Published in final edited form as:
Heart Rhythm. 2007 December ; 4(12): 1542–1543.

The phenotype of a KCNQ1 mutation depends on its KCNE partners: Is the cardiac slow delayed rectifier (I_{Ks}) channel more than a KCNQ1/KCNE1 complex?

Gea-ny Tseng, PhD
Virginia Commonwealth University, Department of Physiology, Medical College of Virginia, Po Box 980551, Richmond, VA 23298-0551, UNITED STATES, 804-828-7382, FAX: 804-828-7382, gtseng@hsc.vcu.edu

I_{Ks} is important for cardiac action potential repolarization, especially under conditions when the β-adrenergic tone is high or when the rapid delayed rectifier (I_{Kr}) channels is suppressed[1]. It has been well established that the I_{Ks} channel has at least two components: a pore-forming component (the KCNQ1 channel, also known as KvLQT1 or Kv7.1), and an auxiliary regulatory component (the KCNE1 subunit, also known as IsK or minK)[2,3]. Things became more complicated when other members of the KCNE family (KCNE2 - KCNE5, also known as minK-related peptides or MiRP1 - MiRP4) were cloned[4]. In heterologous expression systems, KCNQ1 can associate with each of the KCNE2 - KCNE5 subunits. These partnerships lead to distinctively different channel phenotypes[5]. KCNQ1 association with KCNE4 or KCNE5 produces a slowly activating Kv channel with the voltage-range of activation markedly shifted in the positive direction, similar to the effect of KCNE1. On the other hand, KCNQ1 association with KCNE2 or KCNE3 produces largely constitutively active K channels that manifest little time- and voltage-dependence in activation. Furthermore, association of KCNQ1 with KCNE3 increases the current amplitude, similar to the effect of KCNE1, while KCNQ1 association with KCNE2 or KCNE4 has the opposite (current suppressing) effect. The transcripts of KCNE2 - KCNE5 subunits have been detected in human hearts[5-7], raising the possibility that cardiac myocytes may coexpress KCNQ1 with not only KCNE1, but also other KCNE family members. Under these conditions, does KCNQ1 preferentially associate with KCNE1, or does KCNQ1 randomly associate with different KCNE subunits? Can one KCNQ1 channel simultaneously associate with more than one type of KCNE subunits? If a KCNQ1 channel simultaneously binds multiple KCNE subunits that have different or opposite effects on the KCNQ1 channel function, what determines the final channel phenotype?

Among these new KCNE family members, a role of KCNE2 in human cardiac electrical activity seems most certain based on the linkage between KCNE2 mutations and LQT6[8,9]. The initial proposal that KCNE2 serves as an auxiliary subunit of the I_{Kr} channel[8] has been challenged[10]. We have explored the role of KCNE2 in cardiac I_{Ks} channel function, and observed the following[11]: (a) KCNE2 is colocalized with KCNQ1 and KCNE1 in adult rat ventricular myocytes, which expressed a robust I_{Ks} current manifested as an HMR1556-sensitive current. (b) In both oocyte and COS-7 expression systems, coexpressing KCNQ1, KCNE1 and KCNE2 produces an I_{Ks}-like current that has a markedly reduced current amplitude than when KCNQ1 and KCNE1 are coexpressed in the absence of KCNE2. (c) An antibody targeting KCNE2 can coimmunoprecipitate KCNE1 with KCNE2 in the presence of

KCNQ1, but not in its absence, indicating that KCNQ1 can simultaneously bind KCNE1 and KCNE2, forming a ternary complex. In conjunction with the voltage clamp data, we propose that in such a ternary complex, the gating modifying effect of KCNE2 on KCNQ1 (making it constitutively active) is masked by the opposing gating modifying effects of KCNE1 (shifting the activation curve in the positive direction and slowing activation). However, KCNE2 can still exert its current suppressing effect in the KCNQ1/KCNE1/KCNE2 channel complex. Therefore, KCNE2 may function as a kinetically silent I_{Ks} suppressor, reducing the I_{Ks} current amplitude without altering its gating kinetics.

In this issue of the Heart Rhythm journal, Lundby et al report a novel KCNQ1 mutation (Q147R) identified in an 82-year old female patient presenting permanent atrial fibrillation and marginal QT prolongation (QTc interval of 470 ms)[12]. When the KCNQ1-Q147R mutant was expressed alone, it produced a Kv channel similar to that produced by the wild-type KCNQ1. However, when KCNQ1-Q147R was coexpressed with KCNE1, it produced an I_{Ks} current with a significantly smaller current amplitude than KCNQ1-WT/KCNE1 expressed at the same level. Interestingly, when KCNQ1-Q147R was coexpressed with KCNE2, it produced a considerably larger current than that produced by KCNQ1-WT/ KCNE2 at the same expression level. Importantly, this current-augmenting effect of Q147R was seen in the presence of KCNE1. Similar to our observations described above[11], Lundby et al showed that KCNQ1 coexpressed with both KCNE2 and KCNE1 produced an I_{Ks} current with a markedly reduced current amplitude than KCNQ1/KCNE1. It is likely that the Q147R mutation of KCNQ1 reduced the current-suppressing effect of KCNE2 in the KCNQ1/KCNE1/KCNE2 ternary complex.

Therefore, Q147R represents a ‘loss-of-function’ KCNQ1 mutation when coexpressed with KCNE1, but a ‘gain-of-function’ mutation when coexpressed with KCNE2, alone or with KCNE1. The structural basis for these differential effects is not clear. Position 147 is close to two other KCNQ1 positions where mutations have been linked to the short QT syndrome (SQT2) or familial atrial fibrillation (fAF): S140G and V141M[13,14]. Neither mutations alter the KCNQ1 channel function when expressed alone, but produce constitutively active channels when coexpressed with KCNE1, i.e. the gating modifying effects of KCNE1 are drastically altered by the two mutations on KCNQ1. These observations indicate that direct or allosteric interactions between the extracellular S1-S2 linker of KCNQ1 and the associated KCNE1 and/or KCNE2 subunits are important for the KCNQ1/KCNE1 (some with additional KCNE2) channel function. Identifying the spatial relationship between the S1-S2 linker of KCNQ1 and associated KCNE1 and KCNE2 subunits will be useful for building structural models of KCNQ1/KCNEx channel complexes. These structural models can help us better understand what determine KCNQ1/KCNEx association, and what determine the final outcome when the KCNQ1 channel is simultaneously associated with multiple KCNE subunits that have different effects on the KCNQ1 function.

The study by Lundby shows us that the phenotype of KCNQ1 mutations can be very much dependent on its KCNE partner(s)[12]. In turn, these observations suggest that the subunit composition in cardiac I_{Ks} channels may be more complicated than a KCNQ1/KCNE1 complex. This leads to new questions that need to be addressed in future experiments: (a) How are the multiple KCNE subunits expressed in different regions of the heart under normal and pathological conditions? (b) Is there a hierarchy in terms of the preference of KCNQ1 association with different KCNE subunits? (c) What determines the hierarchy in terms of dominance of KCNE effects on the KCNQ1 channel function? (d) How are the phenotypes of other KCNQ1 mutations identified in LQT1, SQT2 or fAF patients modified by the partner KCNE subunits?

Reference List

1. Jost M, Virag L, Bitay M, Takacs J, Lengyel C, Biliczki P, Nagy Z, Bogats G, Lathrop DA, Papp JG, Varro A. Restricting excessive cardiac action potential and QT prolongation. A vital role for I_{Ks} in human ventricular muscle. Circulation 2005;112:1392–1399. [PubMed: 16129791]
2. Barhanin J, Lesage F, Guillemare E, Fink M, Lazdunski M, Romey G. KvLQT1 and IsK (minK) proteins associate to form the I_{Ks} cardiac potassium current. Nature 1996;384:78–80. [PubMed: 8900282]
3. Sanguinetti MC, Curran ME, Zou A, Shen J, Spector PS, Atkinson DL, Keating MT. Coassembly of KvLQT1 and minK (IsK) proteins to form cardiac I_{Ks} potassium channel. Nature 1996;384:80–83. [PubMed: 8900283]
4. Abbott GW, Goldstein SAN. A superfamily of small potassium channel subunits: form and function of the MinK-related peptides (MiRPs). Quart Rev Biophys 1998;31:357–398.
5. Bendahhou S, Marionneau C, Haurogne K, Larroque MM, Derand R, Szuts V, Escande D, Demolombe S, Barhanin J. In vitro molecular interactions and distribution of KCNE family with KCNQ1 in the human heart. Cardiov Res 2005;67:529–538.
6. Lundquist AL, Manderfield LJ, Vanoye CG, Rogers CS, Donahue BS, Chang PA, Drinkwater DC, Murray KT, George AL Jr. Expression of multiple KCNE genes in human heart may enable variable modulation of I_{Ks}. J Mol Cell Cardiol 2005;38:277–287. [PubMed: 15698834]
7. Radicke S, Dotella D, Graf EM, Banse U, Jost N, Varro A, Tseng GN, Ravens U, Wettwer E. Functional modulation of the transient outward current I_{to} by KCNE β-subunits and regional distribution in human non-failing and failing hearts. Cardiov Res 2006;71:695–703.
8. Abbott GW, Sesti F, Splawski I, Buck ME, Lehmann MH, Timothy KW, Keating MT, Goldstein SAN. MiRP1 forms I_{Kr} potassium channels with HERG and is associated with cardiac arrhythmia. Cell 1999;97:175–187. [PubMed: 10219239]
9. Sesti F, Abbott GW, Wei J, Murray KT, Saksena S, Schwartz PJ, Priori SG, Roden DM, George AL Jr, Goldstein SAN. A common polymorphism associated with antibiotic-induced cardiac arrhythmia. Proc Natl Acad Sci USA 2000;97:10613–10618. [PubMed: 10984545]
10. Weerapura M, Nattel S, Chartier D, Caballero R, Hebert TE. A comparison of currents carried by HERG, with and without coexpression of MiRP1, and the native rapid delayed rectifier current. Is MiRP1 the missing link? J Physiol 2002;540:15–27. [PubMed: 11927665]
11. Wu DM, Jiang M, Zhang M, Liu XS, Korolkova YV, Tseng GN. KCNE2 is colocalized with KCNQ1 and KCNE1 in cardiac myocytes and may function as a negative modulator of I_{Ks} current amplitude in the heart. Heart Rhythm 2006;3:1469–1480. [PubMed: 17161791]
12. Lundby A, Raven LS, Svendsen JH, Olesen SP, Schmitt N. KCNQ1 mutation Q147R is associated with atrial fibrillation and prolonged QT-interval. Heart Rhythm. 2007in press
13. Chen YH, Xu SJ, Bendahhou S, Wang XL, Wang Y, Xu WY, Jin HW, Sun H, Su XY, Zhuang QN, Yang YQ, Li YB, Liu Y, Xu HJ, Li XF, Ma N, Mou CP, Chen Z, Barhanin J, Huang W. KCNQ1 gain-of-function mutation in familial atrial fibrillation. Science 2003;299:251–254. [PubMed: 12522251]
14. Hong K, Piper DR, Diaz-Valdecantos A, Brugada J, Oliva A, Burashnikov E, Santos-de-Soto J, Grueso-Montero J, Diaz-Enfante E, Brugada P, Saches F, Sanguinetti MC, Brugada R. De novo KCNQ1 mutation responsible for atrial fibrillation and short QT syndrome in utero. Cardiov Res 2005;68:433–440.