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Progressive External Ophthalmoplegia has an unusual Inheritance Pattern Depending on the Gene Involved

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ABSTRACT

Progressive external ophthalmoplegia (PEO) is characterized by weakness of the eye muscles or mainly by a loss of the muscle functions in the eye (Ophthalmoplegia) and eyelid movement (ptosis). The signs and symptoms typically appear or tend to begin in early adulthood and slowly worsens over time and lead paralysis of one or more extraocular muscles. People with PEO may also have a general weakness of the skeletal muscles used for movement (myopathy). PEO is a disease of mitochondrial origin and it is mainly caused by defects or mutations in any of several mitochondrial proteins. Mitochondria are structures in cells that use oxygen to convert the energy from food into a form that cells can use. It has different inheritance patterns depending on the gene of the affected individual. Mitochondria have their own chromosome and DNA replication system, including a unique DNA polymerase, called polymerase gamma (Pol G). The aim of this literature review is to discuss the types of PEO resulting from mutations in the mitochondrial genome, as well as, how this results in a maternal inheritance pattern.

❖ MITOCHONDRIAL MUTATIONS:

- ❑ Progressive external ophthalmoplegia is transmitted as an autosomal dominant trait. With the onset of symptoms usually occurring between 18 and 40 years of age. The main clinical manifestation of PEO is a progressive weakness of the external eye muscles resulting in blepharoptosis *(an abnormal or low-lying upper eyelid margin)* and ophthalmoparesis *(paralysis or weakness of the eye muscles).*
- ❑ PEO can result from mutations in one of several different genes in the mitochondria. For instance, PEO can be associated with mutations in **the POLG gene** encoding a subunit of the mitochondrial DNA polymerase, which is the only known DNA polymerase in human mitochondria and is essential for mitochondrial DNA replication and repair. It is well established that defects in mtDNA replication lead to mitochondrial dysfunction and disease. .
- ❑ Perhaps surprisingly, mutations in nuclear genes have an effect on mitochondrial DNA replication, but there's not a maternal inheritance pattern because in most cases, there are **4 autosomal dominant mutations** that cause PEO encode the amino acid substitutions **G923D, R943H, Y955C** and **A957S** in the polymerase domain of POLG.

❖ **DEFINITION: Autosomal dominance** is a pattern of inheritance characteristic of some genetic diseases. **"Autosomal"** means that the gene in question is located on one of the numbered, or non-sex, chromosomes. **"Dominant"** means that a single copy of the disease-associated mutation is enough to cause the disease.

Mitochondria structural feature

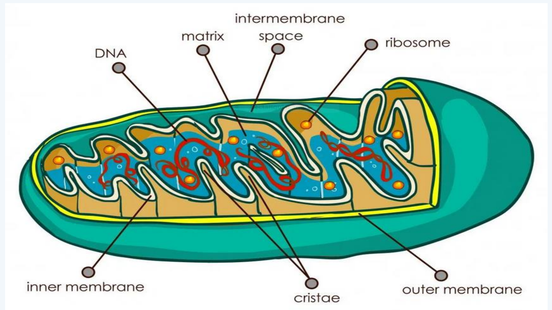

Figure 1:

Progressive External Ophthalmoplegia

Figure 2:

FIGURE 1: The mitochondria is an organelle that can be considered the power generator of the cell, converting oxygen and nutrients into a form that cells can use. Mutations or defects in the nuclear DNA of this organelle are responsible for the condition, including mutations in the POLG resulting in the progressive external ophthalmoplegia (PEO).

FIGURE 2: This individual is affected by a progressive external ophthalmoplegia disease and presents a weakness or paralysis of the eye muscles that move the eyes. Usually, affected individuals have to turn their heads to see in different directions, especially as the ophthalmoplegia worsens.

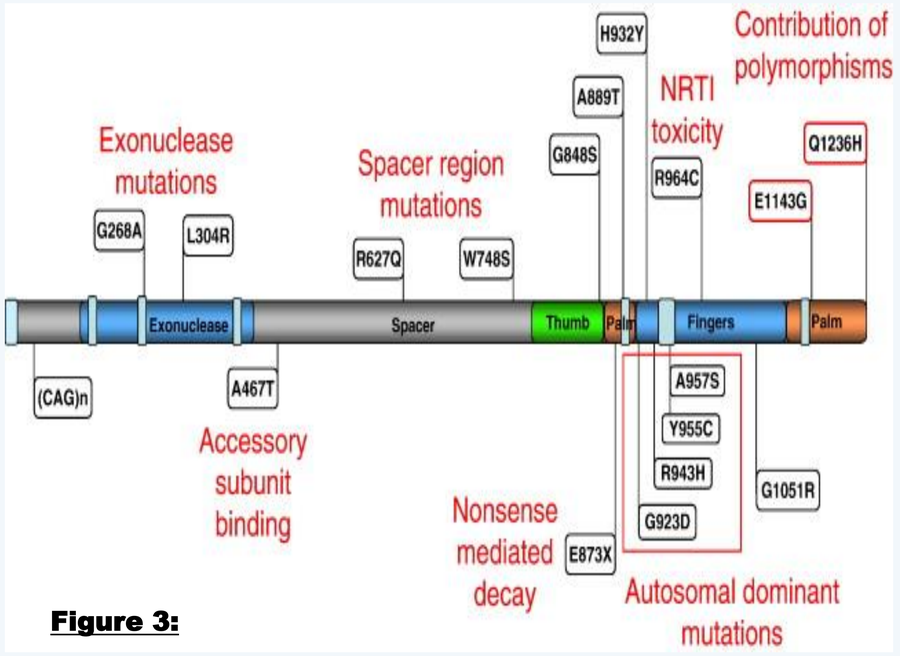

Figure 3:

FIGURE 3: The POLG contains an exonuclease region, spacer, thumb region and a finder region surrounded by two palms. It also illustrates that there are many mutations in the PEO, but mutations in and around the finger domain are autosomal dominant mutations, the only mitochondrial disease that cosegregates with autosomal dominant (ad) mutations in POLG. Nearly all of the adPEO mutations in POLG are located in the polymerase domain of pol γ (Fig.3).

One of the first adPEO mutations to be discovered was the Y955C mutation, and this was the first to be biochemically characterized. The Y955C is a mutation, causing a 10- to 100-fold increase in misinsertion errors, most likely as a consequence of a 45-fold decrease in binding affinity for the incoming nucleoside triphosphate.

This enhanced mutagenesis is mitigated by a functional intrinsic exonuclease activity resulting in only a 2-fold mutator effect for base-pair substitutions by the exonuclease proficient Y955C enzyme.

In a subsequent study of four adPEO mutant variants, the Y955C and R943H substitutions were predicted to interact directly with the incoming dNTP by analysis of a structural model of the polymerase active site based upon the solved crystal structure of T7 DNA polymerase.

Recombinant proteins carrying these substitutions retain less than 1% of the wild-type (WT) polymerase activity and display a severe decrease in processivity. The significant stalling of DNA synthesis and extremely low catalytic activities of both enzymes are the two most likely causes of the severe clinical presentation in R943H and Y955C heterozygotes.

The G923D and A957S substitutions retained less than 30% Wild Type polymerase activity. This is consistent with the reduced clinical severity of PEO in individuals heterozygous for the G923D and A957S mutations.

Although progressive external ophthalmoplegia (PEO) is part of a spectrum of disorders with overlapping signs and symptoms, the primary symptom is muscle weakness which is caused by defects in mitochondria with depletion of mitochondrial DNA (mtDNA). MtDNA replication is important as it explains the formation of deletions and point mutations associated with human disease and aging. It's replicated by an assembly of proteins and enzymes including DNA polymerase γ (pol γ) and its accessory protein, single-stranded DNA binding protein (mtSSB), mtDNA helicase (Twinkle), and a number of accessory proteins and transcription factors.

Ultimately, an autosomal dominant (nuclear) is causing mitochondrial problems with DNA replication and no heteroplasmy ensures that the children will receive a mix of normal and mutant mitochondria. The child will only be affected if a threshold of mutant (critical mutation rate) mitochondria is reached.

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