DOI: https://doi.org/10.53350/pjmhs020241891

REVIEW ARTICLE

Mitochondrial Genetics and Human Health: Implications and Insights

HAMZA ALI[1], ABRAR AHMED RATTAR[2], MAHAM TAQI[1], RAFAY SHAIKH[4], ANOSH GILL[5]
[1]*Institute of Molecular Biology, Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro 76080, Sindh, Pakistan*
[2]*Institute of Medical & Health Sciences, Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro 76080, Sindh, Pakistan*
[3]*Institute of Molecular Biology, Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro 76080, Sindh, Pakistan*
[4]*Institute of Medical & Health Sciences, Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro 76080, Sindh, Pakistan*
[5]*Institute of Medical & Health Sciences, Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro 76080, Sindh, Pakistan*
Correspondence to all writers: E-mails: hmarri38@gmail.com, abrarrattar@gmail.com, zartaqsoomro@gmail.com, zrafayr50@gmail.com, dgill12333@gmail.com

SUMMARY

Mitochondrial genetics is a crucial area of research with major implications for human health. Mitochondria are cellular organelles essential for energy production but also play vital roles in other cellular processes like calcium regulation and redox balance. Certain unique characteristics of the mitochondrial DNA (mt-DNA) including its high mutation rate, maternal inheritance and heteroplasmy make it central to understanding the wide range of genetic and complex diseases.

This review examines the bridge between mt-DNA mutations and various diseases such as mitochondrial myopathies, neurodegenerative disorders and complex diseases like type 2 diabetes and cardiovascular disorders. Mutations in the mt-DNA lead to generation of reactive oxygen species (ROS) which leads to cellular damage and disease progression. The review explores different epigenetic factors such as environment. Lifestyle, aging impact the mitochondrial function with focus on the susceptibility of mt-DNA to oxidative damage due to its proximity to ROS generation sites

The review also highlights the importance of mitochondrial genetics in reproductive health and provides insights on maternal transfer of mt-DNA and inherited mitochondrial disorders. These findings offer foundation for advancement in diagnosing, treating and preventing mitochondrial diseases, ultimately increasing our understanding of human biology and disease mechanism.

Keywords: Mitochondrial genetics, Mitochondrial DNA (mt-DNA,) Mitochondria Genetic diseases, Mitochondrial myopathies, Neurodegenerative disorders, Type 2 diabetes, Cardiovascular disorders

INTRODUCTION

Mitochondria or as more often referred as “powerhouse” of the cell due to their ability to produce ATP via a process called oxidative phosphorylation, mitochondria are also responsible for a range of other biological processes crucial for the cell’s survival like calcium homeostasis, redox balance, signaling pathways, energy production[1,2,3] mitochondria maintain a redox state within the cell by producing reactive oxygen species (ROS) which influence many cellular activities including signaling, gene transcription, apoptosis[4,5,6]. Mitochondria is also actively involved in maintaining an equilibrium of calcium ions within a cell which are important for muscular contraction, neuronal communication and hormone production[7]. They also regulate the metabolic functions of a cell by altering the activity of enzymes related to glycolysis, citric acid cycle, pentose phosphate pathway[3]. Mitochondria are dynamic organelles that change their shape, size and distribution according to the condition within the cell, these changes are necessary to preserve cellular homeostasis and controlling biological process like morphogenesis, cell migration and senescence[8,9,10].

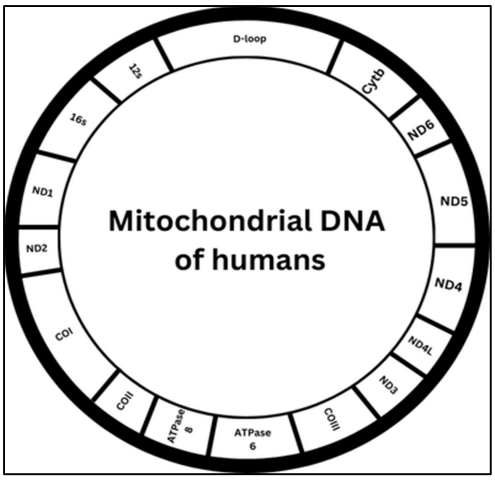
Metabolites produced by the mitochondria have signaling properties contributing to intra cellular communication[5]. These metabolites are also responsible for cellular senescence, which is a condition marked by the buildup of damaged cellular components and continuous stop of cell cycle[9].

Mitochondria are present in most eukaryotes and contain their own genetic material, the study of this genetic material is called mitochondrial genetics[11] for most eukaryotic organisms the process of oxidative phosphorylation is crucial for survival and this process is dependent on the genetic information encoded in the mitochondrial. (mt-DNA)[11,12,13].

Understanding mitochondrial genetics is significant for understanding of many diseases and disorders for example Leber's hereditary optic neuropathy (LHON) is a common genetic mitochondrial condition that leads to vision loss due to optic nerve degeneration, the mutations occur in the gene ND1, ND4, ND6 resulting in higher level of oxidative stress that the optic nerve cells endure causing damage to the nerve cells[12]. Another class of diseases that mitochondrial genetics help in comprehending is the primary mitochondrial myopathies (PMMs) these diseases are characterized by abnormalities in the oxidative phosphorylation process brought on by mutation in nuclear and mt-DNA .[13]Mitochondrial genetics doesn't only help us in understanding diseases but also evolution and diversity of different microorganisms, mitochondrial genetics was used in a study where the larvae and adults of aquatic fireflies matched to determine the relationship between species[14].

The aim of the review is to provide an in-depth analysis of the developing field of mitochondrial genetics and its significance in human health. Recent discoveries in the field link the pathophysiology of many diseases to mt-DNA (mt-DNA). Firstly, we aim to analyze the dynamic role of mt-DNA in cells and then we want to demonstrate that how research is transforming our knowledge of human health in relation to mt-DNA.

Figure 1: Mitochondrial DNA of humans



Received on 14-05-2024
Accepted on 27-08-2024

Mitochondrial DNA (mt-DNA): mt-DNA is circular in shape and has a length of 15-20 kilobases, this circular arrangement allows for efficient replication and maintenance of the genetic material[15]. The mt-DNA is composed of two complimentary strands: the heavy (H-strand) and the light (L-strand), each serving as a template for the synthesis of the other[15]. Mt-DNA 13 highly conserved, protein coding genes. These encoded proteins participate in the electron transport chain and other mitochondrial processes[15].

Table 1: Numerous genes of mitochondria and proteins encoded by them.

GENE	PROTEIN
mt-ATP6	Encodes the ATP synthase subunit 6, which is involved in the production of ATP during cellular respiration
mt-ATP8	Encodes the ATP synthase subunit 8, which is also involved in the production of ATP during cellular respiration
mt-CO1	Encodes the cytochrome c oxidase subunit 1, which plays a crucial role in the electron transport chain
mt-CO2	Encodes the cytochrome c oxidase subunit 2, which is also involved in the electron transport chain
mt-CO3	Encodes the cytochrome c oxidase subunit 3, which is involved in the electron transport chain
mt-CYTB	Encodes the cytochrome b, which is involved in the electron transport chain
mt-ND1	Encodes the NADH dehydrogenase subunit 1, which is involved in the electron transport chain
mt-ND2	Encodes the NADH dehydrogenase subunit 2, which is involved in the electron transport chain
mt-ND3	Encodes the NADH dehydrogenase subunit 3, which is involved in the electron transport chain
mt-ND4	Encodes the NADH dehydrogenase subunit 4, which is involved in the electron transport chain
mt-ND4L	Encodes the NADH dehydrogenase subunit 4L, which is involved in the electron transport chain
mt-ND5	Encodes the NADH dehydrogenase subunit 5, which is involved in the electron transport chain
mt-ND6	Encodes the NADH dehydrogenase subunit 5, which is involved in the electron transport chain

CHARACTERSTICS OF MITOCHONDRIAL-DNA: While the structure of mt-DNA is simple, its characteristics are not, unlike nuclear DNA mt-DNA displays a phenomenon called heteroplasmy. Heteroplasmy is the co-existence of wild type and mutant mt-DNA variants within the same cell, the percentage of the mutant type mt-DNA has significant effect on the severity of disease[16,17]. Another characteristic of mt-DNA is the dramatic variance in the copy number between individuals and within the same cell over a period, such variance confounds our knowledge of how mt-DNA affects cellular health[18,19]. mt-DNA also shows structural changes like linear monomers and circular" head-to-head" dimers [20]. mt-DNA also shows unique evolutionary patterns due to its high genetic drift caused by its high mutation rate[21].

Even though mt-DNA is more susceptible to mutation, mt-DNA contains essential regulatory sequences like the D-loop which plays a key role in the transcription of the mt-DNA. These regulatory areas are highly conserved across species indicating the importance of them in healthy mt-DNA functioning[15,22] of utmost importance is the link between mt-DNA mutations and wide range of human diseases like cardiovascular diseases, type 2 diabetes, hypertension, cardiomyopathies, neurodegenerative disorders and cancer[23-26].

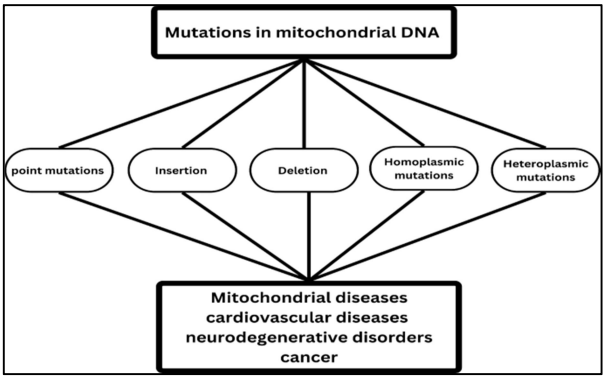
Table 2: Difference between nuclear and mt-DNA

Mitochondrial-DNA	Nuclear DNA
Structure	
Circular DNA	Linear DNA
High mutation rate	Lower mutation rate
Evolutionary pattern	
High genetic drift	Lower genetic drift
Highly conserved	Less conserved

The inheritance pattern of mt-DNA varies between species, in most animals including humans mt-DNA is maternally inherited. This is due to the fact that after fertilization the mitochondria of the sperm are often destroyed leaving only the mitochondria of the egg to contribute to the mt-DNA of the progeny[27,28]. Although followed by most but not all maternal inheritance of mitochondria have exceptions, in other some species an inheritance pattern is seen in which both parents contribute mt-DNA. such inheritance is called the biparental inheritance of mt-DNA and is seen in male blue mussel (Mytilus)[29].

Another unique type of inheritance seen in some bivalve mollusks is doubly uniparental inheritance (DUI) in this pattern the females contribute their mt-DNA to both male and female offsprings while the males only transmit their mt-DNA to their sons[30]. opposed to general consensus over the maternal inheritance of mt-DNA in humans, there may be a bimodal inheritance pattern of biparental inheritance in humans, this suggests that paternal mt-DNA transmission to the progeny is possible. However, concerns over the contamination of mt-DNA with nuclear pseudogenes (NUMTs) raise concerns over the validity of these of these findings[31,32].

Figure 2: Mutations of mt-DNA and their consequence
Mitochondrial Genetics



Mt-DNA is prone to many types of mutation including point, deletions, insertions, heteroplasmic and homoplasmic mutations[33-37]. The mentioned mutation in the mt-DNA lead to a variety of diseases like mitochondrial encephalomyopathies which primarily affect the brain and muscles leading to seizures, cognitive impairment and muscle weakness examples of mitochondrial encephalomyopathies are MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes)[38,39].

Mitochondrial leukoencephalopathies are the disorders that primarily affect white matter in brain leading to gradual neurological decline and cognitive impairment e.g., mitochondrial leukoencephalopathy with brainstem and spinal cord involvement and high lactate (MLBLSL)[39]. Mitochondrial fatty acid oxidation disorders (FAODs) are another type of mitochondrial diseases that impairs the breakdown of the fatty acids for energy production, e.g., carnitine palmitoyl transferase II deficiency, very long chain acyl-CoA dehydrogenase deficiency[40] mitochondrial diabetes is another group of disease characterized by diabetes and deafness e.g. maternally inherited diabetes and deafness (MIDD) and diabetes and deafness (DAD)[41]. Mitochondrial myopathies are disorders characterized by muscle weakness, fatigue and pain e.g. mitochondrial myopathies with lactic acidosis and mitochondrial myopathies with ragged-red fibers[38] mitochondrial disorders that affect the brain and the gastrointestinal system and other organs are called mitochondrial neurogastrointestinal encephalopathy (MNGIE) these disorders often present with seizures, gastrointestinal dysfunction and muscle weakness[38]. Mitochondrial diseases also include neurodegenerative disorders like Parkinson's disease, Alzheimer's and Huntington disease[42,43].

Mt-DNA acquires mutation mainly through two ways; mt-DNA replication and transcription and reactive oxygen species (ROS) production[44,45]. The replication of the DNA of mitochondria occurs by a semiconservative process during which continuous replication of one strand called leading strand occurs, and another

strand's replication occur in short fragments called Okazaki fragments, this strand is known as lagging strand[44]. This replication is prone to error due to its asymmetric nature. The lagging strand spends more time as a single strand than leading strand making the lagging strand susceptible to mutations more specifically point mutations G→A and T→C transitions[46]. Another mechanism of mutation is oxidative damage via ROS, these moieties modify the bases of mt-DNA e.g. formation of 8-oxoguanine[47,48].

To mend these mutations mt-DNA has evolved several DNA repair mechanisms. The bases excision repair is the primary mechanism to repair oxidative damage to mt-DNA, the process starts with recognition of the damaged base followed by excision of the damages base via enzymes like OGG1 and filling the gap created from excision with the correct base[49,50]. Homologous recombination is another mechanism of mt-DNA repair in which the healthy strand of mt-DNA is used as the template to repair the damaged strand[49,50] Microhomology mediated end joining (MMEJ) repairs the double stranded breaks in the mt-DNA by randomly joining ends[49,50].

Mitochondrial Function and Dysfunction

Mitochondria are the principal sites for ATP production within a cell through oxidative phosphorylation[51-54]. The mitochondrial electron transport chain (ETC) is made up of 4 complexes (I-IV), these complexes receive an electron and transfer it to the next one[55-57]. The transfer of electrons is coupled with pumping of hydrogen ions from the matrix to the intermembrane space resulting in a proton gradient[57,58]. This proton gradient is used by ATP synthase to phosphorylate ADP to ATP and inorganic phosphate. This process is called chemiosmosis and is the primary method of ATP synthesis in mitochondria[59]. Mitochondria utilizes many substrates like glucose, amino acid, fatty acids to generate reducing agents e.g., NADH and FADH2.These substrates are oxidized in the tricarboxylic acid cycle and the β-oxidation pathway to generate electrons for the ETC (55,60). During the oxidative phosphorylation some of the electrons may escape from the ETC and react with oxygen forming reactive oxygen species ROS[55,61,62].

Mt-DNA mutations (mt-DNA) play a very important part in effecting mitochondrial function and have been linked to various diseases and disorders[63] emphasized the need of measuring mitochondrial heteroplasmy levels in mice models to better understand the effects of changed one-carbon metabolism on mt-DNA[64]. Furthermore, the effect of proteotoxicity on mitochondrial function has been studied in budding yeast, providing insight into gene dosage responses to mt-DNA depletion and mitochondrial protein stress[65]. MutPred scores have been used to predict the pathogenicity of mt-DNA variations on protein function in the context of neurocognitive performance in persons with HIV, indicating a potential relationship between mt-DNA mutations and cognitive impairment. Furthermore, the effects of iodine supplementation and mt-DNA mutations on papillary thyroid cancer in Saudi women eating a vegetarian diet were investigated, emphasizing the importance of understanding the role of environmental factors in conjunction with genetic mutations[66]. The interaction of iron, dopamine, and mitochondrial activity has been studied in the context of Parkinson's disease, demonstrating that dopamine treatment can improve mitochondrial fitness by increasing mitochondrial respiration and activating the antioxidant stress response[67].

Furthermore, the role of lysine acetylation in the function of mitochondrial ribosomal protein L12 has been investigated as a possible mechanism for regulating mitochondrial gene expression, highlighting the complex relationship between post-translational modifications and mitochondrial function[76]. Mitochondrial function is dependent on the coordinated expression of mitochondrial and nuclear genes, and mito-nuclear incompatibilities may influence nuclear compensatory evolution in response to damaging mt-DNA mutations[77].

Fig. 3 Effect of mitochondrial dysfunction on cells and eventually on organs

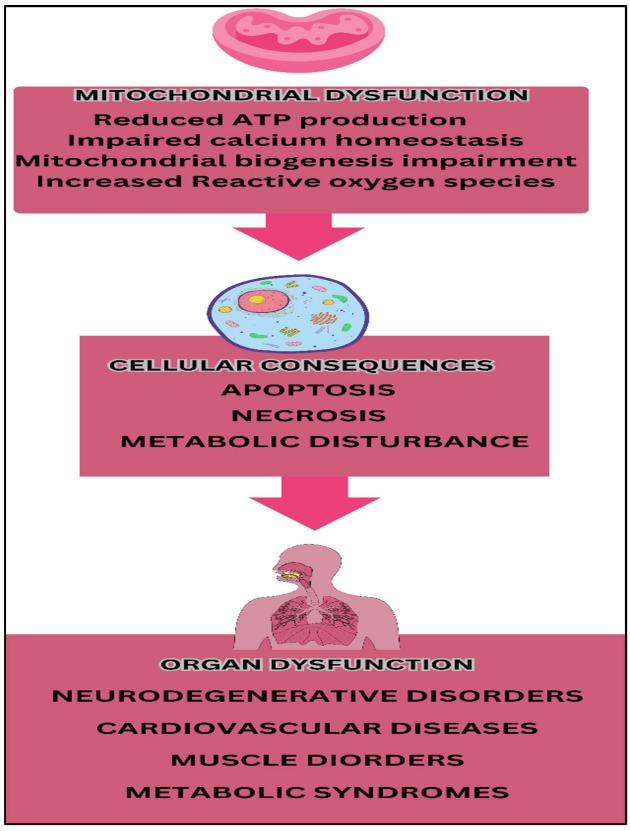


Table3: This table demonstrates the impact of Environmental Factors on mitochondrial DNA and their mechanism of action.

Environmental factors	Mechanism of action	Impact on mitochondria	References
Cigarette Smoke	Induces oxidative stress and mitochondrial DNA damage	decreased mitochondrial respiratory function	[68]
Alcohol Consumption	Increases production of reactive oxygen species (ROS)	Mitochondrial DNA mutations, impaired ATP production	[69]
Pesticide Exposure	Inhibits mitochondrial electron transport chain	Mitochondrial dysfunction, apoptosis	[70]
High-Fat Diet	Alters mitochondrial dynamics and biogenesis	Increased mitochondrial ROS production, insulin resistance	[71]
Ultraviolet (UV) Radiation	Causes direct DNA damage and increases ROS	Mitochondrial DNA deletions, impaired mitochondrial function	[72]
Air Pollution	Triggers oxidative stress and inflammation	Mitochondrial damage, reduced biogenesis	[73]
Heavy Metals (e.g., Lead, Mercury)	Inhibits mitochondrial enzymes, induces oxidative stress	Disrupted mitochondrial function, apoptosis	[74]
Radiation Exposure	Induces double strand breaks in DNA	Mitochondrial DNA mutations, cell death	[75]

Furthermore, the intrinsic complexity of mt-DNA related to genetic analysis has been explored, underlining the necessity for novel approaches to better understand the role of mt-DNA in human health and illness[70]. When mitochondria get debilitated, it can lead to the pathophysiology of many diseases. It produces reactive oxygen species (ROS) in human spermatozoa, causing oxidative stress, reduction in sperm formation, and events like apoptosis. Oxidative stress is leading cause of male infertility[71]**.** The debilitated mitochondria in combination with insufficiency of glymphatic system, is the main cause in the development of neurodegenerative diseases. This situation can cause clumping of misfolded proteins, inability of glymphatic clearance and neuroinflammation which can lead to the development of Alzheimer's Disease[80]. In this disease, failure of mitochondria, oxidative stress, and continuous neuroinflammation develop interrelated cascades that lead to the development of disease. Possible therapies direct oxidative stress and mitochondrial bioenergetics[73]. The collaboration between kidney and heart diseases is linked to impaired mitochondria, which leads to the outcomes such as deprived energy metabolism and cellular stress responses. Sustaining homeostasis of mitochondria can be a therapeutic option for cardiorenal syndrome[82]. In the conditions of cardiac failure, the inability of mitochondria to work properly is more than a failure for production of energy; including blockage of metabolic reactions, redox imbalances, and inflammation, which subsidize to heart diseases[83]. The deteriorated conditions of mitochondria in mesothelial cells is linked to the impairment of peritoneal membrane throughout dialysis of peritoneum, inferring that mt-DNA concentration in dialysate might be a biomarker indicating damage to membrane[84]**.** Pathophysiology of preeclampsia is also linked to disruption of mitochondrial function, even though additional research is required to understand the complete mechanism[85]. In SLE, immunological dysregulation occurs due to impaired mitochondria causing interaction of noncoding RNAs with oxidative stress. This interaction highlights the efficiency of antioxidant medications[86]. In PCOS, impaired mitochondria effects metabolic systems and reproductive organs, pointing towards a complex association between functions of mitochondria and reproductive pathology[63].

Mitochondrial Diseases: Findings have shown that mitochondrial genomics is central to human physiology and has been linked with numerous diseases ranging from metabolic diseases, neurodegenerative diseases or even the aging process. Mitochondrial dysfunction in relation to other complex disorders like diabetes and cardiovascular diseases has received a lot of focus and emphasis in recent studies. Undefined from a genetic point of view, mitochondrial diseases are caused by defects in the mt-DNA that led to impaired mitochondrial oxidative phosphorylation, with mutations, aging, infections, or certain lifestyles among the notable causes of diseases such as cancer, type-2 diabetes, cardiovascular diseases, or Alzheimer's diseases.

The genes of mitochondria have a very important role in many health conditions which include neurodegenerative diseases, metabolic syndromes, aging, diabetes, cardiovascular diseases, and cancer. The Mitochondria can lose its function by various conditions such as mutations, aging, Infections, and sedentary lifestyle can lead to disorders such as cancer, type 2 diabetes, cardiovascular disease, and Alzheimer's disease[87]. One study has shown that the mt-DNA mutations has role in the quality and quantity of mt-DNA which has affected fertility in both males and female gametes, impacting pregnancy[88].

Impact of Mitochondrial Genetics on Health Conditions: Mitochondria are the main cellular component of the production of energy, so decreased production of ATP affects muscle and brain which requires large amount of energy leading to metabolic conditions[88]. The inability of Mitochondria to function effectively has close association with the development of type 1 and type 2 diabetes .The reduction in synthesis of mitochondria other than normal and decreased oxidative phosphorylation is associated with insulin resistance and lost function of b cells of pancreas[88]. Particular mt-DNA variations like mutation in the gene A3243G are linked with a type of diabetes named mitochondrial diabetes which is associated with hearing loss[89]. One study has shown that impaired energy generation in mitochondria can lead to Mitochondrial Myopathy presented withmuscle weakness and exercise intolerance production. Mt-DNA variations like mutation in the gene A3243G is linked with a type of diabetes named mitochondrial diabetes which is associated with hearing loss[89]. One study has shown that impaired energy generation in mitochondria can lead to Mitochondrial Myopathy presented with muscle weakness and exercise intolerance production[90]. The mutations in mitochondrial genes encoding proteins of oxidative phosphorylation (OXPHOS) can lead to disruption in mitochondrial function, which can lead to impairment in ATP production, and increased production of reactive oxygen species (ROS), and metabolic pathways can be altered. The increased production of ROS could damage the components of cell, Including DNA, proteins, lipids of cell membrane that's why oxidative stress is a common characteristic of metabolic diseases[91]. Studies have shown that the mutations in mitochondrial genes especially genes encoding proteins of electron transport chain, have increased risk of metabolic conditions[92]. The mt-DNA variants can also lead to the development of MELAS Syndrome presenting muscle weakness, encephalopathy, lactic acidosis, and stroke-like episodes[93]. The apoptosis and cell death is also regulated by mitochondria, So the defective mitochondria can increase or decrease tissue condition leading to metabolic disorders[94].

The degradation of mitochondria on specific sites is also known as Mitophagy in which defected mitochondria accumulates in nerve cells leading to neurodegenerative diseases[95]. The impairment of mitochondrial function is a crucial sign in many neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). The nerve cells can die due to impaired mitochondria due to mechanisms such as oxidative stress, Impaired calcium homeostasis, and mitochondrial dynamics which can contribute to pathogenesis of these diseases[96,89]. The mitochondrial disorders arise from mutations in mt-DNA and nuclear genome, the connection between mt-DNA mutations and neurodegenerative disorders like Alzheimer's and Parkinson's diseases is still not known. The mitochondria undergo the process of mitochondrial dynamics (fusion and fission) to maintain their shape, distribution and size[98]. The Process of mitochondrial dynamics should be stable to maintain its function otherwise it will lead to neurodegeneration[99].

The important disease linked to impairment of mitochondria especially in substantia nigra is Parkinson's disease contributing to dopaminergic neuron degeneration. The main role of genes in Parkinson's disease are played by PINK1 and Parkin, which play a part in the quality control of mitochondria, are associated with familial variants of Parkinson's disease[100]. The deletions of mt-DNA and the mutations results in accumulation of impaired mitochondria in Nerve cells of Parkinson's Disease[101]. The inability of mitochondria to function properly can lead to the degeneration of motor neurons which leads to the pathogenesis of Amyotrophic Lateral Sclerosis (ALS).It is caused due to mutations in genes like SOD1, TDP-43, and C9orf72[102]. The observed features seen in ALS patients are lack of mitochondrial dynamics, bioenergetics, and increased oxidative stress[103]. Alzheimer's Disease (AD) is also caused due to mutations and deletions in the DNA content of mitochondria leading to its impaired function and death of neurons[104]. The function of mitochondria can be associated due to accumulation of Mitochondria-associated amyloid-beta (Aβ) accumulation which impairs the function of mitochondria, which increases oxidative stress and neuroinflammation[105]. The mutation in HTT gene due to CAG repeat expansion leads to impaired mitochondria and death of nerve cells**.** Study reveals that the synthesis and dynamics of mitochondria are changed in HD, leading to neurodegeneration[106]. The abnormal Huntington protein

weakens the function of mitochondria, dysregulates homeostasis of calcium and increases oxidative stress[107].

The reduction in the copy number and the quality of mt-DNA are linked to improper function of organelle in aging, drawing attention to the need for treatment to pay attention to pathologies resulting from mt-DNA mutations[108]The cells which age have reduced ATP production in mitochondria, influencing the most energy utilizing tissues such as brain and muscle. The impaired mitochondria is a common characteristic of aging[109]. The mutations in the DNA of mitochondria disrupts oxidative phosphorylation ,leads to decreased ATP production which leads to age related decrease in cell function[110]. The improper dynamics of mitochondria, leads to cellular aging and senescence[111]. The lost function of mitochondria is deeply connected to the process of aging .With increased age mt-DNA mutations get together in mitochondria and loss of function of mitochondria occur ,leading to cellular senescence, tissue degeneration, and age-related diseases. The lost function of mitochondria intensifies the oxidative stress and disrupts cellular homeostasis and triggers the aging process[112,113].

The Mitochondria has very important role function and differentiation of lipocytes abnormal conditions of mitochondria can impair lipid metabolism of the body, leading to obesity[114] changes in metabolic rate and the obesity are rare associated with polymorphisms in mt-DNA[115]. The Mitochondria has very important role in function and differentiation of lipocytes abnormal conditions of mitochondria can impair lipid metabolism of the body, leading to obesity[114]. The changes in metabolic rate and the obesity are associated with polymorphisms in mtDNA[115].

Table 4: This table shows the association of genetic defects of mitochondria with Cardiovascular Diseases.

Mitochondrial genetic defect	Associated cardiovascular diseases	References
Mutations in mitochondrial tRNA genes	Hypertrophic Cardiomyopathy	[122]
Mutations in mitochondrial DNA (mtDNA)	Dilated Cardiomyopathy	[123]
Mutations in mitochondrial complex I (ND genes)	Ischemic Heart Disease	[124]
Mitochondrial DNA deletions	Kearns-Sayre Syndrome (Cardiomyopathy)	[125]
Mutations in mitochondrial complex II (SDH genes)	Hypertension	[126]
Mutations in mitochondrial complex III (CYTB gene)	Arrhythmias	[127]
Mutations in mitochondrial complex IV (COX genes)	Cardiomyopathy	[128]
Mutations in ATP synthase (mt-ATP6)	Mitochondrial Myopathy (with Cardiac Involvement)	[129]
Mitochondrial DNA depletion syndrome	Heart Failure	[130]
Mutations in the mitochondrial D-loop region	Atherosclerosis	[131]

Table 1 This table shows the genetic defects of mitochondria that can cause various cancers.

Mitochondrial Genetic Defects	Associated cancer	Reference
Mutations in mitochondrial DNA	Breast cancer	[135]
Mitochondrial DNA deletions	Pancreatic cancer	[136]
Mutations in mitochondrial complex I (ND genes)	Liver cancer	[137]
Mutations in mitochondrial complex II (SDH genes)	Paraganglioma, Pheochromocytoma	[138]
Mutations in mitochondrial complex III (CYTB gene)	Colorectal Cancer	[139]
Mutations in mitochondrial complex IV (COX genes)	Prostate Cancer	[140]
Mitochondrial DNA depletion syndrome	Renal cancer	[141]
Mutations in tRNA genes	Gastric cancer	[142]
Mutations in ATP synthase (mt-ATP6)	Brain Cancer (Glioblastoma)	[143]
Mutations in the mitochondrial D-loop region	Head and Neck Cancers	[144]

The lost function of mitochondria leads to the development of diabetes by disrupting insulin secretion and mode of action, promoting β-cell impairment, and triggers insulin resistance in peripheral tissues. Mutations in mt-DNA and nuclear-encoded mitochondrial genes have related to an increased risk of diabetes and its complications[116,117]. The impairment of mitochondrial function plays a crucial role in the pathogenesis of cardiovascular diseases such as heart failure, ischemic heart disease, and cardiomyopathies. When mitochondria lose its function energy depletion, increased oxidative stress, and impaired calcium handling, occurs which can lead to myocardial dysfunction and cardiac remodeling[118,119]. The dysregulation of function of mitochondria plays a crucial role in the pathogenesis of cardiovascular diseases, including cardiomyopathy and atherosclerosis[92]. The mutations in the genes of mitochondria is associated with impaired oxidative phosphorylation, increasing increased reactive oxygen species (ROS),and cell death, leading to cardiovascular diseases[120]. The DNA of mitochondria codes for 13 proteins which play important role in electron transport chain and oxidative phosphorylation, and also contains genetic information of 22 tRNAs and 2 rRNAs for protein synthesis of mitochondria.mt-DNA is inherited from mothers unlike nuclear DNA that why it is more likely to be mutated because of less repair mechanisms and closeness to ROS production sites[121].

The different conditions of mt-DNA and disruption of its genes are linked with survival outcomes in cancer patients, shows the importance of link between nuclear and mitochondrial genes in cellular function. Mt-DNA variations and dysregulation of mitochondria-encoded genes are associated with cancer [125]. The mt-DNA mutants impact the development of cancer and by many processes, including altered energy metabolism, evasion of apoptosis, and promotion of tumor cell proliferation, facilitating tumor growth and metastasis[133,134].

Current Treatments for Mitochondrial Diseases

1. Nutritional Supplements and Pharmacological Agents: many pharmaceutical drugs and nutrients are being utilized to improve the function of mitochondria and to improve the signs and symptoms. They are hypothesized to aid in the energy synthesis of cell and include antioxidants, vitamins, and co-factors. Many clinical trials are conducted to test the effectiveness of these supportive therapies whose results have been mixed up and further research is required to determine the true impact on human body[145].

2. Biochemical Approaches: Some interventions involve an increase in electron transport and the availability of substrates in electron transport chain. They impact biosynthesis of mitochondria and decrease reactive oxygen species (ROS). Special pharmaceutical strategies are employed to serve these purposes. [146]As oxidative stress is the main cause of the impairment of mitochondrial function, and it is mainly due to ROS so antioxidants are being employed to scratch out ROS and reduce oxidative stress

3. Gene Therapy and Allotopic Expression: Leber Hereditary Optic Neuropathy (LHON), In this type of therapy, a mitochondrial gene named ND4 involved in the electron transport chain of mitochondria is transported to cell nucleus for expression, by mechanism known as allotropic expression. It is a promising strategy toward treating LHON which affects vision[145].

4. Mt-DNA Maintenance Disorders: Some trials are being conducted clinically which have been proven successful. Some approaches include to understand the biochemical process of the replication of DNA of mitochondria which has shown promising treatment aspects, includes enhancement of small molecule substrate and gene therapy with the help of adenovirus or lentivirus vectors[147].

5. Physical Exercise and Lifestyle Interventions: The health of mitochondria can be improved with diet and including daily exercise in life.They have been shown to increase synthesis and function of mitochondria, with the potential of treating symptoms in patients with mitochondrial disease[148].

Researchers are conducting research in transplantation of mitochondria into damaged cells to restore their function which has shown promising results in the treatment of diseases of mitochondria[138]. Most common gene editing techniques such as CRISPR Cas 9 can repair genetic mutations in order to treat mitochondrial diseases, but they are still in the stage of experiments. A novel strategy in the treatment of mitochondrial diseases involves Ibudilast which is inhibitor of phosphodiesterase. Its clinical and preclinical trials are being conducted to treat mitochondrial related neurodegenerative diseases and it has proven successful to reduce inflammation, oxidative stress, and apoptosis[150].

Mitochondrial Gene therapy hopes to replace genes having faults by healthier gene in order to improve the genetic bases of diseases associated with dysfunction of mitochondria and is currently under investigation on effective and targeted methods of delivery[151]. Current investigations have focused on treatments that aim at treating maintenance disorders of mitochondria .These strategies include gene therapies associated with lentivirus or adenovirus ,has been proven successful in evaluating the human health outcomes in clinical and pre-clinical trials[152].

Parkinson's disease shows a main characteristic of impaired mitochondrial function. So, gene therapies are being employed to improve the function of mitochondria, especially in monogenic and idiopathic forms, showing promising results. Still investigations are being conducted on how to develop and deliver these therapies more effectively[153].

A novel strategy is developed to separate synaptic and non-synaptic mitochondria from brain tissue known as Fractionated mitochondrial magnetic separation (FMMS). This technique has proven to detect mitochondrial dysfunction in the inflammation of central nervous system and neurodegenerative disorders, and it is better technique for assessment of brain derived mitochondria because it is better obtained[154].

Another experimental treatment is the PPARγ agonist which penetrates the brain has shown improvements in nervous system of experimental mouse models of X-linked adrenoleukodystrophy (X-ALD). It decreases nervous system related injuries and has shown potential to cure nervous system degeneration and neuroinflammation because of its ability to improve mitochondrial dysfunction[155]. The synthesis of mitochondria is greatly influenced by PGC-1α.Some therapeutic approaches in order to increase PGC-1α have shown great effects in improvement of urinary system in animal models of chronic kidney injury (CKD) or acute kidney injury (AKI).This types of therapies can also be used to treat mitochondria associated diseases by enhancement of mitochondrial synthesis and improvement of its dysfunction[156].

A future research direction is towards the modification of the genetic profiles of individuals with the emergence of personalized medicine. Genome editing systems such as CRISPR-Cas9 have the capability to correct genetic mutations which are responsible for impairment of mitochondrial function. Investigations are now being conducted on the mechanisms of delivery improving the long-term safety and effectiveness of these type of gene therapies[151].

Some drugs target mitochondrial biosynthesis and are in active research. PPARγ agonist decreases nervous system related injuries and has shown potential to cure nervous system degeneration and neuroinflammation because of its ability to improve mitochondrial dysfunction[157]. The synthesis of mitochondria is greatly influenced by PGC-1α.Some therapeutic approaches in order to increase PGC-1α have shown great effects in improvement of urinary system in animal models of chronic kidney injury (CKD) or acute kidney injury (AKI).This types of therapies can also be used to treat mitochondria associated diseases by enhancement of mitochondrial synthesis and improvement of its dysfunction[158].

Challenges in Treatment: The diseases associated with mitochondria have different signs and symptoms, so it is complicated to develop a universal cure. The diagnosis and cure are tough because of the complicity of both mitochondrial and nuclear DNA and genetic heterogeneity. Precision medicine is required to assess the needs of each individual with mitochondrial disease[151]. The most important complication in gene therapy and the transplantation of mitochondria is to make sure that these treatment approaches have reached their targeted cells systematically. Some advances in drug delivery systems such as nanoparticles and viral vectors are required for the enhancement of target and intake of these therapies[159]. The continuous verification of the novel medicines is an obstacle. There can be several side effects which involve unexpected genetic modifications or there can be activation of immune responses towards viral vectors, so they need to be examined in preclinical and clinical trials. So, Research should be continuously carried out in order to reduce these dangers and improve these therapeutic strategies[160]. There is a complication in gathering enough participants in clinical trials to evaluate the health outcomes as mitochondrial diseases are very rare. Further trials should also be designed to describe the genetic and phenotypic diversity of these diseases. Corporative attempts and international registries can knock over these queries and can led to the development of novel therapeutic strategies[157].

CONCLUSION

The study of mitochondrial genetics has evident impact on human health, bridging the gap between mitochondrial function, mutations and a wide range of diseases. Mitochondria are not only essential for energy production but are versatile cellular organelles playing crucial roles in cellular process. The unique characteristics of mt-DNA like high mutation rate, maternal inheritance and the presence of heteroplasmy maki it a vital area of research for understanding the basis of human pathology.

One of the most significant insights gained from research in this field is the link between mt-DNA and various disorders. Mutations in the mt-DNA can lead to a wide range of diseases such as mitochondrial myopathies, encephalopathies and neurodegenerative disorders like Alzheimer's and Parkinson's disease. These mutations disrupt the normal function of mitochondria leading to impaired energy production and the generation of reactive oxygen species (ROS) which damages the cell and contributes to the progression of diseases. The study of mt-DNA has also shone light on its role in complex diseases such as type 2 diabetes, cardiovascular diseases, and certain cancers emphasizing on the broader implication of mitochondrial dysfunction on human health.

Research in this area has also shown that mitochondrial dysfunction is not only associated with genetic mutations but also environmental factors, lifestyles choices and aging. For example, oxidative stress which is due to the imbalance between the production of ROS and the body's ability to detoxify them, has been implicated in in the pathophysiology of several diseases. Mitochondrial-DNA is especially prone to oxidative damage due to its proximity to the electron transport chain, where these ROS are generated.

Mitochondrial genetics also has its influence on reproductive health, with studies showing that mt-DNA mutations can affect fertility and health of an offspring. The maternal inheritance of the mt-DNA means that mutations in the maternal mt-DNA can be inherited by the progeny, potentially leading to inherited mitochondrial disorders. This aspect of mitochondrial genetics is vital for our understanding of inherited disorders and developing interventions to prevent or mitigate these conditions.

In conclusion the study of mitochondrial genetics has revolutionized our understanding of mitochondrial function in human pathology the unique properties of mt-DNA and its central role in cellular processes makes it a critical focus point of research for understanding wide array of disease. As our collective knowledge of mitochondrial genetics continues to grow it opens new frontiers for diagnosing, treating and preventing mitochondrial

diseases and ultimately contributing to better understanding of human health.

Conflict of Interest: The Authors of this Manuscript declared no Conflict of Interest.

REFERENCES

1. S. Madan, B. Uttekar, S. Chowdhary, and R. Rikhy, "Mitochondria Lead the Way: Mitochondrial Dynamics and Function in Cellular Movements in Development and Disease," *Front Cell Dev Biol*, vol. 9, Feb. 2022, doi: 10.3389/fcell.2021.781933.
2. L. Wang *et al.*, "GCN5L1 modulates cross-talk between mitochondria and cell signaling to regulate FoxO1 stability and gluconeogenesis," *Nat Commun*, vol. 8, no. 1, p. 523, Sep. 2017, doi: 10.1038/s41467-017-00521-8.
3. A. V. Kuznetsov, R. Margreiter, M. J. Ausserlechner, and J. Hagenbuchner, "The Complex Interplay between Mitochondria, ROS and Entire Cellular Metabolism," *Antioxidants*, vol. 11, no. 10, p. 1995, Oct. 2022, doi: 10.3390/antiox11101995.
4. S. Yanagida, K. Osabe, T. Nagai, and N. Murakami, "Quantum chemistry molecular modeling for longevity: Importance of antioxidative effects in mitochondria as battery of cells," *Integr Mol Med*, vol. 6, no. 5, 2019, doi: 10.15761/IMM.1000380.
5. J. Cai, F. Wang, and M. Shao, "The Emerging Importance of Mitochondria in White Adipocytes: Neither Last nor Least," *Endocrinology and Metabolism*, vol. 38, no. 5, pp. 493–503, Oct. 2023, doi: 10.3803/EnM.2023.1813.
6. N. K. Bennett, M. Lee, A. L. Orr, and K. Nakamura, "Systems-level analyses dissociate genetic regulators of reactive oxygen species and energy production.," *bioRxiv*, Oct. 2023, doi: 10.1101/2023.10.14.562276.
7. A. Raffaello, C. Mammucari, G. Gherardi, and R. Rizzuto, "Calcium at the Center of Cell Signaling: Interplay between Endoplasmic Reticulum, Mitochondria, and Lysosomes," *Trends Biochem Sci*, vol. 41, no. 12, pp. 1035–1049, Dec. 2016, doi: 10.1016/j.tibs.2016.09.001.
8. S. Madan, B. Uttekar, S. Chowdhary, and R. Rikhy, "Mitochondria Lead the Way: Mitochondrial Dynamics and Function in Cellular Movements in Development and Disease," *Front Cell Dev Biol*, vol. 9, Feb. 2022, doi: 10.3389/fcell.2021.781933.
9. S. K. Ghosh-Choudhary, J. Liu, and T. Finkel, "The role of mitochondria in cellular senescence," *The FASEB Journal*, vol. 35, no. 12, Dec. 2021, doi: 10.1096/fj.202101462R.
10. Y. Luan, Y. Luan, R.-X. Yuan, Q. Feng, X. Chen, and Y. Yang, "Structure and Function of Mitochondria-Associated Endoplasmic Reticulum Membranes (MAMs) and Their Role in Cardiovascular Diseases," *Oxid Med Cell Longev*, vol. 2021, pp. 1–19, Jul. 2021, doi: 10.1155/2021/4578809.
11. V. F. Gonçalves, "Mitochondrial Genetics," 2019, pp. 247–255. doi: 10.1007/978-981-13-8367-0_13.
12. A. Manickam, M. Michael, and S. Ramasamy, "Mitochondrial genetics and therapeutic overview of Leber's hereditary optic neuropathy," *Indian J Ophthalmol*, vol. 65, no. 11, p. 1087, 2017, doi: 10.4103/ijo.IJO_358_17.
13. I. G. Arena, A. Pugliese, S. Volta, A. Toscano, and O. Musumeci, "Molecular Genetics Overview of Primary Mitochondrial Myopathies," *J Clin Med*, vol. 11, no. 3, p. 632, Jan. 2022, doi: 10.3390/jcm11030632.
14. X. Fu and L. Ballantyne, "An Overview of Aquatica Fu et al., a Phylogeny of Aquatic Fireflies Using Mitochondrial Genomes, a Description of Two New Species, and a New Record of Aquatic Fireflies in China (Coleoptera: Lampyridae: Luciolinae)," *Insects*, vol. 15, no. 1, p. 31, Jan. 2024, doi: 10.3390/insects15010031.
15. J.-W. Taanman and A. M. Kroon, "Mitochondrial DNA: Structure, Genetics, Replication and Defects," in *Mitochondria in Obesity and Type 2 Diabetes*, Elsevier, 2019, pp. 127–152. doi: 10.1016/B978-0-12-811752-1.00005-5.
16. Y. Tikochinski, C. Carreras, G. Tikochinski, and S. T. Vilaça, "Population-specific signatures of intra-individual mitochondrial DNA heteroplasmy and their potential evolutionary advantages," *Sci Rep*, vol. 10, no. 1, p. 211, Jan. 2020, doi: 10.1038/s41598-019-56918-6.
17. A. Hahn and S. Zuryn, "The Cellular Mitochondrial Genome Landscape in Disease," *Trends Cell Biol*, vol. 29, no. 3, pp. 227–240, Mar. 2019, doi: 10.1016/j.tcb.2018.11.004.
18. M. Yu, "Somatic Mitochondrial DNA Mutations in Human Cancers," 2012, pp. 99–138. doi: 10.1016/B978-0-12-394384-2.00004-8.
19. M. Yu, "Generation, function and diagnostic value of mitochondrial DNA copy number alterations in human cancers," *Life Sci*, vol. 89, no. 3–4, pp. 65–71, Jul. 2011, doi: 10.1016/j.lfs.2011.05.010.
20. V. Doublet, R. Raimond, F. Grandjean, A. Lafitte, C. Souty-Grosset, and I. Marcadé, "Widespread atypical mitochondrial DNA structure in isopods (Crustacea, Peracarida) related to a constitutive heteroplasmy in terrestrial species," *Genome*, vol. 55, no. 3, pp. 234–244, Mar. 2012, doi: 10.1139/g2012-008.
21. F. Karimian *et al.*, "Phylogenetic Analysis of the Oriental-Palearctic-Afrotropical Members of Anopheles (Culicidae: Diptera) Based on Nuclear rDNA and Mitochondrial DNA Characteristics," *Jpn J Infect Dis*, vol. 67, no. 5, pp. 361–367, 2014, doi: 10.7883/yoken.67.361.
22. D. R. Wolstenholme, "Animal Mitochondrial DNA: Structure and Evolution," 1992, pp. 173–216. doi: 10.1016/S0074-7696(08)62066-5.
23. M. A. Sazonova *et al.*, "Mutations of mtDNA in some Vascular and Metabolic Diseases," *Curr Pharm Des*, vol. 27, no. 2, pp. 177–184, Jan. 2021, doi: 10.2174/1381612826999200820162154.
24. M. Tanaka, Á. Szabó, E. Spekker, H. Polyák, F. Tóth, and L. Vécsei, "Mitochondrial Impairment: A Common Motif in Neuropsychiatric Presentation? The Link to the Tryptophan–Kynurenine Metabolic System," *Cells*, vol. 11, no. 16, p. 2607, Aug. 2022, doi: 10.3390/cells11162607.
25. S. E. Hasnain, "A Link between Mitochondrial DNA Haplogroup and Ischemia," *Medical Principles and Practice*, vol. 20, no. 3, pp. 201–202, 2011, doi: 10.1159/000323839.
26. Schapira and Cock, "Mitochondrial myopathies and encephalomyopathies," *Eur J Clin Invest*, vol. 29, no. 10, pp. 886–898, Oct. 1999, doi: 10.1046/j.1365-2362.1999.00540.x.
27. R. Gyawali and X. Lin, "Prezygotic and Postzygotic Control of Uniparental Mitochondrial DNA Inheritance in Cryptococcus neoformans," *mBio*, vol. 4, no. 2, May 2013, doi: 10.1128/mBio.00112-13.
28. S. Luo *et al.*, "Biparental Inheritance of Mitochondrial DNA in Humans," *Proceedings of the National Academy of Sciences*, vol. 115, no. 51, pp. 13039–13044, Dec. 2018, doi: 10.1073/pnas.1810946115.
29. E. Zouros, A. Oberhauser Ball, C. Saavedra, and K. R. Freeman, "An unusual type of mitochondrial DNA inheritance in the blue mussel Mytilus.," *Proceedings of the National Academy of Sciences*, vol. 91, no. 16, pp. 7463–7467, Aug. 1994, doi: 10.1073/pnas.91.16.7463.
30. F. Alves, C. Beasley, W. Hoeh, R. Rocha, L. Simone, and C. Tagliaro, "Detection of mitochondrial DNA heteroplasmy suggests a doubly uniparental inheritance pattern in the mussel Mytella charruana," *Revista Brasileira de Biociências*, vol. 4849, pp. 176–185, Apr. 2012.
31. S. Luo *et al.*, "Biparental Inheritance of Mitochondrial DNA in Humans," *Proceedings of the National Academy of Sciences*, vol. 115, no. 51, pp. 13039–13044, Dec. 2018, doi: 10.1073/pnas.1810946115.
32. S. Annis *et al.*, "Quasi-Mendelian paternal inheritance of mitochondrial DNA: A notorious artifact, or anticipated behavior?," *Proceedings of the National Academy of Sciences*, vol. 116, no. 30, pp. 14797–14798, Jul. 2019, doi: 10.1073/pnas.1821436116.
33. S. A. Dabravolski, V. A. Khotina, V. N. Sukhorukov, V. A. Kalmykov, L. M. Mikhaleva, and A. N. Orekhov, "The Role of Mitochondrial DNA Mutations in Cardiovascular Diseases," *Int J Mol Sci*, vol. 23, no. 2, p. 952, Jan. 2022, doi: 10.3390/ijms23020952.
34. B. Heuer and D. C. Seibert, "Understanding the nomenclature of mitochondrial DNA mutations through examples of two specific disease entities: Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes and Leber hereditary optic neuropathy," *J Am Assoc Nurse Pract*, vol. 34, no. 2, pp. 217–219, Feb. 2022, doi: 10.1097/JXX.0000000000000693.
35. X.-L. Yu *et al.*, "Clinical, Neuroimaging, and Pathological Analyses of 13 Chinese Leigh Syndrome Patients with Mitochondrial DNA Mutations," *Chin Med J (Engl)*, vol. 131, no. 22, pp. 2705–2712, Nov. 2018, doi: 10.4103/0366-6999.245265.
36. S. Bannwarth *et al.*, "Prevalence of rare mitochondrial DNA mutations in mitochondrial disorders," *J Med Genet*, vol. 50, no. 10, pp. 704–714, Oct. 2013, doi: 10.1136/jmedgenet-2013-101604.
37. S. C. E. H. Sallevelt *et al.*, "Preimplantation genetic diagnosis for mitochondrial DNA mutations: analysis of one blastomere suffices," *J Med Genet*, vol. 54, no. 10, pp. 693–697, Oct. 2017, doi: 10.1136/jmedgenet-2017-104633.
38. N. Wolf, F. Ebinger, D. Rating, and T. Bast, "Epilepsies in mitochondrial disorders: seizure types and history," *Neuropediatrics*, vol. 37, no. 03, Sep. 2006, doi: 10.1055/s-2006-953562.
39. L. Morató *et al.*, "Mitochondrial dysfunction in central nervous system white matter disorders," *Glia*, vol. 62, no. 11, pp. 1878–1894, Nov. 2014, doi: 10.1002/glia.22670.
40. P. Ruiz-Sala and L. Peña-Quintana, "Biochemical Markers for the Diagnosis of Mitochondrial Fatty Acid Oxidation Diseases," *J Clin Med*, vol. 10, no. 21, p. 4855, Oct. 2021, doi: 10.3390/jcm10214855.
41. S. A. Dabravolski *et al.*, "The Role of Mitochondrial Mutations and Chronic Inflammation in Diabetes," *Int J Mol Sci*, vol. 22, no. 13, p. 6733, Jun. 2021, doi: 10.3390/ijms22136733.
42. C. Giorgi, S. Marchi, and P. Pinton, "The machineries, regulation and cellular functions of mitochondrial calcium," *Nat Rev Mol Cell Biol*, vol. 19, no. 11, pp. 713–730, Nov. 2018, doi: 10.1038/s41580-018-0052-8.
43. L. E. Gyllenhammer, S. Entringer, C. Buss, and P. D. Wadhwa, "Developmental programming of mitochondrial biology: a conceptual framework and review," *Proceedings of the Royal Society B: Biological Sciences*, vol. 287, no. 1926, May 2020, doi: 10.1098/rspb.2019.2713.
44. L. A. Zinovkina, "Mechanisms of Mitochondrial DNA Repair in Mammals," *Biochemistry (Moscow)*, vol. 83, no. 3, pp. 233–249, Mar. 2018, doi: 10.1134/S0006297918030045.
45. A. D. N. J. De Grey, "Reactive Oxygen Species Production in the Mitochondrial Matrix: Implications for the Mechanism of Mitochondrial Mutation Accumulation," *Rejuvenation Res*, vol. 8, no. 1, pp. 13–17, Mar. 2005, doi: 10.1089/rej.2005.8.13.
46. M. Sanchez-Contreras *et al.*, "A replication-linked mutational gradient drives somatic mutation accumulation and influences germline polymorphisms and genome composition in mitochondrial DNA," *Nucleic Acids Res*, vol. 49, no. 19, pp. 11103–11118, Nov. 2021, doi: 10.1093/nar/gkab901.
47. D. Schniertshauer, D. Gebhard, and J. Bergemann, "Real-time Base Excision Repair Assay to Measure the Activity of the 8-oxoguanine DNA Glycosylase 1 in Isolated Mitochondria of Human Skin Fibroblasts," *Bio Protoc*, vol. 11, no. 6, 2021, doi: 10.21769/BioProtoc.3954.
48. M. A. Lovell and W. R. Markesbery, "Oxidative DNA damage in mild cognitive impairment and late-stage Alzheimer's disease," *Nucleic Acids Res*, vol. 35, no. 22, pp. 7497–7504, Nov. 2007, doi: 10.1093/nar/gkm821.
49. V. Bazzani, M. Equisoain Redin, J. McHale, L. Perrone, and C. Vascotto, "Mitochondrial DNA Repair in Neurodegenerative Diseases and Ageing," *Int J Mol Sci*, vol. 23, no. 19, p. 11391, Sep. 2022, doi: 10.3390/ijms231911391.
50. K. Allkanjari and R. A. Baldock, "Beyond base excision repair: an evolving picture of mitochondrial DNA repair," *Biosci Rep*, vol. 41, no. 10, Oct. 2021, doi: 10.1042/BSR20211320.
51. P. Andrieux, C. Chevillard, E. Cunha-Neto, and J. P. S. Nunes, "Mitochondria as a Cellular Hub in Infection and Inflammation," *Int J Mol Sci*, vol. 22, no. 21, p. 11338, Oct. 2021, doi: 10.3390/ijms222111338.
52. M. Ott, V. Gogvadze, S. Orrenius, and B. Zhivotovsky, "Mitochondria, oxidative stress and cell death," *Apoptosis*, vol. 12, no. 5, pp. 913–922, May 2007, doi: 10.1007/s10495-007-0756-2.
53. S. B. Yu and G. Pekkurnaz, "Mechanisms Orchestrating Mitochondrial Dynamics for Energy Homeostasis," *J Mol Biol*, vol. 430, no. 21, pp. 3922–3941, Oct. 2018, doi: 10.1016/j.jmb.2018.07.027.
54. E. Kummer and N. Ban, "Mechanisms and regulation of protein synthesis in mitochondria," *Nat Rev Mol Cell Biol*, vol. 22, no. 5, pp. 307–325, May 2021, doi: 10.1038/s41580-021-00332-2.

55. R. Zhao, S. Jiang, L. Zhang, and Z. Yu, "Mitochondrial electron transport chain, ROS generation and uncoupling (Review)," *Int J Mol Med*, May 2019, doi: 10.3892/ijmm.2019.4188.
56. L. K. Billingham *et al.*, "Mitochondrial electron transport chain is necessary for NLRP3 inflammasome activation," *Nat Immunol*, vol. 23, no. 5, pp. 692–704, May 2022, doi: 10.1038/s41590-022-01185-3.
57. D. Nolfi-Donegan, A. Braganza, and S. Shiva, "Mitochondrial electron transport chain: Oxidative phosphorylation, oxidant production, and methods of measurement," *Redox Biol*, vol. 37, p. 101674, Oct. 2020, doi: 10.1016/j.redox.2020.101674.
58. A. Alexandre, B. Reynafarje, and A. L. Lehninger, "Stoichiometry of vectorial H^+ movements coupled to electron transport and to ATP synthesis in mitochondria," *Proceedings of the National Academy of Sciences*, vol. 75, no. 11, pp. 5296–5300, Nov. 1978, doi: 10.1073/pnas.75.11.5296.
59. Y. HATEFI, "ATP synthesis in mitochondria," *Eur J Biochem*, vol. 218, no. 3, pp. 759–767, Dec. 1993, doi: 10.1111/j.1432-1033.1993.tb18431.x.
60. Y. Liu *et al.*, "An Overview: The Diversified Role of Mitochondria in Cancer Metabolism," *Int J Biol Sci*, vol. 19, no. 3, pp. 897–915, 2023, doi: 10.7150/ijbs.81609.
61. J. St-Pierre, J. A. Buckingham, S. J. Roebuck, and M. D. Brand, "Topology of Superoxide Production from Different Sites in the Mitochondrial Electron Transport Chain," *Journal of Biological Chemistry*, vol. 277, no. 47, pp. 44784–44790, Nov. 2002, doi: 10.1074/jbc.M207217200.
62. S. Chenna, W. J. H. Koopman, J. H. M. Prehn, and N. M. C. Connolly, "Mechanisms and mathematical modeling of ROS production by the mitochondrial electron transport chain," *American Journal of Physiology-Cell Physiology*, vol. 323, no. 1, pp. C69–C83, Jul. 2022, doi: 10.1152/ajpcell.00455.2021.
63. K. M. Siemers, A. K. Klein, and M. L. Baack, "Mitochondrial Dysfunction in PCOS: Insights into Reproductive Organ Pathophysiology," *Int J Mol Sci*, vol. 24, no. 17, p. 13123, Aug. 2023, doi: 10.3390/ijms241713123.
64. R.-H. Hsieh, J.-Y. Li, C.-Y. Pang, and Y.-H. Wei, "A novel mutation in the mitochondrial 16S rRNA gene in a patient with MELAS syndrome, diabetes mellitus, hyperthyroidism and cardiomyopathy," *J Biomed Sci*, vol. 8, no. 4, pp. 328–335, Jul. 2001, doi: 10.1007/BF02258374.
65. J. T. McNamara, J. Zhu, Y. Wang, and R. Li, "Gene dosage adaptations to mtDNA depletion and mitochondrial protein stress in budding yeast," *G3: Genes, Genomes, Genetics*, vol. 14, no. 2, Feb. 2024, doi: 10.1093/g3journal/jkad272.
66. M. T. Lin and M. F. Beal, "Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases," *Nature*, vol. 443, no. 7113, pp. 787–795, Oct. 2006, doi: 10.1038/nature05292.
67. M. S. Sharpley *et al.*, "Heteroplasmy of Mouse mtDNA Is Genetically Unstable and Results in Altered Behavior and Cognition," *Cell*, vol. 151, no. 2, pp. 333–343, Oct. 2012, doi: 10.1016/j.cell.2012.09.004.
68. N. Puri and A. W. Karzai, "HspQ Functions as a Unique Specificity-Enhancing Factor for the AAA+ Lon Protease," *Mol Cell*, vol. 66, no. 5, pp. 672-683.e4, Jun. 2017, doi: 10.1016/J.MOLCEL.2017.05.016.
69. B. Rosner, N. Cook, R. Portman, S. Daniels, and B. Falkner, "Determination of blood pressure percentiles in normal-weight children: some methodological issues," *Am J Epidemiol*, vol. 167, no. 6, pp. 653–666, Mar. 2008, doi: 10.1093/AJE/KWM348.
70. D. K. Whynes, R. A. McCahon, A. Ravenscroft, V. Hodgkinson, R. Evley, and J. G. Hardman, "Responsiveness of the EQ-5D health-related quality-of-life instrument in assessing low back pain," *Value Health*, vol. 16, no. 1, pp. 124–132, Jan. 2013, doi: 10.1016/J.JVAL.2012.09.003.
71. H. Christian Riis, M. H. Jensen, S. L. Cichosz, and O. K. Hejlesen, "Prediction of exacerbation onset in chronic obstructive pulmonary disease patients," *J Med Eng Technol*, vol. 40, no. 1, pp. 1–7, Jan. 2016, doi: 10.3109/03091902.2015.1105317.
72. J. O. Lee *et al.*, "Antimelanogenesis and skin-protective activities of Panax ginseng calyx ethanol extract," *J Ginseng Res*, vol. 42, no. 3, pp. 389–399, Jul. 2018, doi: 10.1016/J.JGR.2018.02.007.
73. J. Michely, F. Rigoli, R. B. Rutledge, T. U. Hauser, and R. J. Dolan, "Distinct Processing of Aversive Experience in Amygdala Subregions," *Biol Psychiatry Cogn Neurosci Neuroimaging*, vol. 5, no. 3, pp. 291–300, Mar. 2020, doi: 10.1016/J.BPSC.2019.07.008.
74. R. D. Sonawane, V. B. Deore, S. D. Patil, C. R. Patil, S. J. Surana, and R. K. Goyal, "Role of 5-HT2 receptors in diabetes: Swertiamarin seco-iridoid glycoside might be a possible 5-HT2 receptor modulator," *Physiol Behav*, vol. 144, pp. 66–72, May 2015, doi: 10.1016/J.PHYSBEH.2015.02.036.
75. A. Nordez *et al.*, "Non-Muscular Structures Can Limit the Maximal Joint Range of Motion during Stretching," *Sports Med*, vol. 47, no. 10, pp. 1925–1929, Oct. 2017, doi: 10.1007/S40279-017-0703-5.
76. K. V. Paluch, K. R. Platz, E. J. Rudisel, R. R. Erdmann, T. R. Laurin, and K. E. Dittenhafer-Reed, "The role of lysine acetylation in the function of mitochondrial ribosomal protein <scp>L12</scp>," *Proteins: Structure, Function, and Bioinformatics*, vol. 92, no. 5, pp. 583–592, May 2024, doi: 10.1002/prot.26654.
77. D. Princepe and M. A. M. de Aguiar, "Nuclear compensatory evolution driven by mito-nuclear incompatibilities," Mar. 2024, Accessed: Aug. 20, 2024. [Online]. Available: https://arxiv.org/abs/2403.10411v1
78. L. A. Hyslop *et al.*, "Towards clinical application of pronuclear transfer to prevent mitochondrial DNA disease," *Nature*, vol. 534, no. 7607, pp. 383–386, Jun. 2016, doi: 10.1038/nature18303.
79. C. Castellini *et al.*, "Pathophysiology of Mitochondrial Dysfunction in Human Spermatozoa: Focus on Energetic Metabolism, Oxidative Stress and Apoptosis," *Antioxidants*, vol. 10, no. 5, p. 695, Apr. 2021, doi: 10.3390/antiox10050695.
80. "Glymphatic System and Mitochondrial Dysfunction as Two Crucial Players in Pathophysiology of Neurodegenerative Disorders".
81. F. L. Andronie-Cioara *et al.*, "Molecular Mechanisms of Neuroinflammation in Aging and Alzheimer's Disease Progression," *Int J Mol Sci*, vol. 24, no. 3, p. 1869, Jan. 2023, doi: 10.3390/ijms24031869.
82. S. Shi *et al.*, "Mitochondrial Dysfunction: An Emerging Link in the Pathophysiology of Cardiorenal Syndrome," *Front Cardiovasc Med*, vol. 9, Feb. 2022, doi: 10.3389/fcvm.2022.837270.
83. B. Zhou and R. Tian, "Mitochondrial dysfunction in pathophysiology of heart failure," *Journal of Clinical Investigation*, vol. 128, no. 9, pp. 3716–3726, Aug. 2018, doi: 10.1172/JCI120849.
84. O. Ramil-Gómez *et al.*, "Mitochondrial Dysfunction Plays a Relevant Role in Pathophysiology of Peritoneal Membrane Damage Induced by Peritoneal Dialysis," *Antioxidants*, vol. 10, no. 3, p. 447, Mar. 2021, doi: 10.3390/antiox10030447.
85. R. D. Williamson, F. P. McCarthy, A. S. Khashan, A. Totorika, L. C. Kenny, and C. McCarthy, "Exploring the role of mitochondrial dysfunction in the pathophysiology of pre-eclampsia," *Pregnancy Hypertens*, vol. 13, pp. 248–253, Jul. 2018, doi: 10.1016/j.preghy.2018.06.012.
86. C.-Y. Tsai *et al.*, "Cross-Talk between Mitochondrial Dysfunction-Provoked Oxidative Stress and Aberrant Noncoding RNA Expression in the Pathogenesis and Pathophysiology of SLE," *Int J Mol Sci*, vol. 20, no. 20, p. 5183, Oct. 2019, doi: 10.3390/ijms20205183.
87. D. C. Chan, "Mitochondrial Dynamics and Its Involvement in Disease," *Annu Rev Pathol*, vol. 15, pp. 235–259, Jan. 2020, doi: 10.1146/ANNUREV-PATHMECHDIS-012419-032711.
88. Y. Ma, L. Wang, and R. Jia, "The role of mitochondrial dynamics in human cancers," *Am J Cancer Res*, vol. 10, no. 5, p. 1278, 2020, Accessed: Aug. 19, 2024. [Online]. Available: /pmc/articles/PMC7269774/
89. S. Goyal, J. Rani, M. A. Bhat, and V. Vanita, "Genetics of diabetes," *World J Diabetes*, vol. 14, no. 6, pp. 656–679, Jun. 2023, doi: 10.4239/wjd.v14.i6.656.
90. S. DiMauro and E. A. Schon, "Mitochondrial DNA mutations in human disease," *American Journal of Medical Genetics - Seminars in Medical Genetics*, vol. 106, no. 1, pp. 18–26, 2001, doi: 10.1002/ajmg.1392.
91. M. P. Murphy, "How mitochondria produce reactive oxygen species," *Biochemical Journal*, vol. 417, no. Pt 1, p. 1, Jan. 2009, doi: 10.1042/BJ20081386.
92. S. W. Ballinger, "Mitochondrial dysfunction in cardiovascular disease," *Free Radic Biol Med*, vol. 38, no. 10, pp. 1278–1295, May 2005, doi: 10.1016/J.FREERADBIOMED.2005.02.014.
93. Y. I. Goto, I. Nonaka, and S. Horai, "A mutation in the tRNA(Leu)(UUR) gene associated with the MELAS subgroup of mitochondrial encephalomyopathies," *Nature*, vol. 348, no. 6302, pp. 651–653, 1990, doi: 10.1038/348651A0.
94. D. R. Green, L. Galluzzi, and G. Kroemer, "Mitochondria and the autophagy-inflammation-cell death axis in organismal aging," *Science*, vol. 333, no. 6046, pp. 1109–1112, Aug. 2011, doi: 10.1126/SCIENCE.1201940.
95. C. T. Chu, "Mechanisms of selective autophagy and mitophagy: Implications for neurodegenerative diseases," *Neurobiol Dis*, vol. 122, p. 23, Feb. 2019, doi: 10.1016/J.NBD.2018.07.015.
96. E. A. Schon and S. Przedborski, "Mitochondria: The Next (Neurode)Generation," *Neuron*, vol. 70, no. 6, pp. 1033–1053, Jun. 2011, doi: 10.1016/j.neuron.2011.06.003.
97. R. H. Swerdlow, "Mitochondria and Mitochondrial Cascades in Alzheimer's Disease," *Journal of Alzheimer's Disease*, vol. 62, no. 3, pp. 1403–1416, Mar. 2018, doi: 10.3233/JAD-170585.
98. L. Tilokani, S. Nagashima, V. Paupe, and J. Prudent, "Mitochondrial dynamics: overview of molecular mechanisms," *Essays Biochem*, vol. 62, no. 3, pp. 341–360, Jul. 2018, doi: 10.1042/EBC20170104.
99. E. A. Schon and S. Przedborski, "Mitochondria: the next (neurode)generation," *Neuron*, vol. 70, no. 6, pp. 1033–1053, Jun. 2011, doi: 10.1016/J.NEURON.2011.06.003.
100. N. Exner, A. K. Lutz, C. Haass, and K. F. Winklhofer, "Mitochondrial dysfunction in Parkinson's disease: molecular mechanisms and pathophysiological consequences," *EMBO J*, vol. 31, no. 14, pp. 3038–3062, Jul. 2012, doi: 10.1038/EMBOJ.2012.170.
101. A. M. Pickrell and R. J. Youle, "The Roles of PINK1, Parkin, and Mitochondrial Fidelity in Parkinson's Disease," *Neuron*, vol. 85, no. 2, pp. 257–273, Jan. 2015, doi: 10.1016/j.neuron.2014.12.007.
102. E. F. Smith, P. J. Shaw, and K. J. De Vos, "The role of mitochondria in amyotrophic lateral sclerosis," *Neurosci Lett*, vol. 710, Sep. 2019, doi: 10.1016/J.NEULET.2017.06.052.
103. M. Cozzolino and M. T. Carrì, "Mitochondrial dysfunction in ALS," *Prog Neurobiol*, vol. 97, no. 2, pp. 54–66, May 2012, doi: 10.1016/j.pneurobio.2011.06.003.
104. W. Wang, F. Zhao, X. Ma, G. Perry, and X. Zhu, "Mitochondria dysfunction in the pathogenesis of Alzheimer's disease: recent advances," *Mol Neurodegener*, vol. 15, no. 1, p. 30, Dec. 2020, doi: 10.1186/s13024-020-00376-6.
105. L. Pagani and A. Eckert, "Amyloid-Beta Interaction with Mitochondria," *Int J Alzheimers Dis*, vol. 2011, no. 1, Jan. 2011, doi: 10.4061/2011/925050.
106. J. M. A. Oliveira *et al.*, "Mitochondrial dysfunction in Huntington's disease: the bioenergetics of isolated and *in situ* mitochondria from transgenic mice," *J Neurochem*, vol. 101, no. 1, pp. 241–249, Apr. 2007, doi: 10.1111/j.1471-4159.2006.04361.x.
107. A. Johri and M. F. Beal, "Mitochondrial Dysfunction in Neurodegenerative Diseases," *Journal of Pharmacology and Experimental Therapeutics*, vol. 342, no. 3, pp. 619–630, Sep. 2012, doi: 10.1124/jpet.112.192138.
108. D. R. Green and J. C. Reed, "Mitochondria and Apoptosis," *Science (1979)*, vol. 281, no. 5381, pp. 1309–1312, Aug. 1998, doi: 10.1126/science.281.5381.1309.
109. A. Trifunovic *et al.*, "Premature ageing in mice expressing defective mitochondrial DNA polymerase," *Nature*, vol. 429, no. 6990, pp. 417–423, May 2004, doi: 10.1038/nature02517.
110. J. Nunnari and A. Suomalainen, "Mitochondria: In Sickness and in Health," *Cell*, vol. 148, no. 6, pp. 1145–1159, Mar. 2012, doi: 10.1016/j.cell.2012.02.035.
111. A. Y. Seo, A.-M. Joseph, D. Dutta, J. C. Y. Hwang, J. P. Aris, and C. Leeuwenburgh, "New insights into the role of mitochondria in aging: mitochondrial dynamics and more," *J Cell Sci*, vol. 123, no. 15, pp. 2533–2542, Aug. 2010, doi: 10.1242/jcs.070490.
112. C. López-Otín, M. A. Blasco, L. Partridge, M. Serrano, and G. Kroemer, "The Hallmarks of Aging," *Cell*, vol. 153, no. 6, pp. 1194–1217, Jun. 2013, doi: 10.1016/j.cell.2013.05.039.
113. A. HIONA, "The role of mitochondrial DNA mutations in aging and sarcopenia: Implications for the mitochondrial vicious cycle theory of aging," *Exp Gerontol*, vol. 43, no. 1, pp. 24–33, Jan. 2008, doi: 10.1016/j.exger.2007.10.001.

114. C. S. Choi *et al.*, "Paradoxical effects of increased expression of PGC-1α on muscle mitochondrial function and insulin-stimulated muscle glucose metabolism," *Proceedings of the National Academy of Sciences*, vol. 105, no. 50, pp. 19926–19931, Dec. 2008, doi: 10.1073/pnas.0810339105.
115. J. Nunnari and A. Suomalainen, "Mitochondria: In Sickness and in Health," *Cell*, vol. 148, no. 6, pp. 1145–1159, Mar. 2012, doi: 10.1016/j.cell.2012.02.035.
116. M. Pittelli *et al.*, "Pharmacological Effects of Exogenous NAD on Mitochondrial Bioenergetics, DNA Repair, and Apoptosis," *Mol Pharmacol*, vol. 80, no. 6, pp. 1136–1146, Dec. 2011, doi: 10.1124/mol.111.073916.
117. P.-J. Guillausseau, "Maternally Inherited Diabetes and Deafness: A Multicenter Study," *Ann Intern Med*, vol. 134, no. 9_Part_1, p. 721, May 2001, doi: 10.7326/0003-4819-134-9_Part_1-200105010-00008.
118. G. Siasos *et al.*, "Mitochondria and cardiovascular diseases—from pathophysiology to treatment," *Ann Transl Med*, vol. 6, no. 12, pp. 256–256, Jun. 2018, doi: 10.21037/atm.2018.06.21.
119. M. G. Rosca and C. L. Hoppel, "Mitochondria in heart failure," *Cardiovasc Res*, vol. 88, no. 1, pp. 40–50, Oct. 2010, doi: 10.1093/cvr/cvq240.
120. D. Lebrecht and U. A. Walker, "Role of mtDNA lesions in anthracycline cardiotoxicity," *Cardiovasc Toxicol*, vol. 7, no. 2, pp. 108–113, Jun. 2007, doi: 10.1007/s12012-007-0009-1.
121. D. C. Wallace, "A mitochondrial bioenergetic etiology of disease," *Journal of Clinical Investigation*, vol. 123, no. 4, pp. 1405–1412, Apr. 2013, doi: 10.1172/JCI61398.
122. J. Terrier, Y. Daali, P. Fontana, C. Csajka, and J. L. Reny, "Towards Personalized Antithrombotic Treatments: Focus on P2Y12 Inhibitors and Direct Oral Anticoagulants," *Clin Pharmacokinet*, vol. 58, no. 12, pp. 1517–1532, Dec. 2019, doi: 10.1007/S40262-019-00792-Y.
123. J. F. P. Barber *et al.*, "Pectin-Alginate Does Not Further Enhance Exogenous Carbohydrate Oxidation in Running," *Med Sci Sports Exerc*, vol. 52, no. 6, pp. 1376–1384, Jun. 2020, doi: 10.1249/MSS.0000000000002262.
124. H. Lindroth *et al.*, "Systematic review of prediction models for delirium in the older adult inpatient," *BMJ Open*, vol. 8, no. 4, Apr. 2018, doi: 10.1136/BMJOPEN-2017-019223.
125. P. Ramesh *et al.*, "Batch and column mode removal of the turquoise blue (TB) over bio-char based adsorbent from Prosopis Juliflora: Comparative study," *Chemosphere*, vol. 271, May 2021, doi: 10.1016/J.CHEMOSPHERE.2020.129426.
126. A. Bezawork-Geleta, J. Rohlena, L. Dong, K. Pacak, and J. Neuzil, "Mitochondrial Complex II: At the Crossroads," *Trends Biochem Sci*, vol. 42, no. 4, pp. 312–325, Apr. 2017, doi: 10.1016/j.tibs.2017.01.003.
127. T. Chen *et al.*, "FHL1-related myopathy may not be classified by reducing bodies in muscle biopsy," *Neuromuscular Disorders*, vol. 30, no. 2, pp. 165–172, Feb. 2020, doi: 10.1016/j.nmd.2019.11.011.
128. T. E. Finucane and J. A. Carrese, "Race and Ethnicity in Clinical Case Presentations.," *N Engl J Med*, vol. 386, no. 12, p. 1195, Mar. 2022, doi: 10.1056/NEJMc2201423.
129. B. M. Knoll *et al.*, "Procalcitonin as a biomarker to differentiate bacterial infections from engraftment syndrome following autologous hematopoietic stem cell transplantation for multiple myeloma," *Am J Hematol*, vol. 94, no. 3, pp. E74–E76, Mar. 2019, doi: 10.1002/AJH.25378.
130. M. Peña *et al.*, "Shock Wave Application Increases the Antineoplastic Effect of Molecular Iodine Supplement in Breast Cancer Xenografts," *Ultrasound Med Biol*, vol. 46, no. 3, pp. 649–659, Mar. 2020, doi: 10.1016/J.ULTRASMEDBIO.2019.11.015.
131. R. Mahajan *et al.*, "Clinical profile of hepatitis C virus infection in a developing country: India," *J Gastroenterol Hepatol*, vol. 33, no. 4, pp. 926–933, Apr. 2018, doi: 10.1111/JGH.13995.
132. A. M. Czarnecka and E. Bartnik, "The Role of the Mitochondrial Genome in Ageing and Carcinogenesis," *J Aging Res*, vol. 2011, pp. 1–10, 2011, doi: 10.4061/2011/136435.
133. J. S. Carew and P. Huang, "Mitochondrial defects in cancer," *Mol Cancer*, vol. 1, no. 1, p. 9, 2002, doi: 10.1186/1476-4598-1-9.
134. M. Brandon, P. Baldi, and D. C. Wallace, "Mitochondrial mutations in cancer," *Oncogene*, vol. 25, no. 34, pp. 4647–4662, Aug. 2006, doi: 10.1038/sj.onc.1209607.
135. T. Kovalenko *et al.*, "Ischemia-induced modifications in hippocampal CA1 stratum radiatum excitatory synapses," *Hippocampus*, vol. 16, no. 10, pp. 814–825, 2006, doi: 10.1002/HIPO.20211.
136. L. Zeng, M. J. Lindstrom, and J. A. Smith, "Ankylosing spondylitis macrophage production of higher levels of interleukin-23 in response to lipopolysaccharide without induction of a significant unfolded protein response," *Arthritis Rheum*, vol. 63, no. 12, pp. 3807–3817, Dec. 2011, doi: 10.1002/ART.30593.
137. I. E. Van Der Horst-Bruinsma, "Treatment of non-radiographic axial spondyloarthritis: it is only the beginning," *Ann Rheum Dis*, vol. 72, no. 6, pp. 789–790, Jun. 2013, doi: 10.1136/ANNRHEUMDIS-2012-202908.
138. H. Witt *et al.*, "Mutations in the gene encoding the serine protease inhibitor, Kazal type 1 are associated with chronic pancreatitis," *Nat Genet*, vol. 25, no. 2, pp. 213–216, Jun. 2000, doi: 10.1038/76088.
139. M. Mattioli *et al.*, "Gene expression profiling of plasma cell dyscrasias reveals molecular patterns associated with distinct IGH translocations in multiple myeloma," *Oncogene*, vol. 24, no. 15, pp. 2461–2473, Apr. 2005, doi: 10.1038/SJ.ONC.1208447.
140. D. Baken and C. Stephens, "More dimensions for the multidimensional health locus of control: confirmatory factor analysis of competing models of the structure of control beliefs," *J Health Psychol*, vol. 10, no. 5, pp. 643–656, Sep. 2005, doi: 10.1177/1359105305055310.
141. K. Niiranen *et al.*, "Targeted Disruption of Spermidine/SpermineN 1-Acetyltransferase Gene in Mouse Embryonic Stem Cells," *Journal of Biological Chemistry*, vol. 277, no. 28, pp. 25323–25328, Jul. 2002, doi: 10.1074/jbc.M203599200.
142. L. L. Munn, "Mechanobiology of lymphatic contractions," *Semin Cell Dev Biol*, vol. 38, pp. 67–74, Feb. 2015, doi: 10.1016/J.SEMCDB.2015.01.010.
143. A. Musacchio, E. G. Rodriguez, A. M. Herrera, D. Quintana, and V. Muzio, "Multivalent DNA-based immunization against hepatitis B virus with plasmids encoding surface and core antigens," *Biochem Biophys Res Commun*, vol. 282, no. 2, pp. 442–446, 2001, doi: 10.1006/BBRC.2001.4580.
144. M. Wawro and M. Fathi-Torbaghan, "A parallel framework for the FE-based simulation of knee joint motion," *IEEE Trans Biomed Eng*, vol. 51, no. 8, pp. 1490–1494, Aug. 2004, doi: 10.1109/TBME.2004.827534.
145. T. Liufu and Z. Wang, "Treatment for mitochondrial diseases," *Rev Neurosci*, vol. 32, no. 1, pp. 35–47, Jan. 2021, doi: 10.1515/revneuro-2020-0034.
146. R. Heaton, L. Millichap, F. Saleem, J. Gannon, G. Begum, and I. P. Hargreaves, "Current biochemical treatments of mitochondrial respiratory chain disorders," *Expert Opin Orphan Drugs*, vol. 7, no. 6, pp. 277–285, Jun. 2019, doi: 10.1080/21678707.2019.1638250.
147. J. Ramón *et al.*, "Therapy Prospects for Mitochondrial DNA Maintenance Disorders," *Int J Mol Sci*, vol. 22, no. 12, p. 6447, Jun. 2021, doi: 10.3390/ijms22126447.
148. G. Kuang, M. Halimitabrizi, A.-A. Edziah, R. Salowe, and J. M. O'Brien, "The potential for mitochondrial therapeutics in the treatment of primary open-angle glaucoma: a review," *Front Physiol*, vol. 14, Aug. 2023, doi: 10.3389/fphys.2023.1184060.
149. L. Yue and H. Yao, "Mitochondrial dysfunction in inflammatory responses and cellular senescence: pathogenesis and pharmacological targets for chronic lung diseases," *Br J Pharmacol*, vol. 173, no. 15, pp. 2305–2318, Aug. 2016, doi: 10.1111/bph.13518.
150. T. Motiwala *et al.*, "Caseinolytic Proteins (Clp) in the Genus Klebsiella: Special Focus on ClpK," *Molecules*, vol. 27, no. 1, p. 200, Dec. 2021, doi: 10.3390/molecules27010200.
151. E. Bottani, C. Lamperti, A. Prigione, V. Tiranti, N. Persico, and D. Brunetti, "Therapeutic Approaches to Treat Mitochondrial Diseases: 'One-Size-Fits-All' and 'Precision Medicine' Strategies," *Pharmaceutics*, vol. 12, no. 11, p. 1083, Nov. 2020, doi: 10.3390/pharmaceutics12111083.
152. J. Ramón *et al.*, "Therapy Prospects for Mitochondrial DNA Maintenance Disorders," *Int J Mol Sci*, vol. 22, no. 12, p. 6447, Jun. 2021, doi: 10.3390/ijms22126447.
153. J. Prasuhn and N. Brüggemann, "Gene Therapeutic Approaches for the Treatment of Mitochondrial Dysfunction in Parkinson's Disease," *Genes (Basel)*, vol. 12, no. 11, p. 1840, Nov. 2021, doi: 10.3390/genes12111840.
154. W. B. Hubbard, C. L. Harwood, P. Prajapati, J. E. Springer, K. E. Saatman, and P. G. Sullivan, "Fractionated mitochondrial magnetic separation for isolation of synaptic mitochondria from brain tissue," *Scientific Reports 2019 9:1*, vol. 9, no. 1, pp. 1–13, Jul. 2019, doi: 10.1038/s41598-019-45568-3.
155. P. Pizcueta, C. Vergara, M. Emanuele, A. Vilalta, L. Rodríguez-Pascau, and M. Martinell, "Development of PPARγ Agonists for the Treatment of Neuroinflammatory and Neurodegenerative Diseases: Leriglitazone as a Promising Candidate," *Int J Mol Sci*, vol. 24, no. 4, p. 3201, Feb. 2023, doi: 10.3390/ijms24043201.
156. M. Fontecha-barriuso *et al.*, "The Role of PGC-1α and Mitochondrial Biogenesis in Kidney Diseases," *Biomolecules*, vol. 10, no. 2, p. 347, Feb. 2020, doi: 10.3390/BIOM10020347.
157. P. Pizcueta, C. Vergara, M. Emanuele, A. Vilalta, L. Rodríguez-Pascau, and M. Martinell, "Development of PPARγ Agonists for the Treatment of Neuroinflammatory and Neurodegenerative Diseases: Leriglitazone as a Promising Candidate," *Int J Mol Sci*, vol. 24, no. 4, p. 3201, Feb. 2023, doi: 10.3390/ijms24043201.
158. M. Fontecha-barriuso *et al.*, "The Role of PGC-1α and Mitochondrial Biogenesis in Kidney Diseases," *Biomolecules*, vol. 10, no. 2, Feb. 2020, doi: 10.3390/BIOM10020347.
159. J. Prasuhn and N. Brüggemann, "Gene Therapeutic Approaches for the Treatment of Mitochondrial Dysfunction in Parkinson's Disease," *Genes (Basel)*, vol. 12, no. 11, p. 1840, Nov. 2021, doi: 10.3390/genes12111840.
160. M. Wierdl, L. Tsurkan, M. J. Hatfield, and P. M. Potter, "Tumour-selective targeting of drug metabolizing enzymes to treat metastatic cancer," *Br J Pharmacol*, vol. 173, no. 19, pp. 2811–2818, Oct. 2016, doi: 10.1111/bph.13553

This review article is cited as: Ali H, Ratar AA, Taqi M, Shaikh R, Gill S: Mitochondrial Genetics and Human Health: Implications and Insights. Pak J Med Health Sci, 2024; 18(9):3-11.