Clinical utility gene card for: Long-QT syndrome

Britt M. Beckmann1,2 · Stefanie Scheiper-Welling1 · Arthur A. M. Wilde3,4,5 · Stefan Kääb2,6 · Eric Schulze-Bahr4,7 · Silke Kauferstein1

Received: 7 December 2020 / Revised: 25 March 2021 / Accepted: 23 April 2021 / Published online: 24 May 2021
© The Author(s) 2021. This article is published with open access

1. Disease characteristic

1.1 Name of the disease
Long-QT syndrome (LQT, LQTS, Romano-Ward syndrome, subgroups: Jervell & Lange-Nielsen syndrome, Andersen-Tawil syndrome, Timothy syndrome, Ankyrin-B syndrome, Cardiac-only Timothy syndrome, Triadin knockout syndrome).

Comment: It may be appropriate to limit the use of numbered LQTS to LQTS 1–3 and the remaining to their pathogenic basis, such as CALM-LQTS rather than LQT14 [1].

1.2 OMIM# of the disease

| OMIM# | Gene(s) |
|-------|---------|
| #192500 | LQT1, KCNQ1-LQTS |
| #613688 | LQT2, KCNH2-LQTS |
| #603830 | LQT3, SCN5A-LQTS |
| #600919 | LQT4, ANK2-LQTS |
| #613695 | LQT5, KCNE1-LQTS |
| #613693 | LQT6, KCNE2-LQTS |
| #170390 | LQT7, (KCNJ2-)Andersen-Tawil syndrome |
| #611818 | LQT9, CAV3-LQTS |
| #611819 | LQT10, SCN4B-LQTS |
| #611820 | LQT11, AKAP9-LQTS |
| #612955 | LQT12, SNTA1-LQTS |
| #613485 | LQT13, KCNJ5-LQTS |
| #616247 | LQT14, CALM1-LQTS |
| #616249 | LQT15, CALM2-LQTS |
| #114183 | LQT16, CALM3-LQTS |
| #612347 | JERVELL AND LANGE-NIELSEN SYNDROME 1; JLNS1 |
| #612347 | JERVELL AND LANGE-NIELSEN SYNDROME 2; JLNS2 |

Legend to Table 1.2.: Table 1.2 reflects the previous entries in OMIM. As for several of the entries, there is only disputed evidence for disease causation, those entries that are now regarded as having disputed evidence were presented in italics.

1.3 Name of the analysed genes or DNA/chromosome segments and OMIM# of the gene(s)

| OMIM# | Gene(s) |
|-------|---------|
| #607542 | LQT1: KCNQ1, 11p15.5-p.15.4 |
| #152427 | LQT2: KCNH2, 7q36.1 |
| #600163 | LQT3: SCN5A, 3p22.2 |
| #106410 | LQT4: ANK2, 4q25-q26 |
| #176261 | LQT5: KCNE1, 21q22.12 |
| #110427 | LQT6: KCNE2, 21q22.11 |
| #603796 | LQT7: KCNJ2, 17q2432 |
| #600681 | LQT8: CACNA1C, 12p13.33 |
| #114205 | LQT9: CAV3, 3p25.3 |
| #601005 | LQT10: SCN4B, 11q23.3 |
| #613688 | LQT12: SNTA1-LQTS |
| #114183 | LQT16: CALM3-LQTS |
| #601253 | LQT9: CAV3, 3p25.3 |
| #608256 | LQT10: SCN4B, 11q23.3 |
90% of the positive LQTS cases a variant affecting function is found in these three core genes. In addition, \textit{CALM1}, \textit{CALM2}, \textit{CALM3} and \textit{TRDN} have a definitive or strong evidence for disease causation, but are associated with specific features. For variants affecting function in the three \textit{CALM} genes, LQTS may present during infancy or early childhood with heart block and severe QT prolongation. At least 30% of patients with clinical clear LQTS are genotype elusive. Common variations likely contribute to phenotype in cases without a known Mendelian variant, but it is likely that there are other genetic and non-genetic factors involved [2].

Cases with \textit{TRDN} mutations presented during early childhood with QT prolongation, negative T waves in precordial leads and exercise-induced arrhythmia related to homozygous or compound heterozygous disease-associated variants. Cases with biallelic loss-of-function variants in \textit{TRDN} can present with either a CPVT or LQTS-like phenotype. Prolonged QTc is not always observed. In cases where it is, it can be classified as atypical LQTS but this is not always the case. The gene \textit{CACNA1C} was reported to have a moderate evidence for disease causation in the absence of multiorgan involvement as in Timothy syndrome. The level of evidence for the gene \textit{KCNJ2} was only limited for the cardio-specific phenotype of LQTS, whereas both genes (\textit{CACNA1C} and \textit{KCNJ2}) were classified to have definitive evidence for causing multiorgan syndromes (respectively: Timothy syndrome and Andersen-Tawil syndrome). Timothy syndrome might be associated with distinctive facial features, developmental delay, endocrine abnormalities and congenital heart defects besides bradycardia, QT prolongation and polymorphic arrhythmias [3]. Extracardiac manifestations of Andersen-Tawil syndrome may present as hypo- or hypercalcemic episodes of paralysis (periodic paralysis) and morphological characteristics as low set ears, clinodactyly or hypertelorism. Andersen-Tawil syndrome is still classified as LQTS although prominent U waves tempted to determine a prolonged QT interval due to inclusion of the U wave [4].

Variants affecting function in the genes \textit{AKAP9}, \textit{ANK2}, \textit{CAV3}, \textit{KCNE2}, \textit{KCNJ5}, \textit{SCN4B} and \textit{SNTA1} are classified as having disputed evidence of disease validity and were, therefore, not included in Tables 1–3 [1, 4].

The spectrum of disease-associated variants (of the loss-of-function subtypes) contains practically all types of variants affecting function (missense, nonsense, splice site, deletions and insertions). Most patients are heterozygous for a variant affecting function, but in ~5% of the cases, patients carry two disease-associated variants in the same or different genes.

### 1.5 Analytical validation

Sequencing of all coding exons and intron-exon boundaries of the eligible genes as listed above. Analysis can be performed by Sanger sequencing, (as part of a (cardio) defined gene
(panel) targeted next-generation sequencing or by whole exome/genome sequencing. Deletions/duplications can be identified using different methods. For instance, multiplex ligation-dependent probe amplification, quantitative PCR, etc.

Sequencing by the Sanger method is predicted to detect >99% of variants in the target regions. Sequencing of both strands (forward and reverse) is recommended. An independent analysis of a second sample of the patient is warranted.

Using NGS as the sequencing method, the sensitivity will depend on the characteristics of test, including (sequencing strategy (e.g. panel/exome/genome), enrichment method), coverage of target regions, base quality and read depth.

Classification of detected variants should be performed according to published standards (e.g. standards of the American College of Medical Genetics and Genomics (ACMG) [5] and should be used with customisation for the specific features of LQTS and its associated genes.

### 1.6 Estimated frequency of the disease

(Incidence at birth (‘birth prevalence’) or population prevalence. If known to be variable between ethnic groups, please report):

1:2,000 in the general population. It may be assumed that the prevalence is of comparable magnitude in different populations [6].

### 1.7 Diagnostic setting

|     | Yes. | No. |
|-----|------|-----|
| A. (Differential) diagnostics | ☒ | ☐ |
| B. Predictive Testing | ☐ | ☒ |
| C. Risk assessment in Relatives | ☒ | ☐ |
| D. Prenatal | ☒ | ☐ |

### 2. Test characteristics

| genotype or A: true positives | C: false negative |
|------------------------------|------------------|
| present | absent | B: false positives | D: true negative |

Test:

- pos. A
- B: sensitivity: $A/(A+C)$
- specificity: $D/(D+B)$
- neg. C
- D: pos. predict. value: $A/(A+B)$
- neg. predict. value: $D/(C+D)$

### 2.1 Analytical sensitivity

(proportion of positive tests if the genotype is present in the analyte)
2.1.1 if tested by conventional Sanger sequencing

Close to 100% if complete Sanger sequencing and deletion/duplication (MLPA) analysis of the affected clinically important regions of each gene is performed. MLPA is indicated for KCNQ1, KCNH2 and KCNJ2. In SCN5A there is insufficient evidence for CNV causing a gain-of-function. But this nearly 100% analytical sensitivity includes variants affecting function as well as variants that are just innocent bystanders where the clinical impact has to be proven subsequently. Potential non-coding pathogenic variants in the 3 core genes may remain undetected by standard sequencing approaches, e.g. deep intronic splice variants.

2.1.2 if tested by Next-generation sequencing

Analytical sensitivity for single nucleotide variants, insertions and deletions: >99% at ≥50× read depth if MLPA and bioinformatic copy number variation (CNV) analysis is included (targeted next-generation sequencing panel approach) [14]. Lack of coverage of specific target regions is a common problem of all NGS platforms. In some cases, the problem can be particularly relevant. For example, some exons of KCNH2 are frequently not completely covered due to their high CG-rich sequence. Thus, additional analysis by Sanger sequencing of these uncovered regions is often required [15, 16]. Core genes (KCNQ1, KCNH2, SCN5A) including flanking splice sites should be entirely and sufficiently covered (at least 20x). Potential non-coding pathogenic variants in the 3 main genes may remain undetected by standard sequencing approaches, e.g. deep intronic splice variants.

2.2 Analytical specificity

(proportion of negative tests if the genotype is not present)

2.2.1 if tested by conventional Sanger sequencing

Close to 100% if complete sequencing and MLPA of the affected gene is performed. But not finding a disease-associated variant rejects by no means the diagnosis LQTS in definite clinical cases as in about 30% the underlying cause or causative genes are still not known.

2.2.2 if tested by Next-generation sequencing

See 2.2.1

2.3 Clinical sensitivity (proportion of positive tests if the disease is present)

The clinical sensitivity can be dependent on variable factors such as age or family history. In such cases, a general statement should be given, even if a quantification can only be made case by case.

2.3.1 if tested by conventional Sanger sequencing

On average the detection rate of variants affecting function for the most frequent LQTS disease genes (KCNQ1, KCNH2, and SCN5A) is about 60–70% [17].

2.3.2 if tested by next-generation sequencing

Extra sensitivity due to sequencing additional genes by NGS is minimally higher as each additionally tested gene mentioned in table a.1.3.1 and 1.4 increases sensitivity slightly.

2.4 Clinical specificity (proportion of negative tests if the disease is not present)

The clinical specificity can be dependent on variable factors such as age or family history. For instance, some patients show an incomplete phenotype, in some individuals the diagnosis is established in adulthood, because of a late onset of symptoms. These cases can likely result in a lower sensitivity. In such cases, a general statement should be given, even if a quantification can only be made case by case.

2.4.1 if tested by conventional Sanger sequencing

About 95%, however, the rate of rare variants of uncertain significance (i.e. non-synonymous genetic variation) in Caucasians is about 4–8% in Non-Caucasian in the LQTS 1–3 genes [18].

2.4.2 If tested by next-generation sequencing

See 2.4.1

2.5 Positive clinical predictive value (life time risk to develop the disease if the test is positive)

Before the age of 40 years roughly 40% of (untreated) patients with LQTS1 and LQTS2 become symptomatic. In LQTS3 this is less, but symptoms may be more severe. Phenotypic expression of the disorder is time-dependent and LQTS subjects maintain a high risk for life-threatening cardiac events after age 40 years, which seems to be less high for LQTS1 [19, 20].

2.6 Negative clinical predictive value (Probability not to develop the disease if the test is negative)

(Probability not to develop the disease if the test is negative).
Assume an increased risk based on family history for a non-affected person. Allelic and locus heterogeneity may need to be considered.

Index case in that family had been tested:
If the index case in that family had been tested and a non-equivocal disease-associated variant had been found in the index patient and the non-affected proband is not a carrier of the identified disease-associated variant close to 100%. In those cases the risk remains as small as the prevalence of the disease in the general population.

Index case in that family had not been tested:
If the patient is clinically affected (prolonged QTc with or without syncope) the index patient has a chance of about 60–70% carrying a variant affecting function. But only in very rare cases there is an indication for performing LQTS genetic testing in a clinically unaffected relative when the index case has not been tested.

This could be imaginable when in an index case there is a strong clinical suspicion of LQTS and there is no DNA available or the index patient refuses genetic testing. Usually, there is no indication for genetic testing in a clinically unaffected family member with unclear genetic status of the index patient if the ECG is normal.

3. Clinical Utility

3.1 (Differential) diagnostics: The tested person is clinically affected (To be answered if in 1.9 "A" was marked)

3.1.1 Can a diagnosis be made other than through a genetic test?

| No. | ☐ (continue with 3.1.4) |
|-----|-------------------------|
| Yes. | ☑ |

Clinically ☑
Imaging ☐
Endoscopy ☐
Biochemistry ☐
Electrophysiology ☐
Other (please describe) ECG recording
Measurement of the QTc interval on repeated ECG recordings and typical clinical symptoms (with low sensitivity) [21].

3.1.2 Describe the burden of alternative diagnostic methods to the patient

ECGs are a non-invasive procedure with no risks and little inconvenience for the patient. But for the reason of low sensitivity and specificity the burden is psychological: uncertainty of proper diagnosis as well as appropriate clinical care: individual therapy, individual recommendations for treatment, life style adaption and individual risk stratification based on specific subtype are not possible in the absence of a genetic substrate.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?

As far as a disease-causing mutation is identified in the index patient, genetic testing can be offered to apparently healthy relatives within the family in order to determine if they carry the same variant affecting function and are at risk for malignant ventricular arrhythmias. If the relative carries the known disease-associated variant a prophylactic inexpensive medical treatment can be started and specific advice can be given to gene carriers (avoiding substances/drugs which might trigger arrhythmias, avoidance of genotype-specific triggers for arrhythmias, careful attendance in case of pregnancy and delivery, reproductive counselling, counselling concerning choice of profession). There is a reduction of the relative risk for developing serious cardiac events of about 65% by proper treatment (mostly with an inexpensive beta-blocker therapy) and the cardiac events in untreated patients on the other hand may lead to early invalidity or death in otherwise often healthy young people with putative high economic loss.

3.1.4 Will disease management be influenced by the result of a genetic test?

| No. | ☐ |
|-----|---|
| Yes. | ☑ |

Therapy (please describe) Pharmaceutical treatment (usually beta-blockers) as primary and secondary prevention. In rare individual cases additional pacemaker and/or an implantable cardioverter defibrillator (ICD), and/or left cardiac sympathetic
3.2 Predictive setting: the tested person is clinically unaffected but carries an increased risk based on family history

(To be answered if in 1.9 "B" was marked)
3.4 Prenatal diagnosis

(To be answered if in 1.9 ‘D’ was marked)

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnosis?

Yes, but prenatal diagnostics are not actively offered.

4. If applicable, further consequences of testing

Please assume that the result of a genetic test has no immediate medical consequences. Is there any evidence that a genetic test is nevertheless useful for the patient or his/her relatives? (Please describe)

For every patient (clinically affected or not) there are known specific triggers for arrhythmias to be avoided (e.g. QT prolonging drugs, competitive sports, low potassium serum levels, swimming in LQTS1, sudden loud noise in LQTS2) [7, 8, 23, 24]. Thus, there should be thorough counselling concerning lifestyle modifications and choice of employment.

This work was supported by EuroGentest2 (Unit 2: ‘Genetic testing as part of health care’), a Coordination Action under FP7 (Grant Agreement Number 261469) and the European Society of Human Genetics.

Funding Open Access funding enabled and organized by Projekt DEAL.

Compliance with ethical standards

Conflict of interest The authors declare no competing interest.

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Adler A, Novelli V, Amin AS, Abiusi E, Care M, Nannenberg EA, et al. An international, multicentered, evidence-based reappraisal of genes reported to cause congenital long QT syndrome. Circulation. 2020;141:418–28.
2. Lahrouchi N, Tadros R, Crotti L, Mizusawa Y, Postema PG, Beekman L, et al. Transethnic genome-wide association study provides insights in the genetic architecture and heritability of long QT syndrome. Circulation. 2020;142:324–38.
3. Splawski I, Timothy KW, Sharpe LM, Decher N, Kumar P, Bloise R, et al. Ca(V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. Cell. 2004;119:19–31.
4. Giudicessi JR, Wilde AAM, Ackerman MJ. The genetic architecture of long QT syndrome: a critical reappraisal. Trends Cardiovasc Med. 2018;28:453–64.
5. Richards S, Aziz N, Bale S, Dick 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;17:405–24.
6. Schwartz PJ, Stramba-Badiale M, Crotti L, Pedrazzini M, Besana A, Bosi G, et al. Prevalence of the congenital long-QT syndrome. Circulation. 2009;120:1761–7.
7. Ackerman MJ, Marcou CA, Tester DJ. Personalized medicine: genetic diagnosis for inherited cardiomyopathies/channeopathies. Rev Esp Cardiol (Engl Ed). 2013;66:298–307.
8. 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. Available from: URL: https://pubmed.ncbi.nlm.nih.gov/15840476/.
9. Koopmann TT, Alders M, Jongbloed RJ, Guerrero S, Mannens MMAM, Wilde AAM, et al. Long QT syndrome caused by a large duplication in the KCNH2 (HERG) gene undetectable by current polymerase chain reaction-based exon-scanning methodologies. Heart Rhythm. 2006;3:52–5.
10. Barc J, Bricc F, Schmitt S, Kyndt F, Le Cunff M, Baron E, et al. Screening for copy number variation in genes associated with the long QT syndrome: clinical relevance. J Am Coll Cardiol. 2011;57:40–7.
11. Tester DJ, Benton AJ, Train L, Deal B, Baudhuin LM, Ackerman MJ. Prevalence and spectrum of large deletions or duplications in the major long QT syndrome-susceptibility genes and implications for long QT syndrome genetic testing. Am J Cardiol. 2010;106:1124–8.
12. Eddy C-A, MacCormick JM, Chung S-K, Crawford JR, Love DR, Rees ML, et al. Identification of large gene deletions and duplications in KCNQ1 and KCNH2 in patients with long QT syndrome. Heart Rhythm. 2008;5:1275–81.
13. Stattin E-L, Boström IM, Winbo A, Cederqvist K, Jonasson J, Jonsson B-A, et al. Founder mutations characterise the mutation panorama in 200 Swedish index cases referred for Long QT syndrome genetic testing. BMC Cardiovasc Disord. 2012;12:95.
14. Pua CJ, Bhalshankar J, Miao K, Walsh R, John S, Lim SQ, et al. Development of a comprehensive sequencing assay for inherited cardiac condition genes. J Cardiovasc Transl Res. 2016;9:3–11.
15. Millat G, Chanavat V, Rousson R. Evaluation of a new high-throughput next-generation sequencing method based on a custom AmpliSeq™ library and ion torrent PGM™ sequencing for the rapid detection of genetic variations in long QT syndrome. Mol Diagn Ther. 2014;18:533–9.
16. Novelli V, Gambelli P, Memmi M, Napolitano C. Challenges in molecular diagnostics of channeopathies in the next-generation sequencing era: less is more? Front Cardiovasc Med 2016;3:29.
17. 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;294:2975–80.
18. Kapa S, Tester DJ, Salisbury BA, Harris-Kerr C, Punghiya MS, Alders M, et al. Genetic testing for long-QT syndrome: distinguishing pathogenic mutations from benign variants. Circulation. 2009;120:1752–60.
19. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, et al. Risk stratification in the long-QT syndrome. N Engl J Med. 2003;348:1866–74.
20. Goldenberg I, Moss AJ, Bradley J, Polonsky S, Peterson DR, McNitt S, et al. Long-QT syndrome after age 40. Circulation. 2008;117:2192–201.
21. Hofman N, Wilde AAM, Kääb S, van Langen IM, Tanck MWT, Mannens MMAM, et al. Diagnostic criteria for congenital long QT syndrome in the era of molecular genetics: do we need a scoring system? Eur Heart J. 2007;28:575–80.
22. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggreve M, Camm J, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015;36:2793–867.
23. Wilde AAM, Jongbloed RJE, Doevendans PA, Düren DR, Hauer RNW, van Langen IM, et al. Auditory stimuli as a trigger for arrhythmic events differentiate HERG-related (LQTS2) patients from KVLQT1-related patients (LQTS1). J Am Coll Cardiol. 1999;33:327–32.
24. Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation. 2001;103:89–95.
25. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, regional, and national burden of cardiovascular diseases for 10 Causes, 1990 to 2015. J Am Coll Cardiol. 2017;70:1–25.
26. Rohatgi RK, Sugrue A, Bos JM, Cannon BC, Asirvatham SJ, Moir C, et al. Contemporary outcomes in patients with Long QT syndrome. J Am Coll Cardiol. 2017;70:453–62.
27. Amin AS, Herfst LJ, Delisle BP, Klemens CA, Rook MB, Bezzi CR, et al. Fever-induced QTc prolongation and ventricular arrhythmias in individuals with type 2 congenital long QT syndrome. J Clin Invest. 2008;118:2552–61.
28. Burashnikov A, Shimizu W, Antzelevitch C. Fever accentuates transmural dispersion of repolarization and facilitates development of early afterdepolarizations and torsade de pointes under long-QT Conditions. Circ Arrhythm Electrophysiol. 2008;1:202–8.
29. Boczek NJ, Best JM, Tester DJ, Giudicessi JR, Middha S, Evans JM, et al. Exome sequencing and systems biology converge to identify novel mutations in the L-type calcium channel, CACNA1C, linked to autosomal dominant long QT syndrome. Circ Cardiovasc Genet. 2013;6:279–89.
30. Crotti L, Johnson CN, Graf E, Ferrari GM, de, Cuneo BF, Ovadia M, et al. Calmodulin mutations associated with recurrent cardiac arrest in infants. Circulation. 2013;127:1009–17.
31. Reed GJ, Boczek NJ, Etheridge SP, Ackerman MJ. CALM3 mutation associated with long QT syndrome. Heart Rhythm. 2015;12:419–22.
32. Splawski I, Tristani-Firouzi M, Lehmann MH, Sanguinetti MC, Keating MT. Mutations in the hminK gene cause long QT syndrome and suppress IKs function. Nat Genet. 1997;17:338–40.
33. Curran ME, Splawski I, Timothy KW, Vincen GM, Green ED, Keating MT. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. Cell. 1995;80:795–803.
34. Plaster NM, Tawil R, Tristani-Firouzi M, Canin S, Bendahhou S, Tsunoda A, et al. Mutations in Kir2.1 cause the developmental and episodic electrical phenotypes of Andersen’s syndrome. Cell. 2001;105:511–9.
35. Wang Q, Curran ME, Splawski I, Burn TC, Millholland JM, VanRaay TJ, et al. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. Nat Genet. 1996;12:17–23.
36. Wang Q, Shen J, Splawski I, Atkinson D, Li Z, Robinson JL, et al. SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. Cell. 1995;80:805–11.
37. Altmann HM, Tester DJ, Will ML, Middha S, Evans JM, Eckloff BW, et al. Homozygous/compound heterozygous triadin mutations associated with autosomal-recessive long-QT syndrome and pediatric sudden cardiac arrest: elucidation of the triadin knockout syndrome. Circulation. 2015;131:2051–60.