs199472927	25.8	D	PD	D	DC	N/A	LC
131	c.1711A>G	p.I571V	150648770	rs199472928	24.0	T	PD	N	DC	P/VUS	LC
132	c.1715G>A	p.G572D	150648766	rs199473423	25.8	D	PD	D	DC	N/A	LC
133	c.1745G>T	p.R582L	150648736	rs199473426	25.6	T	PD	D	PO	LP	LC
134	c.1825G>C	p.D609H	150648656	rs199472941	24.9	D	PD	D	DC	N/A	LC
135	c.1843C>T	p.L615F	150648638	rs199472945	24.1	T	PD	D	DC	LP	LC
136	c.1863C>G	p.S621R	150648618	rs199472949	24.4	D	PD	D	DC	N/A	LC
137	c.1877G>C	p.G626A	150648604	rs199472952	23.6	D	PD	D	DC	N/A	LC
138	c.1911G>C	p.E637D	150648570	rs199472966	23.6	T	PD	D	PO	P	LC
139	c.1930G>T	p.V644F	150648551	rs199472972	25.3	T	PD	D	DC	N/A	LC
140	c.1967T>G	p.F656C	150648187	rs199472977	26.7	D	PD	D	DC	N/A	LC
141	c.1979C>T	p.S660L	150648175	rs199472979	28.4	D	PD	D	DC	LP//P/VUS	LC
142	c.2087G>C	p.R696P	150648067	rs199473531	28.8	D	PD	D	DC	N/A	LC
143	c.2231delG	p.F743fs+12X	150647423_150647423	N/A	16	N/A	N/A	N/A	DC	N/A	LC
144	c.2398+3A>G	N/A	150647253	rs1554425151	22	N/A	N/A	N/A	DC	VUS	N/A
145	c.2398+3A>T	N/A	150647253	N/A	26	N/A	N/A	N/A	DC	N/A	N/A
146	c.2398G>T	p.G800W	150647257	N/A	14.11	D	PD	D	DC	N/A	LC
147	c.2452T>C	p.S818P	150646084	rs199473537	26.1	D	PD	D	DC	N/A	LC
148	c.2494A>T	p.K832X	150646042	rs794728393	40	N/A	N/A	N/A	DC	N/A	LC
149	c.2581A>C	p.N861H	150645955	rs199473007	25.3	D	PD	D	DC	N/A	LC
150	c.2638-2648del GGCTTCAGTCG	p.G879fs+35X	150645576_150645586	N/A	N/A	N/A	N/A	N/A	DC	N/A	TR2
151	c.2676-2682del CAGGCGC	p.R892fs+79X	150645542_150645548	N/A	N/A	N/A	N/A	N/A	DC	N/A	TR2
152	c.2738-2739insCGGC	p.A913fs62X	150644920_150644921	N/A	N/A	N/A	N/A	N/A	DC	N/A	TR2

(Continues)

TABLE 1 (Continued)

No.	HGVS DNA	HGVS protein	Chromosome 7 position (hg19)	dbSNP	CADD	SIFT	Polyphen-2	PROVEAN	MutationTaster	ClinVar	Protein region
153	c.2775del	p.G925fs+47X	150644884_150644884	N/A	16	N/A	N/A	N/A	DC	N/A	TR2
154	c.2781G>A	p.W927X	150644878	N/A	42	N/A	N/A	N/A	DC	N/A	TR2
155	c.2895-2905del AGAGCCGCC	p.G965+148X	150644756_150644764	N/A	N/A	N/A	N/A	N/A	PO	N/A	TR2
156	c.2903C>T	p.P968L	150644756	rs199473017	16.73	D	B	N	PO	VUS	TR2
157	c.3045C>A	p.C1015X	150644523	N/A	20.2	N/A	N/A	N/A	DC	N/A	TR3
158	c.3093-3106del TCGGCGGCCCCGGG	p.G1031fs+86X	150644462_150644475	N/A	39	N/A	N/A	N/A	DC	N/A	LC
159	c.3093-3099del/insTTCGC	p.G1031fs+20X	150644470_150644474	N/A	19.2	N/A	N/A	N/A	DC	N/A	LC
160	c.3099delG	p.R1033fs+22X	50644469_150644469	N/A	15.2	N/A	N/A	N/A	DC	N/A	LC
161	c.3100delC	p.P1034fs+63X	150644468_150644468	N/A	20	N/A	N/A	N/A	DC	N/A	LC
162	c.3154del	p.R1051fs+4X	150644141_150644141	N/A	21	N/A	N/A	N/A	DC	N/A	LC
163	c.3304InsC	p.P1101fs+16X	150643990_150643991	N/A	26.2	N/A	N/A	N/A	DC	N/A	LC
164	c.3397-3398del ACA	p.T1133fs+135X	150642534_150642536	N/A	26.7	N/A	N/A	N/A	DC	N/A	LC
165	c.3457C>T	p.H1153Y	150642476	rs199473035	24.2	D	PD	N	DC	VUS	TR4
166	c.2399-28A>G	N/A	150949077	N/A	17.86	D	N/A	N/A	DC	N/A	N/A
167	c.1687T>G	p.W563C*	150951706	rs199472923	0.43	T	N/A	D	DC	N/A	LC
168	c.1697G>T	p.C566F	150951696	rs199472925	4.31	D	PD	D	DC	N/A	LC
169	c.1887C>A	p.N629K	150951506	rs41307295	1.35	T	PD	D	DC	N/A	LC
170	c.3221 del T	p.Val1074f	150644074_150644074	N/A	13.2	D	B	N	DC	N/A	LC
171	c. 3924A>C	p.F106L*	150675406	N/A	16.73	D	B	D	DC	N/A	LC
172	c.1468G>A	p.A490T	150952514	rs28928905	3.06	D	PD	D	DC	P	LC
173	c.1474C>T	p.H492Y*	150649596	rs199472910	26.4	D	PD	D	DC	LP	LC
174	c.1232_1234delinsTTTGAA	p.D411Vfs*2	150649837	N/A	N/A	N/A	N/A	N/A	DC	N/A	LC
175	c.2536C>T	p.P846T*	150646000	rs199473006	27.5	T	N/A	D	DC	LP/VUS	LC
176	c.1478A>T	p.Y493F	150952504	rs199472911	5.80	D	PD	D	DC	N/A	LC
177	c.1285G>C	p.A429P	150952697	rs199473508	4.36	D	B	D	DC	N/A	LC
178	c.2945delAC	p.Pro982fs	150644713_150644714	N/A	26	N/A	N/A	N/A	DC	N/A	TR2
179	c.157G>A	p.G53S	150671949	rs199472842	28.7	D	PD	D	DC	N/A	LC
180	c.182A>G	p.Q61R	150671924	N/A	24.6	D	B	D	DC	N/A	LC
181	c.235_242delGCCGCGCA	p.A79Dfs*63	150671864_150671871	N/A	N/A	N/A	N/A	N/A	DC	N/A	LC
182	c.453delC	p.T151Pfs*	150656679_150656679	N/A	30	N/A	N/A	N/A	DC	N/A	LC

TABLE 1 (Continued)

No.	HGVS DNA	HGVS protein	Chromosome 7 position (hg19)	dbSNP	CADD	SIFT	Polyphen-2	PROVEAN	MutationTaster	ClinVar	Protein region
183	c.526C>T	p.R176W	150655537	rs36210422	23.4	D	PD	D	PO	LB/VUS	LC
184	c.1094A>G	p.E365G	150654413	N/A	25.6	D	PD	D	DC	N/A	LC
185	c.1688G>A	p.W563*	150648793	N/A	40	D	PD	N/A	DC	P	LC
186	c.1706A>G	p.Y569C	150648775	N/A	25.6	D	PD	D	DC	N/A	LC
187	c.2254C>T	p.R752W	150647400	rs199472990	25.6	T	PD	D	DC	P	LC
188	c.2312A>G	p.H771R	150647342	N/A	29.1	T	PD	D	DC	VUS	LC
189	c.2453C>T	p.S818L	150948995	rs121912510	12.76	D	PD	D	DC	LP	LC
190	c.2959_2960del CT	p.L987Vfs*131	150644699_150644700	N/A	27.3	N/A	N/A	N/A	DC	N/A	LC
191	c.3107dupG	p.D1037Rfs*82	150644461	N/A	N/A	N/A	N/A	N/A	N/A	N/A	TR3
192	c.284A>G	p.E95G	150671822	N/A	27.8	D	PD	D	DC	N/A	PAC
193	c.371T>C	p.M124T	150656761	rs199472862	25.2	D	PD	D	DC	N/A	PAC
194	c.547–553delGGCGGCG	p.G185fsX198	150655510_150655516	N/A	N/A	N/A	N/A	N/A	DC	N/A	LC
195	c.2311–2332del/insTC	p.H771fsX796	150647322_150647343	N/A	N/A	N/A	N/A	N/A	DC	N/A	LC
196	c.260T>C	P.L87P*	150671846	rs199473495	26.4	T	N/A	D	DC	N/A	LC
197	c.296A>C	P.Y99S*	150671810	rs199472854	25.6	D	N/A	D	DC	N/A	PAC
198	c.582-587delCCGTG	p.G192fs328*	150655476_150655479	N/A	N/A	N/A	N/A	N/A	DC	N/A	LC
199	c.1039C>T	p.P347S	150654468	rs138776684	22.0	T	PD	N	DC	B /LB/VUS	LC
200	c.1341C>A	p.Y447*	150649729	N/A	0.15	D	N/A	N/A	DC	N/A	LC
201	c.1501G>A	p.D501N*	150649569	rs199472912	27.8	D	N/A	D	DC	LP	LC
202	c.2092G>T	p.E698*	150648062	N/A	41	N/A	N/A	N/A	DC	N/A	LC
203	c.2471insG	p.R823fs828*	150646064_150646065	N/A	13.2	N/A	N/A	N/A	DC	N/A	LC
204	c.2616delC	p.P872fs877*	150645608_150645608	N/A	15.9	N/A	N/A	N/A	DC	N/A	LC
205	c.1467C>T	p.I489I	150649603	rs740952	11.83	T	N/A	N	PO	B	LC
206	c.1539C>T	p.F513F	150649531	rs1805120	8.73	T	N/A	N	PO	B	LC
207	c.1692A>G	p.L564L	150648789	rs1805121	11.50	T	N/A	N	PO	B	LC
208	c.1956T>C	p.Y652Y	150648198	rs1137617	6.86	T	N/A	N	PO	B	LC
209	c.2690A>C	p.K897T	150648198	rs1137617	38	D	B	N	PO	B	LC
210	c.IVS13+22G>A	N/A	150623552	N/A	20	N/A	N/A	N/A	N/A	N/A	N/A
211	c.712G>C	p.G238R	150655351	N/A	8.25	T	B	N	PO	N/A	TR1
212	c.515C>T	p.A172V	150655548	rs794728355	19.89	T	B	N	PO	VUS	LC
213	c.1027delC	p.L343Sfs*17	150654480_150654480	rs1131690873	17	N/A	B	N/A	DC	N/A	LC
214	c.1067G>A	p.R356H	150654440	rs730880118	24.6	D	PD	N	DC	VUS	LC

(Continues)

TABLE 1 (Continued)

No.	HGVS DNA	HGVS protein	Chromosome 7 position (hg19)	dbSNP	CADD	SIFT	Polyphen-2	PROVEAN	MutationTaster	ClinVar	Protein region
215	c.2115delG	c.W705Cfs*9	150950951	rs794728443	13.2	N/A	N/A	N/A	DC	N/A	LC
216	c.2419G>T	p.E807*	150646117	N/A	41	N/A	N/A	N/A	DC	N/A	LC
217	c.2565C>G	p.S855R	150645971	N/A	24.0	D	B	N	DC	N/A	LC
218	c.2639G>T	p.G880V	150645585	N/A	22.2	D	PD	D	DC	N/A	TR2
219	c.2669C>G	p.S890C	150645555	N/A	23.0	D	PD	N	DC	N/A	TR2
220	c.381_408delCAATTTCGAGG TGGTGATGGAGAAGGAC	N/A	150656724_150656751	N/A	N/A	N/A	N/A	N/A	DC	N/A	N/A
221	c.1120G>T	p.V374F	150654387	N/A	24.6	D	PD	D	DC	N/A	LC
222	c.1243-1256delCTGC TGCTGGTCAT	p.I414fs98X	150649814_150649827	N/A	N/A	N/A	N/A	N/A	DC	N/A	LC
223	c.1332G>T	p.E444D	150649738	rs9770044	0.18	D	B	N	PO	N/A	LC
224	c.1387T>C	p.F463L	150649683	rs199472904	27.8	D	PD	D	DC	N/A	LC
225	c.1424A>G	p.Y475C	150649646	rs199472907	26	D	PD	D	DC	N/A	LC
226	c.1515T>G	p.E505D	150649555	N/A	11.90	D	N/A	N/A	DC	N/A	LC
227	c.3110A>T	p.D1037V	150644458	N/A	23.6	D	PD	D	DC	N/A	TR3
228	c.1605G>A	p.V535M	150648876	N/A	10.18	D	PD	D	DC	N/A	LC
229	c.1619-1637delCCGTAC TCTGAGTAGCGAT	p.L539fs47X	150648845_150648862	N/A	N/A	N/A	N/A	N/A	DC	N/A	LC
230	c.1676T>A	p.L559H	150648805	rs199472920	25.3	D	PD	D	DC	N/A	LC
231	c.1800C>A	p.S600R	150648681	N/A	19.31	D	B	D	DC	N/A	LC
232	c.1810G>T	p.G604C	150648671	N/A	26.3	D	PD	D	DC	N/A	LC
233	c.1848C>A	p.Y616X	150648633	N/A	38	N/A	N/A	N/A	DC	N/A	LC
234	c.1956C>A	p.Y652X	150648198	N/A	38	N/A	N/A	N/A	DC	N/A	LC
235	c.2402A>C	p.K801T	150646134	N/A	26.9	D	PD	D	DC	N/A	LC
236	c.2453C>G	p.S818W	150646083	N/A	31	D	PD	D	DC	N/A	LC
237	c.442 C>T	p.R148 W	150656690	rs139544114	24.2	N/A	N/A	N/A	DC	N/A	LC
238	c.2038delG	p.V680Cfs*34	150648116	N/A	N/A	N/A	N/A	N/A	DC	N/A	LC
239	c.1897A>G	p.N633D	150648584	rs199472960	24.8	T	PD	D	DC	N/A	LC
240	c.2532_2533delAC	p.R744fs	150646003_150646004	N/A	N/A	N/A	N/A	N/A	DC	N/A	LC
241	c.2503delC	p.L835fs	150646033_150646033	N/A	21.5	N/A	N/A	N/A	DC	N/A	LC
242	c.1467C>T	p.Asp489=	150649603	rs740952	11.83	D	N/A	N/A	PO	B	LC
243	c.1887C>T	p.Thr629=	150648594	rs41307295	3.58	T	N/A	N/A	DC	B /LB	LC

TABLE 1 (Continued)

No.	HGVS DNA	HGVS protein	Chromosome 7 position (hg19)	dbSNP	CADD	SIFT	Polyphen-2	PROVEAN	MutationTaster	ClinVar	Protein region
244	c.1956T>C	p.His652=	150648198	rs1137617	3.58	T	N/A	N/A	PO	B	LC
245	c.2146-61A>G	N/A	150950481	rs4725983	6.07	N/A	N/A	N/A	PO	B	N/A
246	c.3330+22T>G	N/A	150946855	N/A	3.36	N/A	N/A	N/A	PO	N/A	N/A
247	c.3036-3048del	p.R1014PfsX39	150644520_150644532	N/A	14	N/A	N/A	N/A	DC	N/A	LC
248	c.3065delT	p.L1021fs+34X	150644503_150644503	N/A	13.5	N/A	N/A	N/A	DC	N/A	TR3
249	c.3251delC	p.T1083fs+170X	150647303_150647303	N/A	13.9	N/A	N/A	N/A	DC	N/A	LC
250	c.1417A>C	p.T473P	150649653	rs199473512	26.1	D	PD	D	DC	LP	LC
251	c.527insC	p.R176fsX331	150655535_150655536	N/A	12.5	N/A	N/A	N/A	DC	N/A	LC
252	c. 569–570 insGCGCGGGCG	p.INSGAG189-190	150655493_150655494	N/A	10.5	N/A	N/A	N/A	PO	N/A	LC
253	c. 1746–1747 insGC	p.R582fs/11*	150648734_150648735	N/A	27	N/A	N/A	N/A	DC	N/A	LC
254	c.785delG	p.Gly262fs	150655278_150655278	N/A	32	N/A	N/A	N/A	DC	N/A	TR1
255	c.132C>G	p.C44W	150671974	rs199472838	27.8	D	PD	D	DC	N/A	PAS
256	c.3376dupG	p.E1126Gfs*144	150642557	N/A	N/A	N/A	N/A	N/A		N/A	N/A
257	c.2680_2681insAGGC	p.R894fsX920	150645543_150645544	N/A	N/A	N/A	N/A	N/A	DC	N/A	TR2
258	c.2T>G	p.Met1Arg	150675000	N/A	22.7	D	B	D	DC	N/A	LC
259	c.38C>A	p. T13N	150674964	rs758978727	23.9	D	PD	D	DC	VUS	LC
260	c.45_56delGG	p.Asp16_Ile19del	150674946_150674957	N/A	18	N/A	N/A	D	PO	N/A	LC
261	c.56T>C	p.I19T	150674946	N/A	23.9	D	PD	D	DC	N/A	LC
262	c.59G>T	p. R20L	150674943	N/A	24.3	D	PD	D	DC	N/A	LC
263	c.81delT	p.L28rfs*32	150672025_150672025	N/A	17	N/A	N/A	N/A	DC	P	LC
264	c.125T>G	p. I42S	150671981	N/A	31	D	PD	D	DC	N/A	PAS
265	c.127T>G	P.Y43D	150671979	rs199472837	25.5	D	PD	D	DC	N/A	PAS
266	c.130T>G	P.C44G	150671976	N/A	28.4	D	PD	D	DC	N/A	PAS
267	c.131G>T	P.C44F	150671975	rs199473489	31	D	PD	D	DC	N/A	PAS
268	c.135C>A	P.N45K	150671971	N/A	24.3	D	PD	D	DC	VUS	PAS
269	c.145T>C	p.C49R	150671961	N/A	29.7	D	PD	D	DC	N/A	PAS
270	c.148delG	p.E50Sfs*10	150671958_15067195	N/A	12	N/A	N/A	N/A	DC	N/A	PAS
271	c.158G>A	p. G53D	150671948	rs199473491	28.9	D	PD	D	DC	N/A	PAS
272	c.167G>A	P.R56Q	150671939	rs199472845	29.2	D	PD	D	DC	LP	PAS
273	c.172G>A	p.P.E58K	150671934	rs199473413	25.4	D	B	N	DC	N/A	PAS
274	c.191G>A	P.C64Y	150671915	rs199473415	26.2	D	PD	D	DC	NA	PAS

(Continues)

TABLE 1 (Continued)

No.	HGVS DNA	HGVS protein	Chromosome 7 position (hg19)	dbSNP	CADD	SIFT	Polyphen-2	PROVEAN	MutationTaster	ClinVar	Protein region
275	c.202T>G	p. F68V	150671904	N/A	26.1	D	PD	D	DC	NA	PAS
276	c.211G>A	p.G71R	150671895	N/A	26.4	D	PD	D	DC	VUS	LC
277	c.215C>T	p.P72L	150671891	rs199473421	23.9	D	PD	D	DC	P	LC
278	c.215C>A	p.P72Q	150671891	rs199473421	22.2	D	PD	D	DC	LP/ P	LC
279	c.223C>T	p.Q75*	150671883	N/A	35	N/A	N/A	N/A	DC	LB	LC
280	c.278A>G	p.K93R	150671828	N/A	22.7	T	B	N	DC	LB	PAC
281	c.316T>G	p.F106V	150656816	N/A	23.6	T	B	D	DC	NA	PAC
282	c.332A>T	p.D111V	150656800	rs199472860	23.2	T	B	D	DC	NA	PAC
283	c.343G>A	p.V115M	150656789	rs150988911	24.0	D	B	N	DC	VUS	PAC
284	c.453dupC	p.Thr152Hisfs*180	150656684	N/A	N/A	N/A	N/A	N/A	N/A	CP	LC
285	c.468_469insGCCC	p.P157Afs*176	150656663_150656664	N/A	N/A	N/A	N/A	N/A	DC	NA	LC
286	c.475_476insAGGC	p. R159Qfs*174	150655587_150655588	N/A	N/A	N/A	N/A	N/A	DC	NA	LC
287	c.480dupC	p.Lys161Glnfs*171	150655583	N/A	N/A	N/A	N/A	N/A	NA	NA	LC
288	c.486_487delCT	p.Phe163Profs*168	150655577	N/A	17.5	N/A	N/A	N/A	DC	NA	LC
289	c.525_558delCCGGGAGTCGT CGGTGCGGTCGGGCG GCGCGGGC	p.R176Afs*14	150655505_150655538	N/A	N/A	N/A	N/A	N/A	DC	NA	LC
290	c.529G>T	p.E 177*	150655534	N/A	36	N/A	N/A	N/A	DC	NA	LC
291	c.560_568del GCGCGGGCG	p.G187_G189del	150655495_150655503	N/A	N/A	N/A	N/A	N	PO	NA	LC
292	c.567_575del	p.P191_A193del	150655488_150655496	N/A	12.5	N/A	N/A	D	PO	NA	LC
293	c.589G>T	p. D197Y	150655474	N/A	25.9	D	PD	N	DC	NA	LC
294	c.722C>T	p.P241L	150655341	rs199472871	7.79	D	B	N	PO	NA	TR1
295	c.724delC	P. R242Afs*118	150655339_150655339	N/A	13.2	N/A	N/A	N/A	DC	NA	TR1
296	c.730_742del GCGCCCGGCCAGC	P.A244Sfs*112	150655321_150655333	N/A	N/A	N/A	N/A	N/A	DC	NA	TR1
297	c.754_756delCGG	p.Arg252del	150655307_150655309	N/A	16.3	D	N/A	D	DC	NA	TR1
298	c.760_775del	p.H254Tfs*101	150655307_150655309	N/A	15.2	N/A	N/A	N/A	PO	NA	TR1
299	c.817delC	p.R273Efs*87	150655246_15065524	N/A	19	N/A	N/A	N/A	DC	NA	TR1
300	c.888delGinsAA	P. P297Nfs*64	150655174_150655175	N/A	19	N/A	N/A	N/A	DC	NA	TR1
301	c.889C>T	p.P297S	150655174	rs199472882	7.79	D	B	N	PO	VUS	TR1
302	c.922A>G	p.M308V	150654585	N/A	17.31	D	B	N	DC	NA	TR1
303	c.933-952del	P. R312Hfs*13	150654555_150654574	N/A	23	N/A	N/A	N/A	DC	NA	TR1

TABLE 1 (Continued)

No.	HGVS DNA	HGVS protein	Chromosome 7 position (hg19)	dbSNP	CADD	SIFT	Polyphen-2	PROVEAN	MutationTaster	ClinVar	Protein region
304	c.1001C>T	p.P334L	150654506	rs199472888	28.5	D	PD	D	DC	NA	LC
305	c.1003C>T	p.Q335*	150654504	N/A	41	N/A	N/A	N/A	DC	NA	LC
306	c.1008_1009insT	P.T337Yfs*19	150654498_150654499	N/A	22	N/A	N/A	N/A	DC	NA	LC
307	c.1091_1102delins AGGAGCGAACCC (53)	p.K364Mfs*3	150654405_150654416	N/A	N/A	N/A	N/A	N/A	DC	NA	LC
308	c.1714G>T	p.G572C	150648767	rs9333649	27.2	D	PD	D	DC	NA	LC
309	c.1129-1G>A	N/A	150952854	rs794728478	9.04	N/A	N/A	N/A	N/A	P	N/A
310	c.1193G>A	p.W398*	150649877	rs794728366	40	N/A	N/A	N/A	DC	P	LC
311	c.1205A>G	p.H402R	150649865	rs199473506	23.7	D	PD	D	DC	VUS	LC
312	c.1280A>G	p.Y427C	150649790	rs199472897	28.0	D	PD	D	DC	LP	LC
313	c.1360delG	P.V454Wfs*67	150649710_150649710	N/A	22	N/A	N/A	N/A	DC	NA	LC
314	c.1384_1401dupATGTTCAT TGTGGACATC	p.Met462-Leu467dup	150649669	N/A	N/A	N/A	N/A	D	N/A	NA	LC
315	c.1389C>G	p.P463L	150649681	N/A	25.5	D	PD	D	DC	NA	LC
316	c.1457C>G	p.P486R	150649613	N/A	26.8	D	PD	D	DC	NA	LC
317	c.1491G>A	p.W497*	150649579	N/A	41	N/A	N/A	N/A	DC	NA	LC
318	c.1557+1G>A	N/A	150952424	rs886039043	4.66	N/A	N/A	N/A	PO	NA	N/A
319	c.1657C>G	p.L553V	150648824	N/A	24.0	D	PD	D	DC	NA	LC
320	c.1671delT	P.F557Lfs*8	150648810_150648810	N/A	12	N/A	N/A	N/A	DC	NA	LC
321	c.1672G>C	p.A558P	150648809	rs121912516	25.4	D	PD	D	DC	P	LC
322	c.1685A>G	p.His562Arg	150648796	rs199472922	24.3	D	PD	D	DC	P	LC
323	c.1689G>A	p.W563*	150648792	N/A	38	N/A	N/A	N/A	DC	P	LC
324	c.1689G>T	p.W563C	150648792	rs199473517	27.4	T	PD	D	DC	NA	LC
325	c.1693G>T	p.A565S	150648788	N/A	25.3	D	PD	D	DC	VUS	LC
326	c.1696T>A	p.C566S	150648785	N/A	24.8	T	PD	D	DC	NA	LC
327	c.1704G>A	p.W568*	150648777	N/A	39	N/A	N/A	N/A	DC	P	LC
328	c.1720A>G	p.M574V	150648761	rs199473667	14.65	T	B	N	DC	NA	LC
329	c.1723G>T	p.E575*	150648758	N/A	39	N/A	N/A	N/A	DC	NA	LC
330	c.1732_1746del CACATGGACTCACGC	p.H578-R582del	150648735_150648749	N/A	N/A	N/A	N/A	D	DC	NA	LC
331	c.1736T>C	p.M579T	150648745	rs199473425	14.81	T	B	N	PO	VUS	LC
332	c.1750G>T	p.E584C	150648725	N/A	23.7	D	PD	D	DC	P/CP/VUS	LC

(Continues)

TABLE 1 (Continued)

No.	HGVS DNA	HGVS protein	Chromosome 7 position (hg19)	dbSNP	CADD	SIFT	Polyphen-2	PROVEAN	MutationTaster	ClinVar	Protein region
333	c.1751G>T	p.G584V	150648730	rs199473429	24.7	D	PD	D	DC	NA	LC
334	c.1766T>C	p.L589P	150648715	N/A	26.1	D	PD	D	DC	NA	LC
335	c.1769G>T	p.G590V	150648712	rs199472929	24.2	D	PD	D	DC	NA	LC
336	c.1775delA	p.Q592Rfs*2	150648706_150648706	N/A	18	N/A	N/A	N/A	DC	NA	LC
337	c.1778T>C	p. I593T	150648703	rs28928904	20.9	D	PD	D	DC	P	LC
338	c.1778T>G	p. I593R	150648703	rs28928904	24.6	T	PD	D	DC	P	LC
339	c.1783A>G	p.K595E	150648698	rs199472932	22.8	T	PD	D	DC	NA	LC
340	c.1785A>T	p.K595N	150648696	rs199473521	18.72	T	PD	D	DC	NA	LC
341	c.1790A>G	p. Y597C	150648691	rs199472934	24.7	D	PD	D	DC	LP	LC
342	c.1801G>A	p.G601S	150648680	rs199472936	18.68	T	B	N	DC	P	LC
343	c.1808G>A	p. G603D	150648673	N/A	22.8	T	B	D	DC	VUS	LC
344	c.1825G>A	p. D609N	150648656	rs199472941	24.9	T	PD	D	DC	P	LC
345	c.1833T>G	p.Y611*	150648648	N/A	24.5	N/A	N/A	N/A	DC	NA	LC
346	c.1838C>A	p. T613K	150648643	N/A	24.1	T	PD	D	DC	NA	LC
347	c.1853C>G	p. T618S	150648628	rs199472947	24.1	T	PD	D	DC	NA	LC
348	c.1861A>C	p. S621R	150648620	N/A	25.2	D	PD	D	DC	NA	LC
349	c.1867A>G	p. T623A	150648614	N/A	24.1	D	PD	D	DC	NA	LC
350	c.1874T>A	p. V625E	150648607	rs199472951	24.9	D	PD	D	DC	NA	LC
351	c.1878_1879insCCT	N/A	150648602_150648603	N/A	14	N/A	N/A	N/A	DC	NA	N/A
352	c.1900A>G	p.T634A	150648581	rs794728377	24.1	T	PD	D	DC	NA	LC
353	c.1912A>G	p.S641A	150648560	N/A	23.6	T	PD	D	DC	NA	LC
354	c.1912A>C	p.K638Q	150648569	N/A	25.1	T	PD	D	DC	NA	LC
355	c.1913_1915del AGA	p.K638del	150648566_150648568	N/A	12	T	N/A	D	DC	LP	LC
356	c.1919_1921delTCT	p.F640del	150648560_150648562	N/A	30	D	N/A	D	DC	NA	LC
357	c.1933A>C	p.M645L	150648548	N/A	25.1	D	PD	D	DC	P	LC
358	c.1945T>C	p.S649P	150648536	rs199473530	29.2	T	PD	D	DC	NA	LC
359	c.1951_1952delAT	P. M651Cfs*63	150648203_150648203	N/A	13	N/A	N/A	N/A	DC	NA	LC
360	c.1990C>T	p.Q664*	150648164	N/A	41	N/A	N/A	N/A	DC	NA	LC
361	c.2003C>A	p.S668*	150648151	N/A	41	N/A	N/A	N/A	DC	P	LC
362	c.2006delG	P.G669Afs*45	150648148_150648148	N/A	18	N/A	N/A	N/A	DC	N/A	LC
363	c.2019C>G	p.Y673*	150648135	N/A	39	N/A	N/A	N/A	DC	N/A	LC

TABLE 1 (Continued)

No.	HGVS DNA	HGVS protein	Chromosome 7 position (hg19)	dbSNP	CADD	SIFT	Polyphen-2	PROVEAN	MutationTaster	ClinVar	Protein region
364	c.2026C>T	p.Q676*	150648128	rs794728381	40	N/A	N/A	N/A	DC	P	LC
365	c.2028_2029delAG	P.Q676Hfs*46	150648125_150648126	N/A	19	N/A	N/A	N/A	DC	N/A	LC
366	c.2062C>T	p.Q688*	150648092	N/A	40	N/A	N/A	N/A	DC	P	LC
367	c.2134G>A	p. D712N	150648020	rs199852343	25.3	T	PD	D	DC	NA	LC
368	c.2145G>C	p.ALA715=	150648009	rs794728384	21.1	T	N/A	N/A	DC	VUS	LC
369	c.2146-2A>G	N/A	150950422	N/A	1.94	N/A	N/A	N/A	DC	LP /P	LC
370	c.2162C>G	p.P721R	150647492	N/A	27.9	D	PD	D	DC	NA	LC
371	c.2169_2170dup	p.L724Pfs*10	150950396	N/A	N/A	N/A	N/A	N/A	N/A	NA	LC
372	c.2192A>C	pH731P	150647462	rs794728385	26.8	D	PD	D	DC	LP	LC
373	c.2195T>C	p.L732P	150647459	N/A	28.5	D	PD	D	DC	NA	LC
374	c.2212C>T	p.Q738*	150647442	N/A	39	N/A	N/A	N/A	DC	N/A	LC
375	c.2231G>C	p.R744P	150647423	N/A	27.0	D	PD	D	DC	VUS	LC
376	c.2255G>C	p.R752P	150647399	N/A	29.6	T	PD	D	DC	N/A	LC
377	c.2347T>C	p.S783P	150647307	N/A	29.1	T	PD	D	DC	N/A	LC
378	c.2353G>A	p.G785S	150647301	N/A	28.9	D	PD	D	DC	N/A	LC
379	c.2354delG	p.G85Afs*25	150950212	N/A	14	N/A	N/A	N/A	N/A	N/A	LC
380	c.2398G>C	p.G800R	150647256	N/A	34	T	PD	D	DC	N/A	LC
381	c.2399-2A>G	N/A	150646139	N/A	34	N/A	N/A	N/A	DC	N/A	N/A
382	c.2592+1G>A	N/A	150645943	rs1554424772	34	N/A	N/A	N/A	DC	N/A	N/A
383	c.2436dupT	p.A813Cfs*17	150949012	N/A	N/A	N/A	N/A	N/A	N/A	N/A	LC
384	c.2468G>A	p .R823Q	150646068	N/A	N/A	D	PD	D	DC	LP/VUS/CP	LC
385	c.2492A>C	p.H831P	150646044	N/A	N/A	D	PD	D	DC	P	LC
386	c.2509G>A	p.D837N	150646027	rs199473005	N/A	T	PD	D	DC	LP /P	LC
387	c.2532_2535delinsTTAA	P.Y845Lfs*24	150646002_150646003	N/A	N/A	N/A	N/A	D	DC	N/A	LC
388	c.2559delG	p.Trp853Cysfs*15	150645977	N/A	14	N/A	N/A	N/A	DC	N/A	LC
389	c.2593_2599delACCAACA	p.Thr865*	150645625	N/A	13	N/A	N/A	N/A	DC	N/A	LC
390	c.2594C>T	p.T865I	150645630	N/A	25.7	T	B	N	DC	VUS	LC
391	c.2613_2669delins ACGCCTG	p.P872Rs*31	150645555	N/A	N/A	N/A	N/A	N/A	DC	N/A	TR2
392	c.2647_2659del CGGCAACGCAAGC	P.R883Afs*87	150645565_150645577	N/A	N/A	N/A	N/A	N/A	DC	N/A	TR2
393	c.2648G>A	p.R883Q	150645576	N/A	20.6	D	B	N	PO	VUS	TR2

TABLE 1 (Continued)

No.	HGVS DNA	HGVS protein	Chromosome 7 position (hg19)	dbSNP	CADD	SIFT	Polyphen-2	PROVEAN	MutationTaster	ClinVar	Protein region
394	c.2731_2732dupGG	p.Arg912Alafs*63	150644927	N/A	N/A	N/A	N/A	N/A	DC	N/A	TR2
395	c.2734_2738delCGGGC	P.R912Gfs*6	150644921_150644925	N/A	N/A	N/A	N/A	N/A	DC	P	TR2
396	c.2774_2775delGG	p.G925Afs*14	150644884_150644885	N/A	N/A	N/A	N/A	N/A	DC	N/A	TR2
397	c.2775dupG	p.Pro926Alafs*14	150644884	N/A	N/A	N/A	N/A	N/A	DC	P	TR2
398	c.2775delG	P.P926Rfs*48	150644884_150644884	N/A	25	N/A	N/A	N/A	DC	N/A	TR2
399	c.2843G>A	p.R948H	150644816	rs199473011	21.0	T	B	N	DC	CP/LP/ VUS/P	TR2
400	c.2892dupC	p.G965Rfs*154	150947679	N/A	N/A	N/A	N/A	N/A	N/A	P	TR2
401	c.2918delT	p.L973Rfs*84	150644741_150644741	N/A	N/A	N/A	N/A	N/A	DC	N/A	TR2
402	c.2932G>T	p.E978*	150644727	rs141117135	26	N/A	N/A	N/A	DC	P	TR2
403	c.2942delG	P.S981Tfs*76	150644717_150644717	N/A	22	N/A	N/A	N/A	DC	N/A	TR2
404	c.2959_2960delCT	P.L987Vfs*131	150644699_150644700	N/A	19	N/A	N/A	N/A	DC	P	LC
405	c.2966-3G>C	N/A	150947517	N/A	9.67	N/A	N/A	N/A	PO	P	N/A
406	c.2993delT	P.F998Sfs*59	150644575_150644575	N/A	16	N/A	N/A	N/A	DC	LP	LC
407	c.3002G>A	p.W1001*	150644566	N/A	49	N/A	N/A	N/A	DC	P	LC
408	c. 3007delG	P.D1003Tfs*54	150644561_150644561	N/A	N/A	N/A	N/A	N/A	DC	N/A	LC
409	c.3036_3048del CCCTCGATGCCCC	p.R1014Pfs*39	150644520_150644532	N/A	N/A	N/A	N/A	N/A	DC	N/A	LC
410	c.3060dupC	p.Ser1021Glnfs*98	150644508	N/A	N/A	N/A	N/A	N/A	N/A	LP	TR3
411	c.3090_3102del GGGTCGGCGGCCC	P.R1032Afs*21	150644466_150644478	N/A	N/A	N/A	N/A	N/A	DC	P	TR3
412	c.3091_3101del GGTCGGCGGCC	p. G1031Pfs*84	150644467_150644477	N/A	N/A	N/A	N/A	N/A	DC	N/A	TR3
413	c.3092dupG	p.Arg1032Serfs*87	150644476	N/A	N/A	N/A	N/A	N/A	N/A	N/A	TR3
414	c.3093_3106del TCGGCGGCCCCGGG	p.P1034Gfs*80	150644462_150644475	N/A	N/A	N/A	N/A	N/A	DC	P	TR3
415	c.3094_3113delCGGCGGCC CCGGGGCGAC	p.R1032Gfs*80	150644457_150644474	N/A	N/A	N/A	N/A	N/A	PO	N/A	TR3
416	c.3096_3109del GCGGCCCCGGGGCG	p.P1034Gfs*80	150644459_150644472	N/A	N/A	N/A	N/A	N/A	DC	N/A	TR3
417	c.3096_3097insGCGGG	p.R1033Afs*26	150644471_150644472	N/A	N/A	N/A	N/A	N/A	DC	N/A	TR3
418	c.3103_3125del	p.R1035Gfs*76	150644443_150644465	N/A	23	N/A	N/A	N/A	DC	N/A	TR3
419	c.3104_3105insCC	p. G1036Rfs*22	150644463_150644464	N/A	28	N/A	N/A	N/A	DC	N/A	TR3
420	c.3113delins GGTCGGCGGCCCCGG	p.V1038Gfs*24	150644454_150644455	N/A	N/A	N/A	N/A	N/A	PO	N/A	TR3

TABLE 1 (Continued)

No.	HGVS DNA	HGVS protein	Chromosome 7 position (hg19)	dbSNP	CADD	SIFT	Polyphen-2	PROVEAN	MutationTaster	ClinVar	Protein region
421	c.3190_3199del CTGCAGCTGC	p.L1064Yfs*5	150644096_150644105	N/A	N/A	N/A	N/A	N/A	DC	N/A	LC
422	c.3252_3262del GGGGCCTGGCC	p.G1085Hfs*30	150644033_150644043	N/A	N/A	N/A	N/A	N/A	DC	N/A	LC
423	c.3278C>T	p.P1093L	150644017	rs199473545	20.2	D	B	D	DC	VUS	LC
424	c.3330+1G>A	N/A	150643964	rs1368439403	34	D	B	N	DC	N/A	N/A
425	c.3430G>A	p.A1144T	150642503	rs199473034	20.2	D	B	N	PO	NA	TR4
426	c.308G>T	p.G103V	150656824	N/A	32	D	PD	D	DC	N/A	PAC
427	c.2454G>T	p.S818=	150646082	rs72549418	11.84	T	N/A	N	DC	N/A	LC
428	c.2508C>T	p.D836=	150646028	rs139295242	2.66	T	N/A	N	DC	LB	LC
429	c.2514G>T	p.L838=	150646022	N/A	11.47	T	N/A	N	DC	N/A	LC
430	c.2588G>A	p.R863Q	150645948	N/A	31	D	PD	D	DC	VUS	LC
431	c.1A>T	p.M1L	150675001	rs199473036	23.7	N/A	N/A	N/A	DC	NA	LC
432	c.92T>C	p.I31T	150672014	rs199472833	29.6	D	PD	D	DC	LP	LC
433	c.2635G>C	p.G879R	150645589	rs199473040	19.86	D	B	D	PO	NA	TR2
434	c.3302C>T	p.P1101L	150643993	rs199473041	25.2	D	PD	D	DC	NA	LC
435	C.1764C>G	P.N588K	150648717	rs104894021	20.9	T	B	D	DC	P	LC
436	C.1764C>A	P.N588K	150648717	rs104894021	21.2	T	B	D	DC	P	LC
437	c.1520C>T	p.P507L	150649550	N/A	27.7	D	PD	D	DC	N/A	LC
438	c.1190G>A	p.R397H	150649880	rs368817970	23.3	D	PD	D	DC	N/A	LC
439	c.2173C>T	p.Q725*	150647481	N/A	41	D	N/A	N/A	DC	N/A	LC
440	c.3107_3108insC	P. D1037Rfs*82	150644460_150644461	N/A	26	D	N/A	N/A	DC	N/A	TR4
441	c.1888G>A	p.V630I	150648593	N/A	23.5	T	PD	N	DC	N/A	LC
442	c.135C>G	p.N45K	150671971	N/A	24.2	D	PD	N/A	DC	N/A	PAS
443	c.872T>C	p.M291T	150655191	rs199472881	21.9	D	PD	N	DC	N/A	TR1
444	C.287T>C	P.I96T	150671819	rs199472853	25.6	D	PD	D	DC	NA	LC
445	c.391G>A	P.V131M	150656741	N/A	22.6	D	PD	D	DC	N/A	PAC
446	C.1199T>A	P.I1400N	150649871	rs199472891	28.1	D	PD	D	DC	P	LC
447	C.1714G>C	P.G572R	150648767	rs9333649	26.4	D	PD	D	DC	N/A	LC
448	C.1862G>A	P.S621N	150648619	s199472948	24.7	T	PD	D	DC	N/A	LC
449	C.1886A>G	P.N629S	150648595	rs199472957	23.2	T	PD	D	DC	N/A	LC
450	c.298C>G	p.R100G	150671808	rs121912515	26.5	D	PD	D	DC	CP/VUS	PAC

TABLE 1 (Continued)

No.	HGVS DNA	HGVS protein	Chromosome 7 position (hg19)	dbSNP	CADD	SIFT	Polyphen-2	PROVEAN	MutationTaster	ClinVar	Protein region
451	c.340C>T	p.P114S	150656792	rs199472861	26.0	D	PD	D	DC	NA	PAC
452	c.959 C>A	p.S320C	150654548	N/A	24.9	N/A	N/A	N/A	DC	N/A	LC
453	c.1575G>T	p.K525N	150648906	rs199472913	23.8	T	PD	D	DC	NA	LC
454	c.1778T>C	p.I593T	150648703	rs28928904	20.9	D	PD	D	DC	N/A	LC
455	c.30963112 del GCGGCCCC GGGGCGACG	p.R1032fsa	150644456_150644472	N/A	N/A	N/A	N/A	N/A	DC	N/A	TR3
456	c.65T>C	p.F22S	150674937	rs199472826	27.1	T	PD	D	DC	NA	LC
457	c.301A>G	p.K101E	150671805	rs199472856	24.5	D	PD	D	DC	CP/LP/VUS	PAC
458	c.326T>C	p.L109P	150656806	N/A	24.0	T	PD	D	DC	N/A	PAC
459	c.446insC	p.R148fs	150674957_150674958	N/A	20	D	N/A	N/A	DC	N/A	PAC
460	c.2111_2114dup	p.W705fs	150950952	N/A	N/A	D	N/A	N/A	PO	N/A	LC
461	c.2573T>C	p.I858T	150645963	rs199473539	28.3	D	PD	D	DC	NA	LC
462	c.2768delC	p.P923fs	150947803	rs794728454	13.2	D	N/A	N/A	DC	NA	TR2
463	c.3090-3102del GGGTCGGCGGCCC	P.R1032Afs*21	150644466_150644478	N/A	N/A	D	N/A	N/A	N/A	N/A	TR3
464	c.2068G>A	p. E637K	150648086	N/A	25.6	D	PD	D	DC	N/A	LC
465	c.455C>T	P.T152I	150656677	N/A	20.1	T	B	N	PO	VUS	LC
466	c.490C>T	P. R164C	150655573	N/A	29.5	T	PD	D	N/A	N/A	LC
467	c.2779T>G	P. W927G	150644880	N/A	23.7	D	PD	D	DC	N/A	TR2
468	c.3404G>A	P. R1135H	150642529	rs199473547	24.7	D	PD	N	DC	NA	TR3
469	c.818G>A	P.R273Q	150655245	rs199472877	23.6	D	PD	N	DC	N/A	TR1
470	c.835G>A	P. V279M	150655228	rs199472879	18.51	D	B	N	PO	N/A	TR1
471	c.2653C>T	P. R885C	150645571	rs143512106	24.9	T	PD	D	DC	N/A	TR2
472	c.3118A>G	P. S1040G	150644450	rs199473024	22.9	T	B	N	PO	N/A	LC
473	c. 1330G>A	p. E444K	150649740	rs201268831	14.92	D	B	N	DC	VUS	LC
474	c.815C>T	P. S272F	150655248	N/A	26.8	D	B	N	DC	N/A	TR1
475	c.1342G>A	p.A448T	150649728	N/A	17.43	T	B	N	DC	VUS	LC
476	c.1894C>T	p.P632S	150648587	rs199473527	24.2	D	PD	D	DC	P/LP	LC
477	c.3131G>T	P.A1044V	150644437	N/A	23.0	T	PD	D	DC	N/A	LC
478	c.3161delC	P.R1055Gfs*2	150644134_150644134	N/A	25	T	N/A	N/A	N/A	N/A	LC
479	c. 65T>A	p. F22Y	150674937	N/A	32	D	PD	N	DC	N/A	LC
480	c. 148G>T	p. E50*	150671958	N/A	37	N/A	N/A	N/A	DC	N/A	PAS

TABLE 1 (Continued)

No.	HGVS DNA	HGVS protein	Chromosome 7 position (hg19)	dbSNP	CADD	SIFT	Polyphen-2	PROVEAN	MutationTaster	ClinVar	Protein region
481	c. 174G>C	p. E58D	150671932	rs199473492	21.4	T	B	N	DC	NA	PAS
482	c. 215C>G	p. P72R	150671891	rs199473421	23.5	D	PD	D	DC	VUS	LC
483	c. 442C>T	p. R148W	150656690	rs139544114	24.2	N/A	N/A	N/A	DC	N/A	PAC
484	c. 1096C>T	P. R366*	150654411	N/A	38	N/A	N/A	N/A	DC	P	LC
485	c. 1283C>A	P.S428*	150649787	N/A	42	N/A	N/A	N/A	DC	VUS	LC
486	c. 1468G>C	p. A490P	150649602	rs28928905	28.4	D	PD	D	DC	NA	LC
487	c. 1490G>T	p. W497L	150649580	N/A	28.9	D	PD	D	DC	LB	LC
488	c. 1700T>C	p. I567T	150648781	rs199473519	24.8	D	PD	D	DC	VUS	LC
489	c. 1747A>G	p. I583V	150648734	rs199473427	19.31	T	B	N	DC	NA	LC
490	c. 1810G>A	p. G604S	150648671	rs199473522	25.6	T	PD	D	DC	P	LC
491	c. 1877G>C	p. G626A	150648604	rs199472952	23.6	D	PD	D	DC	NA	LC
492	c. 1898A>G	p. N633S	150648583	rs199472961	24.0	T	PD	D	DC	P/LP	LC
493	c. 1979C>T	p. S660L	150648175	rs199472979	28.4	D	PD	D	DC	CP/LP/ VUSP	LC
494	c. 2230C>T	p. R744*	150647424	rs189014161	38	N/A	N/A	N/A	DC	P	LC
495	c. 2521G>C	p. V841L	150646015	N/A	25.2	D	PD	D	DC	P	LC
496	c. 2932G>T	p. E978*	150644727	rs141117135	42	N/A	N/A	N/A	DC	P	TR2
497	c. 3128A>G	p. D1043G	150644440	N/A	25.3	D	PD	D	DC	P	TR2
498	c. 3139C>T	p. R1047C	150644429	rs377095107	23.9	D	PD	D	DC	VUS	TR2
499	c.3347C>T	p. A1116V	150642586	rs199473032	17.61	D	B	N	DC	VUS	TR2
500	c.1694G>T	p. A565V	150648787	rs794728482	24.5	D	N/A	N/A	DC	N/A	LC
501	c.1519C>A	p. P507T	150649551	N/A	25.6	D	PD	D	DC	N/A	LC
502	c.2009C>T	p. T670I	150648145	N/A	25.8	D	PD	D	DC	N/A	LC
503	c.3208 C>T	P.Q1070*	150644087	N/A	47	D	N/A	N/A	DC	N/A	TR3
504	c.1817 C>T	p.S606F	150648664	N/A	25.0	D	PD	D	DC	VUS	LC
505	c.1883G>A	p.G628D	150648598	N/A	24.5	D	PD	D	DC	N/A	LC
506	c.2117C>G	p. S706C	150648037	rs199472985	25.1	D	PD	D	DC	N/A	LC
507	c.2504G>A	p.R835Q	150646032	N/A	25.1	T	PD	D	DC	VUS	LC
508	c.2684C>T	P. T895M	150645540	rs199473434	24.5	T	PD	D	DC	CP/LP/VUS	TR2

TABLE 1 (Continued)

No.	HGVS DNA	HGVS protein	Chromosome 7 position (hg19)	dbSNP	CADD	SIFT	Polyphen-2	PROVEAN	MutationTaster	ClinVar	Protein region
509	c.2674C>T	p.R892C	150645550	rs201627778	25.9	D	PD	D	DC	CP/LB/VUS	TR2
510	c.3103delC	p.R1035Gfs*22	150644465_150644465	rs794728468	29	N/A	N/A	N/A	N/A	P	TR3
511	c.3140G>T	R1047 L	150644428	rs36210421	22.5	D	B	N	DC	B/LB/VUS	LC

Note: NM_000238.4.

Abbreviations: B, Benign; CADD, Phred≤20, Neutral; CP, Conflicting interpretations of pathogenicity; D, Deleterious; DC, Disease Causing; LB, Likely benign; LC, Low complexity; LP, Likely pathogenetic; N, Neutral; NA, Not Available; P, Pathogenic; PD, Possibly Damaging; Phred>20, Damaging; PO, Polymorphism; POD, Possibly Damaging; T, Tolerated; TR, Transmembrane; VUS, Uncertain signicivance.

criterion was the existence of LQTS-related variants considered damaging by at least one prediction tool.

3 | RESULTS

3.1 | Clinical and genetic findings

The ECG of the normal (II-1) and affected (II-5 and III-4) individuals (Figure 1C) illustrated borderline QTs in II-5 and III-4 (480 ms and 476 ms, respectively) and 425 ms QT in II-1. A bifid T wave was also observed in II-5.

The WES analysis detected a novel pathogenic variant in the heterozygous state, c.1425C>A: p.Tyr475Ter in exon 6 of *KCNH2* in an Iranian pedigree suspected of LQT2 (Figure 1A). The heterozygote/homozygote pathogenic/normal states for this position in the available members of the pedigree were confirmed by PCR and Sanger sequencing (Figure 1B). According to the segregation analysis results, LQT2 was inherited in this pedigree with an autosomal dominant pattern (Figure 1A). The CADD Phred of the c.1425C>A variant was 32. Based on the American College of Medical Genetics guideline, PVS1 was the null variant in the *KCNH2* gene as a loss-of-function variant and was associated with LQT2, and PM2 was a variant not found in gnomAD exomes/genomes. Furthermore, PP3 was a pathogenic computational verdict based on 3 pathogenic predictions from BayesDel addAF, FATHMM-MKL, and MutationTaster. The investigation by BDGP and HSF indicated that this valiant did not affect the splicing process. Moreover, the alignment of the KCNH2 variant region displayed its highly conservative position among the various species.

3.2 | Structural analysis

A 3D model of wild and truncated KCNH2 proteins was obtained through SWISS-MODEL. The best model of KCNH2 was provided with 5va3 by SWISS-MODEL experimental structures with a QMEAN score of 0.75 ± 0.05, which suggested that the model was more definitive with a low local error score. Given the destruction of KCNH2 in the early steps of protein synthesis, resulting from the p.Tyr475Ter variant, no mutant structure model was achieved (Figure 3A).

3.3 | Literature review findings

Our search strategy and data extraction led to the collection of 511 variants causing LQTS. The characteristics of these variants are presented in Table 1, according to which most variants (353 variants) were in the low complexity region. The highest CADD score was for c.3002G>A (Phred = 49), followed by c.3157G>T and c.3208C>T (Phred = 47), as well as c.3040C>T (Phred = 46). These variants were in the low complexity region.

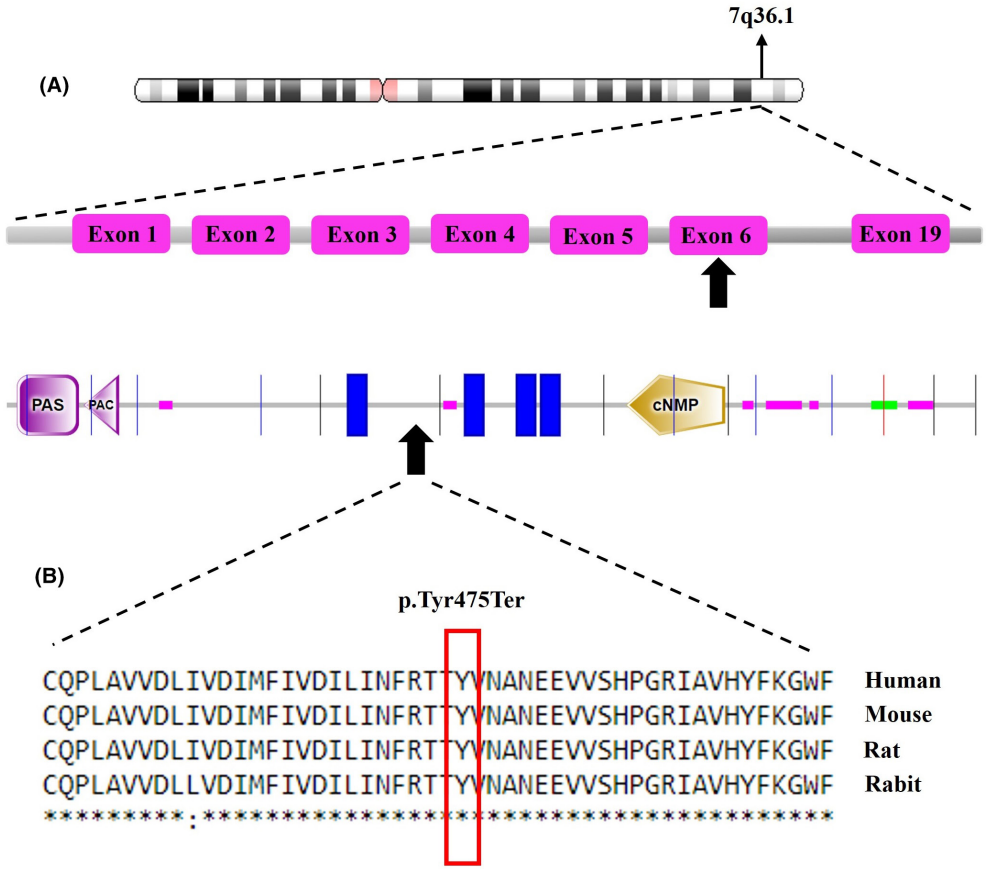

FIGURE 2 A schematic view of the *KCNH2* gene and the KCNH2 protein. (A) The image depicts the location of *KCNH2* on the chromosome and the variant location in the exon. The protein's secondary structure was obtained from SMART web server (https://smart.embl.de/smart/show_motifs.pl?ID=Q12809. The blue boxes are the transmembrane domains, and the pink boxes are the low complexity regions. (B) The image demonstrates the conservation of the p.Tyr475Ter amino acid in the KCNH2 protein among the species.

4 | DISCUSSION

In the current study, we detected that the *KCNH2* c.1425C>A (p.Tyr475Ter) novel variant was related to the LQT2 phenotype in an Iranian pedigree. The most common LQTS-causing genes are *KCNH2*, *KCNQ1*, *KCNE1*, *KCNE2*, and *SCN5A*.[1] Napolitano et al.[11] screened 430 patients with LQTS for 5 common genes and reported that 322 individuals had positive genetic tests. Tester et al.[6] reported a 75% yield among patients with LQTS for genetic testing. These studies underscore the necessity of genetic testing for patients suspected of LQTS and their family members. Research have also demonstrated that *KCNQ1* causes LQT1, *KCNH2* LQT2, *SCN5A* LQT3, *KCNE1* LQT5, *KCNE2* LQT6, *KCNJ2* LQT7, and *CACNA1c* LQT8.[3,12,13] Strong genotype–phenotype correlations have also been reported in LQTS. In other words, there are auditory triggers and/or postpartum accompanying LQT2 and swimming with LQT1, somewhat elucidating the LQTS genetic etiology and improving efficient treatment.[14]

The secondary structure of the KCNH2 protein, Kv11.1, is a tetrameric protein with low complexity regions, PAS, PAC, and 1 transmembrane domain per subunit (Figure 2A). As is shown in Table 1, regarding *KCNH2*, the most pathogenic variant, likely pathogenic variant, and variants of unknown significance were located in low complexity regions. The identified p.Tyr475Ter variant was also located in the low complexity region and seemed to affect the Kv11.1 channel or the plasma membrane traffic. Structural analysis indicated the altered amino acid, Tyrosine 475, was highly conserved in the protein sequence among the species (Figure 2B). Hence, this variant was predicted to be damaging. The 3D structure of the Kv11.1 protein has 6 transmembrane α helices (S1–S6), N and C terminals situated in the cytoplasm, and a pore located between S5 and S6 (Figure 3). A total of 511 variants were found in *KCNH2* that could cause LQTS by different mechanisms such as defects in ion permeation, gating, trafficking from the endoplasmic reticulum to the plasma membrane, and HERG synthesis reduction, all of which impact Ikr, the main cardiac repolarization current.[15,16] Nonsense variants comprised a small percentage of these variants (39/511, 7.6%); still, they exerted a more destructive effect on protein, especially if this cessation of protein synthesis occurred in the early stages of synthesis. The p.Tyr475Ter variant was in the early low complexity region and made truncated Kv11.1 protein (Figure 1A).

The present study indicates the potential effects of *KCNH2* changes on the LQT2 phenotype; nevertheless, it suffers from some limitations. First, the DNA samples of the individuals who had SCD (I-2 and II-3) were not available for a further survey of

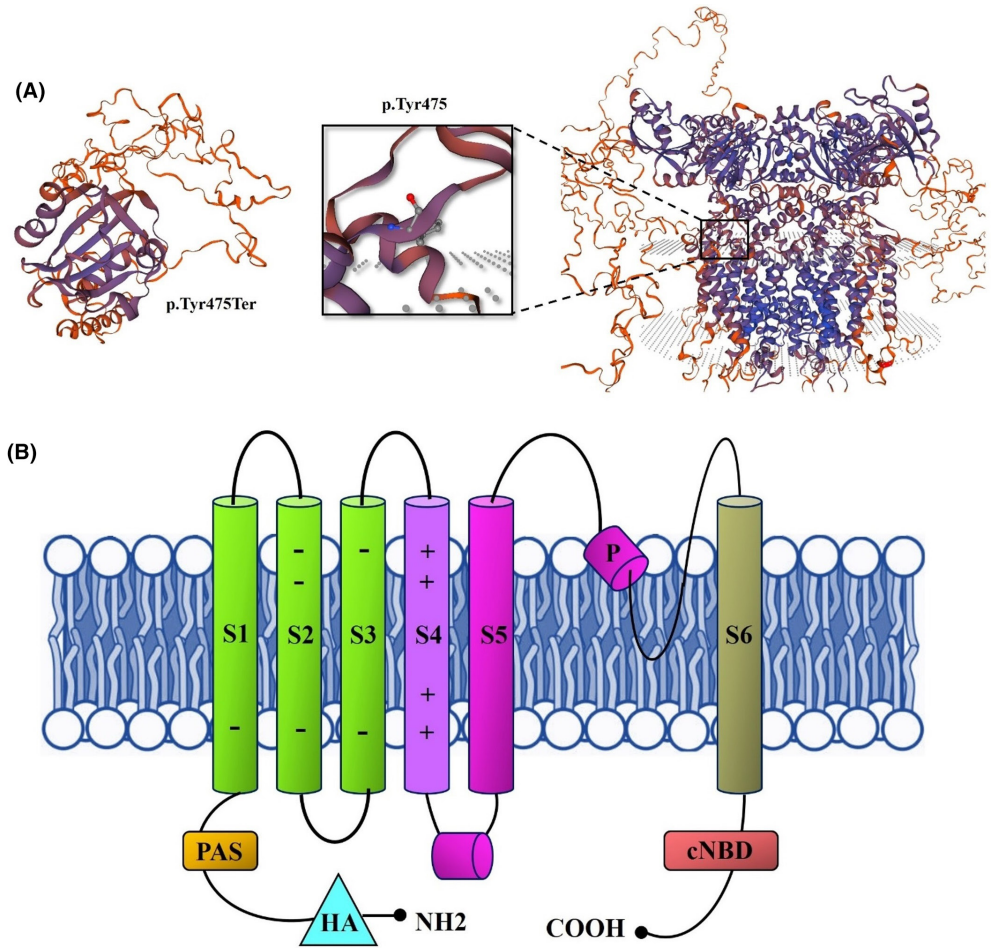

FIGURE 3 The 3D structure of the KCNH2 protein. (A) The image shows the SWISS-MODEL homology modeling of wild (right) and truncated (left) KCNH2. (B) The schematic view of the domains of KCNH2, as a transmembrane protein, is illustrated herein.

genotype–phenotype correlations. Second, although our bioinformatics analysis demonstrated the pathogenic effect of c.1425C>A: p.Tyr475Ter, functional evaluation could have helped to confirm this pathogenicity.

5 | CONCLUSIONS

We have presented the first genetic and clinical assessment of the p.Tyr475Ter *KCNH2* variant.

This finding indicates the importance of potassium support and monitoring in patients with LQTS, especially those developing Kv11.1 dysfunction resulting from loss-of-function variants. NGS has significant potential for clinical and research use. We suggest the application of the WES approach for individuals suspected of LQTS with a family history of sudden death whose genetic etiology has remained unidentified.

AUTHOR CONTRIBUTIONS

Samira Kalayinia, Amir Farjam Fazelifar, and Majid Maleki wrote the article. Maryam Pourirahim and Tannaz Masoumi carried out the experiments. Amir Farjam Fazelifar, Alireza Biglari, and Majid Maleki contributed to the patient's diagnosis. Samira Kalayinia performed WES analysis data interpretation. All the authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data sets generated and/or analyzed during the current study are available in the ClinVar repository [https://www.ncbi.nlm.nih.gov/clinv

ar/variation/1178326/?new_evidence=false]. The accession number of the variant in ClinVar is as follows: NM_000238.4 (KCNH2): c.1425C>A (p.Tyr475Ter): VCV001178326.3.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Ethics Committee of Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran (IR.RHC.REC.1400.113). Written informed consent was obtained from all the available members of the pedigree.

CONSENT FOR PUBLICATION

Not applicable.

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REFERENCES

1. 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(9):1297–303.
2. Moss AJ, Kass RS. Long QT syndrome: from channels to cardiac arrhythmias. J Clin Invest. 2005;115(8):2018–24.
3. Park JK, Oh Y-S, Choi J-H, Yoon SK. Single nucleotide deletion mutation of KCNH2 gene is responsible for LQT syndrome in a 3-generation Korean family. J Korean Med Sci. 2013;28(9):1388–93.
4. 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. 2000;102(10):1178–85.
5. Moss AJ, Zareba W, Kaufman ES, Gartman E, Peterson DR, Benhorin J, et al. Increased risk of arrhythmic events in long-QT syndrome with mutations in the pore region of the human ether-a-go-go–related gene potassium channel. Circulation. 2002;105(7):794–9.
6. Tester DJ, Will ML, Haglund CM, Ackerman MJ. Compendium of cardiac channel mutations in 541 consecutive unrelated patients referred for long QT syndrome genetic testing. Heart Rhythm. 2005;2(5):507–17.
7. Shimizu W, Makimoto H, Yamagata K, Kamakura T, Wada M, Miyamoto K, et al. Association of genetic and clinical aspects of congenital long QT syndrome with life-threatening arrhythmias in Japanese patients. JAMA Cardiol. 2019;4(3):246–54.
8. Anderson CL, Kuzmicki CE, Childs RR, Hintz CJ, Delisle BP, January CT. Large-scale mutational analysis of Kv11. 1 reveals molecular insights into type 2 long QT syndrome. Nat Commun. 2014;5(1):1–13.
9. Zehelein J, Zhang W, Koenen M, Graf M, Heinemann SH, Katus HA. Molecular cloning and expression of cERG, the ether a go-go-related gene from canine myocardium. Pflugers Arch. 2001;442(2):188–91.
10. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405–23.
11. Napolitano C, Priori SG, Schwartz PJ, Bloise R, Ronchetti E, Nastoli J, et al. Genetic testing in the long QT syndrome: development and validation of an efficient approach to genotyping in clinical practice. Jama. 2005;294(23):2975–80.
12. Hedley PL, Jørgensen P, Schlamowitz S, Wangari R, Moolman-Smook J, Brink PA, et al. The genetic basis of long QT and short QT syndromes: a mutation update. Hum Mutat. 2009;30(11):1486–511.
13. Itoh 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(10):1411–8.
14. Van Langen I, Birnie E, Alders M, Jongbloed R, Le Marec H, Wilde A. The use of genotype-phenotype correlations in mutation analysis for the long QT syndrome. J Med Genet. 2003;40(2):141–5.
15. Clancy CE, Rudy Y. Cellular consequences of HERG mutations in the long QT syndrome: precursors to sudden cardiac death. Cardiovasc Res. 2001;50(2):301–13.
16. Thomas D, Kiehn J, Katus HA, Karle CA. Defective protein trafficking in hERG-associated hereditary long QT syndrome (LQT2): molecular mechanisms and restoration of intracellular protein processing. Cardiovasc Res. 2003;60(2):235–41.

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