De novo deletion variant in the GTPase effector domain (GED) of DNM1L leads to Gross motor delay, hypotonia, axonal sensory neuropathy with peroxisomal and mitochondrial abnormalities

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DNM1L encodes dynamin-related protein 1 (DRP1), an 80-kDa GTPase in the dynamin super-family, which is essential for mitochondrial and peroxisomal fission. Dysfunction in DNM1L has been linked to mitochondrial and neurodegenerative disorders, including Alzheimer's, Parkinson's, and Huntington's disease. DNM1L protein has 3 distinct domains the GTPase domain, middle domain and GTPase effector domain (GED). To date, different domain specific variants have been identified in the DNM1L gene among patients. These gene variants exhibit a range of neurological symptoms, from severe hypotonia causing neonatal death to developmental delay, cerebellar atrophy, encephalopathy, profound intellectual disabilities, and gross motor delay. Pathogenic variants in the middle domain and GTPase domain of DNM1L are associated with encephalopathy due to defective mitochondrial and peroxisomal fission 1 (EMPF1, MIM #614388). Additionally, familial pathogenic variants in the GTPase domain have been connected to isolated optic atrophy. Here we report a patient with a novel, de novo deletion variant (Leu700del) in the GED domain exhibiting gross motor delay, onset at infancy with hypotonia, and axonal sensory neuropathy, thereby further expanding the clinical spectrum of DNM1L associated disorders. Here we detail the functional studies involving this novel GED variant (Leu700del) in Drosophila and compare the phenotypes this variant produces in our model system with GTPase domain (A192E), and middle domain (R403C) fly models produced in our lab. We find that our Drosophila model displays large abnormal peroxisomes and mitochondria when overexpressing the GED variant (Leu700del) and middle domain variant (R403C), an effect comparable to that of middle domain missense alleles observed in pediatric subjects with EMPF1. The results clearly indicate that our Drosophila model can produce EMPF1 phenotype, and that current study further enhances our understanding of the natural progression of an increasing number of DNM1L-related disorders.