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A novel *de novo* alteration in *SLC12A6* in a patient with early onset severe progressive sensorimotor polyneuropathy and abnormal EEG.

The *SLC12A6* gene encodes a potassium-chloride cotransporter (KCC3) belonging to a family of transmembrane proteins that regulate cell volume and control neuronal activity by transporting K+ and Cl− ions across the plasma membrane. Biallelic truncating and missense mutations in *SLC12A6* cause autosomal recessive agenesis of the corpus callosum with peripheral neuropathy associated with hydrocephalus, developmental delay, intellectual disability and seizures. However, only one patient with a *de novo* heterozygous missense alteration, c.2971A>G (p.T991A), in the *SLC12A6* gene has been reported till date. This patient presented with progressive, and early-onset axonal motor neuropathy with normal corpus callosum, cognition, and no epilepsy (Kahle *et al.* 2016). Functional studies demonstrated that this alteration results in constitutive KCC3 activity. We report an additional patient with a previously unpublished *de novo* missense alteration c.620G>A (p.R207H) in *SLC12A6* and severe sensorimotor polyneuropathy with distal and proximal weakness, and abnormal EEG. The alteration was identified through diagnostic exome sequencing (DES) and reported as a candidate genetic etiology due to limited clinical validity of the association of monoallelic *SLC12A6* alterations with human genetic disease. A different alteration at the same codon, p.R207C, has been previously reported in a patient with developmental delay and mild intellectual disability, significant hypotonia with areflexia, pyramidal signs, complete agenesis of the corpus callosum, and an axonal and demyelinating neuropathy of the motor and sensory nerves with reduced motor nerve conduction velocity. The patient was found to be homozygous for the alteration and the carrier parents were asymptomatic. *In vitro* functional studies of the p.R207C alteration demonstrated decreased transport activity of the mutant KCC3 when expressed in Xenopus oocytes (Salin-Cantegrel *et al.* 2011). Functional studies of the effect of the p.R207H alteration need to be performed in order to determine whether this alteration has a loss- or gain-of-function effect and hence has been classified as a variant of uncertain clinical significance. There is also the possibility of another alteration on the second allele that could be intronic or located in the regulatory region, and therefore not detected by exome sequencing. RNA-sequencing studies could be pursued to confirm the state of the second allele in this patient.