Abstract: 912

Gain-of-function mutation in the cardiac kv4.2 potassium channel underlies paroxysmal atrial fibrillation

Authors:
M Drabkin¹, N Zilberberg², S Menahem³, W Mulla⁴, D Halperin¹, Y Yoge¹, O Wormser¹, Y Etzion⁴, A Katz⁵, OS Birk¹, ¹Ben Gurion University of the Negev, Faculty of Health Sciences and the National Institute for Biotechnology in the Negev - Beer Sheva - Israel, ²Ben Gurion University of the Negev, Department of Life Sciences and Zlotowski Center for Neuroscience - Beer Sheva - Israel, ³Ben Gurion University of the Negev, Department of Family Medicine - Beer Sheva - Israel, ⁴Ben Gurion University of the Negev, Regenerative Medicine and Stem Cell Research Center and Department of Physiology and Cell Biology - Beer Sheva - Israel, ⁵Ben Gurion University of the Negev, Faculty of Health Sciences - Beer Sheva - Israel,

Topic(s):
Basic Science - Cardiac Diseases: Arrhythmias

Citation:
Background: Three generations of a Jewish-Persian family presented with autosomal dominant early-onset paroxysmal atrial fibrillation (pAF), with recurrent self-terminating palpitations that were predominantly nocturnal.

Methods: Whole exome sequencing and linkage analysis were used to identify the disease-causing mutation. Electrophysiological assays in Xenopus oocytes followed by in-vivo experiments on genetically manipulated (CRISPR-Cas9) mice were used to determine the molecular mechanism of the disease.

Results: Through linkage analysis and sequencing studies we identified the disease-causing missense mutation in KCND2, encoding the pore-forming (a) subunit of the Kv4.2 cardiac potassium channel. Kv4.2, with Kv4.3, contributes to the cardiac fast transient outward K+ current, Ito. Ito underlies the early repolarization phase in the cardiac action potential, setting the initial potential of the plateau phase and governing its duration and amplitude. In Xenopus oocytes, the KCND2 mutation increased inactivation time constant of the channel and affected its regulation: the mutation resides in a protein-kinase C (PKC) phosphorylation site, which normally attenuates Kv4.2 membrane expression. Mutant Kv4.2 exhibited impaired response to PKC, resulting in augmented Kv4.2 membrane expression and enhanced potassium currents. Moreover, in a hybrid channel composed of Kv4.3 and Kv4.2, simulating the mature endogenous hetero-tetrameric channel underlying Ito, the Kv4.2 mutation exerted gain-of-function effect on Kv4.3. Thus, the mutation exerts gain-of-function effect on both Kv4.2 homo-tetramers and Kv4.2-Kv4.3 hetero-tetramers. In mice harboring the human mutation, which we generated using CRISPR-Cas9, basal ECG was normal, but altered response to pharmacological intervention, namely, adrenergic stimulation using phenylephrine, was observed.

Conclusions: Nocturnal pAF can be caused by a gain-of-function mutation in Kv4.2, suggesting targeting Kv4.2 may be effective in the management of nocturnal pAF. Notably, Kv4.2 expression was previously shown to demonstrate circadian variation, possibly relevant to nocturnal occurrence of pAF.