Disturbed mitochondrial and peroxisomal dynamics due to loss of MFF causes Leigh-like encephalopathy, optic atrophy and peripheral neuropathy.

Mitochondria are dynamic organelles which undergo continuous fission and fusion to maintain their diverse cellular functions. Components of the fission machinery are partly shared between mitochondria and peroxisomes, and inherited defects in two such components (dynamin-related protein (DRP1) and ganglioside-induced differentiation-associated protein 1 (GDAP1)) have been associated with human disease. Deficiency of a third component (mitochondrial fission factor, MFF) was recently reported in one index patient, rendering MFF another candidate disease gene within the expanding field of mitochondrial and peroxisomal dynamics. Here we investigated three new patients from two families with pathogenic mutations in MFF. The patients underwent clinical examination, brain MRI, and biochemical, cytological and molecular analyses, including exome sequencing. The patients became symptomatic within the first year of life, exhibiting seizures, developmental delay and acquired microcephaly. Dysphagia, spasticity and optic and peripheral neuropathy developed subsequently. Brain MRI showed Leigh-like patterns with bilateral changes of the basal ganglia and subthalamic nucleus, suggestive of impaired mitochondrial energy metabolism. However, activities of
mitochondrial respiratory chain complexes were found to be normal in skeletal muscle. Exome sequencing revealed three different biallelic loss-of-function variants in MFF in both index cases. Western blot studies of patient-derived fibroblasts indicated normal content of mitochondria and peroxisomes, whereas immunofluorescence staining revealed elongated mitochondria and peroxisomes. Furthermore, increased mitochondrial branching and an abnormal distribution of fission-mediating DRP1 were observed. Our findings establish MFF loss of function as a cause of disturbed mitochondrial and peroxisomal dynamics associated with early-onset Leigh-like basal ganglia disease. We suggest that, even if laboratory findings are not indicative of mitochondrial or peroxisomal dysfunction, the co-occurrence of optic and/or peripheral neuropathy with seizures warrants genetic testing for MFF mutations.