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Pro-arrhythmic features of a novel mouse model of sudden death due to abnormal branched chain amino acid (BCAA) metabolism

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Introduction:
Phenotype-driven ENU (N-ethyl-N-nitrosourea) mutagenesis screens in mice may constitute a powerful tool to uncover new genes and pathways modulating cardiac electrical function and arrhythmia susceptibility. During such a screen, we identified a particular line of mutagenized mice (MPC-91) presenting with sudden death.

Results:
Genetic mapping and whole genome sequencing of the MPC-91 line revealed the presence of a missense mutation in the Bcat2 gene encoding mitochondrial branched chained aminotransferase. Homozygous mutant (HOM) mice showed increased plasma and urine levels of branched chain amino acids (BCAAs). All HOM mice died suddenly between the age of 6-8 weeks, without any overt preceding symptoms. No cardiac abnormalities were observed on histological analysis, and heart weight to tibia length ratios were similar in HOM and wild type (WT) littermates. Compared to WT, HOM mice showed QTc-prolongation in vivo on surface ECG analysis and prolonged action potential duration (APD80) ex vivo in isolated Langendorff-perfused hearts. Moreover, isolated HOM hearts displayed increased inducibility of atrial and ventricular arrhythmias as compared to WT. In line with this, patch clamp measurements revealed significant APD90 prolongation and increased incidence of pro-arrhythmic events in isolated cardiomyocytes from HOM mice as compared to WT, which was prevented by pharmacological inhibition of the late sodium current.

Conclusion:
We describe a novel mouse model of sudden cardiac death with pro-arrhythmic features secondary to increased levels of BCAAs in the absence of cardiac structural abnormalities. Recent studies have linked the increase level of BCAAs to an increased reactive oxygen species (ROS) production involving the mTor pathway. We are now aiming in characterizing the electrophysiological consequences of increased concentrations of BCAAs in the presence of hiPSC-CMs. Overall, our findings point to a potential role for BCAA metabolism in (dys)regulation of cardiac electrophysiological properties, which may contribute to pro-arrhythmia in the setting of metabolic disorders, including heart failure.