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We are pleased to hear that Dr El-Batrawy and his colleagues are interested in our work. We note they are concerned that the sodium current recordings in our patch clamp experiments could have been contributed to by Nav1.5. We do detail in our methods "We assessed expression in HEK293 cells, which do not express endogenous sodium channels". These cells were transfected with mutant and wild type SCN4A DNA as described in the methods. This approach excludes any possibility of Nav1.5 or any other sodium channel isoform, contributing to the sodium current recordings. This is why the composition of patch clamp solution for discussion on isolation of isoform specific currents is not indicated. However, the solutions can be found in in the references to our previous work using this cell system ("…which we have previously used for functional expression[14, 23, 24]"). In addition, we cannot measure action potentials in heterologous expression system, and this is why any discussion of action potential waveforms is omitted.

Our genetic analysis was hypothesis driven and focused on SCN4A variants. We did however additionally analyse 90 cardiac genes with an established role in inherited cardiac disease and SIDS (described in methods and available as supplemental data). We omitted SCN10A from this list as the role of SCN10A variants in Brugada syndrome is uncertain and no association with sudden infant death has been shown. After the initial findings by Hu et al, Behr ER et al performed an extensive analysis of SCN10A variants in patients with Brugada syndrome and a larger number of controls. This study did not identify any significant association of rare SCN10A variants with this disorder and could not support a strong role for SCN10A causing monogenic Brugada Syndrome. A common SNP was associated with Brugada syndrome but the significance of this requires further evaluation. Nav1.8 is widely expressed in the dorsal root ganglion neurones. The expression of Nav1.8 in human cardiomyocytes is low and its role in cardiac conduction has not been clearly established. Clinical genotyping is not recommended as the significance of SCN10A variants for cardiac arrhythmia and sudden death is unclear.

References

1. Hu D, Barajas-Martinez H, Pfeiffer R, et al. Mutations in SCN10A are responsible for a large fraction of cases of Brugada syndrome. J Am Coll Cardiol 2014; 64(1): 66-79.

2. Behr ER, Savio-Galimberti E, Barc J, et al. Role of common and rare variants in SCN10A:results from the Brugada syndrome QRS locus gene discovery collaborative study. Cardiovasc Res 2015; 106(3): 520-9.