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Variations of Mitochondria in Nervous System Disorders

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Abstract

Mitochondria, often referred to as the powerhouse of the cell, predominantly influence highly energy-dependent organs such as the brain, heart, and skeletal muscles. Consequently, mitochondrial disorders are commonly classified as encephalocardiomyopathies. These disorders typically involve multiple organ systems, with neurological dysfunction being one of the most prominent clinical features. The interplay between mitochondrial DNA and nuclear DNA adds another layer of complexity to understanding and diagnosing mitochondrial disorders. Furthermore, clinical heterogeneity—where a single mutation may lead to diverse phenotypes and similar phenotypes with various mutations may arise from different genetic defects—significantly complicates diagnosis. Another major challenge arises from the highly polymorphic nature of the mitochondrial genome, largely attributed to its exposure to a highly oxidative environment. As a result, distinguishing pathogenic or deleterious variants from benign polymorphisms becomes difficult, necessitating the use of specific criteria and computational prediction algorithms. Despite these challenges, substantial progress has been made in recent years. An increasing number of nuclear genes associated with mitochondrial dysfunction have been identified, enriching our understanding of disease mechanisms. The advent of next-generation sequencing (NGS) has further accelerated the field by enabling comprehensive analysis of both mitochondrial and nuclear genomes in a single workflow. This review focuses on the role of mitochondrial polymorphisms in the pathogenesis of major neurological disorders. Recent advancements in genetics and genomics are significantly improving our understanding of mitochondrial disease complexity and are paving the way for more accurate diagnosis and potential therapeutic strategies.

Keywords: mitochondria, variation, parkinson, oxidative stress

Introduction

Mitochondria are known as the power house of cell, their disorders are collectively called encephalocardiomyopathies as they affect most energy dependent organs like brain, heart and muscles. Mitochondria consist of its own circular DNA which is eubacterial in origin [1]. Mitochondria present in multiple copies in the cell and their number can vary depending on the tissue type. Ever since mitochondrial genome sequenced [2], and first pathogenic mutation was identified [3], many mitochondrial variations have been implicated in various disorders [4-6]. Highly oxidative environment of mitochondria, favors the accumulation of variations [7,8]. Both mutated and wild type copies of mitochondrial DNA are present in the cell. State of presence of both mutated and normal copy in the cell is known as heteroplasmy. Ratio of normal to mutated mitochondrial DNA or percent of heteroplasmy (a state where both mutated and wild type mtDNA exists) decides the manifestation of disease. That particular ratio is known as threshold. After crossing a threshold disease gets manifested. Percent heteroplasmy is responsible for variable expressivity in mitochondrial disease. Heteroplasmy varies among different tissues within the same individual i.e 5.1% in red bone marrow, 62% in the bladder for mutation (m.16093T>C) in non coding regulatory region in a study [9]. Similarly, in a preprint study it was shown that heteroplamy was significantly higher in neurons in comparison to muscles [10]. There are examples of certain homoplasmic mutations causing the disease with variable expressivity. To explain this variable expressivity due to homoplasmic mutation two locus hypothesis is suggested where a nuclear gene is acting as modifier in addition to mitochondrial counterpart. Many more nuclear genes are being discovered. These nuclear genes have been modelled in various model organisms including yeast, zebra fish. This review focuses on mitochondrial mutations in relation to neurological disorders. All kinds of mutations e.g. insertions, deletions, rearrangements and point mutations have been reported in various neurological disorders including Alzheimer, Ataxia, Wilson's disease etc. These mutations show variable expressivity, genetic and clinical heterogeneity, a hallmark of mitochondrial disorders. Furthermore, oxidative stress due to mitochondrial dysfunction is a reason for neuronal death in several neurological disorders. Oxidative damage acts in age dependent manner. This age related damage is more in mitochondrial DNA rather than nuclear DNA.

Mitochondrial genome: The double stranded and circular mitochondrial genome is of eubacterial origin, comprising, 16569 bps[2]. Thirteen polypeptides involved in oxidative phosphorylation (OXPHOS), two ribosomal RNAs (rRNAs) and 22 transfer RNAs (tRNAs) that are required for protein synthesis inside mitochondria are encoded by mitochondrial genome[2,](Fig 1). Besides 13 polypeptides, several nuclear encoded proteins are involved for the functioning complex mitochondrial machinery. Mitochondrial genome is haploid, maternally inherited and traditionally thought not to recombine but recent evidence suggest low-frequency

recombination does occur [11,12]. Mitochondrial genome shows codon bias.

Dual genetic control: Variable penetrance is a hallmark feature of mitochondrial disorders which can easily be explained by hetroplasmy. There are certain homoplasmic mutations showing variable penetrance pointing towards the presence of other locus acting as modifier. For example A1555G in 12SrRNA gene implicated in sensorineural hearing loss and A4300G in the $tRNA^{ile}$ involved in maternally inherited hypertrophic cardiomyopathy [13,14]. In addition to playing as modifier, a lot of nuclear gene codes of protein which are essential for mitochondrial functioning. Mitochondria imports around 1500 nuclear encoded protein for its functioning. Out of all, most of the mutations are reported in polymerase gamma. Many complementation studies using cybrids and yeast as a model system shows nuclear – mitochondrial interactions. Nuclear–mitochondrial DNA cross talk can be seen in SNHL (Sensorineural Hearing Loss), where *Saccharomyces cerevisiae* is taken as a model system. Yeast cells harbouring the paramomycin resistance P^R 454 mutation, produce phenotype deficient in respiration only in the presence of a nuclear mutation. This nuclear mutation is present in two highly conserved genes, MTO1 and MSS1 and this paramomycin resistance P^R 454 mutation was homologous to the human mitochondrial A1555G mutation [13]. These nuclear genes probably are required to run translational and the splicing mechanisms optimally. Human homologs of these genes are present but no mutation has been reported in them. These nuclear genes involved in the translational machinery, are thought to be conserved as A1555G, corresponding mutation in human, falls in the highly conserved region of 12S rRNA therefore, can be considered as potential modifier [15]

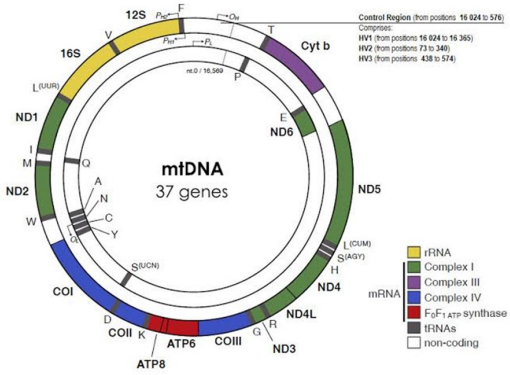


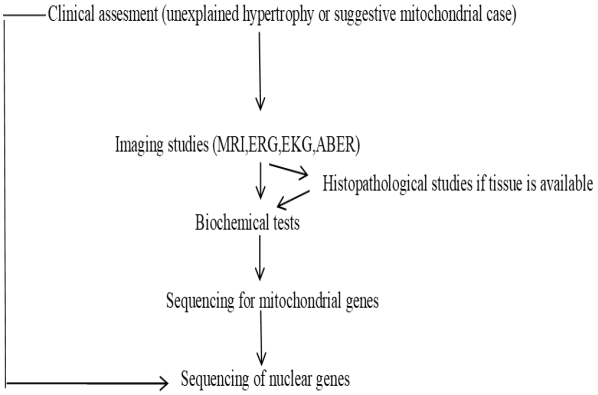
Figure 1 Organization of mitochondrial genome. Reproduced from: Amorim A, Fernandes T, Taveira N. Mitochondrial DNA in human identification: a review. PeerJ. 2019;7:e7314

Heterogeneity in disease presentation: Number of mitochondria varies from 500 to 2000 per cell. Mitochondrion follows the rule of population genetics rather following the mendalian genetics [16]. It is maternally inherited, with rare recombination events. Since recombination is very rare then a question arises what is the genesis of mitochondrial variations? One of the reasons of variations of mitochondria is highly oxidative environment. These variations inherit in different inheritance pattern. Some are sporadic and some are familial. Moreover, mitochondrial disorders show clinical and genetic heterogeneity. There are different mutations which produces identical phenotype known as genetic heterogeneity and also there are mutations where a single mutation producing different phenotypes.

For example, Defect in ATPase 6 gene lead to clinically indistinguishable Leigh syndrome. On the other hand, in case of clinical heterogeneity same genetic defect can results in multiple clinical phenocopies for example classical MELAS (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes), with CPEO, or with deafness and diabetes are the result of one A3243G mutation that is present in mitochondial $tRNALeu^{(UUR)}$ gene. Different clinical presentations in different children of same mother of A3243G mutation can be explained by bottleneck effect (a process where there is a sharp reduction in the mt DNA copies during oogenesis followed by random drift and amplification in mature oocytes resulting in a shift in the percentage of mutant mtDNA from mother to offsprings). Interestingly, sometimes mitochondrial mutations affect multiple organs (Leigh syndrome) whereas in few cases it affect specific organs only e.g. Leber Hereditary Optic Neuropathy (LHON) and aminoglycoside induced deafness [17]. Due to clinical and genetic heterogeneity mitochondrial variations are difficult to prioritize. Moreover, polymorphic nature of mitochondrial genome and variations accumulated due to oxidative environment adds the complexity. Following criterion can be adopted to prioritize the variations.

- Mutation would be novel and not reported in normal individuals
- Base change / variation must occur at a site which is evolutionary conserved. For example in protein coding regions, certain regions of ribosomal or t RNAs and few functionally important regions of D loop. The idea is any change in these conserved region is likely to be deleterious. For protein coding genes the misssense mutation has higher chances of being deleterious. However, a synonymous change can also lead to a reduced expression of the gene.
- Heteroplasmic status of the variation
- For various clinical presentations with different clinical severity, segregation of mutation or mutation load differs i.e severely affected person has high heteroplasmy while normal or asymptomatic individual will has low level of heteroplasmy.
- The mutation segregates biochemically with the disease.

Diagnosing mitochondrial disease is a complex, requiring a multidisciplinary approach combining clinical history, physical exams, biochemical tests (like lactate/pyruvate levels, amino/organic acids), specialized imaging (MRI, EKG), and ultimately definitive genetic testing (mtDNA/nDNA sequencing) to find mutations, often supported by muscle biopsies to assess mitochondrial function directly, because symptoms mimic many other conditions and affect multiple organs. At DNA level genetic heterogeneity of mitochondrial diseases becomes a challenge in diagnosing the disease. No single test confirms the disease therefore a integrative approach should be adopted. (Fig.2)



MRI -Magnetic Resonance Imaging

ERG - Electroretinogram

EKG - Electrokardiogram

ABER – Abduction and External Rota

Figure 2 Schematic diagram showing diagnosis of mitochondrial disorders.

Mitochondrial haplogrups

Mitochondrial genome is haploid, maternally inherited with rare recombinational events. Consequently, it evolves due to accumulation of sequential mutations along different lineages and therefore, all the variations in a lineage remain associated with each other. Based upon the frequency of common variants, the normal mitochondrial genomes can be subdivided into distinct genetic groups (haplogroups). These haplogroups have been defined on the basis of existence of restriction site polymorphisms, which are nothing but single nucleotide polymorphisms in the mtDNA sequences. Study of haplogroups from all over the world suggests one common ancestor of Homo Sapiens which is African in origin. Majority of the reported mutations in mitochondrial genome in modern human populations have occurred on pre-existing haplogroups. Therefore, in addition to be used in phylogenetic studies, it has been shown that certain haplogroups confer disease susceptibility whereas some are protective. For example, there are three main mtDNA mutations are found for LHON out of which two i.e T14484C in the ND6 gene and G11778A in the ND4 gene are associated with haplogroup J, a haplogroup which occur 15% in northern Europeans. It has been suggested that increased penetrance of these two mutations is due to haplogrpoup J [18]. LHON affects males only. The possible explanation of sex bias in LHON is nuclear locus such as PRICKLE3, located on X-chr acting as modifier, altering the clinical severity of LHON mtDNA mutations [19]. Similarly haplogroup J and K are reported to have protective effect to Parkinson disease in European population [20]. Besides disease predisposition, mitochondrial polymorphisms have also been shown to be associated with adaptation to cold climates. This is because, variations in respiratory complexes leading to tightly coupled complexes would generate more energy, a condition advantageous in tropics whereas uncoupled complexes would generate more heat, a condition advantageous in cold climate [21].

Mitochondrial polymorphisms in neurological disorders: Since brain metabolism is one of the high energy requiring processes, therefore role of mitochondria in neurological disorders cannot be ignored. Mitochondrial dysfunction has been reported in many neurological disorders. Key mechanisms involved in these disorders are impaired ATP production, oxidative stress, point

mutations and deletions, calcium dysregulation, apoptosis and defective mitochondrial dynamics (fission, fusion and mitophagy).

Epilepsy: In an epidemiological study by Gourie-Devi [22], epilepsy was the most prevalent neurological disorder especially in rural India. Epilepsy is a common manifestation of the MERRF syndrome, MELAS and POLG associated disorders [23]. Mitochondrial disorders are progressive therefore leading to worsening the symptoms. Several different mtDNA mutations have been identified for epilepsy. Among several mutations for MERRF, very first report was of m.8344A>G mutation present in the tRNA gene of mitochondria coding for lysine [24]. Two more mutations i.e m.8356T>C and m.8361G>A in the same tRNA gene reported to cause same clinical syndrome. There are several other mitochondrial mutations resulting in clinical syndromes with myoclonic epilepsy along with cardiomyopathy or diabetes mellitus. Furthermore, MERRF and MELAS presents the overlapping symptoms showing phenotypic variability characteristic of mitochondrial disorders and poor phenotype–genotype correlation. MELAS is a rare genetic disorder primarily defined by lactic acidosis i.e the accumulation of lactic acid in blood that results in vomiting, stroke-like episodes and temporary muscle weakness (SLEs) [25, 26]. Several different mtDNA mutations, can cause MELAS out of which m.3243A>G in the MTTL1 is a cardinal mutation[27]. This mutation can result mainly in MELAS, CEPO (Chronic Progresive External Opthalmoplagia & MIDD(Maternally Inherited Deafness and Diabetes) along with some additional symptoms [28]. Epilepsy is a presenting symptom in 65% of Mitochondrial spinocerebellar ataxia and epilepsy (MSCAE) patients [29]. This early age onset disorder is characterized by spinocerebellar ataxia, peripheral neuropathy, and epilepsy. MSCAE is different from MELAS in the sense that sensorineural deafness is rare and acute liver necrosis is common in it. MSCAE is caused by the recessive mutations in the catalytic subunit of POLG gene out of them two are very imp i.e the c.1399G>A correspond to p.A467T and the c.2243G>C correspond to p.W748S [30]. A recent study also warrants screening of PolG in epileptic cases [31].

Parkinson disease (PD): Parkinson disease is a progressive neurological disorder characterized by selective degeneration of dopaminergic neurons in substantia nigra [MIM#605909]. Mitochondrial involvement in PD has been documented in several studies but results of these studies are not consistent. A variation at position A10398G was reported in many studies altering the susceptibility towards PD in individual. In some studies this polymorphism is conferring protection to PD while in few studies not [20, 32]. Table 1 [20, 33-41]

Table 1 Effect of polymorphism A10398G on risk of PD in different studies.

S.N	Study	Population	Risk for PD	Odd ratio
1	Huerta C (2007)	Spanish	Protective	0.52(0.34-0.81)
2	Huerta C (2005)	Spanish	Decrease	0.53(0.33-0.86)
3	Vander Walt JM(2003)	Europian	Protective	0.53(0.39-0.73)
4	Chu Q (2015)	Chinese	Increase	1.30 (0.95-1.76)
5	D. Otaegui(2004)	Spanish	No correlation	
6	Clark J (2011)	Caucasian	Inversely associated	1.4-2.0
7	Chen CM (2007) A10398G with in a haplotype	Taiwanese	Decrease	0.44(0.24-1.80)
8	Latsoudis H(2008)	Cretan	No correlation	
9	Liou et al(2016)	Cybrid cells	Resistance against PD	.50(.33-.28)
10	Simon DK (2010)	Non-Hispanic Caucasians	No correlation	

A study in European population reveals that this variation was significantly associated with decreased risk of PD in haplotype J & K. Protective effect was stronger in women(P=.009) than among men(P=.04). A recent meta-analysis suggests that A10398G was not significantly associated with Asian population (G Vs A: OR=1.090, 95%CI=0.939-1.284, P=0.242) while it is protective in Caucasian population (G Vs A: OR=.699, 95%CI=0.546-.895, P=0.005).Reason of these conflicting results can be small sample size or population stratification in case control studies which give false association between gene marker and disease, therefore selection of ethnically matched control and cases are warranted. SNP A10398G results in threonine to alanine amino acid change which is a non-conservative change in the ND3 subunit of complex I. SNPA10398G may act as a surrogate marker for a causative variation present in other mitochondrial gene. One probable reason to explain the protective effect of this polymorphism is the decreased ROS production by complex I is associated with increased oxidative stress, eventually resulting in degeneration of neurons [32].

Alzheimer disease (AD): AD is characterized by the selective loss of neurons of hippocampus or cerebral cortex.AD brain shows the presence of extracellular amyloid plaques and intracellular neurofibrillary tangles of hypophosphorylated tau protein. AD inherits in autosomal dominant fashion which is approximately 5% of all cases. Fifty percent of them has mutations in one of the three genes ie. amyloid precursor protein (APP), presenilin1 (PSEN1) or presenilin 2 (PSEN2) are found. Remaining cases are sporadic. Only one genetic factor is known for sporadic AD is APOE genotype. Variation A433G in this gene has been reported in AD and PD as well in many studies. Mitochondrial haplogroups have been reported to influence AD risk. Haplogroup K and U may modulate the susceptibility to AD by neutralising the effect of APOE4 genotype [42]. However haplogroup K is not associated with decreased risk of AD according to Vander Walt 2004. They also demonstrated that males belonging to haplogroup U and carrying the 10398 A allele showed a increased risk of AD compared to males with G allele. With the same haplogroup U, polymorphism 12308G and 7028 T were associated with decreased risk of AD. Haplogroup U showed the gender dependent risk reported in many studies., e.g this haplogroup was less frequent among male centenarian (4%) than among control males (23%) ans more frequent in AD males (13.3%), as compared to age-matched controls (6.8%) [43-45]. In a study in Han Chinese population haplogroup B5 confers genetic susceptibility to AD and its effect was most likely mediated by ancient variation m8584G>A [46]. While the interaction between the APOE -ϵ4 genotype mtDNA haplogrops has been investigated in multiple studies, there is no consensus on validation by genome-wide association studies (GWAS). Effect of various haplogroups on neurological disorders are compiled in Table 2 [20, 42-49].

Table 2: Effect of haplogroups on neurological disorders in different populations.

S.N.	Study	Haplogroup	Ethnicity	Risk for disease
1	Soini HK(2013)	U5a1(m.15218A>G)	Finnish	Increased risk for epilepsy
2	Van Der Walt(2003)	J and K(A10398G)	European	Decrease risk for PD
3	Carrieri, G (2001)	K	European	No effect on the risk for AD
4	Van Der Walt(2004)	U	Caucasians	Increase risk in males, decrease risk in females in AD
5	De Benedictis G (2000a)	J	Italian	Associated with longevity
6	De Benedictis G (2000)	U	Italian	Associated with longevity
7	Bi, R (2015)	B5	Han Chinese	Suceptible for AD
8	Takasaki S(2009)	M7b2, B4e, B5b	Japanese	Associated with PD
9	Takasaki S(2008)	G2a	Japanese	Associated with AD

Somatic mutations: Mitochondrial genome acquires mutation at higher rate than nucleus due to mitochondrial oxidative environment. These acquired mutations are termed as somatic mutations. Somatic mutations have been reported in various neurodegenerative diseases like Parkinson [50], Huntington [51] and Alzheimer [52] AD. Coskun et al identified T414G, T414C and T477C mutations in control region which were exclusive to AD patients. Out of these three, 65% of examined AD brains had T414 mutations. Few mutations were common between AD and control brains both but more prevalent in AD brains. Moreover these were growing in percentage with the increase in age in comparison to controls. These mutations were heteroplasmic (70-80% hetroplasmy) [53].

Few common mutations in mitochondrial and nuclear genomes are listed in Table 3 [32, 54-60].

Table 3: Important mitochondrial polymorphisms in neurological disorders

Disease	Gene	Mutation	Ref
Mutations in proteins encoded by mitochondrial genome			
NARP (Neuropathy, Ataxia and Retinitis Pigmentosa)	ATPase 6	T899C	Majendar et al 1997
Parkinsonism, deafness and neuropathy	12S RNA	T1095C	Thygarajajan D et al 2000
MELAS	$tRNA^{leu}$	A3243G	Kaufman et al 2004
Parkinson	ND3 subunit of Complex I	A10398G	Hua F et al 2017
Mutations in nuclear encoded mitochondrial proteins			
Alzheimer	Apolipoprotein E	Genotypeε3/ε3	LiuM et 2014
Alzheimer and other neurodegenerative diseases	Apolipoprotein E	e 2 genotype	Goldberg, T.E. et al 2020
Epilepsy	PolG	G1399A(p.A467T), G2243C(p.w748S), G2542A(p.G848S)	Anagnostou EM et al 2016
Infantile onset spinocerebellar ataxia	Twinkle	C1472T A1708G	Nikali K et al 2005

Oxidative stress and neurodegenerative disorders

One of the common mechanisms in neurological disorders is oxidative stress due to mitochondrial dysfunction. Oxidative stress is defined as a disequilibrium between production and accumulation of reactive oxygen species (ROS) and ability of cell to detoxify these reactive products. Mitochondria is major source of ROS. These ROS are produced as a result of defective electron transport chain (complex I and complex III are the major site of ROS production) due to mutation in mitochondrial DNA. Excessive ROS generation disrupts mitochondrial function through multiple mechanisms. It initiates lipid peroxidation and oxidizes amino acids, thereby compromising the electron transport chain and reducing ATP synthesis. ROS also induces DNA strand

breaks, leading to the accumulation of harmful mutations [61]. In addition, it alters the permeability of the inner mitochondrial membrane by promoting the formation of the mitochondrial permeability transition pore (mPTP) [62], and triggers calcium release from the endoplasmic reticulum [63]. Persistent calcium overload enhances superoxide production, creating a self-amplifying cycle that activates signaling pathways such as CaMKII, causes osmotic imbalance, and culminates in swelling and rupture of the outer mitochondrial membrane. These events ultimately drive programmed or unregulated cell death via apoptosis or necrosis [64]. The damaged cells are subsequently eliminated through autophagy.

Oxidative stress and Alzheimer disease (AD)

In a recent study sodium dismutase; a marker for oxidative stress was found elevated in the patients of AD and MCI (mild cognitive impairment) with ApoE polymorphism [65]. A case control study of postmortem brain samples of AD subjects showed increased levels of protein oxidation product (carbonyl) and decreased glutamine synthetase activity in age matched control and AD groups but more profound in AD brains [66].This decreased enzyme activity led to decreased clearance of glutamate, eventually, increase in glutamate toxicity or excitotoxicity in which neurons are killed by overstimulating glutamate receptor like NMDA, causing massive calcium influx, leading to mitochondrial damage, induce oxidative stress(ROS) and activation of destructive enzymes, triggering cell death by both necrosis and apoptosis a common mechanism in Huntington, Alzheimer and ALS(Amyotrophic Lateral Sclerosis) which may lead to cell death [67]. Another study suggests involvement of glycated tau protein in inducing oxidative stress found in neurofibrillary tangles in sporadic AD [68]. Different studies revealed that AβP can generate free radical peptide and produce ROS [69]. Deficiency of cytochrome oxidase, a marker for ROS and reduced expression of mitochondrial Cox1 and Cox 3 subunits have also been observed in AD brains [70].

Oxidative stress and Parkinson disease (PD)

Parkinson is the second most degenerative neurological disorder after Alzheimer. PD and AD shows overlapping symptoms thus suggesting a common etiological mechanism [61]. Mutations in mitochondrial (12S RNA) and nuclear genes (PINK1, PARK2, PARK6, alpha-synuclein &DJ-1) have been shown to be associated with PD [71]. These mutations in these genes make cell susceptible to oxidative stress, one of proposed mechanism for nigrostriatal loss (loss of dopamine neuron in nigrostriatal pathway). This has been corroborated by several studies [72-75]. Activity of complex I and ubiquinone was found reduced in the brain of PD patients which may lead to neurodegeneration [76-78]. Moreover, downregulation of mitochondrial encoded genes in expression studies of dopaminergic neurons of PD patients, thereby further strengthening of

the idea of mitochondrial dysfunction in this disease [79].

Oxidative stress and Amyotrophic lateral sclerosis (ALS)

It has been shown that in ALS or more commonly Charcot disease, oxidative stress play an important role in loss of motor neurons and mitochondrial dysfunction leading to neurodegeneration. People have shown that loss of super oxide dismutase (SOD) activity results in the loss of motor neurons in spinal cord [80]. This can be increased by reduced glutamate transport and situation can be improved by supplementing antioxidants showing that there is involvement of free radicals. Mutant SOD gene in transgenic mice has shown to induce symptoms corresponding to human ALS [81].

Recent advances in mitochondrial genetics:

Disease management of mitochondria can be done either by (a) replacing defective mitochondria or (b) manipulating the mitochondrial genome. A recently emerged technique involves selection of preimplantation embryos with low mutation load. This is an IVF based technique known as preimplantation genetic diagnosis (PGD). PGD fails when mother is homoplasmic for the mutation or fails to produce embryo of low mutation load. There are reports of PGD in case of alzhiemer and other neurological disorders [82, 83]. Mitochondrial donation (MD) techniques also hold potential includes mitochondrial spindle transfer (MST), pronuclear transfer (PNT), polar body transfer and genetic transfer. Out of these MST and PNT most extensively studied MD techniques (Fig3,4) [84]. Both of these techniques involves the removal of nuclear material from patient and donor oocytes either pre or post fertilization. Now the nuclear material from patient oocyte is transferred to donor oocyte resulting in the reconstruction of oocyte or zygote that contains nuclear material of patient and normal mitochondria from donor. There are ethical and regulatory considerations for Mitochondrial Donation (MD) center on safety, "three-parent" identity(refers to an infant born from mother, father and donor. Since contribution of mitochondria is only 37 genes, about 0.1% of the total genome, so it does not affect much on appearance of baby), germline modification, donor consent/rights, equity of access, and regulatory clarity on parenthood, requiring robust oversight like the UK's Human Fertilization and Embryology Authority (HFEA), balancing reproductive freedom against long-term health risks, ensuring donor anonymity or identity access, and addressing societal views on genetic contribution. Key issues involve the permanence of germline changes, ensuring informed consent for donors and recipients, defining parental roles, and managing potential "slippery slope" arguments toward broader genetic editing.

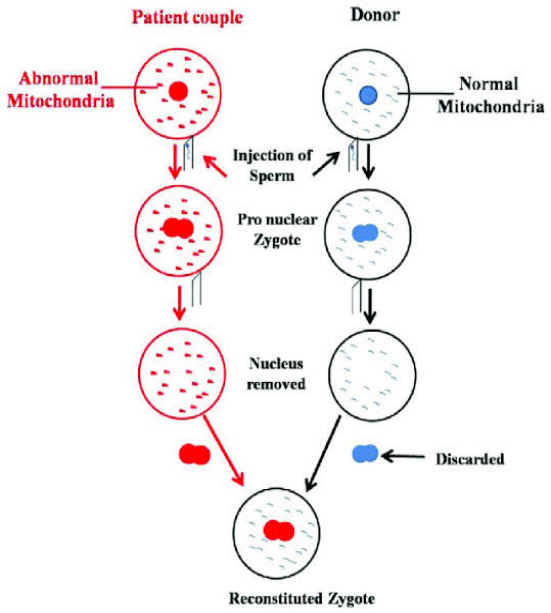


Figure 3: Pronuclear Transfer Technique of mitochondrial donation

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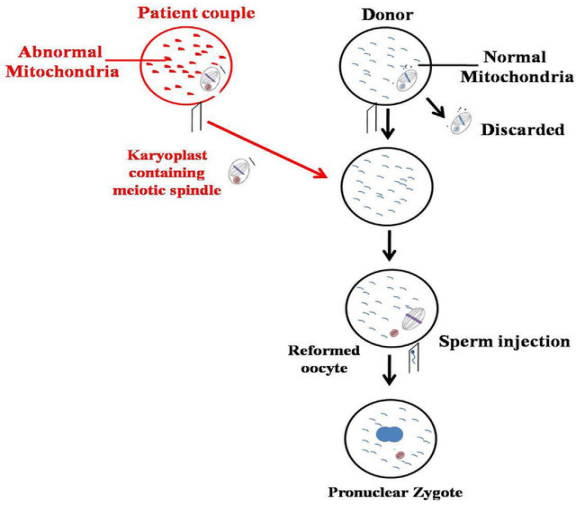

Figure 4 Pronuclear Transfer Technique of mitochondrial donation

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Another approach involves altering mitochondrial heteroplasmy. This can be achieved by many ways like selectively inhibiting the mutant mitochondrial DNA replication, destruction of mutant mt DNA by restriction endonucleases and by gene editing.

With the advent of next generation sequencing (NGS), mitochondrial science witnesses a major change in diagnosis and theraputics as well. NGS enables detection of even low hetroplasmy, therefore, helping in diagnosis [85]. It will reduce the need for an invasive muscle biopsy especially in disorders involving coding sequences however muscle biopsy remains the "gold standard" for certain biochemical assays that NGS can not replace. Furthermore, comprehensive information of disease target enables the formation of homogenous cohorts of patients for clinical trial, therefore, aiding in intervention.

Conclusion:

Mitochondrial disorders represent one of the most challenging disease categories to diagnose and manage due to their clinical complexity and genetic variability. Since mitochondria play essential roles in cellular energy production and apoptosis, they have become a central focus for research on neurological disorders. Numerous mitochondrial polymorphisms have been identified, some directly implicated in disease pathogenesis, while others are associated with altered disease susceptibility. The advent of next-generation sequencing (NGS) has transformed the diagnostic landscape,

enabling accurate detection even with small sample sizes and facilitating the discovery of rare mitochondrial disorders. Additionally, NGS allows rapid analysis of both mitochondrial and nuclear genomes, offering precise and sensitive detection of heteroplasmy. With ongoing advancements in genetic and genomic technologies, significant improvements in the diagnosis and treatment of mitochondrial disorders are expected in the future.

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