Journal of Health, Medicine and Nursing
ISSN 2422-8419 An International Peer-reviewed Journal
Vol.53, 2018

Mitochondrial DNA Analysis and Mitochondrial Diseases

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Abstract
Mitochondria are the organelle in which cellular respiration is carried out in eukaryotic organisms. Cellular respiration is the process of forming ATP energy by breaking down the nutrients with oxygen. Free oxygen radicals coming out in the result of the electrons escaping from the electron transport chain creates damage firstly in the mitochondria and then in the cell. Mutations occur in mitochondrial DNA (Mt-DNA) which are exposed to free oxygen radicals and are specific for mitochondria. In the result of the mutations, single and double branching, abasic areas, base modifications and sugar damage may occur in Mt-DNA, or there may be cross-linking between DNA and protein (Cooke at al. 2003; Evans and Cooke 2004). These mutations cause mainly Alzheimer and Parkinson, many diseases originated from endocrine glands, brain, heart and liver diseases. In this review, the structure and genetics of Mt-DNA and diseases related to Mt-DNA and mechanisms of formation were discussed.
Keywords: Mitochondrial DNA, Free oxygen radicals, Mutation, Insertion, Deletion.

1. Introduction

Mitochondrion, the most important of the cytoplasmic organelles, was defined by Altmann in 1894. That mitochondrion whose structure and function were not yet known at that time had respiratory enzymes was demonstrated by Warburg in 1913 (Arias et al. 2017). Later studies have focused on the internal structure and components of mitochondria. The double membrane structure of mitochondria was shown by Chevremont and et al. by light microscopy in 1956. Mt-DNA was introduced in 1963 by Nass and et al. with the discovery of electron microscopy (Arias et al. 2017). This provided to be had detailed information about Mt-DNA and the structure of mitochondria.

2. Mitochondrial DNA (Mt-DNA)

The base sequence of human Mt-DNA was introduced in 1981 by Anderson and et al. (Arias et al. 2017). According to this, Mt-DNA is much smaller than the nucleus DNA (n-DNA) and a double helix enclosed circular shape (Sahakyan et al. 2017). The number of them is 2-6 depending on the size of the mitochondrion (Ngo et al. 2014). The molecular weight is $10x10^6$ Daltons, its length is approximately 5 millimicrons and contains 16569 base pairs (Sawyera et al. 2015). The genome is consecutive and does not contain an intron. Human Mt-DNA replicates independently from n-DNA. It contains 13 of 60 protein components of the electron transport chain and has 2 r-RNA molecules as 16-S and 12-S required for translation of these proteins, and introns encoding the 22 t-RNA molecule. In Mt-DNA, there are two chains, the heavy chain (H) rich in terms of guanine and the light chain (L) rich in terms of cytosine (Ngo et al. 2014). These chains replicate each other in opposite directions (Sawyera et al. 2015).

The genetic code of Mt-DNA is different from universal code. UGA which is a stop codon in universal code encodes the tryptophan amino acid in the genetic code of Mt-DNA. AUA codon encoding Leucine amino acid in the universal code encodes methionine amino acid in Mt-DNA. AGA and AGG codons encoding arginine in the universal code have function as a stop codon in Mt-DNA. In Mt-DNA, AUA and AUU codons are the start codons such as the AUG codon.

Table: Genetics codes.

CODON	UNIVERSAL KOD	MITOCHONDRIAL CODE
UGA	STOP	TRP
AUA	LEU	MET
CUA	LEU	LEU
AGA	ARG	STOP
AGG	ARG	STOP

2.1. Replication and Transcription of Mt-DNA

All enzymes necessary for replication and transcription of Mt-DNA are encoded by n-DNA (Sahakyan and et al. 2017). Replication of Mt-DNA is based on the Displacement-loop (D-loop) mechanism (Brown and et al. 1992). According to this, replication starts at the H chain origin of Mt-DNA, proceeds clockwise and completes at the L chain origin (Larysa et al. 2013). The D-loop region contains promoter regions of both chains and Conserved Sequence Box (CSB) regions with three conserved base sequences (Arias and et al. 2017; Sahakyan et al. 2017).

Because Mt-DNA is circular, event of replication occurs asynchronously and bi-directionally (Anderson and et al 1981). Transcription also occurs asynchronously and bi-directionally from the two chains (H and L) in the D-loop region as in replication (Larysa et al. 2013; Lagouge and Larsson 2013).

3. Mitochondrial Inheritance

3.1. Features of mitochondrial inheritance

Mitochondrial inheritance does not suit the Mendelian laws. When fertilization occurs, only DNA of the spermine is transferred into the egg, the tail part and the organelle remain outside. Because the sperm mitochondrion is located close to the tail, only mother's mitochondria are in the zygote. Therefore, the embryo takes all its organelles from the egg, consequently from its mother. In mammals, 99.99% of Mt-DNA comes from the mother (Doğan et al. 2017) and mutations of maternal Mt-DNA transfer to child from mother.

The main differences of Mt-DNA inheritance from n-DNA are:

a) Mt-DNA is semi-autonomous and endosymbiotic origin.

b) It shows maternal inheritance. While the sperm contains several hundred Mt-DNA, the egg contains hundreds of thousands of Mt-DNA. A small number of sperms entering the egg have little effect on the genotype of the Mt-DNA.

c) Even if there is heteroplasmic state in the mitochondria, the Mt-DNA genotype shifts to homoplasm. The heteroplasmic rate is important in diseases (Anderson et al. 1981).

d) Mt-DNA damages have differences in regard to organ and system. Systems with the highest ATP requirements (such as central nervous system) are the places where the most frequent damages are seen.

e) Mutation rate in Mt-DNA is 10 times higher than n-DNA. This is due to the fact that Mt-DNA is close to the internal membrane which is the main site of free radicals, does not have protective histones and its repair mechanism is limited (Munn 1974; Hyslop et al. 2016; Takemura et al. 2016).

3.2. The place and importance of mitochondrial heritage in daily life

The Mt-DNA genetics of every living creature is very similar to that of his mother. This is used to be determined his kinship relationship with the ancestors of his mother. Mt-DNA is referenced to be identified of the kinship relations of the societies, to be determined the origins of the species, and to be lightened the evolutionary process by being used variance analysis method (Larysa, et al.2013; Lagouge and Larsson 2013; Douglas 2015, Dogan et al. 2017). Besides all these properties, Mt-DNA is highly resistant to time and environmental conditions. For this reason, Mt-DNA analysis is performed when n-DNA analysis is not possible. The examination of teeth, hairs or bones remaining in high temperature, moisture or acid soil for a long time can be performed by Mt-DNA analysis (Ngo et al. 2014). Mt-DNA analysis can be used to assess many aspects of life such as genetic characteristics, diseases and kinship relationships that have existed centuries ago. By means of Mt-DNA analysis, it is possible to evaluate many topics such as the genetic characteristics, diseases and kinship relations of living creatures who lived centuries ago.

4. Mutations of DNA and Mitochondrial Diseases

Mutations happening in Mt-DNA in humans occur in the genes of cellular respiratory enzymes or in t-RNA genes and show maternal inheritance (Larysa et al. 2013; Lagouge and Larsson 2013). It causes many degenerative diseases in the brain, heart, liver and endocrine glands (Douglas et al. 2013; Hyslop et al. 2016; Takemura et al. 2016). Mt-DNA mutations are basically investigated into two titles: base exchange and deletion-insertion mutations.

4.1. Base exchange mutations

4.1.1. Missense mutations

Point mutations causing amino acid changes are called missense mutations. They lead to ophthalmologic and neurological diseases and show maternal inheritance (Newman et al. 1990; Lood et al. 2016). These mutations can be detected by Mt-DNA analysis both in prenatal and postnatal genetic tests (Sayıner and Kısmalı 2016). There are two phenotypes of them.

4.1.1.1. LHON (Lebers hereditary optic neuropaty)

It comes out at the nucleotide 11778 of Mt-DNA with the transition of Guanine → Adenine. In the result of this, the Arginine amino acid takes place of Histinin in the 4th subunit of the NADH dehydrogenase (Wallace 1997). LHON leads to bilateral visual loss with the death of the optic nerve (Itsara et al. 2014). Because it is carried by a mutant gene linked to X, it is four times more common in women than in men (Newman and Wallace 1990). Generally, age of its appearance is 27 years old. Other indications of maternal heredity are heart failure and behavioral disability (Wallace 1997).

4.1.1.2. NARP (Neurogenic muscle weakness ataxia and retinis pigmentosa)

It comes out at the nucleotide 8993 of ATPase-6 gene with the transition of Thymine → Guanine. In the result of this,

Arginine takes place of the leucine amino acid at the 156th subunit of the produced protein (Wallace 1997). Paralysis, deafness, muscle weakness, developmental disorders and deletions are seen in the disease having maternal inheritance (Rao et al. 2017).

4.1.2. Biogenesis mutations (Point mutations)

Usually, these mutations are the point mutations observed in the t-RNA genes of mitochondrion. It is characterized by mitochondrial myopathies and shows maternal inheritance.

4.1.2.1. MERRF (Myoclonic epilepsy and ragged-red fiber)

It comes out at the nucleotide 8344 of t-RNA with the transition of Adenine → Guanine. In the result of this, a decrease in the level of protein synthesized by the ribosome complex-1st and complex-3rd units are seen (Brown et al. 1992). In patients, functional disorders in the brain and muscles, myoclonic epilepsy, hearing loss, respiratory insufficiency, cardiomyopathy, renal dysfunction and height shortness are observed (Rao et al. 2017). The disease is proportional to the percentage of mutant mitochondria and age.

4.1.2.2. MELAS (Mitokondrial encephalomyopaty lactic acidosis and stroke-like episodes)

80% of the MELAS cases with Diabetes mellitus come out with transition of Adenine → Guanine at nucleotide 3243 affecting the dihydrouidine branch (Fetterman et al. 2016). It is a muscle disease characterized as mitochondrial myopathies with deficiency of complex-1 and oxidase enzymes involved in the electron transport chain. The most important symptoms are vomiting after a sudden headache, muscle weakness, shortness of height, vision defects and blindness (Rao et al. 2017).

4.1.2.3. MMC (Maternally inherited myopaty and cardiomyopathy)

The disease occurs with transition of Adenine → Guanine at nucleotide 3260 affecting the anticodon arm of t-RNA. MMC is characterized by cardiomyopathy and mitochondrial myopathy with ribosome complex-1 and 4 defects. It shows maternal inheritance and it is not related to age (Fetterman et al. 2016).

4.1.2.4. LIMM (Lethall infantile mitokondrial miyopaty)

It occurs with transition of Adenine → Guanine at nucleotides 15923 and 15924 of t-RNA (Douglas et al. 2013; Takemura et al. 2016). It causes cardiomyopathy and respiratory failure.

4.2. Deletion-insertion mutations

4.2.1. Deletions

Damage in to the nucleus DNA leads to Mt-DNA deletions. Delesions; mutation result Mt-DNA in both h and L replication origin points disappear status (Holt et al 1998). H and L deletions are associated with Pearson's syndrome, ocular myopathies, Choronic Progressive External Opthalmoplegia (CPEO) and Kearns Sayre Syndrome (KSS) (Hyslop et al. 2016). Deletions do not have familial heredity (Lood et al. 2016; Rao et al. 2017; Valdes and Goldring 2017).

4.2.1.1. Pearson syndrome

Pearson's syndrome appears with loss of all blood cells (pancytopenia) or loss of bone marrow precursor cells. It has been reported that 95% of the deletions observed in patients with Pearson syndrome are located between the origins of replication of H and L chains or on the right side of the origin of replication (Igor et al. 2016). It is a childhood disease that does not show familial heredity but is usually fatal (Fetterman et al. 2016; Ruggiero et al. 2017).

4.2.1.2. KSS (Kearns sayre sendromu)

KSS is an adult disease characterized by ophthalmoplegia, ptosis and mitochondrial myopathy. It causes hearing loss, muscle weakness and height shortness (Brown et al. 1992).

4.2.2. Insertions

Inserts are the opposite of deletions (Aksoy and Soydemir 2017). It causes duplications in Mt-DNA regions and does not show familial heredity (Paulton et al. 1989).

5. Discussion

Mutation in Mt-DNA in tissues with high ATP consumption in mammals increases proportionally with age (Barja 2002). This is due to the fact that free oxygen radicals, which are the result of cellular respiration, accumulate in the cell over time and cause oxidative damage (Burçak and Andiçan 2004). Depending on the oxidative damage, the mt-DNA protective and reparative proteins diminish or damage. This can lead to mutations, as well as accelerate cellular aging (Luft 1994; Burçak and Andiçan 2004). Therefore, mitochondria in which this process occurs play a key role in aging (Miquel et al. 1980). Studies that have been done so far have found that diseases that increase in frequency with aging such as physiological aging, premature aging symptoms, Alzheimer's disease, diabetes, heart failure, deafness, optic nerve degeneration, many progressive muscle diseases and cancer are related to the presence of dysfunctional mitochondria containing mutated DNA (Mecocci et al. 1993; Luft 1994; Lunec et al. 1994; Shimoda et al. 1994; Dandona et el. 1996; Wallace 1997; Farinati et al. 1998; Martin and Oshima 2000; Martinet et al. 2001; Burçak and Andiçan 2004). Similarly, although mutations that cause LHON disease usually occur in childhood, blindness in the result of disease is

seen in older ages (Wallace 1997). It has been reported that oxidative Mt-DNA damage is inversely associated with maximum life span and potential of maximum life span decrease with increasing of oxygen consumption (Wallace 1997; Burçak and Andiçan 2004).

6. Conclusion

Free oxygen radicals occur in the result of exposure of living organisms to environmental agents and oxygen respiratory happening in the cells. The most important targets of these radicals are mitochondria and Mt-DNA. While mitochondrial dysfunction results in decrease production of ATP energy, organ dysfunction and apoptosis, it causes mutations in Mt-DNA. It is impossible to eliminate the effects of free oxygen radicals, but it is possible to reduce this effect to minimum, or treat some of them by determining early the mutations that they cause. The Mt-DNA analysis method applied in missense mutants aims to be determined the level of free oxygen radicals in cells and to be identified the diseases that may be caused in advance. With this method, it is possible to detect and treat many diseases caused by mutations that have risk of seeing at future generations (Rao et al. 2017). The same method provides important clues in the early diagnosis of diseases caused by Mt-DNA mutations in infants with amniotic fluid analysis during pregnancy. This is important to be prevented infant and maternal deaths and to be provided early diagnosis and treatment of preventable diseases.

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