NF-kB pathway via OPTN and TBK1. The muscle biopsy specimens of sporadic inclusion body myositis (n = 14), GNE myopathy (n = 5), and oculopharyngeal muscular dystrophy (n = 2), polymyositis (n = 10), sporadic ALS (n = 6) and histologically normal control (n = 5) were examined. These specimens were subjected to immunohistochemistry and immunofluorescent technique using antibodies against phosphorylated TDP-43 (p-TDP-43), OPTN, and TBK1. RVs were immunopositive for TBK1. Necrotic fibers had diffuse cytoplasmic immunoreactivities for TBK1. Fibers without RVs or necrosis were not positive for TBK1. Immunofluorescent study showed that TBK1, OPTN and pTDP-43 were colocalized around RVs. This study suggests that RVs might work as necrosomes via TBK1 and OPTN.

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MITOCHONDRIAL DISEASES

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Neuromyopathy with cataracts and glaucoma: A novel syndrome caused by recessive mutations in POLG1

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Mutations in DNA polymerase gamma (POLG1), an enzyme involved in the replication of human mitochondrial DNA, are known to cause a wide array of pathologies, ranging from progressive external ophthalmoplegia to fatal Alpers syndrome. We identified three patients with compound heterozygous mutations in POLG1 in the same exons causing a homogeneous phenotype of neuromyopathy. The onset was congenital in all the three patients, with cataracts, delayed walking and distal weakness. When performed, muscle biopsy showed neurogenic findings and ragged red fibers, and muscle MRI showed similar features across the patients. All the patients also developed glaucoma. This report expands the clinical spectrum of POLG1-related disorders, and identifies a novel phenotype of neuromyopathy with glaucoma and cataracts.

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Clinical, molecular, radiological investigations in patients with SURF1 mutations and muscle biopsy findings

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Leigh syndrome (LS) is a mitochondrial disease that typically presents in infancy with subacute neurodegenerative encephalopathy. In this study, SURF1 gene was sequenced in patients with clinical suspicion of LS, complex IV deficiency, or clinical features of mitochondrial disorders. The study included seven patients with SURF1 mutations identified from a study of 21 children with Leigh syndrome findings in magnetic resonance imaging who had been underwent muscle biopsy. All the patients underwent a detailed neurological assessment, muscle biopsy, and sequencing of the complete mitochondrial genome and SURF1. The differential diagnosis of organic acidurias and fatty acid beta-oxidation defects were performed. The patients had various forms of metabolic encephalomyopathy. All of the patients had the typical neuroradiological features of Leigh syndrome. The SURF1 analysis identified previously reported mutations in all the patients. Diffuse decreased activity or total deficit of COX was revealed histochemically in 4 of 7 examined muscles. No ragged red fibres (RRFs) were seen. Lipid accumulation and fibre size variability were found in four of six specimens. Ultrastructural assessment showed several mitochondrial abnormalities, lipid deposits, myofibrillar disorganisation and other minor changes. On follow-up four patients expired and three had a stable course. Patients with Leigh syndrome and SURF1 mutation often have skin and hair abnormalities. Bilateral symmetrical hypertrophic olivary degeneration could be a specific clue for SURF1 deficiency. Histological and histochemical features of muscle of genetically homogenous SURF1-deficient LS were reproducible in detection of COX deficit. It should be kept in mind that muscle biopsy changes are not specific if COX staining is not employed.

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Exercise intervention in a family with exercise intolerance and a novel mutation in the mitochondrial POLG gene

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Mutations in the POLG gene, encoding the mitochondrial DNA (mtDNA) polymerase subunit gamma-1, have been identified in severe mtDNA depletion syndromes and mtDNA deletion disorders which include ataxia neuropathy spectrum disorders and AR and AD forms of progressive external ophthalmoplegia (PEO) and PEO-plus disorders. We report on a family with exercise intolerance. The proband was a 50-year-old man with severe muscle pain and premature fatigue after exercise of mild to moderate intensity. Serum CK ranged from 400 to 4500 U/L. Her mother, 3 out of 4 siblings, and two uncles showed the same symptoms and hyper-CK-emia (>500 U/L). Neurological examination, and brain and lower limbs MRI were normal. Presence of muscle RRF-COX- and mild respiratory chain complex I deficiency prompted us to suspect a mitochondrial disorder. Muscle whole mtDNA sequencing by NGS showed no pathogenic variants, whereas multiple mtDNA deletions were found by long-range PCR. A novel heterozygous mutation (p.Thr585Ile) in the POLG gene that segregated with the phenotype was identified through a targeted NGS panel of nuclear genes involved in mtDNA maintenance. In silico algorithms and protein structure analysis suggested pathogenicity, however very low frequency was found in ExAC database. A 8-week exercise intervention protocol in the proband combining aerobic and resistance training induced improvements in functional tests (6-minute walking distance, 15-step climbing, and get up and go), maximal strength tests (bench press, legs press, maximal inspiratory pressure), peak oxygen uptake (VO2peak), and DXA-determined femur mineral density. Isolated exercise intolerance has not been associated so far with POLG mutations and multiple mtDNA deletions. Supervised exercise interventions seem to help improving the functional capacity of these patients.

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Pathogenic mutations in TMEM126B, a recently discovered complex I assembly factor, identified in four siblings from two Belgian families

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