Available online at www.garmian.edu.krd

Passer Journal of Basic and Applied Sciences

Passer 7 (Issue 1) (2025) 179-191

Original Article

Mitochondrial DNA from Genotype to Phenotype Related to Maternally Inherited Syndromes

Sakar Ahmed Abdullah*[1]

[1]*Medical laboratory department, College of Health and Medical Technology, Sulaimani Polytechnic University, Kurdistan Region, Iraq.*

Received 06 October 2024; revised 29 December 2024;
accepted 01 April 2025; available online 04 May 2025

DOI: 10.24271/PSR.2025.482148.1769

ABSTRACT

Mitochondrial DNA (mtDNA) mutations cause maternally inherited diseases; the symptoms appear in late childhood or adulthood. The pathogenicity of the mtDNA differs among individuals within the same family due to the difference between mitochondrial phenotype and genotype modulated by heteroplasmy, which refers to the presence of both mutated and normal mtDNA within the cell.

Monoploidy and the lack of compensation alleles lead to a higher risk of mtDNA mutations than nuclear DNA. Point mutation and large-scale deletion disrupt mitochondrial function, such as oxidative phosphorylation, leading to syndromes like MELAS, Leigh syndrome, and Kearns-Sayre syndrome. They also underlined that heteroplasmy influences the severity of symptoms in offspring, often leaving mothers asymptomatic.

This study aims to determine the pathogenic role of mtDNA mutations, their contributions to maternally inherited syndromes, and their implications for genetic counselling and premarital testing. For this purpose, mtDNA mutations associated with maternally inherited syndromes are underlined, focusing on their impact on mitochondrial function and the phenotypic expression influenced by heteroplasmy. We collected data from existing research and databases, including MITOMAP.

Due to mitochondria's heteroplasmic nature, even if the mother is asymptomatic, premarital carrier testing and genetic counselling for mtDNA mutations should be considered necessary to ascertain the mother's genotype and identify thirteen disorders the offspring may inherit. However, the heterogeneity resulting from heteroplasmy and non-Mendelian inheritance patterns makes it challenging to predict the manifestation of a disease. More studies are required to enhance mtDNA disease diagnostic and therapeutic strategies.

Keywords: Autophagy, DNA methylation, Heteroplasmy, Kearns-Sayre syndrome, Leigh syndrome, Mitochondrial DNA.

1 Introduction

Mitochondrial DNA, called mitogenomes, is a circular double-stranded DNA molecule nearly 5 µm long and consists of 16.5 kb with a molecular mass of 10^7 Dalton. Each mitochondrion contains 2-10 copies of mtDNA, and each cell almost consists of thousands of mtDNA [1, 2].

All human single cells, except red blood cells, contain approximately 1000 to 10,000 mtDNA molecules. The number of mitochondria varies depending on the type of cell and its energy requirements. For instance, liver cells contain more mitochondria than other cell types [3]. The primary function of mtDNA is converting the food molecules to energy through adenosine triphosphate (ATP) by oxidative phosphorylation [4].

* Corresponding author
E-mail address sakar.ahmed@spu.edu.iq (Instructor).
Peer-reviewed under the responsibility of the University of Garmian.

1.1 Structure of mitochondria

The mtDNA double strands consist of heavy (guanine-rich) and light (cytosine-rich) strands. Unlike nDNA, the coding region of the mitochondrial genome lacks intron sequences, and there is only one noncoding region in the mitochondrial genome called the displacement loop (D loop) with 1.1 kb. The D loop consists of an origin of replication and two promoters, a light strand promoter (LSP) and a heavy strand promoter (HSP) [5, 6].

The mtDNA encodes for 37 genes; among these genes, two encode for 12S and 16S ribosomal RNA (rRNA), twenty-two genes encode for transfer RNA (tRNA), and thirteen genes encode for proteins involved in the respiratory chain for ATP production through oxidative phosphorylation. Among thirteen protein-coding genes, the IV complex is encoded by three genes,

the V complex is encoded by two genes and the III complex is encoded by one gene [7]. The names and functions of all 37 genes are listed in Table 1.

Table 1: Mitochondria genes and function.

No	Gene	Location	Function	Type
1	*MT-ND1*	Oxidative phosphorylation enzymes, Complex I	electron transport chain.	NADH dehydrogenase subunit 1
2	*MT-ND2*		Electron transport chain.	NADH dehydrogenase subunit 2
3	*MT-ND3*		Electron transport chain.	NADH dehydrogenase subunit 3
4	*MT-ND4*		Electron transport chain.	NADH dehydrogenase subunit 4
5	*MT-ND4L*		Electron transport chain.	NADH dehydrogenase subunit 4L
6	*MT-ND5*		Electron transport chain.	NADH dehydrogenase subunit 5
7	*MT-ND6*		Electron transport chain.	NADH dehydrogenase subunit 6
8	*MT-CYB*	Oxidative phosphorylation enzymes, Complex III	Encodes cytochrome b, a part of complex III in the electron transport chain	Cytochrome b
9	*MT-CO1*	Cytochrome *c* oxidase	Encodes cytochrome c oxidase I, a subunit of complex IV of the mitochondria	Cytochrome c oxidase I
10	*MT-CO2*		Encodes cytochrome c oxidase II, a subunit of complex IV, is also involved in electron transport and oxidative phosphorylation.	Cytochrome c oxidase II
11	*MT-CO3*		Encodes cytochrome c oxidase III, a subunit of complex IV, involved in oxidative phosphorylation and ATP synthesis.	Cytochrome c oxidase III
12	*MT-ATP6*	ATP Synthase	Encodes a subunit of ATP synthase	ATP Synthase subunit 6
13	*MT-ATP8*		Encodes subunit of ATP synthase	ATP Synthase subunit 8
14	*MT-TA*	tRNAs	Transfers alanine amino acid to ribosomes during mitochondrial protein synthesis	
15	*MT-TC*		Transfers cysteine amino acid	
16	*MT-TD*		Transfers aspartic acid amino acid	
17	*MT-TE*		Transfers glutamic acid amino acid	
18	*MT-TF*		Transfers phenylalanine amino acid	
19	*MT-TG*		Transfers glycine amino	
20	*MT-TH*		Transfers histidine amino acid	

No	Gene	Location	Function	Type
21	*MT-TI*		Transfer RNA (tRNA) called tRNA-Ile (isoleucine) within the mitochondria.	
22	*MT-TK*		Encodes the mitochondrial tRNA for lysine	Mitochondrial tRNA Lys
23	*MT-TL1*		Encodes the mitochondrial tRNA for leucine (UUR)	Mitochondrial tRNA Leu(UUR)
24	*MT-TL2*		Encodes the mitochondrial tRNA for leucine (CUN)	Mitochondrial tRNA Leu(CUN)
25	*MT-TM*		Transfers methionine amino acid to ribosomes during mitochondrial protein synthesis	
26	*MT-TN*		Transfers asparagine amino acid	
27	*MT-TP*		Transfers proline amino acid	
28	*MT-TQ*		Transfers glutamine amino acid	
29	*MT-TR*		Transfers arginine amino acid	Mitochondrial tRNAs for various amino acids
30	*MT-TS1*		Transfers serine amino acid	tRNA-Ser(UCN)
31	*MT-TS2*		Transfers serine amino acid	tRNA-Ser(AGY)
32	*MT-TT*		Transfers threonine amino acid	
33	*MT-TV*		Transfers valine amino acid	
34	*MT-TW*		Transfers tryptophan amino acid	
35	*MT-TY*		Transfers tyrosine amino acid	
36	*MT-RNR1*	Ribosomes	Encodes the mitochondrial 12S rRNA, which is involved in mitochondrial protein synthesis.	Mitochondrial 12S rRNA
37	*MT-RNR2*		Encodes the mitochondrial 16S rRNA, which is involved in mitochondrial protein synthesis.	Mitochondrial 16S rRNA

1.2 Replication of mtDNA

Mitochondria and their genome are semi-autonomous, making them divide and replicate independently of the nuclear division cycle. De novo mitochondrial mutations can occur during replication, leading to heteroplasmy [8].

During periods of high energy demand, the mitochondria grow and replicate. In contrast, when less energy is required, mitophagy destroys mitochondria or becomes inactive [9].

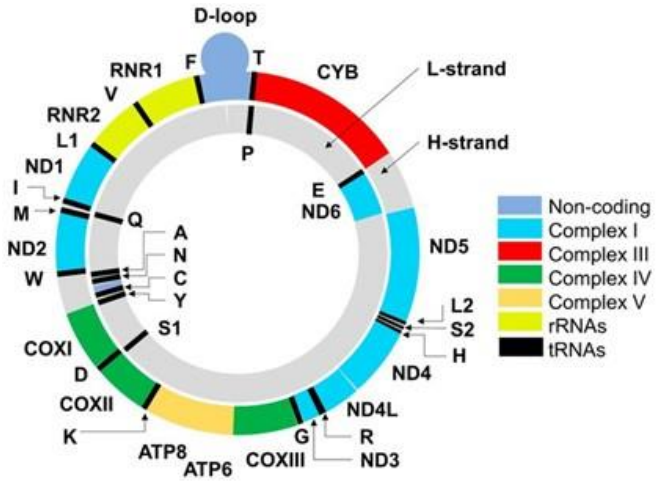
During cell division, mitochondria are randomly separated between the two daughter cells, each receiving half of the total mitochondria. After cell division, the new cells produced more copies of mitochondria through binary fission [10].

Mitochondrial DNA replication occurs in two ways, starting in the D-loop region. At first, replication of the heavy strand begins and forms a substantial part of the circular DNA. Then the light strand begins to replicate [11, 12], as shown in Figures 1[13].

1.3 Mitochondrial fusion

Mitochondrial fusion facilitates the mixing of the mitochondrial components in a cell. This fusion eliminates the mutant gene in heteroplasmic cells. As a consequence of this process, mutant

mtDNA inhibits reaching a crucial threshold level in the cell and protects the integrity of the mtDNA [14].



Figures 1: Replication site (D-loop), sites of genes, heavy and light stand of the mitochondria.

Some disorders occur due to defective proteins responsible for mitochondrial fusion, such as the dynamin-1-like (Drp1) protein, which is a GTPase that results in the loss of mtDNA wild-type. Also, defective mitochondrial proteins responsible for mtDNA segregation during mitotic division are a causative agent for *de novo* oocyst mutations. *De novo* mutation in germ cells causes a maternally inherited disorder that is asymptomatic in the mother; these de novo mutations increase with the mother's age [15].

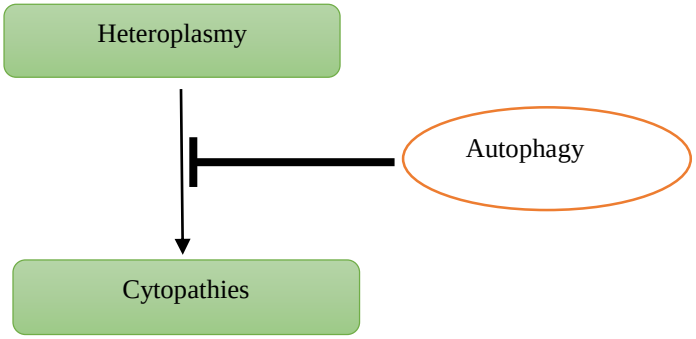


Figure 2: Autophagy eliminates the mutant mtDNA that makes mutation under the threshold level, and the disorder becomes asymptomatic.

1.4 Autophagy process

Autophagy is the intracellular repair mechanism for renewing cells through isolating, degrading, and delivering defective organelles and damaged or energy-deficient mitochondria to the lysosomal compartment. Alteration in the autophagy process causes abnormal mitochondria accumulation in cells, leading to mitochondrial-mediated cell death[16]. Figure 2 illustrates the effects of autophagy on eliminating cytopathies.

In the study by [17], when the number of mitochondria was measured by using mitochondrial marker enzymes, the result of the study showed that the fibroblast cells from MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) patients with A:G 3243 mutation in the tRNA and MERRF (myoclonic epilepsy and ragged-red fibres) patients with an A:G point mutation at nucleotide 8344 in the tRNA, the mutated cells were depleted compared to the control cells. This result indicated that the autophagy process or fusion occurred in the mutated cell to remove defective mitochondria and regulate the degradation of mitochondria, as shown in Figure 3 [18].

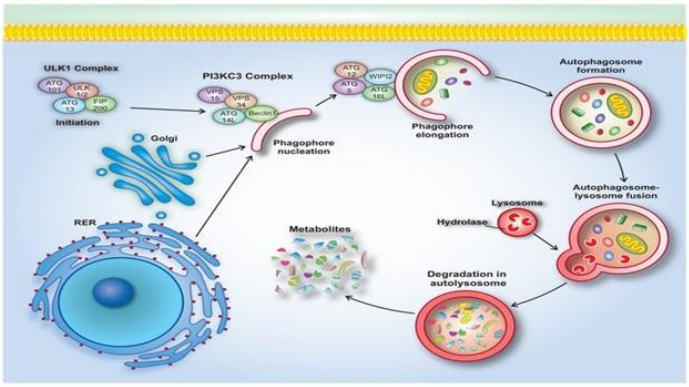


Figure 3: The mechanism of autophagy for elimination of mutant mitochondria.

1.5 Paternal mtDNA

Human mitochondrial DNA is predominantly maternally inherited. Sperm contains 50-75 mitochondria forming a sheath around the flagellar axoneme, providing adenosine triphosphate (ATP) for the axonemal movement. During fertilization, the sperm lose mitochondria, making offspring homozygous for maternal mtDNA. In contrast, the oocyte contains 100,000 copies of mtDNA, ensuring that the mitochondrial genome in the offspring is predominantly inherited from the mother [19, 20]. Nevertheless, a study has detected heterologous mtDNA from paternal and maternal sources in the muscle tissue, possibly due to the recombination of the paternal and maternal mitochondrial genomes [21].

1.6 DNA profiling

During DNA profiling, sometimes it is impossible to get a complete profile of the 20 regions of the short tandem repeats (STRs) of nDNA using DNA Index System CODIS software due to degraded samples. For this purpose, hypervariable segment 1 (HV1) and hypervariable segment 2 (HV2) regions of the mtDNA are used by forensic scientists due to the enormous copies of mtDNA in a cell. Since mtDNA is maternally inherited, mtDNA determines identities by comparing maternal mtDNA [22].

1.7 Mutations

According to the human mitochondrial genome database MITOMAP, about 260 mutations have been characterized [23]. These mutations include point mutations, duplications, insertions, and DNA rearrangements that cause large-scale deletions that remove one or more essential genes that can affect respiratory chain protein-coding genes and tRNA- or rRNA-coding genes [24].

Mutation can be a pathogenic mutation that causes various disorders or polymorphic variants that contribute to genetic diversity within the population; these mutations are typically maternally inherited or *de novo* mutations [25].

The mtDNA has a mutation rate 10–17 times higher than that of the nDNA [6] because the mtDNA replicates frequently; insufficient proofreading and the limited capacity of the repair mechanism make mtDNA more prone to damage, and there is increased oxidative damage produced by reactive oxygen species [26]. According to the MitoCarta 3.0 database, 1,136 human nDNA and mtDNA genes are responsible for mitochondrial function [27].

1.8 Maternally inherited mtDNA methylation

Epigenetics plays an important role in maternally inherited disorders; unlike nDNA, mtDNA lacks histone protein, so histone modification is absent, while mtDNA methylation is obvious. Cytosine methylation in mtDNA occurs through the mtDNA methyl transferase enzyme 1 (mtDNMT1) activity. The expression of the gene MtDNMT1 is controlled by oxidative stress. Alteration of mtDNMT1 expression directly affects the transcription of the tRNA gene, 12S rRNA gene, and D-loop gene[28, 29].

1.9 Mitochondrial cytopathies

Both inherited and sporadic mtDNA mutations cause various disorders known as mitochondrial cytopathies in high-energy-demand cells, such as those in the nervous and muscular systems [19].

The decline in mitochondrial function affects the nervous system, which causes developmental and mental disorders, migraines, stroke-like episodes, dementia, cramps, disturbance of thermoregulation, hearing disorders, and vision loss. In addition to muscles, the decline in mitochondrial function may also affect the nerves, resulting in muscle weakness and aches. In addition, defective mitochondria affect other organs, causing Cardiomyopathy, cardiac arrhythmias, liver failure, hypoglycemia, and atrophy of the kidney's proximal tubule, as well as endocrine problems like diabetes and exocrine issues due to pancreatic insufficiency[30, 31].

Females produce various oocysts with homoplasmic and heteroplasmic mtDNA (wild-type and mutant mtDNA). Mutant mtDNA is transmitted to offspring in different levels, ranging from low-level, intermediate-level, and high-level mtDNA mutations. During meiosis, the separation of mitochondria occurs randomly. That leads to a genetic bottleneck when females with heteroplasmic mtDNA mutations pass on High-level mtDNA mutation to the next generation, which may cause a rapid shift of mutant level in a single generation [32].

The offspring become more symptomatic of the disease, which becomes more clinically apparent once the number of affected mtDNA reaches a threshold of expression. Direct molecular diagnosis of genotype-phenotype is limited due to three mtDNA thresholds, including phenotypic, biochemical, and translational thresholds [5]. This phenomenon is called *de novo* mutations (DNMs), an important source of genetic variation in human evolution [33].

Defective mtDNA sometimes causes life-threatening diseases and increases the frequency of age-related disorders because mitochondria control several cell functions, such as oxidative phosphorylation, supply energy, intracellular signalling, centrosome homeostasis, apoptosis, cell development, differentiation, and proliferation [34].

1.10 Gene therapy

Gene therapy involves transferring nDNA from a mother with mutant mtDNA to a healthy mitochondrial cell from a different female to eliminate a maternally inherited mutation. However, ethical restrictions forbid this method regarding biological motherhood since the child receives genes from two women. The use of genetic engineering to produce offspring with free mtDNA syndrome is controversial and requires ethical approval [35].

Transgenic tRNAs were used in a study by [36] to improve mitochondrial translation and raise mitochondrial protein levels in people with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). Several techniques involve compensating the mutant genes, as shown in Table 2.

1.11 Diagnosis

Clinical signs of cytopathies may be rare due to mitophagy, mtDNA polyploidy, and heteroplasmy, which makes understanding the pathogenesis of mitochondrial disease more complicated than the nDNA [24]. The disorder's severity and risk depend on the tissue distribution and the number of inherited abnormal mtDNA [41].

In Leigh syndrome and neuropathy, ataxia, and retinitis pigmentosa syndrome (NARP), the mother is usually asymptomatic, while all offspring are at risk of inheriting the pathogenic variant.

Diagnosing mitochondrial syndrome is complicated because of the similarity of several syndromes of mitochondrial cytopathies, such as KSS, CPEO/PEO, and ophthalmoplegia-plus syndrome disorder. When symptoms appear at the age of 20, the symptom is diagnosed as Kearns–Sayre syndrome KSS, while in elderly persons, the same symptoms are diagnosed as an ophthalmoplegia-plus syndrome[42, 43]. The most common

disorder caused by mutant mtDNA is shown in Table 3 [6, 44, 45].

Table 2: Gene therapy methods used for treating mtDNA mutation and nDNA mutations that involve mitochondrial function.

Gene Therapy Approach	Description	Target	Method	Source
Mitochondrial gene therapy	Directly targets and modifies mtDNA within mitochondria.	Mutations in mtDNA	targeting mitochondrial zinc finger nucleases (mtZFNs) and transcription activator-like effector nucleases (TALENs) for editing mtDNA	[37]
Protein replacement therapy	Delivers functional mitochondrial proteins into cells to compensate for defective or missing proteins.	Defective mitochondrial proteins	Delivering viral vectors to express proteins in cells	[38]
Nuclear gene therapy	Targets and modifies nuclear DNA to correct gene defects that encode mitochondrial proteins.	Mutations in nDNA genes affecting mitochondrial function	Using CRISPR-Cas9 to edit nuclear genes and inserting corrected copies of nuclear genes into cells	[39]
RNA interference (RNAi)	It uses small interfering RNAs (siRNAs) to silence the expression of mutant genes or genes contributing to mitochondrial dysfunction.	Mutant genes or genes involved in mitochondrial dysfunction	Silencing mutant mtDNA, including oxidative stress genes	[40]

2. Materials and Methods

This study used review articles using Google Scholar, PubMed, and other academic search engines to determine mtDNA mutations associated with maternally inherited syndromes. For this purpose, several keywords were used in the search, such as mitochondrial DNA mutations, cytopathies, genetic counselling, maternally inherited syndromes, heteroplasmy, MELAS, Leigh syndrome, Kearns-Sayre syndrome, MERRF, and NARP.

In addition, the database MITOMAP (mitomap.org) is used to collect data, and it is a catalogue of human mtDNA variations and clinical syndromes. Besides the MitoCarta 3.0 database, for gathering information on nuclear and mitochondrial genes involved in mitochondrial function.

2.1. Inclusion Criteria

We considered clinical reports and case studies that detected the phenotypic effects on mitochondrial function, focusing on their roles in heteroplasmy and phenotypic variability.

2.2. Data Extraction and Analysis

Relevant information from the articles and databases, including types of mtDNA mutations, their functions, and clinical symptoms, was extracted. The role of heteroplasmy in phenotypic expression is also discussed. The impact of mtDNA on gene-encoding components of oxidative phosphorylation, tRNA, and rRNA was analyzed.

2.3. Focus Areas

The study focused on the impact of mtDNA mutations on mitochondrial function and the role of heteroplasmy in the phenotypic expression of mtDNA-related disorders. The importance of mtDNA mutations for genetic counselling and premarital testing, besides several general information like mtDNA replication, mitochondrial fusion, autophagy, paternal mtDNA inheritance, mtDNA profiling, and mtDNA methylation.

2.4 Epidemiological Data

Prevalence rates of mitochondrial disorders were listed from published epidemiological studies across different geographic regions to provide context for mutation frequency and syndrome occurrence.

Table 3: Materially inherited syndromes with the mutant gene and defective amino acid.

NO	Syndrome/Disease	Symptoms	Gene/complex	Mutation	Position of mutant nucleotide/amino acid
1.	**MELAS Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes**	Neurodegenerative disease causes Cardiomyopathy during childhood. The gradual death of neurons causes hearing loss, ptosis, epilepsy, and muscle fatigue [46].	*MT-TL1, tRNA*	m.3243A.G	DHU loop at Nucleotide 14, localized in the mitochondrial transcription termination factor mTERF binding site
				m.3256C.T	Nucleotide 25, localized in the region of transcription termination of the stem of DHU loop [47]
				m.3271T.C	Nucleotide 40, localized in the stem of the anticodon loop, wobbles.
			MT-ND3, complex 1	m.10197G.A	Amino acid (codon) 47 protein impact Alanine (A) → Threonine (T)
			MT-ND5, complex 1	m.13042A.T	a substitution of Alanine (A)-Threonine (T) at 236:
2.	**CPEO chronic progressive external ophthalmoplegia syndrome**	The disease appears in childhood and causes visual muscle myopathy and ptosis, pigmentary degeneration of the retina (retinitis pigmentosa), dementia, and cerebral ataxia [42].	*MT-TV*	m.1658T.C	Nucleotide 61, localized in the stem of T-loop
			MT-TL2	m.12315G.A	Nucleotide 52, localized in the stem of T-loop
3.	**KSS Kearns–Sayre syndrome**	cardiac arrhythmia, proximal muscle weakness, retinopathy, and ataxia [48, 49].	A large deletion of the mitochondrial genome at positions from 8,469 to 13,447		
4.	**MIDD Maternally inherited diabetes and deafness.**	Cause hearing loss and diabetes type 1 and 2 during adulthood, Cardiomyopathy, pigments, ptosis, myopathy, retinitis, and psychoneurological symptoms. [50, 51]	A large deletion of the mitochondrial genome at positions from 4,398 to 14,822		
			MT-TL1 tRNA	m.3243A.G	Nucleotide 14, localized in the mTERF binding site
			MT-ND1, complex 1	m.3421A.G	Amino acid 39: a substitution of V.I*
5.	**MERRF myoclonic epilepsy is associated with ragged red fibres**	Symptoms include Myoclonus, seizures, cerebellar ataxia, dementia, Cardiomyopathy, cardiac arrhythmia, neuropathies, optic atrophy, and hearing loss [52].	*MT-TK*	m.8344A.G	Nucleotide 55, localized in the T-loop [53]
				m.8356T.C	Nucleotide 65, localized in the stem of T-loop.
				m.8363G.A	Nucleotide 72, localized in the stem of the acceptor.
			MT-ND5, complex 1	m.13042A.T	Amino acid 236: a substitution of A.T* CoQ reductase and cytochrome C-oxidase (COX) in the mitochondrial genome
6.	**NIDDM noninsulin-dependent diabetes mellitus**	A metabolic disorder characterized by insulin resistance and progressive beta-cell dysfunction.	*MT-RNR2*	m.3200T.C	Nucleotide 1529
			MT-TL1	m.3242G.A	Nucleotide 13, localized in the region of transcription termination of DHU loop (dihydrouridine arm of transfer RNA)
				m.3252A.G	Nucleotide 23 is localized in the region of transcription termination of the DHU loop.
				m.3264T.C	Nucleotide 33, localized in the anticodon loop.
			MT-ND1, complex 1	m.3316G.A	Amino acid 4: a substitution of A.T*
				m.3394T.C	Amino acid 30: a substitution of Y.H*
			MT-ND6, complex 1	m.14577T.C	Reverse direction of synthesis: a substitution of I.V*
			MT-ND2, complex 1	m.4833A.G	Amino acid 122: a substitution of A.T*
7.	**LHON**	Causes a sudden, painless, complete loss of central vision due to optic nerve atrophy from	*MT-ND1*, complex 1	m.3460G.A	Amino acid 52: a substitution of A.T*
			MT-CO3, complex 4	m.9804G.A	Amino acid 200: a substitution of A.T*

	Leber hereditary optic neuropathy	age 15 to 35 years due to increased oxidative stress in the nerve endings of cells [54]	*MT-ND4*, complex 1	m.11778G.A	Amino acid 340: a substitution of R.H*
			MT-ND6, complex 1	m.14459G.A	Reverse direction of synthesis. Amino acid 72: a substitution of A.V*
				m.14484A.G	Reverse direction of synthesis. Amino acid 64: a substitution of M.V*
			MT-CYTB, complex 3	m.15257G.A	Amino acid 171: a substitution of D.N*
8.	**MILS Maternally inherited Leigh syndrome.**	Neuroradiological evidence in the child causes movement disorders and peripheral neuropathy, hypotonia, spasticity, and cerebellar ataxia [41, 55].	*MT-ATP6*, complex 5	m.8993T.C	Amino acid 156: a substitution of L.P* [56, 57].
			MT-ATP6	m. 9176T.G	
			MT-ATP6, complex 5	m.8993T.G	Amino acid 156: a substitution of L.R*
			MT-ND3, complex 1	m.10197G.A	Amino acid 47: a substitution of A.T*
			MT-ND5, complex 1	m.13513G.A	Amino acid 393: a substitution of D.N*
9.	**Maternally inherited aminoglycoside-induced deafness**	Hearing Loss, Vestibular Dysfunction. In some cases, Hearing impairment and deafness increase with age [58].	*MT-RNR1*	m.1095T.C	Nucleotide 448
				m.1494C.T	Nucleotide 847
				m.1555A.G	Nucleotide 908 in the 12S rRNA
				m.961ins/del C	Nucleotide 314, duplication/deletion C
10.	**NARP Neuropathy, Ataxia, and Retinitis Pigmentosa**	Muscle weakness, sensory neuropathy, ataxia, Cardiomyopathy, developmental delay, learning problems, and retina degeneration. [59].	*MT-ATP6*, complex 5	m.8993T.G	Amino acid 156: a substitution of L.R* [44]
			MT-ATP6, complex 5	m.8993T.C	Amino acid 156: a substitution of L.P* [59]
			MT-RNR1	m.1541G.A	Nucleotide 894
11.	**Maternally inherited Cardiomyopathy and encephalomyopathy.**	Cause defect in coenzyme Q10 biosynthesis, Encephalopathy-hypertrophic cardiomyopathy-renal tubular disease syndrome causes neonatal lactic acidosis, tonus disorder, seizures and global developmental delay.	*MT-TV*	m.1634C.T	Nucleotide 35, localized in the anticodon
			MT-TL1	m.3243A.G	DHU nucleotide 14, localized in the mTERF binding site
				m.3260A.G	Nucleotide 29, localized in the stem of the anticodon loop.
			MT-TI	m.4269A.G	Nucleotide 7, localized in the stem of the acceptor
			MT-CO2, complex 4	m.7587T.C	Amino acid 1: a substitution of M.T*
			MT-TK	m.8296A.G	Nucleotide 2, localized in the stem of the acceptor
				m.8348A.G	Nucleotide 59, localized in the stem of T-loop
				m.8363G.A	Nucleotide 72, localized in the stem of the acceptor.
			MT-CO3, complex 4	m.9957T.C	Amino acid 1: a substitution of F.L*
			MT-TG	m.9997T.C	Nucleotide 7, localized in the stem of the acceptor
			MT-TH	m.12192G.A	Nucleotide 59, localized in the stem of T-loop
			MT-TL2	m.12297C.T	Nucleotide 33, localized in the anticodon loop
			MT-ND6, complex 1	m.14484A.G	Reverse direction of synthesis. Amino acid 64: a substitution of M.V*
			MT-CYTB, complex 3	m.15059G.A	Amino acid 105: a substitution of G.R*
12.	**Pearson syndrome PS**	sideroblastic anaemia, pancreatic insufficiency impairs the heart, kidneys, liver, eyes, and nervous system. Often fatal in infancy [45].			**large-scale deletions in mitochondrial DNA**
13.	**MIEH Maternally inherited essential hypertension**	Hypertension, hearing loss, diabetes, and Renal Dysfunction [60]	*MT-TM gene*	m.4467C.A	It affects the tRNA for methionine

2.5. Ethical Considerations

Ethical implications surrounding genetic testing and counselling for mtDNA disorders were reviewed, highlighting the challenges in predictive diagnostics due to non-Mendelian inheritance patterns.

2.6. Limitations

This study is based on a review of articles and databases. It does not involve primary data collection or experimental research. Heteroplasmy makes predicting the exact mutation that causes the disorder challenging, and there is a conflict between articles. Further research is important to reveal the exact role of mutation.

3 Results

This study identified several mitochondrial DNA (mtDNA) mutations, including point mutations, large-scale deletions, and duplications that cause thirteen maternally inherited syndromes, such as MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes), Leigh Syndrome, Kearns-Sayre Syndrome (KSS), and Myoclonic Epilepsy with Ragged Red Fibers (MERRF).

These mutations are often asymptomatic in mothers, while offspring have severe clinical symptoms due to the random segregation of mutated mtDNA.

Our review found that mutations such as m.3243A>G in MELAS and m.8344A>G in MERRF display varying phenotypic disorders.

Epidemiological data showed differences in prevalence across geographic regions. For example, MELAS prevalence ranged from 0.001% in Japan to 0.00236% in Australia. Global estimates put the incidence of KSS at 1-3 per 100,000. However, maternally inherited diabetes and deafness (MIDD) prevalence was up to 1% globally, as shown in Table 4.

Mutations in genes encoding oxidative phosphorylation, such as MT-ND1 and MT-ATP6, impair energy production, leading to multisystemic disorders. Syndromes like Leigh syndrome were linked to mutations like m.8993T>G in the MT-ATP6 gene that affect ATP synthesis. Clinical symptoms appeared only after a critical threshold of mutated mtDNA was reached in tissues.

A review of multiple studies indicated regional differences in syndrome occurrence, possibly influenced by population genetics and environmental factors.

Table 4: Estimated prevalence of the mitochondria inherited syndrome in different countries.

Syndrome	Country/Region	Estimated Prevalence	Source
MELAS Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes	North East England	0.001.41%	[61]
	Sweden	0.002%	[61]
	Finland	0.0018.4%	[61]
	Australia	0.00236%	[61]
	Canada	0.002.51%	[62]
	Japan	0.000.18%	[63]
CPEO chronic progressive external ophthalmoplegia syndrome	United Kingdom	0.00339%	[64]
	Hong Kong	0.00102%	[65]
	United Kingdom	Estimated 1 in 30,000 (0.0033%)	[64]
	Worldwide	Incidence estimated at 1-2 per 100,000 (0.001-0.002%)	[66]
KSS Kearns–Sayre syndrome	General Estimate	0.001–0.003%	
	Worldwide	Estimated 1-3 per 100,000 (0.001-0.003%)	[67]
	Europe	Estimated 1-3 per 100,000 (0.001-0.003%)	[68]
Maternally inherited diabetes and deafness	Europe	0.5%–2.8%	[69]
	Cyprus	Approximately 0.5%–2.8%	[70]
	Global Estimate	Up to 1%	[71]

myoclonic epilepsy associated with ragged red fibers	Northern Europe	Approximately 1 in 400,000	[72]
	Northern Finland	0–1.5	[73]
	Northern England	0.39	[73]
	Western Sweden	0–0.25	[73]
	Northeast England	0.7	[73]
	Hong Kong	1.02	[65]
	Global Estimate	Less than 1 in 100,000	[73]
noninsulin-dependent diabetes mellitus	Global	8.5% (adults aged 18+)	International Diabetes Federation. IDF Diabetes Atlas
	China	12.8% (adults)	[74]
	India	8.9% (adults)	[75]
	United States	11.3% (adults)	[76]
	Europe	Varies by country, generally between 6-10%	[77]
Leber hereditary optic neuropathy	Europe	1 in 30,000 to 1 in 54,000	[78]
	Finland	1 in 50,000	[79]
	Denmark	1 in 54,000	[78]
	Australia	1 in 68,000	[78]
	Japan	1 in 50,649	[78]
	United States	Approximately 1 in 50,000	[80]
	Global Estimate	Approximately 1 in 50,000	[78]
Maternally inherited Leigh syndrome.	Portugal	Approximately 1 in 25,000 live births	[81]
	China	Approximately 1 in 100,000 children	[82]
Maternally inherited aminoglycoside-induced deafness	China	0.5 - 1.5%, much higher in some specific ethnic groups	
	Europe	Lower prevalence compared to Asian populations (generally <0.1%)	[83]
Maternally inherited Cardiomyopathy and encephalomyopathy	Worldwide	Estimated 1 in 40,000 to 1 in 100,000 (0.0025% to 0.001%)	[84]
	Europe	Similar prevalence to global estimates	[85]
	North America	likely similar to global estimates	[86]
Pearson syndrome PS	Worldwide	Estimated 1 in 1,000,000 (0.0001%)	
	Italy	1 case/million newborns	[87]
	Generally	Less than 200 cases have been reported worldwide	[88]

4 Discussion

This study identifies mtDNA mutations contributing to thirteen maternally inherited syndromes, including MELAS, Leigh syndrome, and Kearns-Sayre syndrome. mtDNA is heteroplasmic and characterized by the random distribution of mutated and wild-type DNA among cells, impacting the phenotypic expression of these disorders. Due to this variability, asymptomatic mothers transmit severe symptoms to offspring. These phenomena make diagnosing and predicting these conditions challenging.

mtDNA mutation in m.3243A>G that causes MELAS and m.8344A>G that contribute with MERRF mutations indicates the heteroplasmy effect on clinical entity.

Oxidative phosphorylation defects such as in (MT-ND1 and MT-ATP6) lead to the inability to produce energy correlated with multisystem dysfunctions. The research also implicated the heterogeneous prevalence of syndromes within regions that environmental factors may trigger. Variations in incidence, for example, MELAS, range from 0.001% in Japan to 0.00236% in Australia, indicating the need for population-specific studies.

The findings indicate the importance of genetic counselling and premarital testing for decreasing the risk of mtDNA-associated syndromes that can help identify carriers. However, the non-Mendelian inheritance patterns and the influence of heteroplasmy complicate predictive diagnostics. Current limitations in understanding genotype-phenotype correlations need further research to develop reliable diagnostic tools and therapeutic strategies.

Several techniques, such as gene therapy and protein replacement therapies, are new treatments for compensating for the mtDNA mutations. However, ethical issues and technical challenges must be considered.

Future studies need to explore the mechanisms of heteroplasmy, enhance diagnostic methods, and investigate therapeutic approaches to improve the quality of life for affected individuals. The continued integration of epidemiological data, advanced molecular techniques, and patient-centred approaches will be pivotal in managing mtDNA disorders' clinical and genetic effects.

Conclusion

MtDNA mutations are critical in inherited syndromes, the phenotype affected by heteroplasmy. The variability makes diagnosis and prediction of the syndrome challenging.

The mitochondrial genome exhibits more evidence of mutation than nDNA due to impaired DNA repair mechanisms, and the presence of monoallelic mutations in addition to tissue-specific phenotypes makes prediction difficult.

Genetic counselling is crucial in families with a history; however, prediction is challenging due to the random segregation of mtDNA during mitosis, non-Mendelian inheritance patterns, and the threshold for symptoms to appear.

Future efforts should prioritize improving diagnostic techniques, conducting population-specific research, and optimizing therapeutic strategies like gene editing and protein replacement therapies. Gaining deeper insights into the monoallelic expression of mtDNA mutations and its role in disease progression will enhance our capacity to tackle these challenges. By combining ethical considerations with innovative methodologies, researchers can advance the diagnosis, prevention, and treatment of mtDNA-related disorders, ultimately improving outcomes for individuals and their families.

Table of Symbols

Symbol	Definition
A	Alanine
D	Aspartic Acid
F	Phenylalanine
G	Glycine
H	Histidine
I	Isoleucine
L	Leucine
M	Methionine
N	Asparagine
P	Proline
R	Arginine
T	Threonine
V	Valine
Y	Tyrosine

Author Contribution

I became interested in maternally inherited syndromes, which inspired me to write this article. I undertook the task of collecting all known mitochondrial mutations that are transmitted from mother to offspring. Although this required significant effort and dedication, I was committed to completing the work independently.

Acknowledgement

I want to express my special thanks to all who helped throughout this work.

References

[1] Filograna, R., Mennuni M., Alsina, D. & Larsson, N. G. Mitochondrial DNA copy number in human disease: the more the better? *FEBS lett* **595**, 976-1002, (2021).
[2] Zhang, Y., Qu, Y., Gao, K., Yang Q., Shi B., Hou P., et al. High copy number of mitochondrial DNA (mtDNA) predicts good prognosis in glioma patients. *Am J Cancer Res* **5**, 1207, (2015).

[3] Lareau C. A., Ludwig L. S., Muus C., Gohil S. H., Zhao T., Chiang Z., et al. Massively parallel single-cell mitochondrial DNA genotyping and chromatin profiling. *Nat. Biotechnol* **39**, 451-461, (2021).
[4] Giles, R. E., Blanc, H., Cann, H. M.& Wallace, D. C. Maternal inheritance of human mitochondrial DNA. *Proc. Natl. Acad. Sci* **77**, 6715-6719, (1980).
[5] Craven, L., Alston, C. L., Taylor, R. W.& Turnbull, D. M. Recent advances in mitochondrial disease. *Annu. Rev Genomics Hum Genet* **18**, 257-275, (2017).
[6] Ryzhkova, A. I., Sazonova, M. A., Sinyov, V. V., Galitsyna, E. V., Chicheva, M. M., Melnichenko. Mitochondrial diseases caused by mtDNA mutations: a mini-review. *Ther Clin Risk Manag* **14**, 1933, (2018).
[7] Yarham, J. W., Elson, J. L., Blakely, E. L., McFarland, R.& Taylor, R. W. Mitochondrial tRNA mutations and disease. *Wiley Interdiscip Rev RNA* **1**, 304-324, (2010).
[8] Hu G.-B. Whole cell cryo-electron tomography suggests mitochondria divide by budding. *Microsc. Microanal*, **20**, 1180, (2014)
[9] Seo A. Y., Joseph A.-M., Dutta D., Hwang J. C., Aris J. P.& Leeuwenburgh C. New insights into the role of mitochondria in aging: mitochondrial dynamics and more. *J Cell Sci* **123**, 2533-2542, (2010).
[10] Lewis, S. C., Uchiyama, L. F.& Nunnari, J. ER-mitochondria contacts couple mtDNA synthesis with mitochondrial division in human cells. *Sci* **353**, aaf5549, (2016).
[11] Doda, J. N., Wright, C. T.& Clayton, D. A. Elongation of displacement-loop strands in human and mouse mitochondrial DNA is arrested near specific template sequences. *Proc Natl Acad Sci* 78, 6116-6120, (1981).
[12] Fish, J., Raule, N.& Attardi, G. Discovery of a major D-loop replication origin reveals two modes of human mtDNA synthesis. *Sci* **306**, 2098-2101, (2004).
[13] Buneeva, O., Fedchenko, V., Kopylov, A.& Medvedev, A. Mitochondrial dysfunction in Parkinson's disease: focus on mitochondrial DNA. *Biomedicines* **8**, 591, (2020).
[14] Chen, H.& Chan, D. C. Mitochondrial dynamics–fusion, fission, movement, and mitophagy–in neurodegenerative diseases. *Hum Mol Genet* **18**, R169-R176, (2009)
[15] Bogenhagen, D. F. Does mtDNA nucleoid organization impact aging? *Exp Gerontol* **45**, 473-477, (2010).
[16] Yorimitsu, T.& Klionsky, D. J. Autophagy: molecular machinery for self-eating. *Cell Dea Differ* **12**, 1542-1552, (2005).
[17] JAMES, A. M., WEI, Y.-H., PANG, C.-Y.& MURPHY, M. P. Altered mitochondrial function in fibroblasts containing MELAS or MERRF mitochondrial DNA mutations. *Biochem J* **318**, 401-407, (1996).
[18] Ahmadi F., Mohammadi, P., Valipour, E., Pournaghi, P., Kiani, S.& Mansouri, K. Autophagy: A challengeable paradox in cancer treatment. *Cancer Med* **12**, 11542-11569, (2023).
[19] Ankel-Simons, F.& Cummins, J. M. Misconceptions about mitochondria and mammalian fertilization: implications for theories on human evolution. *Proc Natl Acad Sci* **93**, 13859-13863, (1996).
[20] Ladoukakis, E.& Eyre, -Walker A. Evolutionary genetics: direct evidence of recombination in human mitochondrial DNA. *Nat Publ Group* **10**, 102-108, (2004).
[21] Kraytsberg, Y., Schwartz, M., Brown, T. A., Ebralidse, K., Kunz, W. S., Clayton. Recombination of human mitochondrial DNA. *Sci* **304**, 981-981, (2004).
[22] Kashyap, V., Sitalaximi, T., Chattopadhyay, P.& Trivedi R. DNA profiling technologies in forensic analysis. *Int J Hum Genet* **4**, 11-30, (2004).
[23] Lott, M. T., Leipzig, J. N., Derbeneva, O., Xie, H. M., Chalkia, D., Sarmady, M. mtDNA variation and analysis using MITOMAP and MITOMASTER. *Curr Protoc Bioinform* **44**, 21-21, (2013).
[24] Chinnery, P. F., Elliott, H. R., Hudson, G., Samuels, D. C.& Relton, C. L. Epigenetics, epidemiology and mitochondrial DNA diseases. *Int J Epidemiol* **41**, 177-187, (2012).
[25] Sallevelt, S. C., de Die-Smulders, C. E., Hendrickx, A. T., Hellebrekers, D. M., de Coo I. F., Alston. De novo mtDNA point mutations are common and have a low recurrence risk. *J Med Genet* **54**, 73-83, (2017).
[26] Chinnery, P. F. Mitochondrial disorders overview. Gene Reviews: University of Washington, Seattle; (2014).
[27] Rath, S., Sharma, R., Gupta, R., Ast, T., Chan, C., Durham, T. J., et al. MitoCarta3. 0: an updated mitochondrial proteome now with sub-organelle localization and pathway annotations. *Nucleic Acids Res* **49**, 1541-1547, (2021).
[28] Bellizzi, D., D'Aquila, P., Giordano, M., Montesanto, A.& Passarino, G. Global DNA methylation levels are modulated by mitochondrial DNA variants. *Epigenomics* **4**, 17-27, (2012).
[29] Iacobazzi, V., Castegna, A., Infantino V.& Andria G. Mitochondrial DNA methylation as a next-generation biomarker and diagnostic tool. *Mol Genet Metab* **110**, 25-34, (2013).
[30] Ballinger, S. W., Shoffner, J. M., Hedaya, E. V., Trounce, I., Polak, M. A., Koontz, D. A., et al. Maternally transmitted diabetes and deafness associated with a 10.4 kb mitochondrial DNA deletion. *Nat Genet* **1**, 11-15, (1992).
[31] Finsterer, J. Treatment of central nervous system manifestations in mitochondrial disorders. *Eur. J. Neurol* **18**, 28-38, (2011).
[32] Wai, T., Teoli D.& Shoubridge, E. A. The mitochondrial DNA genetic bottleneck results from replication of a subpopulation of genomes. *Nat Genet*, **40** 1484-1488, (2008).
[33] Kessler, M. D., Loesch, D. P., Perry, J. A., Heard-Costa, N. L., Cade B. E., Wang, H., et al. De novo mutations across 1,465 diverse genomes reveal novel mutational insights and reductions in the Amish founder population. *BioRxiv* 553214, (2019).
[34] Donthamsetty, S., Brahmbhatt, M., Pannu, V., Rida, P., Ramarathinam, S., Ogden A., et al. Mitochondrial genome regulates mitotic fidelity by maintaining centrosomal homeostasis. *Cell cycle* **13**, 2056-2255, (2014).
[35] Hamzelou, J. Exclusive: World's rst baby born with new "3 parent" technique. (2016).
[36] Karicheva, O. Z., Kolesnikova, O. A., Schirtz, T., Vysokikh, M. Y., Mager-Heckel, A.-M., Lombès A., et al. Correction of the consequences of mitochondrial 3243A> G mutation in the MT-TL1 gene causing the MELAS syndrome by tRNA import into mitochondria. *Nucleic acids Res* **39**, 8173-8186, (2011).
[37] Di Donfrancesco, A., Massaro, G., Di Meo I., Tiranti, V., Bottani, E.& Brunetti, D. Gene therapy for mitochondrial diseases: Current status and future perspective. *Pharmac*, **14**, 1287, (2022).
[38] Faria, R., Boisguérin, P., Sousa, Â.& Costa, D. Delivery systems for mitochondrial gene therapy: a review. *Pharmac*, **15**, 572, (2023).
[39] Prasuhn, J.& Brüggemann, N. Gene therapeutic approaches for the treatment of mitochondrial dysfunction in parkinson's disease. *Genes* **12**, 1840, (2021).
[40] Soldatov, V., V Kubekina, M., Yu Skorkina, M., E Belykh, A., V Egorova, T., V Korokin, M., et al. Current advances in gene therapy of mitochondrial diseases. *J Transl Med* **20**, 1-23, (2022).
[41] Thorburn, D. R., Rahman, J.& Rahman, S. Mitochondrial DNA-associated Leigh syndrome and NARP. Gene Reviews: University of Washington, Seattle; 2017.
[42] Schmiedel, J., Jackson, S., Schäfer, J.& Reichmann, H. Mitochondrial cytopathies. *J Neurol* **250**, 267-277, (2003).
[43] Schon, E. A., DiMauro, S.& Hirano M. Human mitochondrial DNA: roles of inherited and somatic mutations. *Nat Rev Genet* **13**, 878-890, (2012).
[44] Lopez-Gallardo, E., Solano, A., Herrero-Martin, M., Martinez-Romero, I., Castano-Perez M., Andreu A., et al. NARP syndrome in a patient harbouring an insertion in the MT-ATP6 gene that results in a truncated protein. *J Med Genet* **46**, 64-67, (2009).
[45] Tumino, M., Meli, C., Farruggia, P., La Spina, M., Faraci, M., Castana, C., et al. Clinical manifestations and management of four children with Pearson syndrome. *Am J Med Genet A* **155**, 3063-3066, (2011).
[46] El-Hattab, A. W., Adesina A. M., Jones J.& Scaglia F. MELAS syndrome: Clinical manifestations, pathogenesis, and treatment options. *Mol Genet Metab A* **116**, 4-12, (2015).
[47] EAlmannai, M., Alfadhel, M., & El-Hattab, A. W. Carnitine Inborn Errors of Metabolism. *Molecules* **24**(18), 3251. https://doi.org/10.3390/molecules24183251 (2019).
[48] Moraes, C. T., DiMauro S., Zeviani M., Lombes A., Shanske S., Miranda A. F., et al. Mitochondrial DNA deletions in progressive external ophthalmoplegia and Kearns-Sayre syndrome. *N Engl J Med* **320**, 1293-1299, (1989).
[49] Zeviani, M., Moraes, C. T., DiMauro, S., Nakase H., Bonilla E., Schon E., et al. Deletions of mitochondrial DNA in Kearns-Sayre syndrome. *Neurology* **38**, 1339-1339, (1988).
[50] Murphy, R., Turnbull, D., Walker M.& Hattersley A. Clinical features, diagnosis and management of maternally inherited diabetes and deafness (MIDD) associated with the 3243A> G mitochondrial point mutation. *Diabet Med* **25**, 383-399, (2008).
[51] Vanden, Ouweland, J., Lemkes, H., Gerbitz K. D.& Maassen J. Maternally inherited diabetes and deafness (MIDD): a distinct subtype of diabetes associated with a mitochondrial tRNALeu (UUR) gene point mutation. *Muscle & Nerve. J of the Amer Asso of Electrod Med* **18**, S124-S130, (1995).

[52] Boulet, L., Karpati G.& Shoubridge, E. Distribution and threshold expression of the tRNA (Lys) mutation in skeletal muscle of patients with myoclonic epilepsy and ragged-red fibers (MERRF). *Am J Hum Genet* **51**, 1187, (1992).
[53] Dela, Mata, Garrido-Maraver J., Cotán D., Cordero M. D., Oropesa-Ávila M., Izquierdo L. G., et al. Recovery of MERRF fibroblasts and cybrids pathophysiology by Coenzyme Q 10. *Neurotherap* **9**, 446-463, (2012).
[54. Hudson, G., Carelli, V., Spruijt, L., Gerards, M., Mowbray, C., Achilli, A., et al. Clinical expression of Leber hereditary optic neuropathy is affected by the mitochondrial DNA–haplogroup background. *Am J Hum Genet* **81**, 228-233, (2007).
[55] Kucharczyk, R., Salin, B.& di Rago, J.-P. Introducing the human Leigh syndrome mutation T9176G into Saccharomyces cerevisiae mitochondrial DNA leads to severe defects in the incorporation of Atp6p into the ATP synthase and in the mitochondrial morphology. *Hum Mol Genet* **18**, 2889-2898, (2009).
[56] Benit, P., Slama, A., Cartault, F., Giurgea I., Chretien D., Lebon S., et al. Mutant NDUFS3 subunit of mitochondrial complex I cause Leigh syndrome. *J Med Genet* **41**, 14-17, (2004).
[57] de Vries, D., van Engelen, B. G., Gabreëls, F. J., Ruitenbeek, W.& van Oost, B. A. A second missense mutation in the mitochondrial ATPase 6 gene in Leigh's syndrome. *Ann Neurol*, **34**, 410-412, (1993).
[58] Usami, S.-i., Abe S., Akita, J., Namba, A., Shinkawa, H., Ishii, M., et al. Prevalence of mitochondrial gene mutations among hearing impaired patients. *J Med Genet* **37**, 38-40, (2000).
[59] Rawle, M.& Larner, A. NARP Syndrome: A 20-YearFollow-Up. *Neurol* **5**, 204-207, (2013).
[60] Liu, Y., Li, Y., Zhu, C., Tian, L., Guan, M.& Chen, Y. Mitochondrial biogenesis dysfunction and metabolic dysfunction from a novel mitochondrial tRNA Met 4467 C> A mutation in a Han Chinese family with maternally inherited hypertension. *Sci Rep* **7**, 1-11, (2017).
[61] Fan, H.-C., Lee, H.-F., Yue, C.-T.& Chi C.-S. Clinical characteristics of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes. *Life* **11**, 1111, (2021).
[62] Buajitti, E., Rosella, L. C., Zabzuni, E., Young, L. T.& Andreazza, A. C. Prevalence and health care costs of mitochondrial disease in Ontario, Canada: a population-based cohort study. *PLoS One* **17**, e0265744, (2022).
[63] Yatsuga, S., Povalko, N., Nishioka, J., Katayama, K., Kakimoto, N., Matsuishi, T., et al. MELAS: a nationwide prospective cohort study of 96 patients in Japan. *Biochim. Biophys Acta Gen Subj* **1820**, 619-624, (2012).
[64] YuWaiMan, P., l Clements, A., Nesbitt, V., Griffiths, P. G., Gorman, G. S., Schaefer, A. M., et al. A national epidemiological study of chronic progressive external ophthalmoplegia in the United Kingdom-molecular genetic features and neurological burden. *Invest Ophthl Vis Sci* **55**, 5109-5109, (2014).
[65] Wong, T.-s., Belaramani, K. M., Chan, C.-k., Chan, W.-k., Chan, W.-l. L., Chang, S.-k., et al. Mitochondrial diseases in Hong Kong: prevalence, clinical characteristics and genetic landscape. *Orphanet J Rare Dis* **18**, 43, (2023).
[66] Gorman, G. S., Schaefer, A. M., Ng, Y., Gomez, N., Blakely, E. L., Alston, C. L., et al. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. *Ann Neurol* **77**, 753-759, (2015).
[67] Gorman, G. S., Chinnery, P. F., DiMauro, S., Hirano, M., Koga, Y., McFarland, R., et al. Mitochondrial diseases. *Nat Rev Dis. Primers* **2**, 1-22, (2016).
[68] Chinnery, P., Schaefer, A.& Turnbull, D., editors. The epidemiology of mitochondrial disorders. Biochimica et Biophysica Acta: Bioenergetics. 6th European Meeting on Mitochondrial Pathology (Euromit 6); 2004: Newcastle University.
[69] Guillausseau, P.-J., Massin, P., Dubois-LaForgue, D., Timsit J., Virally M., Gin H., et al. Maternally inherited diabetes and deafness: a multicenter study. *Ann Intern Med* **134**, 721-728, (2001).
[70] Kyriakidou, A., Hadjivassiliou, M., Papapostolou, A.& Picolos, M. K. Maternally Inherited Diabetes and Deafness (MIDD)–Atypical Clinical Diabetes Features Leading to the diagnosis. *JCEM Case Reports* **1**, luad047, (2023).
[71] Agrawal, P. K., Pursnani, N., Gautam, A., Singh, A. P.& Singh, A. K. Maternally inherited diabetes mellitus and deafness (MIDD): A case report and review of literature. *J Diabetol* **14**, 173-176, (2023).
[72 Park, S. Y., Kim, S. H.& Lee, Y.-M. Molecular diagnosis of myoclonus epilepsy associated with ragged-red fibers syndrome in the absence of ragged red fibers. *Front Neurol* **8**, 520, (2017).
[73] Velez-Bartolomei, F., Lee, C.& Enns, G. Merrf. Myoclonic Epilepsy with Ragged-red Fibers with Intranuclear Inclusions. *Intern Med* **4**, 7767-21, (2021).
[74] Wang, L., Peng, W., Zhao, Z., Zhang, M., Shi, Z., Song, Z., et al. Prevalence and treatment of diabetes in China, 2013-2018. *Jama* **326**, 2498-2506, (2021).
[75] Anjana, R. M., Deepa, M., Pradeepa, R., Mahanta, J., Narain, K., Das, H. K., et al. Prevalence of diabetes and prediabetes in 15 states of India: results from the ICMR–INDIAB population-based cross-sectional study. *Lancet Diab Endo* **5**, 585-596, (2017).
[76] Control, C. f. D.& Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States. *MMWR Morb Mortal Wkly Rep* **201**, 2568-2569, (2011).
[77] Linnenkamp, U., Guariguata, L., Beagley, J., Whiting D.& Cho N. The IDF Diabetes Atlas methodology for estimating global prevalence of hyperglycaemia in pregnancy. *Diabe Res Clin Pract* **103**, 186-196, (2014).
[78] Sathianvichitr, K., Sigkaman, B., Chirapapaisan, N., Laowanapiban, P., Padungkiatsagul, T., Apinyawasisuk, S., et al. The epidemiology and mutation types of Leber's hereditary optic neuropathy in Thailand. *Ann Med* **54**, 1601-1607, (2022).
[79] Puomila, A., Hämäläinen, P., Kivioja, S., Savontaus, M.-L., Koivumäki, S., Huoponen, K., et al. Epidemiology and penetrance of Leber hereditary optic neuropathy in Finland. *Eur J Hum Genet* **15**, 1079-1089, (2007).
[80] Man, P. Y. W., Turnbull, D.& Chinnery, P. Leber hereditary optic neuropathy. *J of med gene* **39**, 162-169, (2002)
[81] Baldo, M. S., Nogueira, C., Pereira, C., Janeiro, P., Ferreira, S., Lourenço, C. M., et al. Leigh syndrome spectrum: A Portuguese population cohort in an evolutionary genetic era. *Genes* **14**, 1536, (2023).
[82] Stenton, S. L., Zou, Y., Cheng, H., Liu, Z., Wang, J., Shen, D., et al. Leigh syndrome: a study of 209 patients at the Beijing Children's hospital. *Ann Neurol* **91**, 466-482, (2022).
[83] Estivill, X., Govea, N., Barceló, A., Perelló, E., Badenas, C., Romero, E., et al. Familial progressive sensorineural deafness is mainly due to the mtDNA A1555G mutation and is enhanced by aminoglycoside treatment. *Am J Hum Genet* **62**, 27-35, (1998).
[84] Mustafa, M. F., Fakurazi, S., Abdullah, M. A.& Maniam, S. Pathogenic mitochondria DNA mutations: current detection tools and interventions. *Genes* **11**, 192, (2020).
[85] Zeviani, M.& Di Donato, S. Mitochondrial disorders. *Brain* **127**, 2153-2172, (2004).
[86] Jackson, M., Schaefer, J., Johnson, M., Morris, A., Turnbull, D.& Bindoff, L. Presentation and clinical investigation of mitochondrial respiratory chain disease. A study of 51 patients. *Brain* **118**, 339-357, (1995).
[87] Farruggia, P., Di Catald A., Pinto, R. M., Palmisani, E., Macaluso, A., Valvo, L. L., et al. Pearson syndrome: a retrospective cohort study from the marrow failure Study group of AIEOP (Associazione Italiana Emato-Oncologia Pediatrica). *JIMD Reports* **26** 37-43 (2016).
[88] Yoshimi, A., Ishikawa, K., Niemeyer, C.& Grünert, S. C. Pearson syndrome: a multisystem mitochondrial disease with bone marrow failure. *Orphanet J Rare Dis* **17**, 379, (2022).