Journal of Cardiology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

A challenge for mutation specific risk stratification in long QT syndrome type 1

Noriaki Yagi (MD)[a], Hideki Itoh (MD, PhD, FJCC)[a,b], Takashi Hisamatsu (MD, PhD)[c], Yukinori Tomita (MD)[a], Hiromi Kimura (MD, PhD)[a], Yusuke Fujii (MD, PhD)[a], Takeru Makiyama (MD, PhD)[d], Minoru Horie (MD, PhD)[a], Seiko Ohno (MD, PhD)[a,e,*]

[a] Department of Cardiovascular and Respiratory Medicine, Shiga University of Medical Science, Otsu, Japan
[b] Medical Safety Section, Shiga University of Medical Science, Otsu, Japan
[c] Department of Environmental Medicine and Public Health Faculty of Medicine, Shimane University, Izumo, Japan
[d] Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan
[e] Center for Epidemiologic Research in Asia, Shiga University of Medical Science, Otsu, Japan

ARTICLE INFO

Article history:
Received 29 September 2017
Received in revised form 5 December 2017
Accepted 20 December 2017
Available online xxx

Keywords:
Long QT syndrome
KCNQ1
Mutation location
Sudden death

ABSTRACT

Background: The relationship between mutation locations in *KCNQ1* which is a major gene in long QT syndrome (LQTS) and phenotype has been analyzed and used for risk stratification. Mutations in the transmembrane region (TM) or cytoplasmic-loop (C-loop) are associated with more frequent cardiac events than those in other regions. However, accumulation of LQTS type 1 (LQT1) patients poses the question of whether the location specific risk stratification is really effective.
Methods: The study cohort consisted of 67 KCNQ1 mutation carriers and 13 family members who were suspected as having LQTS due to sudden cardiac death or syncope from 36 unrelated families. The KCNQ1 mutations were L250H, V254M, H258P, and R259C located in segment 4–5 linker (C-loop), G269S, and S277L in segment 5 (TM).
Results: More than half of the patients with V254M or S277L suffered sudden cardiac death or syncope. In contrast, those with other mutations showed mild phenotype. In these two mutations related to severe phenotype, gender frequency and the age of onset were contrasting, 14 out of 23 patients with V254M were male, 19 out of 22 patients with S277L were female. In the patients we could confirm the age of onset, all of the patients with V254M showed symptoms at less than 15 years old, while 5 out of 12 patients with S277L suffered symptoms after 16 years old.
Conclusion: Clinical characteristics were not specific for mutation locations but specific for respective mutations in our LQT1 patients. Patients should be evaluated by their own mutations to prevent severe cardiac events.

Introduction

Long QT syndrome (LQTS) is an inherited arrhythmic disease associated with prolonged QT interval and fatal arrhythmias such as torsade de pointes (TdP) or ventricular fibrillation (VF) [1]. *KCNQ1* is a causative gene of LQTS type 1 (LQT1), which encodes α-subunit of the slow component of delayed rectifier potassium current channel, and its mutations cause the loss of function in I_{Ks} [2]. Correlations between mutation sites and phenotypes in LQT1 have been well studied [3,4]. Missense mutations in the C-loop which represented inner linkers between segment 2 and 3 or segment 4 and 5 have been shown to be associated with malignant phenotypes [5].

We however realized that S277L located in the segment 5 (S5), a non-C-loop mutation which was frequently identified in our cohort [6] (Fig. 1A), showed a more severe phenotype. Based on the frequency and the location of the mutations, we chose six mutations for the analysis (Fig. 1B), four mutations in the segment 4–5 (S4-5) linker (C-loop) and two mutations including S277L in the S5 (transmembrane, TM), and compared clinical features of the patients with these mutations.

* Corresponding author at: Department of Cardiovascular and Respiratory Medicine, Shiga University of Medical Science, Seta-Tsukinowa, Otsu, Shiga 520-2192, Japan. Tel.: +81 77 548 2212; fax: +81 77 543 5839.
E-mail address: seikoono@belle.shiga-med.ac.jp (S. Ohno).

https://doi.org/10.1016/j.jjcc.2017.12.011
0914-5087/

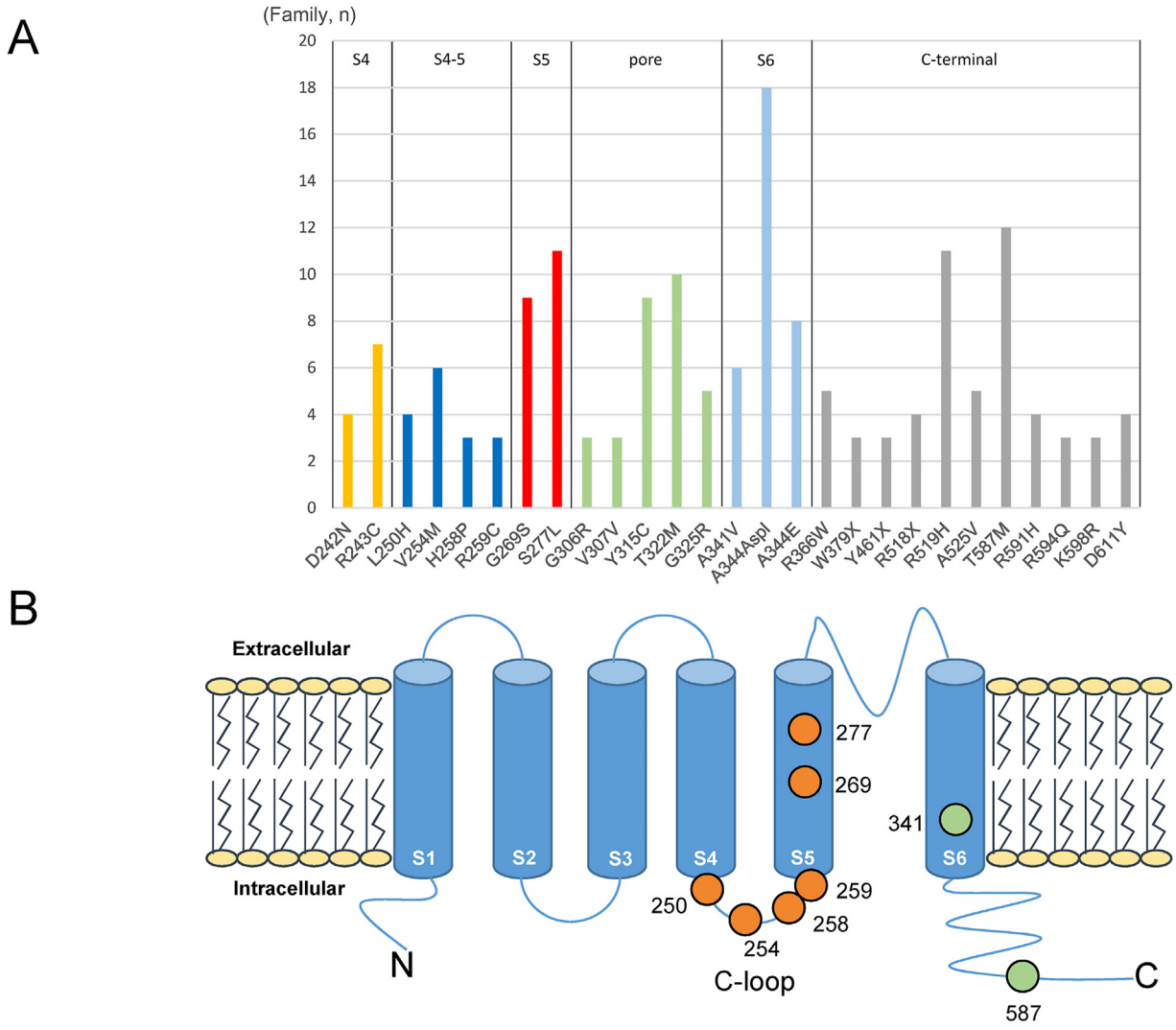

Fig. 1. Mutation frequency (A) and locations (B) in KCNQ1. (A) All the KCNQ1 mutations in our cohort identified in more than 2 families and family numbers with the mutation. Mutations in N-terminal to S3-4 linker were identified only in 2 and less. (B) The location of each mutation is indicated on the transmembrane topology model. Orange circles display mutations we analyzed. Green ones are mutations discussed in Discussion section.

Methods

Study population

From 1996 to 2014, we performed genetic analysis for LQTS probands in 2 centers, Shiga University of Medical Science and Kyoto University Graduate School of Medicine. This study cohort consisted of 67 carriers with one of the six KCNQ1 mutations and 13 family members who were not genotyped but suspected of having LQTS due to sudden cardiac death or syncope from 36 unrelated families. Six mutations were all the mutations identified in S4-S5 linker (C-loop) and S5 TM domain in our LQT1 patients, and they were identified in more than 2 families (Fig. 1A). The mutations were L250H (c.749T>A), V254M (c.760G>A), H258P (c.773A>C), R259C (c.775C>T), G269S (c.805G>A), and S277L (c.830C>T). Fig. 1B shows the KCNQ1 morphology showing the position of the mutations in this study. Compound or double mutation carriers were excluded from this study [6].

Clinical information included gender, age, cardiac events such as syncope, TdP, and cardiac arrest prior to β blocker therapy, family history of sudden cardiac death and LQTS, age at onset of first cardiac symptoms, and electrocardiographic (ECG) findings [6,7]. The prolongation of QTc intervals were defined as being over 450 ms in males and 460 ms in females.

The QT interval was manually measured as the time period between QRS onset (Q) and the point at which the isoelectric line intersected a tangential line drawn at the maximal downslope of the positive T wave or the maximal upslope of the negative T wave (Tend). Data were basically obtained from the V5 lead in the 12-lead ECG during stable sinus rhythm and corrected by the Bazett's formula [8].

Genetic analysis

The protocol for genetic analysis was approved by and performed under the guidelines of the Institutional Ethics Committee at each institute. Written informed consent to participate in the study including the collection and use of DNA samples for genetic analysis was obtained in each center. Genomic DNA was isolated from peripheral white blood cells using conventional methods. Genetic analysis was performed as previously reported [9]. Briefly, we screened for *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, and *KCNE2* corresponding to LQT1, LQT2, LQT3, LQT5, and LQT6 genes, using polymerase chain reaction/single-

Please cite this article in press as: Yagi N, et al. A challenge for mutation specific risk stratification in long QT syndrome type 1. J Cardiol (2018), https://doi.org/10.1016/j.jjcc.2017.12.011