

Characterization of a novel LQT3 variant with a selective efficacy of mexiletine treatment

Kim: Functional study of a novel LQT3 mutation

Hyun-Ji Kim^{1,3*}, Bok-Geon Kim^{2,3*}, Jong Eun Park⁴, Chang-Seok Ki⁵, June Huh⁶, Jae Boum Youm⁷, Jong-Sun Kang^{2,3}, Hana Cho^{1,3}

¹Department of Physiology, ²Department of Molecular Cell Biology, ³Single Cell Network Research Center, Sungkyunkwan University, Suwon, Korea;

⁴Department of Laboratory Medicine, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, Republic of Korea; ⁵GC Genome, Yongin, Republic of Korea; ⁶Division of Pediatric Cardiology, Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; ⁷Department of Physiology, College of Medicine, Cardiovascular and Metabolic Disease Center, Inje University, Busan, Korea.

* These authors contributed equally to this work.

Corresponding author address:

Prof. Hana Cho MD, PhD

Department of Physiology, Sungkyunkwan University School of Medicine, 2066, Seobu-Ro, Jangan-gu, Suwon, Gyunggi-do, Korea 16419

Phone: +82-31-299-6104,

E-mail address: hanacho@skku.edu

1. PolyPhen-2

Protein sequence in FASTA format:

>NP_932173.1 sodium channel protein type 5 subunit alpha isoform a
[Homo sapiens]

MANFLLPRGTSSFRRFTRESLAAIEKRMAEKQARGSTTLQESREGLPEEEAPRPQL
DLQASKKLPDLYGNPPQELIGEPLDLPFYSTQKTFIVLNKGKTIFRFSATNALYVL
SPFHPIRRAAVKILVHSLFNMLIMCTILTNCVFMAQHDPWPWKYVEYTFTAIYTFESL
VKILARGFCLHAFTFLRDPWNWLDVSVIIMAYTTEFVDLGNVSALRTFRVLRALKTIS
VISGLKTIVGALIQSVKKLADVMVLTVFCLSVFALIGLQLFMGNLRHKCVRNFTALNG
TNGSVEADGLVWESLDLYLSDPENYLLKNGTSDVLLCGNSSDAGTCPEGYRCLKA
GENPDHGYTSFDSFAWAFALFRLMTQDCWERLYQQTLRSAGKIYMIFFMLVIFLG
SFYLVNLI LAVVAMAYEEQNQATIAETEEKEKRFQEAMEMLKKEHEALTIRGVDTVS
RSSLEMSPLAPVNSHERRSKRRKRMSSGTEECGEDRLPKSDSEDGPRAMNHLSL
TRGLSRTSMKPRSSRGSIFTFRRRDLGSEADFADDENSTAGESESHHTSLLVPWPL
RRTSAQQQPSPGTSAPGHALHGKKNSTVDCNGVVSLGAGDPEATSPGSHLLRP
VMLEHPPDTTTPSEEPGGPQMLTSQAPCVDGFEEPGARQRALS AVSVLTSALEEL
EESRHKCPPCWNR LAQRYLIWECCPLWMSIKQGVKLVMDPFTDLTITMCIVLNTLF
MALEHYNMTSEFEEMLQVGNLVFTGIFTAEMTFKIIALDPYFFFQGGWNIFDSIIVILS
LMELGLSRMSNLSVLR SFRLRVFKLAKSWPTLNTLIKIIGNSVGALGNLTLVLAIVFI
FAVVGMLFGKNYSELRDSDSGLLPRWHMMDFFHAFLIIFRILCGEWIETMWDCME
VSGQSLCLLVFLLVMVIGNLVVNLFLALLSSFSADNLTAPDEDREMNNLQLALARI
QRGLRFVKRTTWDFCCGLLRQRPQKPAALAAQGQLPSCIATPYSPPPPETEKVPP
TRKETRFEEGEQPGQGTPGDPEPVCVPIAVAESDTDDQEEDEENSLGTEEESSKQ
QESQPVSGGPEAPPDSRTWSQVSATASSEAEASASQADWRQQWKAEPQAPGCG
ETPEDSCSEGSTADMTNTAELLEQIPDLGQDVKDPEDCFTEGCVRRCPCCAVIDTT
QAPGKVVWR LRKTCYHIVEHSWFETFIIFMILLSSGALAFEDIYLEERKTIKVLLEYA
DKMFTYVFLVLEMLLKWVAYGFKKYFTNAWCWLDLIVDVSLVSLVANTLGFAEMGPI
KSLRTLRLRPLRALS RFEGMRVVNALVGAIPSIMNVLLVCLIFWLIFSIMGVNLFAG
KFGRCINQTEGDLPLNYTIVNKSQCESLNTGELYWTKVKVNF DNVGAGYLALLQ
VATFKGWMDIMYAAVDSRGYEEQPQWEYNLYMYIYFVIFIFGSFFTLNLFIVIIDNF
NQQKKKLGGQDIFMTEEQKKYYNAMKKLGSKKPQKPIRPLNKYQGFIFDIVTKQA
FDVTIMFLICLNMTMMVETDDQSPEKINILAKINLLFVAIFTGECIVKLAALRHYYFTN
SWNIFDFVVVILSIVGTVLSDIIQKYFFSPTLFRVIRLARIGRILRLIRGAKGIRTL LFALM
MSLPALFNIGLLLFLVMFIYSIFGMANFAYVKWEAGIDDMFNFTFANSMLCLFQITTS
AGWDGLLSPILNTGPPYCDPTLPNSNGSRGDCGSPAVGILFFTTYIIISFLIVVNMYIAI
ILENFSVATEESTEPLSEDDFDMFYEIWEKFDPEATQFIEYSVLSDFADALSEPLRIAK
PNQISLINMDLPMVSGDRIHCMDILFAFTKRVLGESGEMDALKIQMEEKFMAANPSK
ISYEPITTTLRRKHEEVSAMVIQRAFRRHLLQRSLKHASFLFRQQAGSGLSEEDAPE
REGLIAYVMSENF SRPLGPPSSSSISSTSFPFSDSVTRATSDNLQVRGSDYSHSE
DLADFPPSPDRDRESIV

Position: 1656

Substitution: AA1-A; AA2-D

Results:

| Prediction Model | Score | | Prediction Report |
|------------------|-------------|-------------|--------------------------|
| | Sensitivity | Specificity | |
| HumDiv | 1.000 | | Probably Damaging |
| | 0.00 | 1.00 | |
| HumVar | 0.999 | | Probably Damaging |
| | 0.09 | 0.99 | |

2. SIFT

Protein query sequence:

>NP_932173.1 sodium channel protein type 5 subunit alpha isoform a
[Homo sapiens]

MANFLLPRGTSSFRRFTRESLAAIEKRMAEKQARGSTTLQESREGLPEEEAPRPQL
DLQASKKLPDLYGNPPQELIGEPLEDLDPFYSTQKTFIVLNKGKTIFRFSATNALYVL
SPFHPIRRAAVKILVHSLFNMLIMCTILTNCVFMAQHDPWPWKYVEYTFTAIYTFESL
VKILARGFCLHAFTFLRDPWNWLDVSVIIMAYTTEFVDLGNVSALRTFRVLRALKTIS
VISGLKTIVGALIQSVKKLADVMVLTVFCLSVFALIGLQLFMGNLRHKCVRNFTALNG
TNGSVEADGLVWESLDLYLSDPENYLLKNGTSDVLLCGNSSDAGTCPEGYRCLKA
GENPDHGYTSFDSFAWAFLALFRLMTQDCWERLYQQTLRSAGKIYMIFFMLVIFLG
SFYLVNLLAVVAMAYEEQNQATIAETEEKEKRFQEAMEMLKKEHEALTIRGVDTVS
RSSLEMSPLAPVNSHERRSKRRKRMSSGTEECGEDRLPKSDSEDGPRAMNHL
SLTRGLSRTSMKPRSSRGSIFTFRRRDLGSEADFADDENSTAGESESHHTSLLVPWPL
RRTSAQQQPSPGTSAPGHALHGKKNSTVDCNGVVSLLGAGDPEATSPGSHLLRP
VMLEHPPDTTTPSEEPGGPQMLTSQAPCVDGFEEP GARQRALS AVSVLTSALEEL
EESRHKCPPCWNRLAQRyliweccplwmsikqgvklvmdpftdltitmcivlntlf
MALEHYNMTSEFEEMLQVGNLVFTGIFTAEMTFKIIALDPY Y Y F Q Q G W N I F D S I I V I L S
LMELGLSRMSNLSVLR SFRLRVFKLAKSWPTLNTLIKIIGNSV GALGNLTLVLAIVFI
FAVGMQLFGKNYSEL R D S D S G L L P R W H M M D F F H A F L I I F R I L C G E W I E T M W D C M E
VSGQSLCLLVFLLVMVIGNLVVNLFLALLLSSFSADNLTAPDEDREMNNLQLALARI
QRGLRFVKRTTWDFCCGLLRQRPQKPAALAAQGQLPSCIATPYSPPPPETEKVPP
TRKETRFEEGEQPGQGTGDPPEPVCVPIAVAESDTDDQEEDENSLGTEEESSKQ
QESQPVSSGGPEAPPDSRTWSQVSATASSEAEASASQADWRQQWKAEPQAPGCG
ETPEDSCSEGSTADMTNTAELLEQIPDLGQDVKDPEDCFTEGCVRRCPCCA V D T T
QAPGKVVWR LRKTCYHIVEHSWFETFIIFMILLSSGALAFEDIYLEERKTIKVLL EYA
DKMFTYVFVLEMLLKWVAYGFKKYFTNAWCWLD FLIVDVSLVSLVANTLGFAEMGPI
KSLRTL RALRPLRALS RFEGMRVVNALVGAIPSIMNVLLVCLIFWLIFSIMGVNL FAG
KFGRCINQTEGDLPLNYTIVNNKSQCESLNTGELYWTKVKVNF DN VGAGYLALLQ
VATFKGWMDIMYAAVDSRGYEEQPQWEYNLYMYIYFVIFIIFGSFFTLNLFIGVIIDNF
NQQKKKLGGQDIFMTEEQKKYYNAMKKLGSKKPQKPIRPLNKYQGFIFDIVTKQA
FDVTIMFLICLNMTMMVETDDQSPEKINILAKINLLFVAIFTGECIVKLAALRHYYFTN
SWNIFDFVVVILSIVGTVLSDI IQKYFFSPTLFRVIRLARIGRILRLIRGAKGIRTL LFALM
MSLPALFNIGLLLFLVMFIYSIFGMANFAYVKWEAGIDDMFNFQTFANSMLCLFQITTS
AGWDGLLSPILNTGPPYCDPTLPNSNGSRGDCGSPAVGILFFTTYIIISFLIVVNMYIAI
ILENFSVATEESTEPLSEDDFDMFYEIWEKFDPEATQFIEYSVLSDFADALSEPLRIAK
PNQISLINMDLPMVSGDRIHCMDILFAFTKRVLGESGEMDALKIQMEEKFMAANPSK
ISYEPITTTLRKHEEVSAMVIQRAFRRHLLQRSLKHASFLFRQQAGSGLSEEDAPE
REGLIAYVMSENF SRPLGPPSSSSISSTSFPPSYDSVTRATSDNLQVRGSDYSHSE
DLADFPPSPDRDRESIV

The substitutions of interest: A1656D

Database to search: UniProt-SwissProt + TrEMBL 2010_09

Median conservation of sequences: 3.00

Remove sequences more than (90) percent identical to query

Results:

Substitution at pos 1656 from A to D is predicted to AFFECT PROTEIN FUNCTION
with a score of 0.00.

Median sequence conservation: 3.04

Sequences represented at this position: 129

*Amino acids with probabilities <0.05 are predicted to be deleterious.