Review of: "Increased early sodium current provokes familial atrial fibrillation and reduces effectiveness of sodium channel block"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

Comments for the Authors

The study by O'Reilly M, Sommerfeld LC, and Fabritz L entitled "Increased early sodium current provokes familial atrial fibrillation and reduces effectiveness of sodium channel block" investigates the cardiac consequences of a mutant of the cardiac voltage-gated sodium channel $Na_V1.5$ p.M1875T, previously reported in a Japanese family with atrial fibrillation, using a transgenic mouse model expressing this mutant. This is a very well written and conducted study with interesting observations. Based on the impressive amount of patch clamp data collected (sodium current measurements), the statistic approach used (A hierarchical nested t-test) is powerful and extremely convincing. However, I have few comments.

Major comments:

1. Although mentioned in the material and methods in lane 79 and further: '' Functional experiments were conducted on hearts of male and female young adult mice (8-20 weeks), heterozygous for the knock-in mutation M1875T in the Scn5a gene (Scn5a-M1875T+/-) and their WT littermates.'' There is not data comparing/showing male versus/and female.

1. One of remaining question, already raised by the searchers describing for the first time this variant in heterologous expression system, is: why a mutant of Nav1.5 expressed in atria and ventricles has an effect only/mainly in atrium. Knowing that the mouse model is available it will be interesting to record the sodium current in ventricle.

1. Lane 266: '' In contrast to findings in HEK293 cells, there was no leftward shift of channel activation in murine left atrial cardiomyocytes''. Perhaps I missed something but, in the paper cited, the shift

observed is on the steady state inactivation and not on activation (see figure 5 of the paper cited). Moreover, it is a right shift (more precisely a shift toward depolarizing membrane voltages).

1. Lane 276 you discussed about the dimerization of Nav1.5 which has been proposed to occur at the C-terminal part of the channel via the calmodulin which is a relevant information based on the localization of this point mutation investigated in you study. Nevertheless, this mechanism is still under debate and other searchers also proposed that the dimerization occurs via the 143-3 protein ‘’far away’’ from the C-terminal part of Nav1.5 (PMID: 29233994). Based on this observation I will be caution with this part of the discussion. Perhaps can you rewrite this part to avoid any misleading for the further readers not aware about those hypotheses.

Minor comments:

1. In methods section 3.1, please add the substrain of the C57Bl6 mice. Are they coming from Janvier, Charles River etc…

1. In methods section 3.1, please add if the animals are on pure background or not.

1. In methods section 3.3. Which was the aesthesia used to sedate the animals?

1. In methods section 3.4. Please add an explanation how you maintained the heart rate during the echocardiography.

1. In methods section 3.5. Please add the information concerning the activity for the protease and the collagenase used for the isolation of cardiomyocytes.

1. In methods section 3.6. Please explain briefly why you focused on the LA and not the RA.

In methods section 3.9. Please add the formula used to fit the patch clamp data (Boltzmann fit).