# Supplementary Online Content

Shimizu W, Makimoto H, Yamagata K, et al. Association of genetic and clinical aspects of congenital long QT syndrome with life-threatening arrhythmias in Japanese patients. *JAMA Cardiol.* Published online February 13, 2019. doi:10.1001/jamacardio.2018.4925

## **eAppendix.** Methods

### Data acquisition institutions:

National Cerebral and Cardiovascular Center, Suita Osaka;
Shiga University of Medical Science, Otsu;
Kyoto University, Kyoto;
Kagoshima Medical Center, Kagoshima;
Kanazawa University, Kanazawa;
Niigata University, Niigata;
Okayama University, Okayama;
Nagasaki University, Nagasaki;
Keio University, Tokyo;
Nihon University, Tokyo;
Tokyo Women's Medical University, Tokyo

### Genetic screening institutions:

National Cerebral and Cardiovascular Center,
Shiga University of Medical Science Hospital,
Kyoto University Hospital,
Kagoshima Medical Center,
Kanazawa University Hospital,
Niigata University Hospital,
Okayama University Hospital,
Nagasaki University Hospital,
Keio University Hospital.

### Bioinformatic Analysis

Pathogenicity of variants was by frequency referring to the NCBI dbSNP database (http://www.ncbi.nlm.nih.gov/snp/), the Human Genetic Variation Browser (an SNP database in Japanese; http://www.genome.med.kyoto-u.ac.jp/SnpDB/), the 1000 Genomes database (http://www.1000genomes.org/home) and our in-house data compiled from 1,000 Japanese individuals.[1]

### eReference

1. Shigemizu D, Aiba T, Nakagawa H, et al. Exome analyses of long QT syndrome reveal candidate pathogenic mutations in calmodulin-interacting genes. *PloS one*. 2015;10:e0130329.

**eTable 1.** LQT1 Mutations or Rare Variants

| | Mutation | site | Site | N | Female (n) | Proband (n) | Mean QTc (proband) | Syncope (n) | CA/VF (n) |
|---|---|---|---|---|---|---|---|---|---|
| c.153C>A | p.Y51X | N | N/C-term | 1 | 0 | 1 | 443 | 1 | 0 |
| c.332A>G | p.Y111C | N | N/C-term | 1 | 1 | 1 | 551 | 1 | 1 |
| c.350C>T | p.P117L | N | N/C-term | 5 | 2 | 3 | 520 | 2 | 1 |
| c.377A>C | p.H126P | N | N/C-term | 2 | 1 | 1 | 495 | 0 | 0 |
| c.521G>A | p.R147H | MS | non-pore MS | 2 | 1 | 1 | 444 | 1 | 0 |
| c.502G>A | p.G168R | MS | non-pore MS | 8 | 7 | 2 | 500 | 0 | 0 |
| c.520C>T | p.R174C | C-loop | non-pore MS | 7 | 4 | 3 | 466 | 1 | 0 |
| c.521G>A | p.R174H | C-loop | non-pore MS | 1 | 0 | 1 | 476 | 0 | 0 |
| c.530C>A | p.S177T | C-loop | non-pore MS | 2 | 1 | 1 | 440 | 0 | 0 |
| c.532G>A | p.A178T | C-loop | non-pore MS | 5 | 1 | 2 | 528 | 1 | 1 |
| | * p.A178-G189del | C-loop | non-pore MS | 1 | 1 | 1 | 471 | 0 | 0 |
| c.557G>A | p.G186D | C-loop | non-pore MS | 2 | 2 | 1 | 458 | 0 | 0 |
| c.566G>A | p.G189A | C-loop | non-pore MS | 2 | 1 | 1 | 474 | 1 | 0 |
| c.565G>A | p.G189R | C-loop | non-pore MS | 2 | 1 | 1 | 521 | 0 | 0 |
| c.568C>T | p.R190W | C-loop | non-pore MS | 2 | 1 | 2 | 471 | 1 | 0 |
| c.569G>A | p.R190Q | C-loop | non-pore MS | 9 | 3 | 6 | 478 | 3 | 0 |
| c.739T>C | p.F193L | MS | non-pore MS | 4 | 2 | 1 | 480 | 0 | 0 |
| c.589C>T | p.P197S | MS | non-pore MS | 3 | 1 | 1 | 511 | 0 | 0 |
| c.657 delG | p.G219fsX236 | MS | non-pore MS | 3 | 0 | 1 | 470 | 0 | 0 |
| c.674C>T | p.S225L | MS | non-pore MS | 2 | 0 | 1 | 448 | 2 | 0 |
| c.677C>T | p.A226V | MS | non-pore MS | 6 | 5 | 3 | 466 | 3 | 0 |
| c.691C>T | p.R231C | MS | non-pore MS | 1 | 1 | 1 | 493 | 1 | 1 |
| | p.R237P | MS | non-pore MS | 1 | 1 | 1 | 598 | 1 | 0 |
| c.724G>A | p.D242N | C-loop | non-pore MS | 9 | 6 | 5 | 494 | 2 | 0 |
| c.727C>T | p.R243C | C-loop | non-pore MS | 9 | 6 | 5 | 476 | 5 | 1 |
| c.728G>A | p.R243H | C-loop | non-pore MS | 5 | 4 | 2 | 447 | 1 | 1 |
| | ** p.W248F | C-loop | non-pore MS | 1 | 1 | 1 | 460 | 1 | 0 |
| c.749T>A | p.L250H | C-loop | non-pore MS | 4 | 2 | 3 | 459 | 2 | 0 |
| c.760G>A | p.V254M | C-loop | non-pore MS | 28 | 13 | 11 | 495 | 22 | 4 |
| c.773 A>C | p.H258P | C-loop | non-pore MS | 5 | 3 | 3 | 455 | 3 | 1 |
| c.775C>T | p.R259C | C-loop | non-pore MS | 3 | 3 | 2 | 480 | 2 | 0 |
| c.781G>T 782A>T | p.E261L | C-loop | non-pore MS | 2 | 1 | 1 | 524 | 1 | 0 |
| c.805G>T | p.G269C | MS | S5-pore-S6 | 1 | 1 | 1 | 516 | 1 | 0 |
| c.805G>A | p.G269S | MS | S5-pore-S6 | 20 | 10 | 10 | 472 | 6 | 2 |
| c.815G>A | p.G272D | MS | S5-pore-S6 | 2 | 1 | 1 | 476 | 0 | 0 |
| c.815G>T | p.G272V | MS | S5-pore-S6 | 3 | 2 | 2 | 437 | 2 | 0 |
| c.828-830delCTC | p.276delS | MS | S5-pore-S6 | 2 | 1 | 1 | 566 | 0 | 0 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| c.830C>T p.S277L | MS | S5-pore-S6 | 10 | 6 | 7 | 488 | 3 | 0 |
| c.916G>C p.G306R | MS | S5-pore-S6 | 2 | 0 | 1 | 474 | 0 | 0 |
| c.931A>G p.T311A | MS | S5-pore-S6 | 2 | 2 | 1 | 439 | 1 | 0 |
| c.938T>A 939C>A p.I313K | MS | S5-pore-S6 | 8 | 4 | 2 | 484 | 8 | 2 |
| c.940G>A p.G314S | MS | S5-pore-S6 | 7 | 4 | 4 | 506 | 5 | 3 |
| c.941G>C p.G314A | MS | S5-pore-S6 | 1 | 1 | 1 | 582 | 1 | 0 |
| c.944A>G p.Y315C | MS | S5-pore-S6 | 5 | 4 | 3 | 521 | 2 | 1 |
| c.947G>A p.G316E | MS | S5-pore-S6 | 2 | 2 | 2 | 490 | 1 | 0 |
| c.1111G>T p.D317Y | MS | S5-pore-S6 | 2 | 1 | 1 | 495 | 2 | 0 |
| c.959C>G p.P320R | MS | S5-pore-S6 | 1 | 1 | 1 | 490 | 1 | 0 |
| *** p.T322M +**** p.637fsx665 | MS | S5-pore-S6 | 4 | 2 | 1 | 514 | 1 | 0 |
| c.965C>T p.T322M | MS | S5-pore-S6 | 10 | 6 | 6 | 488 | 2 | 0 |
| c.973G>A p.G325R | MS | S5-pore-S6 | 9 | 6 | 5 | 464 | 5 | 0 |
| c.974G>A p.G325E | MS | S5-pore-S6 | 2 | 2 | 1 | 490 | 2 | 0 |
| c.976A>G p.K326E | MS | S5-pore-S6 | 1 | 0 | 1 | 446 | 1 | 0 |
| c.1016T>C p.F339S | MS | S5-pore-S6 | 3 | 2 | 2 | 466 | 0 | 0 |
| c.1017-1019del CTT p. 340del F | MS | S5-pore-S6 | 5 | 4 | 2 | 564 | 2 | 0 |
| c.1022C>T p.A341V | MS | S5-pore-S6 | 35 | 20 | 11 | 500 | 23 | 7 |
| c.1022C>A p.A341E | MS | S5-pore-S6 | 1 | 0 | 1 | 480 | 0 | 0 |
| c.1028C>T p.P343L | MS | S5-pore-S6 | 2 | 1 | 2 | 571 | 2 | 1 |
| c.1031C>A p.A344E | MS | S5-pore-S6 | 20 | 14 | 11 | 496 | 2 | 2 |
| c .1031C>T p.A344V | MS | S5-pore-S6 | 1 | 1 | 1 | 480 | 1 | 0 |
| c.1032 G>A p.A344A splicing | MS | S5-pore-S6 | 47 | 26 | 24 | 494 | 23 | 4 |
| c.1040T>G p.L347R | MS | S5-pore-S6 | 1 | 1 | 1 | 487 | 0 | 0 |
| ***** p.K358_Q359del | C | N/C-term | 2 | 1 | 1 | 493 | 1 | 0 |
| ****** p.Q361_K362 ins RQ | C | N/C-term | 1 | 1 | 1 | 470 | 1 | 0 |
| c.1096C>T p.R366W | C | N/C-term | 13 | 6 | 8 | 488 | 3 | 0 |
| c.1097G>C p.R366P | C | N/C-term | 4 | 2 | 2 | 525 | 3 | 0 |
| c.1097G>A p.R366Q | C | N/C-term | 2 | 2 | 2 | 454 | 0 | 0 |
| c.1111 G>A p.A371T | C | N/C-term | 1 | 1 | 1 | 460 | 0 | 0 |
| p.G417A splicing error | C | N/C-term | 1 | 1 | 1 | 481 | 1 | 0 |
| c.1265A>C p.K422T | C | N/C-term | 3 | 3 | 2 | 519 | 0 | 0 |
| c.1309A>G p.M437V | C | N/C-term | 3 | 2 | 1 | 380 | 0 | 0 |
| c.1352G>A p.R451Q | C | N/C-term | 1 | 0 | 1 | 440 | 1 | 1 |
| c.1382-1383ins A p.T461X | C | N/C-term | 1 | 1 | 1 | 480 | 1 | 0 |
| c.1550T>C p.I 517T | C | N/C-term | 3 | 1 | 1 | 410 | 1 | 0 |
| c.1552C>G p.R518G | C | N/C-term | 6 | 4 | 4 | 443 | 4 | 0 |
| c.1552C>T p.R518X | C | N/C-term | 1 | 0 | 1 | 453 | 0 | 0 |
| c.1556G>A p.R519H | C | N/C-term | 1 | 0 | 1 | 400 | 1 | 1 |
| ******* p.Q521-Y522 del T | C | N/C-term | 1 | 1 | 1 | 448 | 0 | 0 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| c.1574C>T p.A525V | C | N/C-term | 13 | 5 | 10 | 494 | 6 | 0 |
| c.1615C>T p.R539W | C | N/C-term | 3 | 1 | 3 | 464 | 1 | 0 |
| c1634A>G p.Y545C | C | N/C-term | 4 | 3 | 2 | 487 | 0 | 0 |
| c.1661T>G p.V554G | C | N/C-term | 1 | 1 | 1 | 523 | 0 | 0 |
| c.1663C>T p.R555C | C | N/C-term | 6 | 2 | 2 | 454 | 1 | 0 |
| c.1664G>A p. R555H | C | N/C-term | 1 | 1 | 1 | 431 | 0 | 0 |
| c.1667T>A p. I556N | C | N/C-term | 1 | 1 | 1 | 490 | 0 | 0 |
| c.1679A>T p. Q560L | C | N/C-term | 1 | 1 | 1 | 481 | 0 | 0 |
| c.1683G>T p.R561S | C | N/C-term | 3 | 2 | 0 | | 1 | 0 |
| c.1700T>C p.I567T | C | N/C-term | 1 | 0 | 1 | 604 | 0 | 0 |
| c.1714delC p.L572fsx592 | C | N/C-term | 4 | 2 | 2 | 461 | 1 | 1 |
| c.1719C>A p.F573L | C | N/C-term | 1 | 1 | 1 | 440 | 0 | 0 |
| c.1760C>T p.T587M | C | N/C-term | 39 | 26 | 19 | 492 | 20 | 3 |
| c.1772G>A p.R591H | C | N/C-term | 13 | 8 | 7 | 479 | 3 | 0 |
| c.1781G>A p.R594Q | C | N/C-term | 6 | 3 | 3 | 474 | 0 | 0 |
| c.1793A>G p.K598R | C | N/C-term | 1 | 1 | 1 | 402 | 0 | 0 |
| c.1805T>C p.L602P | C | N/C-term | 1 | 1 | 0 | | 0 | 0 |
| c.1807 del G p.D603fsX665 | C | N/C-term | 1 | 0 | 1 | 447 | 0 | 0 |
| c.1831G>T p.D611Y | C | N/C-term | 19 | 9 | 6 | 510 | 5 | 1 |
| c.1893delC p.P631fsX664 | C | N/C-term | 3 | 2 | 0 | | 0 | 0 |
| c.1128+1G>A Splicing Error | | | 4 | 4 | 3 | 469 | 1 | 0 |
| c.1514+1G>A Splicing Error | | | 1 | 1 | 1 | 496 | 0 | 0 |
| c.1732+2T>C Splicing Error | | | 3 | 1 | 2 | 458 | 1 | 0 |

N: N-terminus, C: C-terminus, TM: transmembrane, MS: membrane spanning, CA/VF:cardiac arrest/ ventricular fibrillation

*c.533-565del CCGGCTGCCGCAGCAAGTACGTGGGCCTCTGGG

** c.743G>T(homo) c.744G>C(homo)

*** c.965C>T

**** c.1909delC

***** c.1073_1078 del AGCAGA

****** c.1084_1085 ins GGCAGA

*******c.1561-1564 del CAGTinsC

eTable 2. LQT2 Mutations or Rare Variants

| Mutation | site | Site | N | Female (n) | Proband (n) | Mean QTc (proband) | Syncope (n) | CA/VF (n) |
|---|---|---|---|---|---|---|---|---|
| c.58C>G p.R20G | N | N/C-term | 1 | 0 | 1 | 490 | 0 | 0 |
| c.59G>T p.R20L | N | N/C-term | 3 | 2 | 1 | 490 | 0 | 0 |
| c.65T>A p.F22Y | N | N/C-term | 1 | 0 | 1 | 558 | 1 | 1 |
| c.80G>C p.R27P | N | N/C-term | 1 | 0 | 1 | 496 | 0 | 0 |
| c.100delG p.A34fsX59 | N | N/C-term | 1 | 1 | 1 | 574 | 1 | 1 |
| c. 122 T>C p. V41A | N | N/C-term | 1 | 0 | 1 | 451 | 0 | 0 |
| c. 127T>G p. Y43D | N | N/C-term | 3 | 2 | 1 | 480 | 1 | 0 |
| c.133A>G p.N45D | N | N/C-term | 2 | 0 | 0 |  | 0 | 0 |
| c.139G>T p.G47C | N | N/C-term | 2 | 0 | 2 | 513 | 0 | 0 |
| c. 148delG p. E50fsX59 | N | N/C-term | 1 | 0 | 1 | 478 | 1 | 0 |
| c. 157G>A p. G53S | N | N/C-term | 6 | 3 | 3 | 538 | 1 | 1 |
| c. 157G>A p. G53R | N | N/C-term | 1 | 1 | 1 | 460 | 1 | 1 |
| c.164C>T p.S55L | N | N/C-term | 1 | 1 | 1 | 474 | 1 | 0 |
| c.172G>A p.E58K | N | N/C-term | 3 | 3 | 2 | 462 | 3 | 1 |
| c.179T>C p.M60T | N | N/C-term | 1 | 1 | 1 | 480 | 1 | 0 |
| c.193A>C p.T65P | N | N/C-term | 5 | 5 | 3 | 525 | 3 | 2 |
| c.196T>C p.C66R | N | N/C-term | 1 | 1 | 1 | 517 | 1 | 0 |
| c.211G>A p.G71R | N | N/C-term | 2 | 2 | 2 | 533 | 2 | 1 |
| c.215C>A p.P72Q | N | N/C-term | 2 | 2 | 1 | 508 | 1 | 0 |
| c.233C>T p.A78V | N | N/C-term | 1 | 0 | 1 | 470 | 0 | 0 |
| c.232G>A p.A78T | N | N/C-term | 1 | 0 | 1 | 520 | 0 | 0 |
| c.252-253ins *1 p.82-84insIAQ | N | N/C-term | 1 | 1 | 1 | 536 | 1 | 0 |
| c.318C>A p. F106L | N | N/C-term | 1 | 1 | 1 | 520 | 1 | 0 |
| c.316T>G p.F106V | N | N/C-term | 2 | 2 | 1 | 510 | 2 | 0 |
| c. 332A>T p. D111V | N | N/C-term | 3 | 3 | 1 | 416 | 1 | 0 |
| c.340C>T p.P114S | N | N/C-term | 8 | 4 | 2 | 513 | 2 | 0 |
| c.343G>A p.V115M | N | N/C-term | 2 | 1 | 1 | 458 | 1 | 0 |
| c.371T>C p.M124T | N | N/C-term | 6 | 4 | 1 | 480 | 2 | 0 |
| c.388G>A p.E130K | N | N/C-term | 3 | 1 | 2 | 483 | 0 | 0 |
| c.437 del A p.N146fsX165 | N | N/C-term | 1 | 1 | 1 | 506 | 0 | 0 |
| c.453-454insC p.P151fsX330 | N | N/C-term | 1 | 1 | 1 | 466 | 1 | 1 |
| c.453 del C p.P151fsX165 | N | N/C-term | 1 | 1 | 1 | 495 | 1 | 1 |
| exon3 c.454inC p.H152 fsX331 | N | N/C-term | 2 | 2 | 1 | 542 | 0 | 0 |
| c.453delC p.T152fsX165 | N | N/C-term | 2 | 2 | 1 | 530 | 1 | 0 |
| c.486-487delCT p.T162fsX330 | N | N/C-term | 2 | 0 | 1 | 490 | 1 | 0 |
| c.527insC p.R176fsX331 | N | N/C-term | 1 | 1 | 1 | 474 | 1 | 1 |
| c.547-533del *2 p.G183fsX198 | N | N/C-term | 1 | 0 | 1 | 482 | 0 | 0 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| c.560-568del [*3] p.G187-A190del | N | N/C-term | 3 | 2 | 1 | 548 | 1 | 0 |
| c.589G>T p.D197Y | N | N/C-term | 4 | 1 | 1 | 542 | 1 | 1 |
| c.715_719 del TCTCC p.S239fsX329 | N | N/C-term | 14 | 8 | 4 | 477 | 2 | 1 |
| c.724del C p.R242fsX359 | N | N/C-term | 4 | 4 | 1 | 464 | 1 | 0 |
| c.730〜742del [*4] p.243fsX355 | N | N/C-term | 1 | 1 | 1 | 436 | 1 | 0 |
| c.760-775del [*5] p.H254fsX354 | N | N/C-term | 2 | 2 | 1 | 520 | 1 | 1 |
| c.804C>T p.R269W | N | N/C-term | 1 | 1 | 1 | 427 | 0 | 0 |
| p.H302fsX339 | N | N/C-term | 2 | 0 | 1 | 472 | 1 | 0 |
| c.929-930insC p.P310fsX331 | N | N/C-term | 1 | 1 | 1 | 475 | 1 | 1 |
| c. 1000-1020 del p. R312-S318 del | N | N/C-term | 2 | 2 | 1 | 505 | 1 | 0 |
| c.934C>T p.R312C | N | N/C-term | 3 | 2 | 1 | 517 | 0 | 0 |
| c. 959 C>T p. S320L | N | N/C-term | 1 | 1 | 1 | 467 | 1 | 0 |
| c. 1001C>T p. P334L | N | N/C-term | 2 | 2 | 2 | 536 | 2 | 0 |
| c.1003C>T p.Q335X | N | N/C-term | 3 | 2 | 1 | 481 | 2 | 0 |
| c. 1025 A>T p. D342V | N | N/C-term | 1 | 1 | 1 | 475 | 1 | 0 |
| c.1091-1102del[*6]ins53[*7] p.K364fsX366 | N | N/C-term | 7 | 3 | 2 | 491 | 2 | 1 |
| c.1171c>T p.Q391X | N | N/C-term | 2 | 1 | 1 | 540 | 1 | 0 |
| c.1190_1191 del GC p.R397fsX517 | N | N/C-term | 1 | 1 | 1 | 480 | 1 | 1 |
| c.1193G>A p.W398X | N | N/C-term | 3 | 2 | 1 | 541 | 1 | 1 |
| c.1205A>G p.H402R | TM | non-pore MS | 3 | 1 | 2 | 488 | 2 | 1 |
| c.1277C>A p.P426H | TM | non-pore MS | 3 | 1 | 1 | 597 | 1 | 0 |
| c.1280A>G p.Y427C | TM | non-pore MS | 2 | 1 | 1 | 470 | 0 | 0 |
| c.1283C>T p.S428L | TM | non-pore MS | 1 | 0 | 1 | 450 | 0 | 0 |
| c.1401-1402ins [*8] p.I467 L468insMFIVDI | TM | non-pore MS | 1 | 1 | 1 | 566 | 0 | 0 |
| c.1403T>G p.L468R | TM | non-pore MS | 1 | 1 | 1 | 594 | 0 | 0 |
| c.1403 ins C p.L468fsX518 | TM | non-pore MS | 2 | 1 | 1 | 515 | 0 | 0 |
| c.1413delC p.F471fsX520 | TM | non-pore MS | 1 | 1 | 1 | 506 | 1 | 1 |
| c.1417A>C p.T473P | TM | non-pore MS | 2 | 0 | 2 | 511 | 1 | 1 |
| c.1421C>T p.T474I | TM | non-pore MS | 4 | 1 | 1 | 509 | 3 | 0 |
| c.1454_1455 ins [*9] p.H485fsX524 | TM | non-pore MS | 3 | 2 | 2 | 484 | 2 | 0 |
| c.1465A>T p.I489F | TM | non-pore MS | 1 | 0 | 1 | 443 | 1 | 0 |
| c. 1468 G>A p. A490T | TM | non-pore MS | 1 | 1 | 1 | 549 | 1 | 0 |
| c.1474C>T p.H492Y | TM | non-pore MS | 8 | 7 | 4 | 495 | 4 | 1 |
| c.1478A>G p.Y493C | TM | non-pore MS | 1 | 0 | 1 | 529 | 0 | 0 |
| c.1483_1484 del AA p.K495fsX517 | TM | non-pore MS | 2 | 2 | 1 | 491 | 0 | 0 |
| c.1491G>A p. W497X | TM | non-pore MS | 3 | 2 | 1 | 500 | 1 | 0 |
| c.1501G>A p.D501N | TM | non-pore MS | 1 | 0 | 1 | 548 | 1 | 0 |
| c.1511C>T p.A504V | TM | non-pore MS | 2 | 1 | 1 | 492 | 1 | 1 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| c.1520C>T p.P507L | TM | non-pore MS | 1 | 1 | 1 | 536 | 1 | 1 |
| c.1582C>T p.R528W | TM | non-pore MS | 1 | 0 | 1 | 454 | 0 | 0 |
| c.1600C>T p.R534C | TM | non-pore MS | 11 | 3 | 5 | 484 | 4 | 1 |
| c.1607_1608 del CG p.A536fsX653 | TM | non-pore MS | 1 | 1 | 1 | 558 | 1 | 0 |
| c. 1682C>T p. A561V | S5 | S5-pore-S6 | 7 | 5 | 5 | 545 | 6 | 2 |
| c.1681G>A p.A561T | S5 | S5-pore-S6 | 1 | 1 | 1 | 503 | 0 | 0 |
| c.1682-1683insAGC p.561-562insA | S5 | S5-pore-S6 | 1 | 0 | 1 | 601 | 1 | 1 |
| c.1686 C>G p.H562Q | S5 | S5-pore-S6 | 2 | 2 | 1 | 459 | 0 | 0 |
| c.1685A>G p.H562R | S5 | S5-pore-S6 | 1 | 0 | 1 | 555 | 0 | 0 |
| c.1687T>G p.W563G | S5 | S5-pore-S6 | 2 | 2 | 1 | 475 | 2 | 0 |
| c.1689G>T p.W563C | S5 | S5-pore-S6 | 2 | 1 | 1 | 460 | 1 | 0 |
| c. 1697G p. C566F | S5 | S5-pore-S6 | 1 | 1 | 1 | 524 | 1 | 0 |
| c.1714G>T p.G572C | pore | S5-pore-S6 | 1 | 1 | 1 | 500 | 1 | 0 |
| c.1714G>A p.G572S | pore | S5-pore-S6 | 9 | 5 | 5 | 496 | 5 | 2 |
| c.1715G>A p.G572D | pore | S5-pore-S6 | 3 | 2 | 2 | 493 | 1 | 0 |
| c.1720A>G p.M574V | pore | S5-pore-S6 | 3 | 3 | 1 | 519 | 1 | 1 |
| c.1736T>C p.M579T | pore | S5-pore-S6 | 3 | 1 | 1 | | 0 | 0 |
| c. 1744 C>T p. R582C | pore | S5-pore-S6 | 5 | 2 | 3 | 490 | 2 | 1 |
| c. 1745 G>T p. R 582L | pore | S5-pore-S6 | 2 | 1 | 1 | 510 | 1 | 0 |
| c.1750G>T p.G584C | pore | S5-pore-S6 | 5 | 4 | 2 | 510 | 2 | 1 |
| c.1769G>T p.G590V | pore | S5-pore-S6 | 3 | 2 | 1 | 435 | 1 | 0 |
| c.1769G>A p.G590D | pore | S5-pore-S6 | 1 | 1 | 1 | 548 | 1 | 0 |
| c.1775 del A p.Q592fsX593 | pore | S5-pore-S6 | 6 | 2 | 2 | 528 | 4 | 1 |
| c.1777A>G p.I 593V | pore | S5-pore-S6 | 2 | 1 | 1 | 495 | 0 | 0 |
| c.1785A>T p.K595N | pore | S5-pore-S6 | 2 | 1 | 1 | 506 | 1 | 1 |
| c. 1783 A>G p. K595E | pore | S5-pore-S6 | 2 | 2 | 1 | 474 | 1 | 0 |
| c.1790A>G p.Y597C | pore | S5-pore-S6 | 3 | 1 | 1 | 469 | 1 | 0 |
| c. 1801 C>A p. G601S | pore | S5-pore-S6 | 8 | 6 | 4 | 479 | 3 | 0 |
| c.1802G>A p.G601D | pore | S5-pore-S6 | 2 | 2 | 1 | 424 | 2 | 1 |
| c.1808G>A p.G603D | pore | S5-pore-S6 | 3 | 2 | 1 | 445 | 2 | 1 |
| c.1811G>A p.G604D | pore | S5-pore-S6 | 1 | 1 | 1 | 521 | 1 | 1 |
| c. 1810 G>A p. G604S | pore | S5-pore-S6 | 3 | 1 | 3 | 506 | 3 | 2 |
| c.1814C>T p.P605L | pore | S5-pore-S6 | 1 | 1 | 1 | 502 | 1 | 0 |
| c.1816 T>C p.S606P | pore | S5-pore-S6 | 1 | 1 | 1 | 269 | 1 | 0 |
| c. 1831 T>G p.Y611D | pore | S5-pore-S6 | 1 | 0 | 1 | 524 | 1 | 1 |
| c.1838C>T p.T613M | pore | S5-pore-S6 | 5 | 3 | 4 | 528 | 3 | 1 |
| c.1840G>A p.A614T | pore | S5-pore-S6 | 3 | 2 | 1 | 553 | 1 | 0 |
| c.1841C>T p.A614V | pore | S5-pore-S6 | 6 | 5 | 5 | 496 | 6 | 1 |
| c.1843C>T p.L615F | pore | S5-pore-S6 | 2 | 2 | 1 | 448 | 1 | 0 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| c.1847A>C | p.Y616S | pore | S5-pore-S6 | 3 | 1 | 1 | 520 | 3 | 0 |
| c.1849T>C | p.F617L | pore | S5-pore-S6 | 3 | 1 | 2 | 505 | 2 | 1 |
| c.1853C>G | p.T618S | pore | S5-pore-S6 | 6 | 3 | 3 | 497 | 2 | 0 |
| c.1868C>T | p.T623I | pore | S5-pore-S6 | 2 | 2 | 1 | 604 | 1 | 0 |
| c.1882G>A | p.G628S | pore | S5-pore-S6 | 5 | 2 | 4 | 603 | 3 | 2 |
| c. 1882G>C | p.G628R | pore | S5-pore-S6 | 1 | 1 | 1 | 542 | 1 | 1 |
| c.1886A>G | p.N629S | pore | S5-pore-S6 | 4 | 4 | 1 | 500 | 1 | 1 |
| c. 1887 C>A | p. N629K | pore | S5-pore-S6 | 1 | 1 | 1 | 596 | 1 | 0 |
| c.888G>C | p.V630L | pore | S5-pore-S6 | 1 | 0 | 1 | 577 | 1 | 0 |
| c.1892C>T | p.S631F | pore | S5-pore-S6 | 1 | 1 | 1 | 576 | 1 | 0 |
| c.1894C>T | p.P632S | pore | S5-pore-S6 | 1 | 1 | 1 | 512 | 1 | 0 |
| c.1898A>T | p.N633I | pore | S5-pore-S6 | 3 | 3 | 1 | 493 | 2 | 0 |
| c.1898A>G | p.N633S | pore | S5-pore-S6 | 1 | 1 | 1 | 535 | 1 | 0 |
| c.1899C>A | p.N633K | pore | S5-pore-S6 | 1 | 0 | 1 | 490 | 0 | 0 |
| c.1900A>T | p.T634S | pore | S5-pore-S6 | 1 | 1 | 1 | 565 | 0 | 0 |
| c.1900A>G | p.T634A | pore | S5-pore-S6 | 1 | 1 | 1 | 510 | 1 | 0 |
| c.1909G>A | p.E637K | S6 | S5-pore-S6 | 3 | 2 | 1 | 469 | 2 | 0 |
| c.1908-1909delAG | p. E637fsX653 | S6 | S5-pore-S6 | 1 | 1 | 1 | 472 | 1 | 0 |
| c.del 1913-1915 | p.K638del | S6 | S5-pore-S6 | 4 | 2 | 3 | 528 | 3 | 1 |
| c.1916T>A | p.I639N | S6 | S5-pore-S6 | 2 | 0 | 1 | 439 | 2 | 0 |
| c. 1989-1991del TTC | p. F640del | S6 | S5-pore-S6 | 3 | 2 | 2 | 354 | 3 | 1 |
| c. 1922C>T | p. S641F | S6 | S5-pore-S6 | 3 | 0 | 1 | 657 | 1 | 0 |
| c.1930G>T | p.V644F | S6 | S5-pore-S6 | 6 | 2 | 3 | 550 | 4 | 2 |
| c.1935G>A | p.M645I | S6 | S5-pore-S6 | 1 | 0 | 1 | 618 | 1 | 1 |
| c.1952T>A | p.M651K | S6 | S5-pore-S6 | 1 | 0 | 1 | 486 | 1 | 0 |
| c. 1956C>A | p. Y652X | S6 | S5-pore-S6 | 1 | 0 | 1 | 540 | 1 | 0 |
| c.1970G>T | p.G657V | S6 | S5-pore-S6 | 1 | 1 | 1 | 512 | 1 | 0 |
| c.1969G>A | p.G657S | S6 | S5-pore-S6 | 1 | 1 | 1 | 450 | 1 | 0 |
| c.2062C>T | p.Q676X | C | N/C-term | 3 | 2 | 1 | 493 | 0 | 0 |
| c.2054-2055GC>CT | p.R685P | C | N/C-term | 1 | 1 | 1 | 499 | 1 | 0 |
| c.2090 del T | p.L697fsX713 | C | N/C-term | 1 | 1 | 1 | 510 | 1 | 0 |
| c. 2117 C>T | p. S706F | C | N/C-term | 1 | 1 | 1 | 406 | 1 | 0 |
| c.2170_2171 ins CC | p. L724fsX733 | C | N/C-term | 2 | 1 | 1 | 477 | 1 | 0 |
| c.2145G>C | p.A715A | C | N/C-term | 2 | 2 | 1 | 458 | 2 | 0 |
| c.2192A>G | p.H731R | C | N/C-term | 1 | 1 | 1 | 521 | 1 | 0 |
| c.2210T>C | p.L737P | C | N/C-term | 2 | 0 | 1 | 500 | 0 | 0 |
| c.2212C>T | p.Q738X | C | N/C-term | 2 | 2 | 1 | 562 | 1 | 0 |
| c.2230C>T | p.R744X | C | N/C-term | 4 | 3 | 3 | 544 | 2 | 0 |
| c.2235-2245delinsTTT | p.G745fsX800 | C | N/C-term | 3 | 0 | 2 | 490 | 1 | 0 |
| c.2250C>A | p.C750X | C | N/C-term | 1 | 1 | 1 | 549 | 1 | 0 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| c.2254C>T | p.R752W | C | N/C-term | 2 | 1 | 1 | 427 | 1 | 0 |
| c. 2266C>G | p. M756V | C | N/C-term | 1 | 0 | 1 | 453 | 1 | 0 |
| c.2311-2332delinsTC | p.H771fsX796 | C | N/C-term | 3 | 3 | 1 | 495 | 0 | 0 |
| c.2354G>A | p.G785D | C | N/C-term | 1 | 1 | 1 | 527 | 1 | 0 |
| c.2385-2387delCGT | p.V796del | C | N/C-term | 1 | 1 | 1 | 482 | 0 | 0 |
| c. 2453C>T | p. S818L | C | N/C-term | 5 | 3 | 4 | 495 | 3 | 0 |
| c.2467C>T | p.R823W | C | N/C-term | 3 | 3 | 1 | 482 | 2 | 0 |
| c.2477C>T | p.T826I | C | N/C-term | 1 | 1 | 1 | 507 | 0 | 0 |
| c.2476A>G | p.T826A | C | N/C-term | 1 | 1 | 1 | 457 | 0 | 0 |
| c.2509G>A | p.D837N | C | N/C-term | 3 | 2 | 1 | 447 | 0 | 0 |
| c. 2536 C>A | p.P846 T | C | N/C-term | 1 | 1 | 1 | 491 | 1 | 0 |
| c. 2559del G | p.W853fsX867 | C | N/C-term | 4 | 2 | 1 | 464 | 2 | 0 |
| 2587C>T | p.R863X | C | N/C-term | 1 | 1 | 1 | 472 | 1 | 0 |
| c.2591A>G | p.D864G | C | N/C-term | 1 | 1 | 1 | 458 | 1 | 0 |
| c.2613-2669del/ins *10 | p.S871fs31X | C | N/C-term | 2 | 2 | 1 | 506 | 2 | 0 |
| c. 2637-2638 del TG | | C | N/C-term | 2 | 1 | 1 | 502 | 0 | 0 |
| c.2680-2681insAGGC | p.R894fsX920 | C | N/C-term | 3 | 3 | 1 | 443 | 1 | 0 |
| c.2684C>T | p.T895M | C | N/C-term | 1 | 0 | 1 | 474 | 0 | 0 |
| c.2719 2792del | p.A907fsX949 | C | N/C-term | 1 | 1 | 1 | 496 | 0 | 0 |
| c.2728-2729ins*11 | p.G909fsX975 | C | N/C-term | 1 | 0 | 1 | 514 | 0 | 0 |
| c.2732_2766 del *12 | p.G911fsX927 | C | N/C-term | 1 | 1 | 1 | 508 | 0 | 0 |
| c.2734-2738delCGGGC | p.R912 fsX917 | C | N/C-term | 4 | 1 | 2 | 495 | 1 | 0 |
| c.2737-2738ins *13 | p.R912fsX975 | C | N/C-term | 2 | 2 | 1 | 511 | 1 | 0 |
| c.2768C>T | p.P923L | C | N/C-term | 1 | 1 | 1 | 478 | 1 | 0 |
| c.2770_2771 ins T | p.G924fsX939 | C | N/C-term | 1 | 1 | 1 | 502 | 1 | 1 |
| c.2775delG | p.G925fsX973 | C | N/C-term | 3 | 1 | 1 | 523 | 0 | 1 |
| c.2780G>A | p.W927X | C | N/C-term | 1 | 0 | 1 | 511 | 1 | 1 |
| c.2892-2893insC | p.964fsX1118 | C | N/C-term | 2 | 1 | 1 | 442 | 0 | 0 |
| c.2901-2902ins *14 | p.P967fsX975 | C | N/C-term | 2 | 1 | 1 | 461 | 0 | 0 |
| c.2918del T | p.L973fsX1056 | C | N/C-term | 2 | 1 | 1 | 497 | 1 | 0 |
| c.2930G>A | p.C977Y | C | N/C-term | 1 | 0 | 1 | 474 | 0 | 0 |
| c.2930G>C | p.C977S | C | N/C-term | 1 | 1 | 1 | 460 | 1 | 0 |
| c.2948-2947del | p.R983fsX1112 | C | N/C-term | 1 | 1 | 1 | 551 | 1 | 0 |
| c.2959_2960 del CT | p.L987fsX1117 | C | N/C-term | 2 | 1 | 1 | 530 | 1 | |
| c.2993delT | p.I997fs59X | C | N/C-term | 1 | 1 | 1 | 440 | 1 | 0 |
| c.3002del G | p.W1001fsX1056 | C | N/C-term | 7 | 4 | 2 | 509 | 5 | 3 |
| c.3019delC | p.R1007fsX1056 | C | N/C-term | 1 | 1 | 1 | 500 | 0 | 0 |
| c.3027C>G | p.Y1009X | C | N/C-term | 1 | 0 | 1 | 515 | 0 | 0 |
| c.3040C>T | p.R1014X | C | N/C-term | 1 | 1 | 1 | 480 | 1 | 0 |
| c.3090-3102 del *15 | p. P1030fsX1052 | C | N/C-term | 3 | 3 | 1 | 572 | 1 | 0 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| c.3092 del G p.G1031fsX1056 | C | N/C-term | 1 | 1 | 1 | 640 | 1 | 1 |
| c.3091-3101del*16 p.G1031fsX1114 | C | N/C-term | 2 | 2 | 1 | 525 | 1 | 0 |
| c.3093 insG p.G1031fsX 1118 | C | N/C-term | 2 | 2 | 1 | 452 | 1 | 1 |
| c.3096-3109del *17 p.R1032fsX1113 | C | N/C-term | 2 | 1 | 1 | 540 | 1 | 1 |
| c.3103delC p.R1035fsX1056 | C | N/C-term | 5 | 2 | 3 | 491 | 2 | 2 |
| c.3104-3105ins CC p. R1035fs×1057 | C | N/C-term | 3 | 2 | 1 | 469 | 2 | 1 |
| c.3115G>T p.E1039X | C | N/C-term | 1 | 0 | 0 | 420 | 0 | 0 |
| c.3190-3199del *18 p.L1064fsX1068 | C | N/C-term | 4 | 2 | 1 | 480 | 1 | 0 |
| c.3252-3262del *19 p.P1084fsX1114 | C | N/C-term | 2 | 1 | 1 | 522 | 1 | 0 |
| c.3278C>T p.P1093L | C | N/C-term | 1 | 0 | 0 | | 0 | 0 |
| c. 3430G>A p A1144T | C | N/C-term | 2 | 1 | 1 | 463 | 1 | 0 |
| c.1557+2T>G Splicing Error | | | 1 | 1 | 1 | 490 | 0 | 0 |
| c.2692+1G>T Splicing Error | | | 3 | 3 | 1 | 516 | 1 | 0 |
| c.1832_1945 del *20 | | | 2 | 1 | 1 | 580 | 1 | 0 |
| c.2966-2A>T Splicing Error | | | 2 | 2 | 1 | 525 | 2 | 1 |

N:N-terminus, TM: transmembrane, C: C-terminus, Abbreviations are same as Supplemental TableS1.

*1 ATCGCGCAG

*2 GGCGGCG

*3 GCGCGGGCG

*4 GCGCCCGGCCAGC

*5 CACAGCCTCAACCCCG

*6 AGGAGCGAACCCA

*7 TGTCTTGAGTCTATGTCATTGTCATAGCTTGAGACATTGTCATAGCACCTAAGA

*8 ATGTTCATTGTGGACATC

*9 ACGAGGAGGTGGTCAGCCA

*10 ACGCCTG

*11 GGGGC

*12 GCCGGGCGGGGGCAGGGCCGAGTAGCCGGGGCCGG

*13 CCGGG

*14 AGCCG

*15 GGG TCG GCG GCCC

*16 GGTCGGCGGCC

*17 GCG GCC CCG GGGCG

*18 CTGCAGCTGC

*19 GGGGCCTGGCC

*20

ATGTGACGGCGCTCTACTTCACCTTCAGCAGCCTCACCAGTGTGGGCTTCGGCAACGTCTCTCCCAACACCAACTCAGAGAAGATCTTCTCCATCTGCGTCATGCTCATTGGCTgtgagtgtgcccaggggcgggcggcggggagagcccacggtggaggaacccaagt eTable 3. LQT3 Mutations or Rare Variants

| **Mutation or rare variant** | location | S5-pore-S6 | N | female (n) | Proband (n) | QTc mean (proband) | syncope (n) | CA/VF (n) | Other phenotypes (n) |
|---|---|---|---|---|---|---|---|---|---|
| c.337G>A p.V113I | N | | 1 | 1 | 1 | 496 | 0 | 0 | |
| c.1231G>A p.V411M | DI | S5-S6 | 7 | 4 | 3 | 555 | 5 | 4 | AT (1) |
| c.1273 G>A p.A425T | DI-DII | | 1 | 1 | 1 | 470 | 1 | 0 | |
| c.1603C>T, p.R533X | DI-DII | | 2 | 2 | 1 | | 2 | 0 | SSS (1) |
| c.2335C>A p.Q779K | DII | | 3 | 0 | 2 | 506 | 2 | 0 | |
| c.2441G>A p.R814Q | DII | | 3 | 2 | 1 | 463 | 0 | 0 | |
| c.2497G>A p.G833R | DII | | 4 | 3 | 2 | 464 | 2 | 0 | AVB (1) |
| c.2923C>T p.R975W | DII-DIII | | 1 | 1 | 0 | | 0 | 0 | |
| c. 3067 C>T, R1023C | DII-DIII | | 1 | 0 | 1 | 458 | 1 | 0 | |
| c.3292G>T p.V1098L | DII-DIII | | 3 | 1 | 1 | 439 | 0 | 0 | |
| c.3988G>A p.A1330T | DIII | | 2 | 2 | 1 | 447 | 0 | 0 | |
| c.3995C>T p.P1332L | DIII | | 2 | 1 | 2 | 520 | 2 | 1 | |
| c.4282G>T p.A1428S | DIII | S5-S6 | 3 | 2 | 1 | 474 | 1 | 0 | |
| c.4396A>T p.I1466F | DIII | S5-S6 | 1 | 0 | 1 | 490 | 1 | 1 | |
| c.4490T>C p.M1498T | DIII-DIV | | 1 | 0 | 1 | 548 | 0 | 0 | |
| c.4513-4521 dup CAGAAGCCC, p.K1505-Q1507dup | DIII-DIV | | 1 | 1 | 1 | 602 | 1 | 1 | SSS (1) |
| c.4519-4527del CAGAAGCCC p.Q1507-p1509del | DIII-DIV | | 3 | 1 | 3 | 550 | 2 | 0 | |
| c.4527-4528ins CAGAAGCCC p.P1509-I1510insQKP | DIII-DIV | | 1 | 1 | 1 | 470 | 1 | 1 | AF,SSS (1) |
| c.4850-4852del TCT p.F1616del | DIV | | 4 | 3 | 1 | 480 | 1 | 0 | SSS (1) |
| c.4892G>A p.G1631D | DIV | | 1 | 0 | 1 | 553 | 1 | 1 | |
| c.4931G>A p.R1644H | DIV | | 3 | 2 | 2 | 502 | 0 | 0 | |
| c.4937T>G p.L1646R | DIV | | 1 | 0 | 1 | 456 | 0 | 0 | |
| c.5236G>A p.A1746T | DIV | S5-S6 | 4 | 1 | 1 | 481 | 1 | 1 | BrS (1) |
| c.5284-5286del ATC p.I1762del | DIV | S5-S6 | 1 | 0 | 1 | 550 | 1 | 1 | |
| c.5287G>A p.V1763M | DIV | S5-S6 | 3 | 2 | 2 | 507 | 3 | 2 | AVB (1) |
| c.5313C>G p. I1771M | DIV | S5-S6 | 1 | 1 | 1 | 580 | 1 | | |
| c.5314C>G p.L1772V | DIV | S5-S6 | 1 | 0 | 1 | 542 | 1 | 1 | AVB (1) |
| c.5319A>G p.N1774D | C | | 1 | 0 | 1 | 582 | 1 | 1 | AVB (1) |
| c.5348C>A p.T1783N | C | | 2 | 1 | 1 | 476 | 1 | 0 | |
| c.5350G>A p.E1784K | C | | 50 | 23 | 26 | 481 | 5 | 0 | BrS(7),AF(1) SSS (6) |
| c.5357T>G p.L1786R | C | | 1 | 0 | 1 | | 0 | 0 | BrS (1) |
| c.5384A>G p.Y1795C | C | | 1 | 0 | 1 | 535 | 0 | 0 | AF (1) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| c.5474T>C | p.L1825 P | C | | 2 | 2 | 2 | 428 | 2 | 0 | SSS (1) |

AF: atrial fibrillation, SSS: sick sinus syndrome, AVB: atrial-ventricular block, BrS: Brugada syndrome

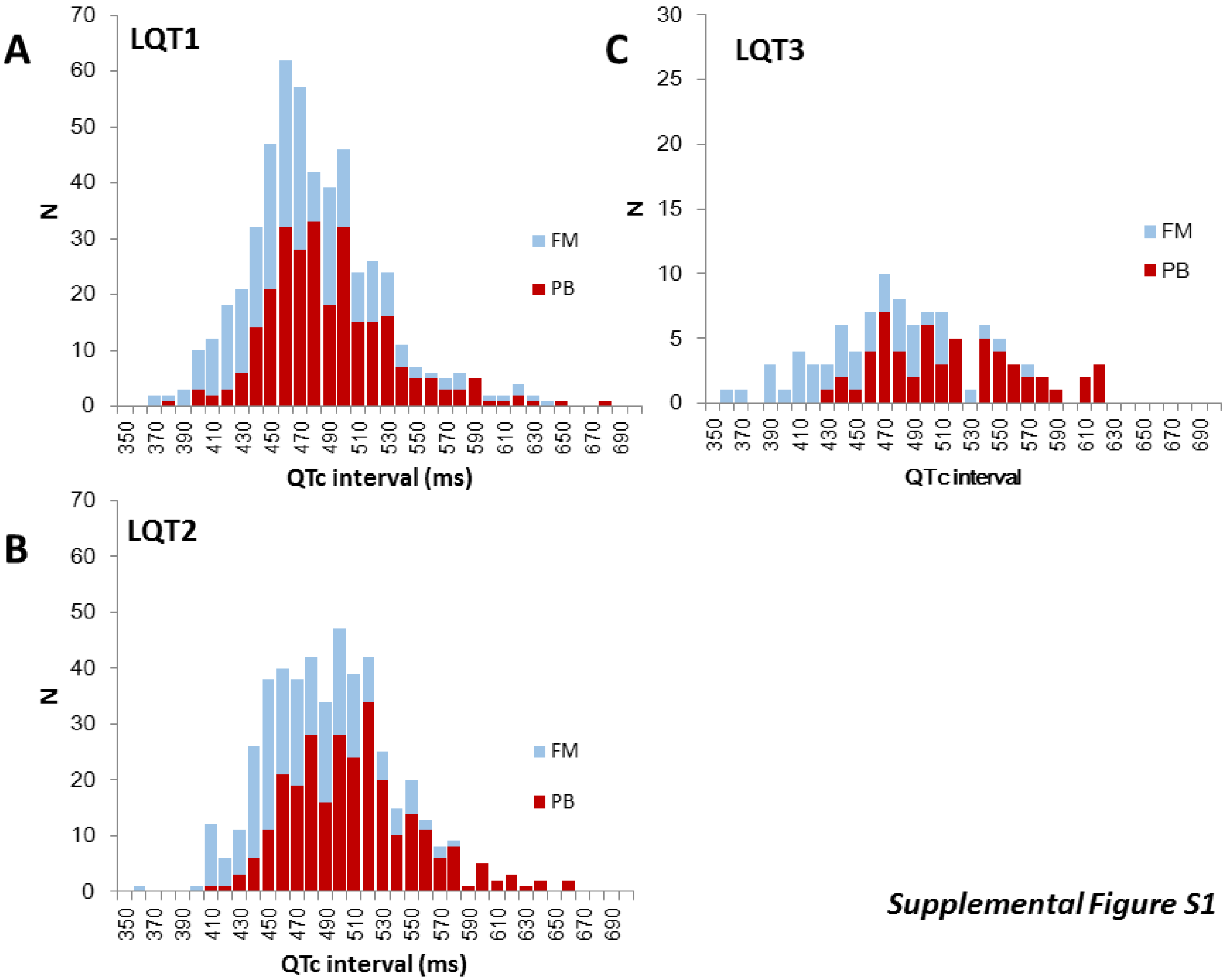
**eTable 4.** *SCN5A* Mutations/Variants in Japanese LQTS Registry

| Mutation or rare variant | location | S5-pore-S6 | N | Clinical Significance (ClinVar) | Conditions (ClinVar) | J- BrS registry * | Polyphen2 | Score | RS# | MAF (ExAC) | MAF (HGVD) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| c.337G>A p.V113I | N | | 1 | not provided | | | Benign | 0.000 | rs199473555 | n/a | n/a |
| c.1231G>A p.V411M | DI | S5-S6 | 7 | Pathogenic (8) | LQT(5), BrS(1) Others(2) | | Probably D | 1.000 | rs72549410 | n/a | n/a |
| c.1273 G>A p.A425T | DI-DII | | 1 | Likely pathogenic | not provided | | Probably D | 0.985 | rs761117662 | 0.000008 | 0.0004 |
| c.1603C>T, p.R533X | DI-DII | | 2 | - | | | - | | - | n/a | n/a |
| c.2335C>A p.Q779K | DII | | 3 | not provided | LQT(1) | yes | Benign | 0.005 | rs199473583 | n/a | n/a |
| c.2441G>A p.R814Q | DII | | 3 | Likely pathogenic (2);<br>Pathogenic (1);<br>Uncertain (2) | BrS(4),<br>Others(2) | yes | Probably D | 0.999 | rs199473584 | 0.00002 | n/a |
| c.2497G>A p.G833R | DII | | 4 | Uncertain (5) | LQT(2), BrS(1) | | Probably D | 1.000 | rs45475899 | 0.00017 | 0.0008 |
| c.2923C>T p.R975W | DII-DIII | | 1 | Uncertain (2) | BrS(1) | | Probably D | 1.000 | rs41311135 | 0.00002 | n/a |
| c. 3067 C>T, p.R1023C | DII-DIII | | 1 | - | | | Probably D | 0.996 | - | 0.000025 | n/a |
| c.3292G>T p.V1098L | DII-DIII | | 3 | Likely benign (2) | BrS(1) | | Benign | 0.021 | rs199473191 | 0.00015 | n/a |
| c.3988G>A p.A1330T | DIII | | 2 | Pathogenic / Likely pathogenic (4) | LQT(1),<br>Others(2) | | Probably D | 1.000 | rs199473224 | n/a | n/a |
| c.3995C>T p.P1332L | DIII | S5-S6 | 2 | Pathogenic (3) | BrS(2) | | Probably D | 1.000 | rs199473225 | n/a | n/a |
| c.4282G>T p.A1428S | DIII | S5-S6 | 3 | Likely pathogenic (1);<br>Uncertain (2) | BrS(1) | yes | Probably D | 1.000 | rs200034939 | 0.000025 | n/a |
| c.4396A>T p.I1466F | DIII | S5-S6 | 1 | - | | | Possibly D | 0.945 | - | n/a | n/a |
| c.4490T>C p.M1498T | DIII-DIV | | 1 | Likely pathogenic (2);<br>Uncertain (1) | LQT(1), BrS(1)<br>Others(1) | | Probably D | 0.998 | rs199473263 | n/a | n/a |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| c.4513-4521 dup CAGAAGCCC, p.K1505-Q1507dup | DIII-DIV | | 1 | - | | | - | | - | n/a | n/a |
| c.4519-4527del CAGAAGCCC p.Q1507-P1509del | DIII-DIV | | 3 | Pathogenic/Likely pathogenic (3) | LQT(1), BrS(1) | | | | rs397514251 | n/a | n/a |
| c.4527-4528ins CAGAAGCCC p.P1509-I1510insQKP | DIII-DIV | | 1 | - | | | | | | n/a | n/a |
| c.4850-4852del TCT p.F1616del | DIV | | 4 | - | | | | | | n/a | n/a |
| c.4892G>A p.G1631D | DIV | | 1 | not provided | LQT(1) | | Possibly D | 0.954 | rs199473285 | n/a | n/a |
| c.4931G>A p.R1644H | DIV | | 3 | Pathogenic (7) | LQT(4), BrS(1) Others(1) | yes | Probably D | 0.995 | rs28937316 | 0.000008 | n/a |
| c.4937T>G p.L1646R | DIV | | 1 | - | | | Probably D | 1.000 | | n/a | n/a |
| c.5236G>A p.A1746T | DIV | S5-S6 | 4 | not provided | LQT(1) | | Possibly D | 0.592 | rs199473306 | n/a | n/a |
| c.5284-5286del ATC p.I1762del | DIV | S5-S6 | 1 | - | | | | | | n/a | n/a |
| c.5287G>A p.V1763M | DIV | S5-S6 | 3 | Pathogenic (2) | LQT(1) | | Probably D | 0.999 | rs199473631 | n/a | n/a |
| c.5313C>G p. I1771M | DIV | S5-S6 | 1 | - | | | Probably D | 1.000 | | n/a | n/a |
| c.5314C>G p.L1772V | DIV | S5-S6 | 1 | not provided | LQT(1) | | Probably D | 0.999 | rs199473312 | n/a | n/a |
| c.5319A>G p.N1774D | C | | 1 | not provided | LQT(1) | | Probably D | 0.998 | rs199473633 | n/a | n/a |
| c.5348C>A p.T1783N | C | | 2 | - | | | Benign | 0.449 | | n/a | n/a |
| c.5350G>A p.E1784K | C | | 50 | Pathogenic (13) | LQT(4), BrS(4) SSS(1), | yes | Possibly D | 0.820 | rs137854601 | 0.00000 | n/a |
| c.5357T>G p.L1786R | C | | 1 | - | | | Probably D | 1.000 | | n/a | n/a |
| c.5384A>G p.Y1795C | C | | 1 | - | | | Probably D | 1.000 | | n/a | n/a |
| c.5474T>C p.L1825 P | C | | 2 | not provided | LQT(1) | | Probably D | 1.000 | rs79299226 | n/a | n/a |

( ) number of subject, Uncertain = uncertain significance, D= damaging

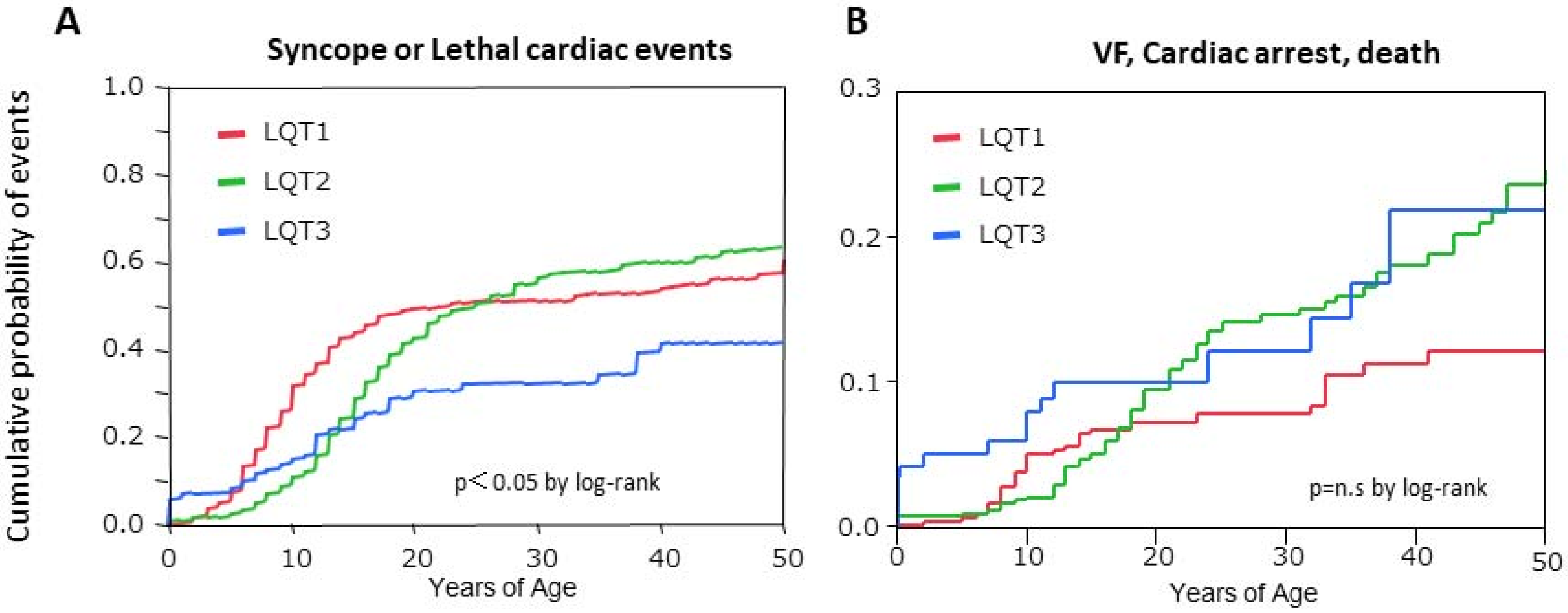
J-BrS : Japanese Brugada syndrome registry (Yamagata K, et al.. Circulation. 2017 Jun 6;135(23):2255-2270.)



***Supplemental Figure S1***

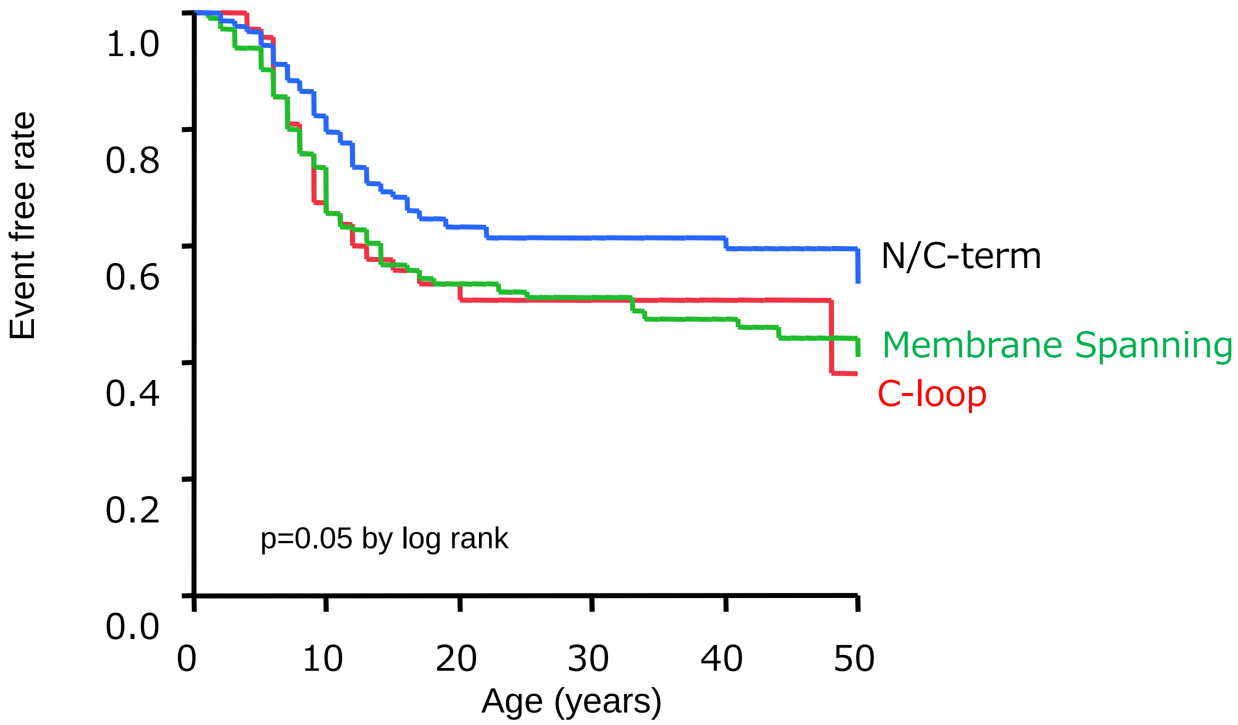
**eFigure 1.** Distribution of QTc Intervals in Genotyped Congenital Long QT Syndrome

**A**: LQT1, **B**: LQT2, and **C**: LQT3. Red bar: probands (PB), Blue bar: family members (FM).



**eFigure 2.** Cumulative Probability of First Event in Each Genotype of Congenital Long-QT Syndrome

A, Syncope or lethal cardiac events. B, Only lethal cardiac event such as ventricular fibrillation, cardiac arrest or death.



**eFigure 3.** Mutation Site-Specific Difference in Syncope or Lethal Cardiac Events in LQT1