Autosomal dominant progressive external ophthalmoplegia

Autosomal dominant progressive external ophthalmoplegia (adPEO) is a late-onset, Mendelian mitochondrial disease characterised by paresis of the extraocular muscles, ptosis and skeletal-muscle restricted multiple mitochondrial DNA (mtDNA) deletions. While dominantly-inherited, pathogenic variants in POLG, TWNK and RRM2B are among the most common genetic defects of adPEO, identification of novel candidate genes and the underlying pathomechanisms remain challenging. We report the clinical, genetic and molecular investigations of a patient who presented in the seventh decade of life with PEO. Oxidative histochemistry revealed cytochrome c oxidase deficient fibres and occasional ragged red fibres showing subsarcolemmal mitochondrial accumulation in skeletal muscle, while molecular studies identified the presence of multiple mtDNA deletions. Negative candidate screening of known nuclear genes associated with PEO prompted diagnostic exome sequencing, leading to the prioritisation of a novel heterozygous c.547G > C variant in GMPR (NM_006877.3) encoding guanosine monophosphate reductase, a cytosolic enzyme required for maintaining the cellular balance of adenine and guanine nucleotides. We show that the novel c.547G > C variant causes aberrant splicing, decreased GMPR protein levels in patient skeletal muscle, proliferating and quiescent cells and is associated with subtle changes in nucleotide homeostasis protein levels and evidence of disturbed mtDNA maintenance in skeletal muscle. Despite confirmation of GMPR deficiency, demonstrating marked defects of mtDNA replication or nucleotide homeostasis in patient cells proved challenging. Our study proposes that GMPR is the nineteenth (19th) locus for PEO and highlights the complexities of uncovering disease mechanisms in late-onset PEO phenotypes [1)].

1)
Sommerville EW, Dalla Rosa I, Rosenberg MM, Bruni F, Thompson K, Rocha M, Blakely EL, He L, Falkous G, Schaefer AM, Yu-Wai-Man P, Chinnery PF, Hedstrom L, Spinazzola A, Taylor RW, Gorman GS. Identification of a novel heterozygous guanosine monophosphate reductase (GMPR) variant in a patient with a late-onset disorder of mitochondrial DNA maintenance. Clin Genet. 2019 Oct 10. doi: 10.1111/cge.13652. [Epub ahead of print] PubMed PMID: 31600844.