A recurrent mutation in *KCNA2* in complicated autosomal dominant spastic paraplegia: an expansion of the channelopathy spectrum and a novel disease mechanism

Authors: K.L. Helbig1 , U.B.S. Hedrich2 , A.C. Teichmann3 , J. Hentschel3 , D.N. Shinde1 , W.A. Alcaraz1 , S. Tang1 , C. Jungbluth4 , S.L. Dugan4,5, R. Schüle6 , H. Lerche2 , J.R. Lemke3 . 1) Division of Clinical Genomics, Ambry Genetics, Aliso Viejo, CA., USA; 2) Department of Neurology and Epileptology, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany; 3) Institute of Human Genetics, University Hospital Leipzig, Leipzig, Germany; 4) Department of Medical Genetics, Children's Hospitals and Clinics of Minnesota, Minneapolis, MN, USA; 5) Division of Medical Genetics, University of Utah, Salt Lake City, UT, USA; 6) Department of Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany

The hereditary spastic paraplegias (HSPs) are a genetically and clinically heterogeneous group of neurodegenerative disorders characterized by spasticity and weakness in the lower extremities. Over 50 genes have been identified for HSPs, involved in a variety of cellular processes. However approximately 20% of familial HSPs remain unsolved. To date ion channels have not been implicated in HSPs. Diagnostic exome sequencing was performed on DNA from the peripheral lymphoblasts of a three-generation family with three affected individuals with HSP (Family 1). Family 2 with two affected individuals across two generations underwent exome sequencing as part of an ongoing research study on the genetic basis of HSP. Both families were found to have the identical c.881G>A (p.R294H) mutation within the voltage sensor of KCNA2, encoding the voltage-gated potassium channel Kv 1.2, a member of the shaker potassium channel family. This mutation segregated with childhood onset spasticity and intellectual disability in five affected individuals from two unrelated families in an autosomal dominant fashion. Onset of spasticity was as early as two years. Cognitive outcomes were variable, with all three affected individuals in Family 1 displaying mild intellectual disability; one individual additionally had a diagnosis of autism spectrum disorder. In Family 2 the proband had mild intellectual disability but the affected mother had normal intellect. The p.R294H mutation is absent from all population databases (ExAC, 1000 Genomes, and EVS), and is predicted to be deleterious by in silico prediction models. The R294 amino acid is the first of seven gating charges in the Kv 1.2 potassium channel S4 transmembrane segment, which forms the voltage sensor domain. Two-electrode voltage-clamp recordings of Xenopus laevis oocytes expressing mutant channels showed a loss of the Kv 1.2 channel's function with a dominant-negative effect causing a decrease in current amplitude and a small depolarizing shift of the activation curve in comparison to wildtype channels. In addition, it has been shown previously for the shaker potassium channel that replacement of the first arginine within the S4 voltage sensor with a histidine causes the formation of a proton pore at hyperpolarized potentials. This finding expands the channelopathy spectrum to include HSP and represents a novel HSP disease mechanism.