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The Role of Kcnb for Neurodevelopmental Disorders

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Approximately 13% of all children are diagnosed with some form of neurodevelopmental disorder. We recently identified genetic variants of KCNB2 in nine patients suffering from neurodevelopmental disorders. Genetic variants in KCNB1, on the other hand, lead to developmental epileptic encephalopathy. Both KCNB isoforms are expressed in the soma and proximal dendrites of most neurons, where they take up a dual role of repolarization and adjusting membrane excitability. They are 97% identical in the transmembrane region but differ in the C-terminus. Using electrophysiology and voltage-clamp fluorometry, we studied the molecular mechanisms underlying disease development and the differential effects of KCNB1 and -B2. We progressively truncated the C-termini of KCNB1 and -B2, since this is the region where the two channels differ. We found that in KCNB2 closed state inactivation is increased in genetic variants leading to neurodevelopmental disorders. We studied the use dependence of KCNB activation by repeated action potential stimulation and determined the slow adaptation of the channels as a function of action potential frequency, amplitude and duration.