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The Relevance of mitochondrial DNA mutation in Human Diseases and Forensic Sciences: Review Article

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Abstract
Several studies have been carried out on mitochondrial DNA mutation in human diseases. Mitochondria are self-contained organelles with their DNA. The primary function of mitochondria is oxidative phosphorylation (OXPHOS), which is how the Electron Transport Chain (ETC) provides energy to the cell. Reactive oxygen species (ROS), which can oxidatively destroy DNA, proteins, and macromolecules like lipids, are one of the process's potentially hazardous byproducts. Compared to mitochondrial DNA (mtDNA), nuclear DNA is better protective and has more repair mechanisms, making it more susceptible to oxidative damage that might result in mutations**.**
This review focuses on the illnesses caused by mtDNA mutations known as "mitochondrial diseases. Numerous characteristics of (mtDNA), mainly those related to matrilineal heredity, a high duplicate number, and the absence of recombination, are advantageous for forensic study. Old bones, teeth, and hair are used as forensic samples for analysis, along with other biological samples with low levels of DNA. Different mtDNA haplogroups can affect longevity and risk of infection, in addition to being used to determine a person's geographic origin.

Keywords: Mitochondrial DNA (mtDNA), diseases, forensic sciences, mtDNA mutations

1. Introduction
Mitochondria are inimitable organelles that have evolved from the addition of endosymbiotic alphaproteobacteria into a host eukaryotic cell of the Archaea phylum [1]. Due to their symbiotic relationship, these organelles are essential for operating eukaryotic cells. They play a crucial role in cellular processes, such as ATP synthesis, acetyl CoA synthesis, fatty acid oxidation, and redox balance [2]. Their unique structural characteristics, including double membrane structures with inner membrane folds named cristae, enable these tasks. The dual membrane structure and placement of the electron transport chain (ETC) components of the inner mitochondrial membrane are crucial for creating a proton motive force during electron transport for ATP production [3]. The outer mitochondrial membrane is a diffusion barrier for molecules and aids in creating rate-dependent concentration gradients [4]. Outer membrane proteins are essential for mitophagy, mitochondrial fusion, and fission [5]. The existence of mitochondrial DNA is another unique property of these organelles.
DNA is found in the organelle's matrix. The matrix contains many duplicates of this circular, double-stranded genome that codes for 13 ETC proteins, mitochondria-specific ribosomal RNA, and transfer RNA (tRNA) [6].
Identifying human genetic material for forensic applications relies on establishing genetic profiles, also known as genetic fingerprints. The European DNA Profiling Group (EDNAP) recommends using only autosomal short tandem repeats (STRs) for genetic fingerprinting. However, autosomal DNA is often absent or damaged, leading to using (mtDNA) for human identification [2]. MtDNA is resilient when there is exclusion or no identity among sequences. Still, when results show sequence identity, they don't correspond to a single person but to a group sharing similar maternal heredity, unlike nuclear markers. Analysis of mitochondrial genome polymorphisms and SNPs related to ancestry and physical and psychological characteristics provide important information for forensic investigations (Figure 1).

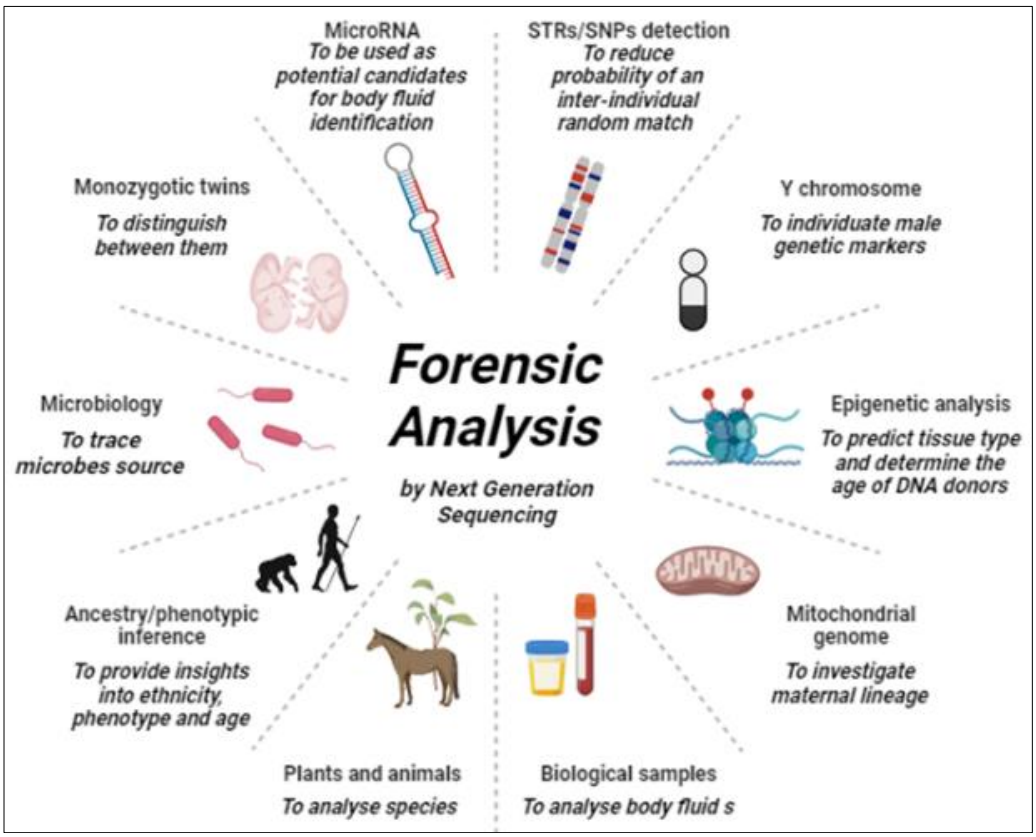

Fig 1: Forensic Analysis is assembled using dynamic created with BioRender.com.

2 Main text

In this section, we present some basic concepts and definitions that will be used in this article.

2.1 biological and genetic aspects of mitochondrial DNA

Mitochondria are cellular organelles with an extra chromosomal genome that is different from and separate from the nuclear genome. The discovery of mitochondrial DNA (mtDNA) in 1963 by Margit Nass and Sylvan Nass led to the release of the first mtDNA sequence in 1981, but it took 18 years for the entire first mtDNA sequence to be released. MtDNA is a circular, double-stranded DNA molecule with no histones, measuring five millimeters in diameter, weighing 107 Daltons, and having about 16,569 base pairs. MtDNA Cambridge Reference Sequence (CRS) was released in 1981 [4, 7].

MtDNA strands have diverse densities due to the varying G+T and base structure. The light (L) strand contains eight tRNA and one polypeptide, while the heavy (H) strand contains more details, including a pair of genes rRNA, twelve polypeptides, fourteen tRNA, and 12S and 16S rRNA. The oxidative phosphorylation system's 13 protein-based goods are all included in the complexes of enzymes that make up this system. Other distinguishing characteristics of mtDNA include intron-less genes and little to no intragenic sequences, except one regulatory region [8].

One of the mtDNA genome's largest non-coding regions (NCR) is the mitochondrial D-loop, generated by the steady insertion of a third, 680-base DNA strand called 7S [9]. According to CRS numeration, the D-loop area, which has Base pairs of 1, 121 and is located at addresses 16,024 and 576, is where replication starts [7]. Two transcription promoters exist in the D-loop region, one for each strand. The locations of nucleotides in the mtDNA genome are numbered using the procedure for replacing CRS updated for RCRS is that the H strand is where each base pair's numeral designation begins, and it continues there for roughly 16,569 base pairs around the molecule [10].

The mitochondrial genome has an advanced mutation ratio to the nuclear genome due to the absence of mtDNA reparation pathways and the conformity of mtDNA polymerase. The mutation rate in people's mtDNA regulatory areas is estimated to be 0.32 x 10_6/site/year [11]. Compared to 0.5 x 10_9/site/year in the nuclear genome [12]. Hyper variable regions (HV1, coordinates 16,024 to 16, 365) and 2 (HV2, locations 73 to 340) of the control region contain the most sequence variation across people [8]. To resolve indistinguishable HV1/HV2 samples, additional polymorphism sites are present in the third hyper variable region (HV3, positions 438 to 574) and may be helpful to [1]. Forensic testing can benefit from the HV areas' modest size and significant inter-person variability. The mtDNA sequence and the dissimilar base pairs regarding the RCRS mtDNA sequence report define the individual haplotype. Haplogroups were created as a result of the successive addition of mutations through maternal lineage and are characterized by the collection of related haplotypes defined by the combination of Single Nucleotide Polymorphisms (SNPs) in mtDNA inherited from a common ancestor [13]. Apiece somatic cells can have up to 1,000 mitochondria, and each mitochondrion comprises 2 to 10 copies of the mtDNA [14, 15]. Typing the mtDNA is more likely to yield a result than typing polymorphic areas discovered in nuclear DNA when the amount of recovered DNA is small or damaged.

MtDNA, transmitted from the mother, can explain why siblings and other maternal relatives share identical mtDNA sequences unless a mutation occurs [16]. Reference samples

can be obtained from known maternal relatives, which can be helpful in forensic situations like examining missing individuals' remains [16]. Most mtDNA is haploid and monoclonal, making DNA sequencing easier. However, Heteroplasm can be discovered in rare circumstances [17]. Heteroplasm has two types: Point substitutions and length variations. The latter is the only factor that matters for (FHID).

Furthermore, forensic laboratories don't record length polymorphisms, and recommendations for using mtDNA to identify people do not specifically include them as information.

Additionally, information about length polymorphisms does not affect the explanation of haplogroups [18]. Heteroplasm, a type of DNA found in human tissue, can manifest in various ways, such as heteroplasmy in one tissue sample, homoplasmy in another, or one form of mtDNA in one tissue and another type in another [19]. The likelihood of heteroplasmy is the lowest when it is found in an individual's mtDNA. Heteroplasm is often seen with one base in HV1 or HV2 [20]. The mitochondrial genome is typically passed down from a mother; despite two or three mitochondria in the neck and sperm tail area, male mitochondrial genome degeneration occurs each through or immediately following conception. Early embryogenesis sees the selective destruction, deactivation, or dilution of sperm mitochondria [21]. However, recent research has shown rare mtDNA inheritance from both parents. Luo and colleagues reported direct or indirect biparental mtDNA inheritance in 17 individuals from three families with many generations [22]. Some cases also involve animals passing down their mitochondrial genomes from father to son [23]. Despite the lack of indication for the fatherly legacy of the human mitochondrial genome, this could encourage courts to minimize the use of mtDNA evidence in court cases. This raises questions about the potential for genetically modified organisms to inherit their mitochondrial DNA.

2.2 Mitochondrial DNA mutations

In 1988, the first harmful mtDNA mutations were discovered [24]. Since then, over 250 harmful point mutations and rearrangements of mtDNA have been identified, causing various illnesses with a wide range of phenotypes. According to the table, mitochondrial diseases are characterized by flaws in any element of mitochondrial activity, such as Leber Hereditary Optic Neuropathy (LHON) and nuclear or mitochondrial DNA abnormalities [25, 15, 26].

Table 1: Mitochondrial disorders, the classification for mtDNA mutations, nuclear DNA errors, and mitochondrial gene mutations [27].

Type	Subtype	Diseases
mtDNA mutations	Rearrangement mutations	Progressive external ophtalmoplegia (PEO) Kearns-Sayre Syndrome (KSS) Pearson Syndrome (PS)
	Point mutation tRNA or rRNA	Mitochondrial Encephalopathy lactic acidosis, and stroke-like episodes (MELAS) Myoclonus Epilepsy and Ragged-Red Fibers (MERRF)
	Point mutation proteins	Neurogenic muscle weakness, ataxia and retinitis pigmentosa (NARP) Leber Hereditary Optic Neuropathy (LHON) Leigh Syndrome
Nuclear DNA defects	Replication mutation proteins	Chromosome 15-linked Autosomal Dominant Progressive External Ophtalmoplegia (adPEO) Chromosome 10-linked adPEO Chromosome 4-linked adPEO
	Mutation in Thymidine kinase2	mtDNA depletion Syndrome (MDS)
	Mutation in Thymidine phospholipase	Mitochondrial Neurogastroinstestinal Encephalomyopathy (MNGIE)

The precise incidence of mtDNA illness is challenging to determine owing to the clinical variety of these disorders and the abundance of known causal mutations. Approximations suggest that 1 in 6000 persons may be at risk for developing mtDNA illness, and up to 1 in 10,000 may already have it [15]. Recent studies on birth pervasiveness have found mutation incidences of 0.14% for the m.3243A > G mutation and 0.2% for the m.1555A > G MT-RNR1 mutation linked to aminoglycoside-induced sensorineural hearing loss, suggesting that the perceived prevalence of mtDNA mutations is still understated [28]. The human mitochondrial genome is shown as a circular, double-stranded structure, with frequent mtDNA mutations indicated. These illnesses include chronic progressive external ophthalmoplegia, Leigh syndrome, mitochondrial myopathy, Leber hereditary optic neuropathy encephalopathy, lactic acidosis, stroke-like episodes, myoclonic epilepsy, and ragged red fibres, maternally inherited Leigh syndrome (MILS), neurogenic weakness, ataxia, and retinitis pigments, and Pearson syndrome [29]. The mitochondrial genome experiences 10- to 17-fold more mutations than nuclear DNA. However, there are mtDNA repair systems. The mitochondrial genome's proximity to the RC complexes in the IMM and the ROS they produce make it unable to prevent the oxidative damage it suffers. Neutral polymorphisms, which comprise the majority of mtDNA variations, help trace human migrations [29]. The majority of mtDNA mutations found to be associated with human diseases are hetero plasma, which means that a cell or tissue coexists with both mutant and wild-type mtDNA [30]. mtDNA is susceptible to mutations, just like any other genetic material, and some of these mutations can cause a diverse range of human disorders known as mitochondrial syndromes or mitochondrial encephalo myopathies [31]. Mitochondrial diseases affect the brain, skeletal muscles, endocrine system, and other tissues with high energy requirements. Clinical signs include muscle weakness, blindness, mental retardation, dementia, progressive epilepsy, sensory neuropathies, ataxia and renal dysfunction. Other metabolic disorders like diabetes, obesity, cardiovascular disease, neurodegenerative syndromes, and cancer have also been linked to mitochondrial changes. Nuclear DNA mutations can also be the source of mitochondrial disorders, impacting the composition or structure of proteins that enter mitochondria. mtDNA flaws exist in multiple cell copies and can coexist with mutant and wild-type alleles [32].

A single disease-causing mtDNA mutation may result in altered mitochondrial morphology and reduced mtDNA transcription, simulating moderate mitochondrial malfunction in conditions like diabetes and autism. It may cause broad changes in the expression of genes involved in signal transduction, epigenetic control, and pathways linked to neurodegenerative disorders when present in relatively

high concentrations. This presents a problem for mtDNA investigations, as different downstream phenotypes may result from different fractions and abundances of mutations and tissue sites [33]. mtDNA copy number, sometimes called mtDNA content or the total amount of mtDNA molecules present in a cell, can impact mitochondrial function and mtDNA sequence differences. Figure2

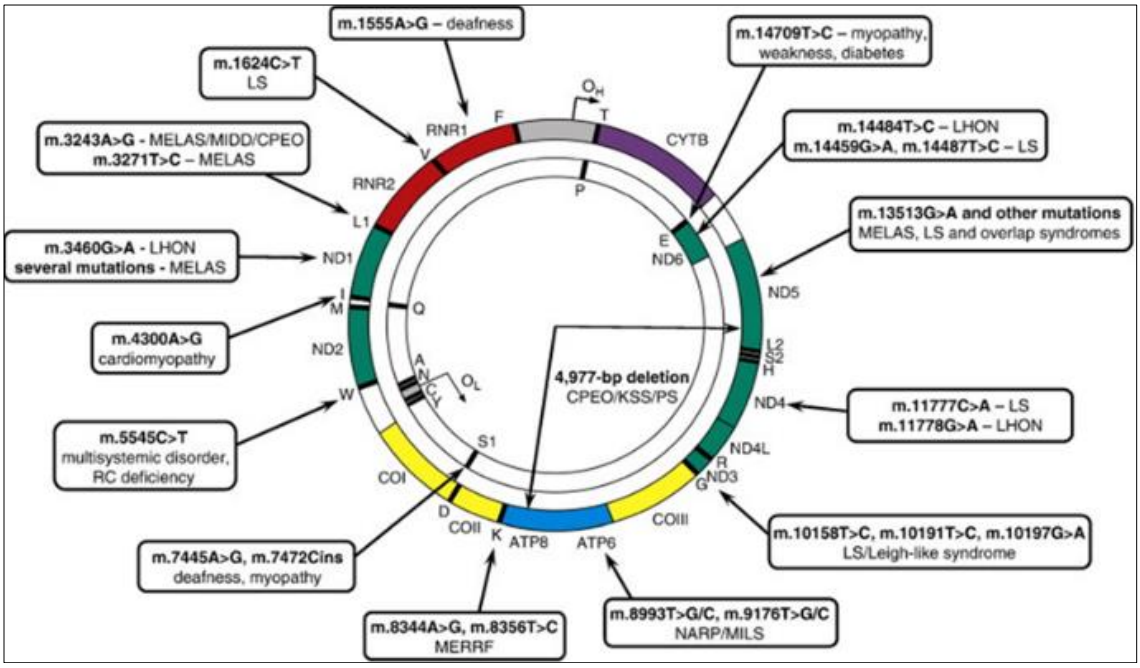

Fig 2: The role of the mitochondrial genome in energy generation [34].

2.3 Mutations of the mtDNA in forensic science estimation of the death age

Forensic inquiry aims to estimate a person's age at death to identify a victim. However, determining an adult's age can be challenging due to the natural aging process that alters organs and tissues on various biochemical levels [35].

One such change is mtDNA mutations; only a few authors have explored the link between mitochondrial mutations and age in forensics, research in skeletal muscle revealed a relationship between age and the prevalent mutation, providing a rough estimate of the age at death [24]. Additionally, tissue that has experienced significant putrefaction can be employed with this technology, which employs Polymerase Chain Reaction.

Three methods were used to analyze A189G mutations: Automated DNA sequencing, blot hybridization with an oligonucleotide probe labeled with digoxigenin, and peptide nucleic acid (PNA)/real-time PCR. They found that mutation accumulates to extremely high levels in post-mitotic muscular tissue and mitotic buccal cells in people 60 or older. Similar methodologies were used by umbuugh *et al.* [31]. To demonstrate that this age-related somatic point mutation occurs in bone tissue.

Similar to the transition mutation in the MERRF syndrome, other authors searched for disease mutations using PCR technology [36]. They discovered a correlation between this mutation and age in healthy persons' extra ocular and skeletal muscle postmortem samples.

Other researchers have also looked for deletions in mitochondrial DNA, using blood and bone samples from patients who had undergone orthopedic surgery [37]. They found mtDNA deletions in bone but not in blood in patients with osteoporosis/rheumatoid arthritis up to 70 years old [38]. PCR amplification of the mitochondrial D-loop's hyper variable region 2 (HV2) demonstrated a reduction in mtDNA content in dentine with aging in wisdom teeth from healthy people.

In bone and muscle samples, three different forms of mini-duplications were found [39]. They are using capillary electrophoresis. The oldest individuals never had evidence of the three duplications in their bones, but anyone over 38 can see at least one. On the other hand, duplicate fragments have been seen in people around 20 and accumulated in older people, carrying several duplicates. This kind of rearrangement has a strong tissue selectivity. Although this process may be straightforward, inexpensive, and valuable for forensic laboratories, and even though it can be applied to tissue that has rotted or putrefied, further research is required before it can be used in forensic cases.

2.4 Haplogroups their function in forensic sciences, illnesses, and aging

According to Salas *et al.* [39] identified haplogroups as mutations widely spread among human populations. mtDNA from various human populations has been studied using restriction fragment-length polymorphisms, revealing ancestor mutations that identify these haplogroups. These haplogroups have a common ancestor but evolve separately due to uniparental inheritance. The classification of mtDNA molecules within a particular population is made possible by the specific sets of associated mutations [40]. Human populations worldwide can be divided into over 20 mtDNA haplogroups, with the human mtDNA tree having roots in Africa and branches spreading across other geographical areas [42, 43]. mtDNA the most ancient and diverse form of DNA, originates from Africa and has four main haplogroups: L0, L1, L2, and L3. Migrations from Africa to Europe and Asia have led to the emergence of new haplogroups, enriching existing ones. 35% of mutations are confined to specific continents [44], making this

phylogeographic distribution useful in forensic research. Studies have linked mtDNA variants to human longevity and aging [45], with C150T polymorphisms describing hereditary mtDNA haplogroups and longer longevity in Finland and Japan. Haplogroup J is overrepresented in northern Italian males who live long lives and reach centenarian age [46], while Irish nonagenarians, centenarians, and long-lived Finns are overrepresented in this haplogroup. Nonagenarian Chinese Uygurs are underrepresented in this haplogroup [47]. Disease risk is also correlated with haplogroups, with Japanese centenarians and supercentenarians being resistant to conditions like Parkinson's disease, type 2 diabetes, myocardial infarction, cerebrovascular infarction, and Alzheimer's dementia [48]. Male members of haplogroup U among Europeans had an increased danger of AD, whereas female members of these haplogroups had a decreased risk. Compared to people with the most prevalent H, haplogroup J had a lower risk of Parkinson's disease [49]. Several research studies have described the risk of cancer-related to various haplogroups. In a Japanese hospital, 30 different haplotypes were examined regarding their relationship to cancer [50]. They found that the haplogroup M7b2, a risk factor for hemopoietic malignancy, increased the likelihood of developing leukemia. According to Young *et al.* [51], the haplogroup U was linked to a higher risk of kidney cancer in Northern Americans. Indian populations are at increased risk for this cancer due to the polymorphism mtG10398A in haplogroups N and its sublineages [52]. This risk is also present in breast and esophageal cancers.

Based on their discovery, the significant haplogroups have been named A through Z alphabetically. The most recent common ancestor, or "Mitochondrial Eve," is a hypothetical root that emerged between 120,000 and 156,000 years ago and represents an individual from whom all living things today have descended. However, she was not the "first" or "only" woman of the species. Haplogroup L was Mitochondrial Eve's group [7]. Figure 3 shows the significant haplogroups and probable migration paths over time.

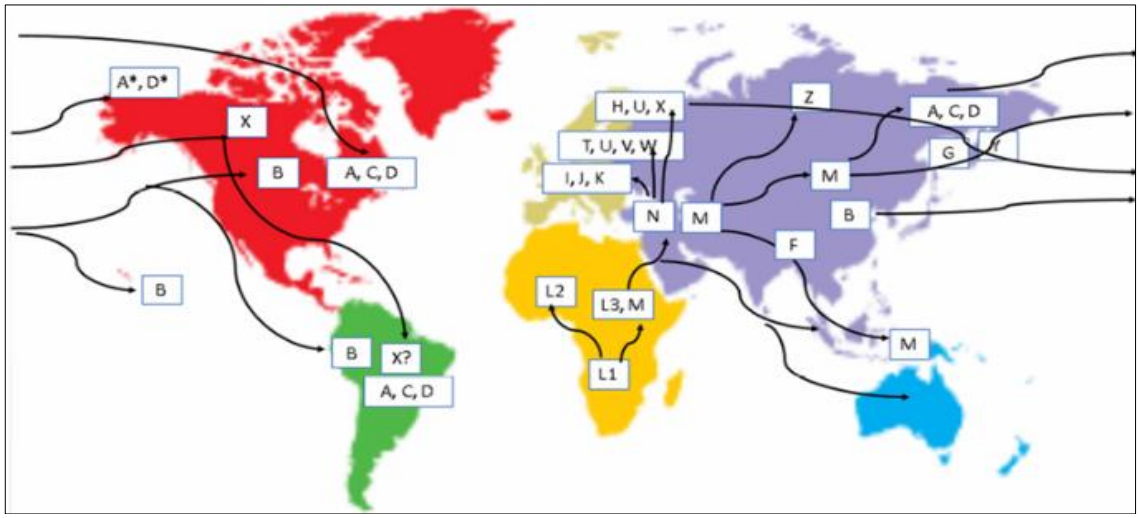

Fig 3: Main mt DNA haplogroups across the world and probable migration routes [7].

These research findings are consistent with the hypothesis that mtDNA variations and haplogroups have a population- and perhaps sex-dependent impact on longevity and disease risk.

2.5 Forensic application of mitochondrial DNA for person identification

The mtDNA sequences of an evidentiary sample(s) and a reference sample are compared to forensic analysis. The result is that they can be rejected as having originated from the same source when the sequences are distinct. A sample cannot be dismissed if the mtDNA sequences match since they must share a common ancestor or come from a common maternal lineage. When hetero plasma is present in both samples at the exact nucleotide locations, samples cannot be excluded. If one specimen is heteroplasmic and the other is homoplasmic, but both share at least one type of mtDNA, the specimens cannot be excluded because they may have the exact origin. According to numerous authors [18], mtDNA samples that differ by a single base should be further examined, especially concerning mutation rate [53]. In 2017, the recommended protocols and guidelines of the International Society of Forensic Genetics were still followed for identifying the remains of victims from the terrorist attack on the World Trade Center, which occurred on 11 Sep 2001 [54].

2.6 Recognizing and reducing the spread of pathogenic mtDNA variations

Most individuals with mtDNA illness experience increasing symptoms, which frequently result in severe morbidity or early mortality. The obvious priority is attempting to stop the transmission of harmful variations during pregnancy because there are no disease-modifying medications currently available. The alternatives available have improved due to the development of new *in vitro* fertilization (IVF) methods, which bring several obstacles. There are several different aspects to take into account when providing reproductive counselling for females with harmful mtDNA variants. Thus, families must get guidance on their options for having children from professionals aware of the associated hazards. Oocytes will inherit variant levels far below the disease threshold [55]. Preimplantation genetic diagnosis (PGD) presents much more of a difficulty for other hetero plasma types. For instance, women with high amounts of a variant and little germ line segregation might not exhibit any symptoms-embryos with levels of variation below those considered to carry a low risk of disease [56].

2.7 Treatment of disease

Significant strides have been made in our comprehension of mtDNA illness. Treatment progress for mtDNA is moving more slowly. The treatment of sick people has significantly improved in recent years. In recent years, there has been a noticeable improvement in patient care. The growth of significant clinical cohorts in numerous countries can now create clinical leaders. These include improved monitoring practices to identify clinical symptoms before they become severe and select the best treatments for mitochondrial illness. Numerous minor molecule treatments are being investigated through clinical studies [57]. However, mtDNA sickness currently has no effective treatment; people have been interested in orthodontics for many years, eliminating genetic defects with gene therapy, and it looks simpler. Lack of nuclear gene therapy Because of misleading the mitochondrial genome's simplicity. However, it has been very challenging to study the inner membrane of the mitochondrion, which is highly specialized for OXPHOS and impenetrable to most molecules, including DNA. However, several strategies have been considered, and recent developments have been very significant.

Using viral vectors, allotropic expression requires introducing wild-type copies of the altered mtDNA gene to the cytosol [58]. This would be translated into the cytosol, and the mitochondria would use a mitochondrial targeting sequence to import the protein. In this study, one patient's eye's damaged retinal ganglion cells received the MT-ND4 by a local viral vector injection. Throughout a 96-week follow-up, the authors noted consistent vision improvement in both eyes, demonstrating the possibility that the viral vector DNA has passed the ocular barrier. Targeting the pathogenic mtDNA variation is another strategy for manipulating variant levels. To stop the replication of altered genomes, peptide nucleic acid oligomers were initially used to test this [59]. Initial results employing *in vitro* replication systems were intriguing, but they could not demonstrate absorption into mitochondria, and cell responses were poor. Using endonucleases that can specifically eliminate harmful mutations by crossing mitochondrial membranes and targeting mitochondria is an alternative strategy [60].

3 Conclusions

Several diseases are linked to mtDNA mutations. Different mtDNA haplogroups can affect longevity and disease risk and can also be used to identify a person's geographic origin. To better understand the role mtDNA mutation plays in illness and how it applies to forensic science, further research is required. Regarding the mtDNA testing's legal admissibility, some questions remain, especially regarding the problem of hetero plasma fusion and, more recently, the potential for parental inheritance. The ability to predict the circumstances in which this is most likely to happen, the capacity to identify and define hetero plasma with great precision, and the comprehensive understanding of cellular mechanisms underlying parental inheritance of mtDNA are significant concerns that need to be addressed.

4. Declarations

Ethics approval and consent to participate

Not applicable.

5. Consent for publication

Not applicable because this manuscript does not contain any individual personal data.

6. Availability of Data and Material

All the data were collected from Scopus, google scholar and PubMed for this study.

7. Competing interests

The author declare no conflict of interest.

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9. Author contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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List of abbreviations

Deoxyribonucleic acid DNA
Oxidative phosphorylation OXPHOS
Electron transport chain ETC
Reactive oxygen species ROS
Mitochondrial DNA mtDNA
Adenosine triphosphate ATP
Coenzyme A CoA
European DNA Profiling Group EDNAP
Short tandem repeats STR
Cambridge Reference Sequence CRS
Light L
Heavy H
Ribosomal ribonucleic acid rRNA
Transfer RNA (Ribonucleic acid) tRNA
Non-coding regions NCR
Rotator cuff related shoulder pain RCRS
Sequence-specific oligonucleotide probes SSO
SNPs Single Nucleotide Polymorphisms
Maternally inherited Leigh syndrome MILS
In vitro fertilization IVF
Pre-implantation Genetic Diagnosis PGD
Polymerase chain reaction PCR
Peptide nucleic acid PNA
MERRF syndrome Myoclonic epilepsy with ragged red fibers
HV2 Hyper variable region2
LHON Leber Hereditary Optic Neuropathy
Parkinson disease PD
Alzheimer dementia AD
Forensic Human Identification (FHID)
Human Identification (HID)

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