Mitochondria are peculiar organelles with their own genome that is composed of a 16.5 kb circular double-stranded DNA molecule (mtDNA). It encodes two rRNAs, 22 tRNAs and 13 structural proteins [1]. Interestingly, a great majority of the proteins in mitochondria -approximately 1500 in number- are encoded by nuclear DNA, which makes these delicate and vulnerable organelles inevitably and highly dependent to the eukaryotic cells’ internal environment.

Nuclear DNA-encoded proteins are transcribed in the nucleus, synthesized in the ribosomes and then actively transported into the mitochondria. Besides, mitochondria have some unique enzymes for their basic genetic needs. For example, mtDNA replication is mediated by a special DNA polymerase, DNA polymerase γ (pol γ) [1]. Among the known 16 different DNA polymerases in eukaryotic cells, pol γ is the only one which is functional in the mitochondria. Pol γ is encoded by POLG1 gene on chromosome 15q25. This exceptional polymerase has an accessory subunit which is encoded by POLG2 gene at chromosomal locus 17q24.1 [2]. The accessory domain of pol γ itself is 55 kDa and is required for tight DNA binding for processive DNA synthesis [2].

The first disease-related mutations in POLG1 were identified and reported in 2001 [3]. These firstly discovered mutations were associated with progressive external ophthalmoplegia (PEO). To date, about 150 disease-related mutations in POLG1 have been documented. The most common disease-related mutation is A467T substitution resulting clinically either Alpers’ syndrome, ataxia-neuropathy syndromes, or PEO. A high incidence of psychiatric conditions, a Parkinson-like syndrome and a primary gonadal failure have also been reported in some families transmitting dominant POLG1 mutations [4, 5].

In addition to that, some cases may exhibit a profound peripheral neuropathy and ataxia (similar to sensory ataxic neuropathy with dystarthis and ophalmoparesis, which is known as SANDO). Recessive POLG1 mutations were also described in patients exhibiting the symptomatology consistent with the adult onset ataxia without ophalmoplegia (mitochondrial recessive ataxia syndrome)[6].

**Alpers’ syndrome** is characterized by severe seizures and generally appears in infancy, although late-onset cases are known. Growth retardation and hypotonia in infants, and mental deterioration as well as progressive cognitive disturbances with increasing age are typical. Epilepsia partialis continua, a kind of intractable myoclonic seizure is also a characteristic finding. Blindness and hearing-loss may occur if optic and acoustic nerves are affected. Depletion of mtDNA is usual [7] and many patients suffer from impaired liver functions, too.

**PEO** becomes evident during adulthood, in general. Its main characteristics are muscle weakness, exercise intolerance, sensory ataxic neuropathy, and respiratory failure. Muscle biopsy reveals prevalent mtDNA depletion in most of the patients [8].

**SANDO**, on the other hand, is a complex multisystem disease due to severe mitochondrial dysfunction associated with mitochondrial depletion in both skeletal muscle and peripheral nerves. Clinically, sensory ataxic neuropathy, dystarthis, and ophalmoparesis constitute the classical triad, although the symptoms can be very polymorphic. An atypical form of the disease has also been reported [9].

The abovementioned entities are the major POLG1 mutation-related diseases. But, mutations in POLG1, both known and undiscovered ones, may underlie some undefined complex clinical symptoms. These symptoms have been grouped by Wong et al [7] as follows: (1) a rather ill-defined childhood myocerebrohepatopathy spectrum disorder; (2) Alpers’ syndrome; (3) ataxia neuropathy spectrum; (4) myoclonus - epilepsy - myopathy - sensory ataxia; (5) autosomal recessive PEO-plus; and (6) autosomal dominant PEO-plus.

In this issue of the *Journal of Experimental and Integrative Medicine*, Kurt et al reports a c.1774C>T substitution, a novel missense mutation in the exon 10 of the POLG1 gene [10]. The patient was a 48-year old woman presenting sensory ataxic neuropathy, dystarthis, ophalmoplegia, and dysphagia (SANDO). They have also found a second mutation, c.3286C>T substitution, in the exon 21 of the same gene in this patient. The latter
one was a known mutation of the POLG1 gene, though. I enjoyed reading their article, and brushed up my knowledge in this field of research. It is my belief that most of the readers will also find this study interesting.

I am of the opinion that mutation screening on the genes related to the mitochondrial functions will provide a fertile soil to the scientists, and may uncover more unidentified links between the molecules and diseases in the near future.

References

Key words: Mitochondrial disease; POLG gene; Polymerase gamma

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