In vitro model of febrile seizures and epilepsy using patient-specific induced pluripotent stem cells-derived neurons

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Febrile seizures (FS), i.e. seizures occurring during fever in children, are classified as simple or complex based on the duration of the convulsive event. FS are often related to missense loss-of-function mutations in the SCN1A gene, coding for voltage-gated sodium channel NaV1.1. Although it has been demonstrated that these mutations lead to a decrease in the Na+ current density, mainly affecting the inhibitory neuronal transmission, it is not clear why the same SCN1A mutation gives rise to more or less severe symptoms in different subjects. To address this issue, we generated human induced pluripotent stem cell (hiPSCs)- derived forebrain neurons from two siblings, SCN1Amut-1 and SCN1Amut-2, carrying the same c.434T>C mutation in SCN1A, but suffering from complex and simple FS, respectively. Our differentiation protocol gave a prevalence of inhibitory GAD1-positive neurons, expressing high levels of Na V1.1. We could not detect significant differences in the expression of NaV1.1 protein between the two patients and a healthy control; however, we found that the chloride transporters NKCC1 and KCC2, which are responsible for depolarization (NKCC1) and hyperpolarization (KCC2) of neurons by chloride flux through the GABA receptor-channel, resulted differentially expressed between the two brothers and with respect to the unaffected control. These data suggest that FS subjects can show different degrees of “brain dysmaturity” causing the neurological disease. The electrophysiological characterization of the hiPSC-derived neurons of the patients, currently undergoing, will help to highlight mechanisms underpinning the generation of different epileptic-like phenotypes in subjects with identical mutation in SCN1A.