DYT3 (ATP1A3): Also known as rapid-onset dystonia-parkinsonism (RDP), this condition presents with abrupt onset dystonia and parkinsonism. Dominant mutations of ATP1A3, a neuronal Na,K-ATPase α subunit isoform, cause neurological disorders with an exceptionally wide range of severity. Several new mutations and their phenotypes are reported here (p.Asp366His, p.Asp742Tyr, p.Asp743His, p.Leu924Pro, and a VUS, p.Arg463Cys). Mutations associated with mild or severe phenotypes [rapid-onset dystonia-parkinsonism (RDP), alternating hemiplegia of childhood (AHC), or early infantile epileptic encephalopathy (EIEE)] were expressed in HEK-293 cells. Paradoxically, the severity of human symptoms did not correlate with whether there was enough residual activity to support cell survival. We hypothesized that distinct cellular consequences may result not only from pump inactivation but also from protein misfolding. Biosynthesis was investigated in four tetracycline-inducible isogenic cell lines representing different human phenotypes. Two cell biological complications were found. First, there was impaired trafficking of αβ complex to Golgi apparatus and plasma membrane, as well as changes in cell morphology, for two mutations that produced microcephaly or regions of brain atrophy in patients. Second, there was competition between exogenous mutant ATP1A3 (α3) and endogenous ATP1A1 (α1) so that their sum was constant. This predicts that in patients, the ratio of normal to mutant ATP1A3 proteins will vary when misfolding occurs. At the two extremes, the results suggest that a heterozygous mutation that only impairs Na,K-ATPase activity will produce relatively mild disease, while one that activates the unfolded protein response could produce severe disease and may result in death of neurons independently of ion pump inactivation [1].

1)
Arystarkhova E, Haq IU, Luebbert T, Mochel F, Saunders-Pullman R, Bressman SB, Feschenko P, Salazar C, Cook JF, Demarest S, Brashear A, Ozelius LJ, Sweadner KJ. Factors in the disease severity of ATP1A3 mutations: Impairment, misfolding, and allele competition. Neurobiol Dis. 2019 Aug 16:104577. doi: 10.1016/j.nbd.2019.104577. [Epub ahead of print] PubMed PMID: 31425744.