Abstract: **P618**

**INa characterization from compound variants in SCN5A from a large founder population with excess sudden cardiac death**

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Recent clinical investigations in a Dutch-German founder population with excess sudden cardiac death, revealed striking phenotypic heterogeneity: long QT-syndrome, cardiac conduction disease, (drug-induced) Brugada syndrome, isorhythmic atrioventricular dissociation and overlap. Ventricular tachyarrhythmia often occurred during mental or physical stress. DNA sequencing identified the pathogenic SCN5A deletion c.4850_4852delTCT, encoding for Nav1.5-DelF1617, and a common polymorphism c.1673A>G, Nav1.5-H558R.

In the present study, we characterized the sodium current by performing whole-cell patch-clamp on Chinese hamster ovary cells (CHO), transiently transfected with wild-type (WT) Nav1.5, Nav1.5-DelF1617 or Nav1.5-DelF1617-H558R. Furthermore, given the location of the F1617, we investigated the interaction of the (mutant) channels with the β1 subunit, which was co-transfected with the aforementioned variants on Nav1.5. The data we generated were used to run in-silico action potential (AP) simulations, in order to evaluate the impact of the differential biophysical properties of the mutant channels on the AP.

The characterization of the Nav1.5-DelF1617 showed overall a marked loss-of-function phenotype, with a significant reduction in the current density, only partially recovered by the presence of the H558R. The voltage dependence of the mutant channels was not altered, but the time constant of inactivation was slower in Nav1.5-DelF1617(-H558R) and recovery from inactivation faster. No TTX-sensitive persistent current was detected. AP simulation confirmed a reduction of the phase 0 upstroke velocity for Nav1.5-DelF1617 and Nav1.5-DelF1617-H558R, due to a decreased peak INa. AP duration was slightly prolonged, especially at low pacing rate (1Hz). When the β1 subunit was co-expressed, the current density of Nav1.5-DelF1617 was not different from WT, but, interestingly Nav1.5-DelF1617-H558R showed a significant reduction. The voltage dependence of activation was shifted towards more positive potentials, causing, together with an incomplete inactivation, a 3-fold increase in the window current.

Taken together, these data suggest a differential interaction of the mutant channels with the β1 subunit, stressing the importance of the modulatory effect of other proteins (i.e. interacting protein forming the sodium channel macromolecular complex) on the cellular electrophysiological phenotype. Further investigation addressing the role of the β1 subunit and other modifier genes that might be of interest in this family is ongoing.