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Review article

Mitochondrial complex I subunit *MT-ND1* mutations affect disease progression

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ABSTRACT

Mitochondrial respiratory chain complex I is an important component of the oxidative respiratory chain, with the mitochondrially encoded NADH:ubiquinone oxidoreductase core subunit 1 (MT-ND1) being one of the core subunits. MT-ND1 plays a role in the assembly of complex I and its enzymatic function. *MT-ND1* gene mutation affects pathophysiological processes, such as interfering with the early assembly of complex I, affecting the ubiquinone binding domain and proton channel of complex I, and affecting oxidative phosphorylation, thus leading to the occurrence of diseases. The relationship between *MT-ND1* gene mutation and disease has been has received increasing research attention. Therefore, this article reviews the impact of *MT-ND1* mutations on disease progression, focusing on the impact of such mutations on diseases and their possible mechanisms, as well as the application of targeting *MT-ND1* gene mutations in disease diagnosis and treatment. We aim to provide a new perspective leading to a more comprehensive understanding of the relationship between *MT-ND1* gene mutations and diseases.

1. MT-ND1 gene expression and biological function

Mitochondrial complex I is the first enzyme complex in the mitochondrial oxidative respiratory chain. It receives electrons from nicotinamide adenine dinucleotide (NAD) + hydrogen (H) (NADH) and transfers them to ubiquinone. The energy obtained is used to pump protons from the matrix side of the inner mitochondrial membrane to the cytoplasmic side, which is important for the oxidative phosphorylation process [1–3]. Complex I consists of 45 subunits encoded by nuclear DNA and mitochondrial DNA (mtDNA), of which 7 subunits encoded by mtDNA (ND1–ND6 and ND4L) are located on the membrane arm of complex I, and are related to the ubiquinone reduction and proton translocation mechanisms [4–6]. Mitochondrially encoded NADH:ubiquinone oxidoreductase core subunit 1 (MT-ND1) is encoded by the guanine-rich heavy chain (H) between nucleotide pair (NPS) 3307 and 4262 in the mtDNA, and is a 36 kDa protein. MT-ND1 is located in the mitochondrial membrane where it provides mitochondrial complex I with NADH dehydrogenase activity and participates in mitochondrial electron transport and the assembly of the mitochondrial respiratory chain complex I.

The expression level of MT-ND1 varies among tissues. The MT-ND1 protein level is high in the heart, brain, kidneys, liver, as well as in malignant tumors, such as myeloid leukemia, thyroid cancer, and early pancreatic ductal adenocarcinoma (PDAC) [7–9]. Functionally, MT-ND1 is a potential testosterone target, and lack of testosterone leads to downregulation of MT-ND1 expression, reduction

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of complex I activity, damage to mitochondrial function, oxidative damage to the substantia nigra striatum, and damage to the dopaminergic system [10]. In addition, MT-ND1 is closely related to DNA oxidative damage and the rapid proliferation of tumor cells [11].

In cells, mtDNA is not protected by histones; therefore, it is more vulnerable to stress damage caused by excessive reactive oxygen species (ROS) and free radicals. Moreover, the repair mechanism of mtDNA is inefficient, resulting in a higher mutation rate compared with nuclear DNA. In addition, there is a heteroplasmy phenomenon in which harmful mutations coexist with normal mtDNA molecules [12,13]. Previous studies have shown that *MT-ND1* has mutations in Leber hereditary optic neuropathy (LHON) disease, diabetes, malignant tumors, and other diseases, and its mutations affect the body's pathophysiological processes [8,14–16].

2. *MT-ND1* mutation affects the body's physiological processes

MT-ND1 plays an important role in maintaining the normal physiological function of the body. It is mainly involved in the assembly of respiratory chain complex I, the ubiquinone binding domain and proton pump structure of complex I, and affects oxidative phosphorylation in the electron transport chain [17]. Mutations in the *MT-ND1* causing defects in the MT-ND1 protein can affect normal physiological activities [18–20], and mutations in different regions of *MT-ND1* can cause varying degrees of enzyme damage [20].

2.1. *Mutations in MT-ND1 affect the assembly of the mitochondrial respiratory chain complex I*

MT-ND1 participates in the formation of the 400 kDa subcomplex required for early assembly of respiratory chain complex I, which plays an important role in the biogenesis of complex I [20]. Based on the analysis of MT-ND1 mutants, some studies suggested that the early assembly model of mitochondrial respiratory chain complex I might involve the formation of intermediate 1 by the nuclear encoded subunits NADH:ubiquinone oxidoreductase core subunit S2 (NDUFS2) and NDUFS3, the addition of NDUFS7 and NDUFS8 to form intermediate 2, and the addition of NDUFA9 to form intermediate 3. Intermediate 3 is fixed on the membrane by assembly factors NADH:ubiquinone oxidoreductase complex assembly factor 3 (NDUFAF3) and NDUFAF4, and combines with the intermediate containing the MT-ND1 subunit to form the 400 kDa subcomplex before the next step of assembly [21]. In addition, through complexome profiling, it is found that the 170 kDa subassembly of the Q module containing NDUFAF 3 and NDUFAF 4 is combined with the assembly factor TIMMDC 1 and the subunit MT-ND 1 of the adjacent P-module, producing 237 kDa complex, and then combine with NDUFA 3, NDUFA 8 and NDUFA 13 to form a 283 kDa complex. This subassembly is called Q/Pp-a [22].

The m.3394T > C mutation in *MT-ND1* disrupts the electrostatic force between the MT-ND1 protein and the nuclear coding subunit NDUFA1 [23]; the m.3955G > A mutation interferes with the expression of *MT-ND1*, resulting in a significant decrease in MT-ND1 levels in mutant cell lines [24]; and m.3946G > A/ND1 (p.E214K) leads to a decrease in the stability of the MT-ND1 protein [25].

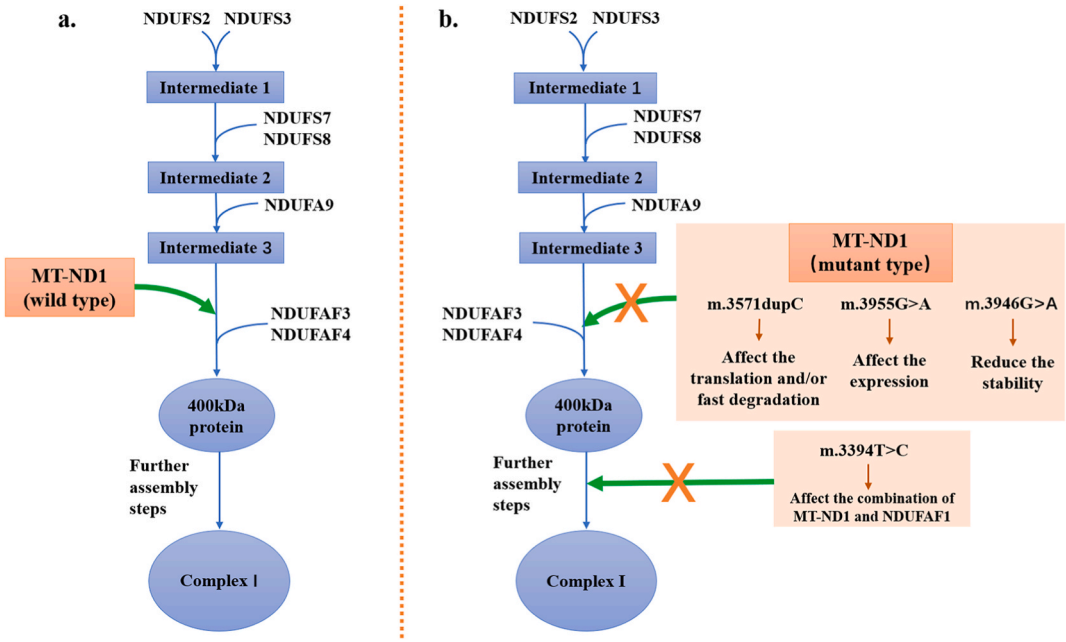

Fig. 1. (a) The wild type MT-ND1 is involved in the early assembly of complex I. ND1 participates in the 400 kDa protein which is necessary for the assembly of complex I. (b) The mutant MT-ND1 may interfere with the formation of the 400 kDa subcomplex or affect the interaction of the 400 kDa subcomplex with other subunits. The mutant MT-ND1 will inhibit the complete assembly of complex I. Deficiency of complex I affects oxidative phosphorylation of mitochondria.

These mutations will affect the assembly of complex I, resulting in a decrease in its level and enzyme activity. If a mutation in *MT-ND1* leads to a decrease in normal MT-ND1 levels, the inability of complex I to assemble properly will also lead to the degradation of other subunits. A deficiency of MT-ND1 and a decrease in steady-state levels of other nuclear encoded subunits were observed in the m.3571dupC mutant cell line [21]; a decrease in the steady-state level of the NDUFB8 subunit was observed in cells with a m.3946G > A/ND1 mutation [26]; and the m.4160T > C/ND1 mutation not only damages the MT-ND1 protein, but also might affect the stability of MT-ND4, MT-ND5, and the nuclear DNA-encoded subunits NDUFB8 and succinate dehydrogenase complex iron sulfur subunit B (SDHB) [19]. Thus, a lack of MT-ND1 can affect the assembly of respiratory chain complex I and inhibit the assembly of complete enzymes. In addition, the absence of MT-ND1 can also affect the formation and stability of respirasomes. The supercomplex comprising complex I, complex III, and complex IV is called a respirasome (CI + $CIII_2$+CIV), which promotes electron transfer and prevents the generation of ROS. The m.3571dupC mutation (m.3571insC) of *MT-ND1* does not affect its transcription, but can affect its translation and/or rapid degradation, leading to a lack of the MT-ND1 protein, decreased activity of mitochondrial complexes I and IV, and disrupted assembly of the CI + $CIII_2$+CIV and CI + $CIII_2$ supercomplexes in mitochondria, affecting the occurrence of respirasomes [21]. Mutation of m.3571insC above the threshold (85–93%) in *MT-ND1* will result in complete loss of MT-ND1, and early assembly of complex I cannot proceed normally. A small amount of wild-type MT-ND1 ectopic expression can restore the partially interrupted assembly of complex I [18] (Fig. 1a and b).

The assembly of mitochondrial respiratory chain complex I (CI) is complicated, and many studies have been dedicated to analyzing its specific assembly process, to better understand its functional structure. MT-ND1 is involved in its early assembly, and the loss of MT-ND1 can lead to incomplete assembly of complex I, resulting in enzyme defects. Currently, the general assembly process of MT-ND1 in complex I has been clarified, and mutations in *MT-ND1* can alter the charged residues on the protein, affecting the binding and interaction between MT-ND1 and other subunits, thereby affecting the generation of complex I. As a result, the decreased level of complex I and functional defects become a pathogenic factor in many diseases.

2.2. MT-ND1 participates in the ubiquinone binding domain and proton channel that constitute complex I, and its gene mutation affects oxidative phosphorylation

Mitochondrial respiratory chain CI of the electron transport chain receives electrons from NADH+H^+, and transfers them to ubiquinone to be reduced. The energy obtained is used to pump protons into the membrane, playing a key role in the process of oxidative phosphorylation-mediated production of ATP [27–29]. The electron transfer sequence in complex I is NADH→flavin mononucleotide (FMN)→FeS→co-enzyme Q (CoQ) (i.e., ubiquinone) [30–33]. The MT-ND1 subunit, as a part of CI, participates in the formation of ubiquinone binding domains and proton channels, which are crucial for the reduction and energy conversion of ubiquinone [5,6,34]. According to the crystal diffraction results of CI, PSST (also known as NDUFS7), and the 49 kDa and MT-ND1 subunits form a narrow and closed ubiquinone reaction chamber, which is close to Fe–S cluster N2 to facilitate the redox reaction, and MT-ND1 is involved in the process of transmitting conformational changes to the four proton channels of CI [5]. Experiments by Uno et al. using artificial ubiquinone also confirmed that MT-ND1 residues interact with quinone and form part of the narrow head of the quinone cavity [6]. The half-channel on MT-ND1 is connected to the half-channel in the MT-ND6 and MT-ND4L subunits, and also participates in the proton channel of CI [5]. The reduction site of ubiquinone is far from the proton pump; therefore, CI can switch conformations to change the binding site of ubiquinone for energy transfer. This process requires the MT-ND1, 49 kDa, and MT-ND3 subunits to respond to quinone reduction and undergo synergistic structural rearrangements, thereby driving proton translocation [17,34,35] (Fig. 2).

MT-ND1 is a part of the ubiquinone domain in CI, which is of great significance to the whole enzyme activity; therefore, *MT-ND1* mutations might affect the activity of CI, resulting in damage to the oxidative phosphorylation process of the electron transport chain, thereby affecting the energy supply of mitochondria. *MT-ND1* and *MT-ND5* mutations, such as 4216T > C/MT-ND1, 13708G > A/MT-

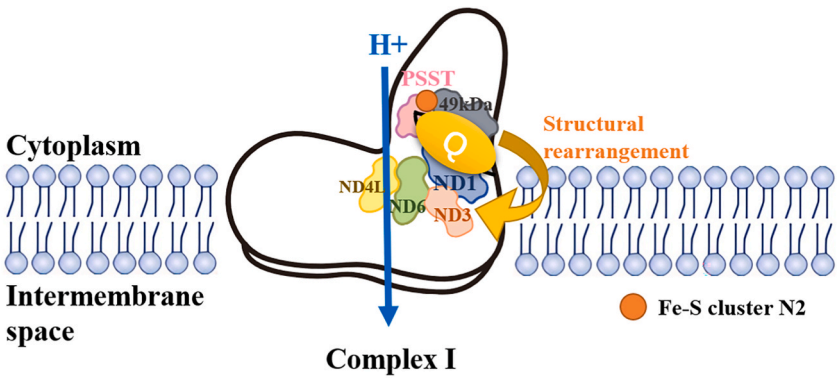

Fig. 2. MT-ND1 and 49 kDa, PSST subunits participate in the ubiquinone cavity and proton channel of complex I. The ubiquinone cavity is close to the N2 iron-sulfur cluster, which will facilitate the reduction of ubiquinone. ND1, together with ND3 and 49 kDa subunits, promotes proton translocation by transferring energy to the proton pump through conformational transformation.

ND5, and 12506T > A/MT-ND5, affect oxidative phosphorylation-mediated mitochondrial energy supply, which is negatively related to the results of intracytoplasmic sperm injection (ICSI), sperm vitality, and fertilization rate decline, which might cause male asthenospermia [36]. In summary, *MT-ND1* mutations affect the process of oxidative phosphorylation, which might cause mitochondrial dysfunction.

MT-ND1, located at the junction of hydrophilic and hydrophobic domains in CI, contributes to the ubiquinone binding and proton pump structure of complex I, and is also related to their coupling mechanism. To date, the fine structure of complex I has been analyzed in detail, and we have some understanding of how MT-ND1 binds and interacts with surrounding subunits. However, there is still no consensus on its contribution to the reduction of ubiquinone and its long-range coupling mechanism with proton pumps. At this level, mutations in *MT-ND1* can cause abnormal binding with other subunits of CI or affect the functional domain of CI, leading to CI dysfunction. Studying the contribution of MT-ND1 to the function of CI will help to enhance our understanding of the function of CI in the mitochondrial respiratory chain (Fig. 3).

3. The impact of *MT-ND1* mutations on diseases and their possible mechanisms

The amino acid sequence of MT-ND1 is highly conserved in evolution. *MT-ND1* mutations mainly comprise m.3460G > A [37], m.3394T > C [16,38], and m.3635G > A [39,40]. Most pathogenic mutations alter the structure of MT-ND1 protein, leading to a decrease in its stability and level, resulting in enzyme defects in CI, thereby promoting various diseases. The different demands for mitochondrial energy supply in different parts of the body mean that *MT-ND1* mutations have significant impacts on organs such as the brain, skeletal muscles, eyes, and heart. *MT-ND1* mutations are closely related to the occurrence and development of LHON; type 2 diabetes; mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS); and other diseases (Table 1) (Fig. 4).

3.1. *MT-ND1 mutation and LHON*

LHON is a mitochondrial genetic disease characterized by maternal inheritance. The disease exhibits significant heterogeneity at both the phenotype and genotype levels. LHON can cause rapid unilateral or bilateral visual loss, mainly affecting central vision. The mitochondria of cells in the optic nerve and retina are dense and require large amounts of energy. Defects in the energy supply of

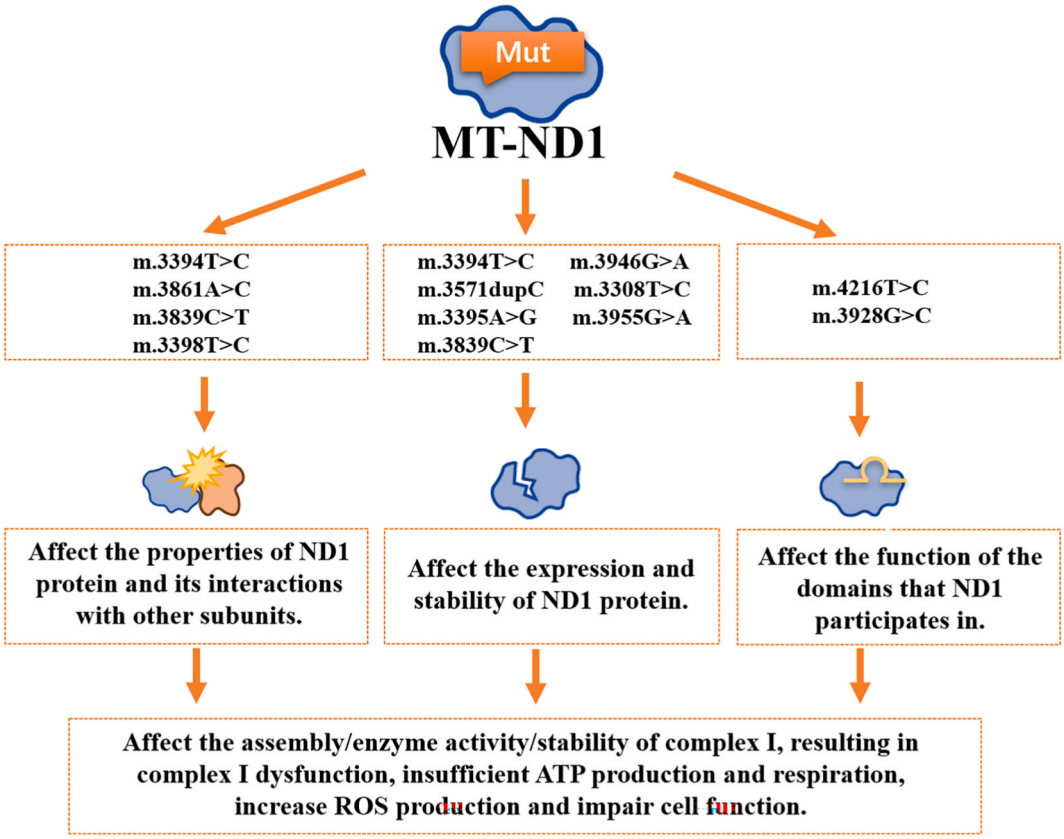

Fig. 3. Effects of MT-ND1 mutation on physiological processes. MT-ND1 affects complex I assembly and enzyme activity by altering the structure of ND1 protein. This will affect the expression and stability of ND1 protein, and cause the dysfunction and alteration of protein properties. This will lead to physiological dysfunction, such as decreased production of ATP, overproduction of ROS, and cell dysfunction.

Table 1
The impact of MT-ND1 mutations on diseases.

Gene	Position	Nucleotide change	Amino acid change	Related Disease
MT-ND1	3308	T > C	Met to Thr	T2D, MELAS, Cardiovascular disease
MT-ND1	3337	G > A	Val to Met	Cardiovascular disease
MT-ND1	3376	G > A	Glu to Lys	LHON, MELAS
MT-ND1	3394	T > C	Tyr to His	T2D, LHON
MT-ND1	3395	A > G	Tyr to Cys	Cardiovascular disease, Hearing impairment
MT-ND1	3397	A > G	Met to Val	Neurological disorders
MT-ND1	3398	T > C	Met to Thr	LHON
MT-ND1	3460	G > A	Ala to Thr	LHON
MT-ND1	3571	dupC	null	MELAS
MT-ND1	3635	G > A	Ser to Asp	LHON
MT-ND1	3736	G > A	Val to Ile	LHON
MT-ND1	3839	C > T	Ser to Leu	Cardiovascular disease
MT-ND1	3861	A > C	Trp to Cys	Hearing impairment
MT-ND1	3866	T > C	Ile to Tys	LHON
MT-ND1	3890	G > A	Arg to Gln	LHON
MT-ND1	3928	G > C	Val to Leu	Neurological disorders
MT-ND1	3946	G > A	Glu to Lys	Neurological disorders
MT-ND1	3955	G > A	Ala to Thr	Neurological disorders
MT-ND1	3959	G > A	Gly to Asp	MELAS
MT-ND1	3995	A > G	Asn to Ser	MELAS
MT-ND1	4171	C > A	Leu to Met	LHON
MT-ND1	4216	T > C	Val to Leu	T2D, Cancer

MT-ND1 mutation will disturb the protein structure, affect the function of mitochondrial complex I, lead to mitochondrial electron transport chain dysfunction, affect energy metabolism in cells. MT-ND1mutations are associated with the onset and progression of a variety of diseases, including LHON, MELAS, T2D and so forth. Disease-associated MT-ND1 mutation sites and amino acid changes are listed here.

mitochondria are more likely to damage the retina and lead to the onset of LHON. Susceptibility to LHON involves many factors. The level of heteroplasmy of mtDNA mutations, nuclear modification factors, epigenetic factors, and the environment all affect the penetrance and phenotype of LHON.

MT-ND1 is considered a mutation hotspot gene in the LHON family, including numerous common or rare mutations, such as m.3460G > A [37], m.3394T > C [38], m.3866T > C [41], and m.3736G > A [42]. The MT-ND1 protein has multiple transmembrane α-helices and is highly hydrophobic. Most pathogenic *MT-ND1* mutations alter the charge and polarity of conserved amino acid residues in the transmembrane region, disrupting the three-dimensional conformation of the protein, and the interaction between MT-ND1 and other subunits, resulting in functional defects. For example, the putative pathogenic variant m.3398T > C (Met-31-Thr) might result in the failure of the mutant residue to form an α-helix and induces a change in hydrophobicity [43]. Mutations in *MT-ND1* lead to CI assembly defects or a decrease in CI levels, activity, and stability. According to a previous report, the m.3394T > C mutation disrupts the interaction between MT-ND1 and NDUFA1, affecting the assembly and activity of CI [38]. When a CI defect occurs, mitochondrial oxidation dysfunction will reduce ATP synthesis efficiency, reduce mitochondrial membrane potential, and overproduce ROS. The excessive generation of ROS creates a vicious cycle of oxidative stress in mitochondria, damaging mitochondrial and cellular proteins, lipids, and nucleic acids, and leading to the degeneration of retinal ganglion cells, resulting in the clinical phenotype of LHON. The mutant cell line carrying the T3866 C/MT-ND1 mutation which related to LHON shows respiratory insufficiency, reduced ATP synthesis, and increased ROS generation [41]. A decrease in autophagy ability was observed in hybrid cells carrying m.3460G > A/MT-ND1, which interferes with the autophagy-mediated degradation of ubiquitinated proteins. The accumulation of autophagic substrates will poison cells [37], representing another possible mechanism of LHON. The rare occurrence of m.4160T > C/MT-ND1 can lead to a decrease in MT-ND1 levels and the CI oxygen consumption rate (OCR), which is a pathogenic mutation of LHON [19]. Therefore, *MT-ND1* mutation is one of the important pathogenic factors of LHON.

Meanwhile, many major *MT-ND1* mutations, including m.3460G > A/MT-ND1 [44], are not sufficient to lead to the generation of the LHON phenotype; however, the synergistic effect of secondary mutations related to LHON might aggravate the mitochondrial dysfunction of carriers, leading to increased penetrance of optic neuropathy. There are interactions between different mtDNA mutations and nuclear modification genes, which together affect the clinical phenotype and disease progression. For example, it was observed that secondary mutations m.3394T > C, m.3866T > C, etc. work synergically with m.11778G > A/MT-ND4, m.14484T > C/MT-ND6 mutations, aggravating mitochondrial dysfunction and resulting in higher penetrance of LHON in families carrying both primary and secondary mtDNA mutations [23,45–47]. The synergistic effect of polymorphism m.4171C > A/MT-ND1 and m.14568C > T/ND6 results in the LHON phenotype [48]. Mutations in mitochondrial tRNA genes might worsen the mitochondrial dysfunction caused *MT-ND1* mutations, while homoplasmic 14693 A > G mutations might cause tRNAGlu metabolism failure through structural changes, exacerbating LHON caused by the primary m.3460G > A/MT-ND1 mutation [49]. The m.3635G > A/MT-ND1 mutation can lead to a decrease in the activity of intracellular mitochondrial CI and a decrease in ATP synthesis efficiency [39,40]. The p.191 Gly > Val mutation of the nuclear modification gene *YARS2* (encoding tyrosyl-tRNA synthetase 2) exacerbates the biochemical defects caused by m.3635G > A/MT-ND1 and cell lines carrying double mutations exhibit more severe respiratory disorders and enhanced autophagy [50]. The C7868T (L95F) mutation of *COII* (encoding mitochondrially encoded cytochrome C oxidase II) might increase the penetrance of LHON in families carrying m.3635G > A/MT-ND1 [51]. A heteroplasmic *NDUFV1* mutation has been reported to

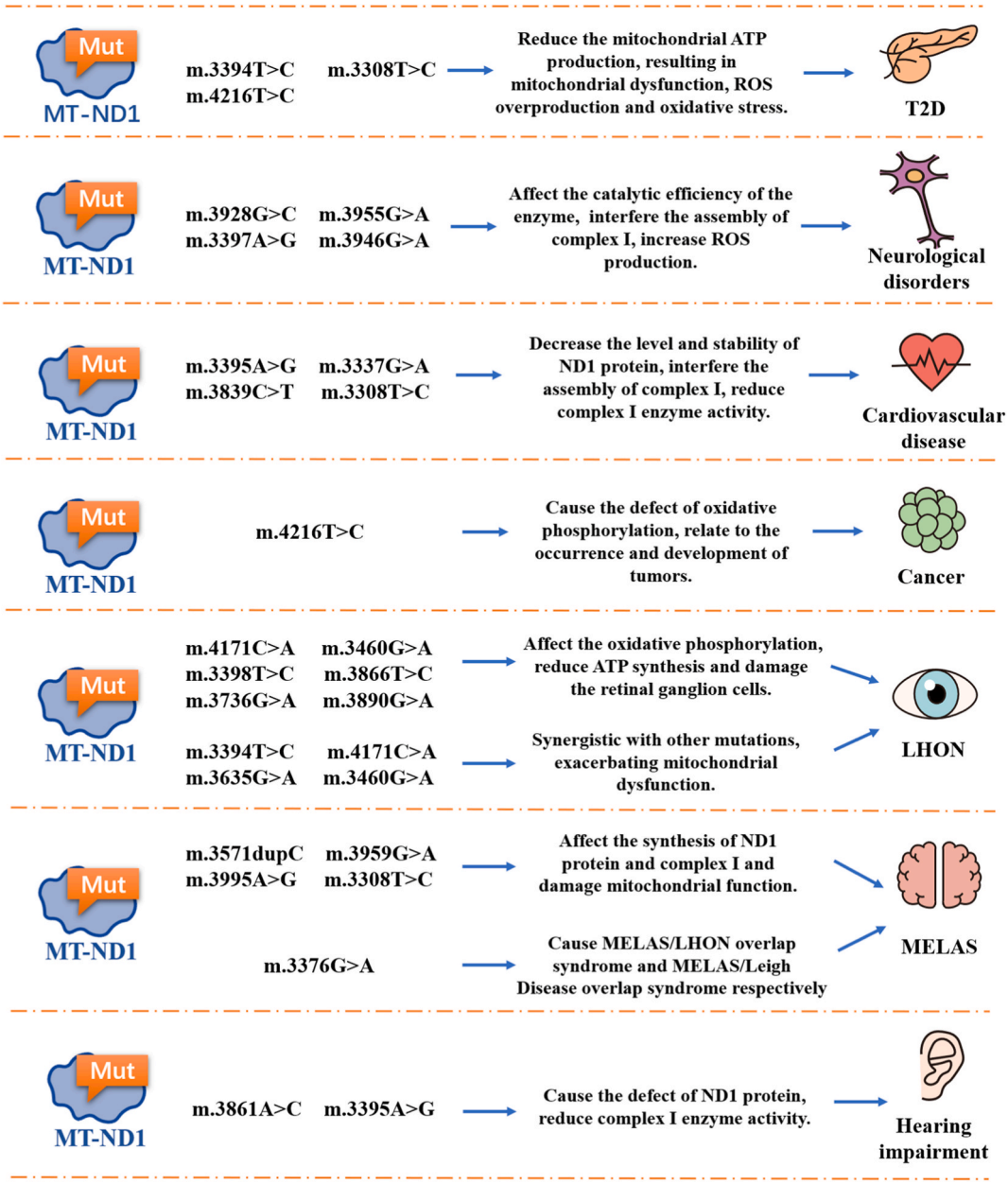

Fig. 4. MT-ND1 mutations are involved in the pathological processes of many diseases. MT-ND1 mutations impair the enzyme function of complex I, resulting in mitochondrial respiratory disorders, reduced ATP production efficiency, increased ROS, and cell dysfunction. It is associated with a wide range of diseases, including LHON, MELAS, T2D, neurological disorders, cardiovascular disease, hearing impairment and cancer.

exacerbate the phenotype of mitochondrial genetic diseases in families carrying homoplasmic m.3460G > A/MT-ND1 mutations [52]. Other gene mutations in cells might have a significant impact on the phenotype caused by *MT-ND1* mutations; however, the mechanism of this synergistic effect is currently unclear.

Different mutations in *MT-ND1* lead to a decrease in respiratory chain CI levels and/or enzyme activity, which is one of underlying mechanisms of LHON. Most *MT-ND1* mutations are not sufficient to generate disease phenotypes, but rather act synergistically with heteroplasmy, different population nuclear backgrounds, and other gene mutations, to exacerbate CI defects, and lead to the occurrence of LHON. The phenotypes caused by *MT-ND1* mutations partially explain the symptoms observed in patients with LHON, and can be used to develop diagnostic and therapeutic methods. However, the influence of multiple pathogenic factors makes the pathology of LHON complex. In future research, we need to acquire a clearer understanding of how *MT-ND1* mutations interact with other genetic factors to affect the phenotype of LHON.

3.2. MT-ND1 mutations and MELAS

MELAS is a common matrilineal mitochondrial disease. *MT-ND1* is considered as a mutation hotspot gene in MELAS. *MT-ND1* frameshift mutation m.3571_3572insC truncates the MT-ND1 protein, causing a decrease in its level and interfering with the assembly and enzyme function of CI, which is a pathogenic mutation of MELAS [53]. In MT-ND1 mutations, the close substitution sites of amino acids might lead to different clinical phenotypes. Two *MT-ND1* mutations, m.3959G > A and m.3995 A > G, were reported in two cases of MELAS. The two mutations are located in functionally similar regions and both affect the structure and function of MT-ND1; however, they cause different disease phenotypes. m.3959G > A results in encephalomyopathy, while m.3995 A > G results in encephalomyopathy combined with sensorineural hearing loss [54]. Partial *MT-ND1* mutations might cause an overlap syndrome, such as the MELAS/Leigh disease overlap syndrome caused by m.3376G > A, which is associated with LHON/MELAS overlap syndrome [55]. Thus, the phenotype of diseases caused by MT-ND1 mutations varies significantly among different individuals.

On the one hand, similar mutations in *MT-ND1* can lead to diverse MELAS disease phenotypes. On the other hand, the neurological symptoms of MELAS might be related to the change of antigenicity caused by *MT-ND1* mutations. The mitochondrial peptide encoded by mitochondrial DNA in mice plays an immune role as a maternally inherited mouse small histocompatibility antigen (MTF) [56]. MTF is caused by variation of MT-ND1 protein residue 6, which makes cells vulnerable to MTF-specific cytotoxic T cell lysis [56]. The m.3308T > C mutation related to MELAS can alter the first amino acid of MT-ND1, which might hinder the initiation of MT-ND1 translation and affect its anchoring on the mitochondrial membrane. Mutation m. 3308T > C will also change the antigenicity of the MT-ND1 N-terminal peptide. A structural change to the MT-ND1 subunit can be recognized by the immune system and might lead to autoimmunity, possibly causing the neurological symptoms of MELAS [57]. Therefore, mutations in *MT-ND1* can also have an impact on the MELAS phenotype in the body's immune system.

In summary, the *MT-ND1* mutations that lead to MELAS overlap with those that cause LHON; however, further research is needed to reveal why there are differences in disease phenotypes. At the same time, mutations in *MT-ND1* might also be related to autoimmunity; however, this is rarely mentioned in human disease research. Whether *MT-ND1* mutations cause a change in its antigenicity, contributing to the occurrence of neurological symptoms of diseases such as MELAS, has yet to be confirmed.

3.3. MT-ND1 mutations and T2D

Type 2 diabetes (T2D) can be caused by environmental and genetic factors. In terms of genetic factors, reported cases of maternal transmission of diabetes suggest that mitochondrial dysfunction caused by mtDNA mutations, such as mt-tRNA gene mutation m.3243 A > G, will affect the process of T2D and participate in multiple organ dysfunction. Moreover, there is evidence that mutations in *MT-ND1* might also cause T2D. Research has shown that m.3394T > C/MT-ND1 is not only associated with the occurrence of LHON [38], but also with T2D. This mutation leads to a decrease in mitochondrial ATP production, a significant decrease in membrane potential, and mitochondrial dysfunction, which are the main factors for patients with T2D, although it is not sufficient to produce a clinical phenotype [16]. Similar to the occurrence of LHON, nuclear genes, the environment, and other factors might play a role in the phenotype of diabetes. Mutations in *MT-ND1*, such as m.4216T > C [58] and m.3308T > C [59], are considered risk factors for the development of T2D. Mutations in *MT-ND1* may lead to metabolic failure of *MT-ND1* mRNA, leading to a decrease in CI and promotion of disease progression. Oxidative stress caused by excessive ROS production is considered as a sign of the onset and progression ofT2D. *MT-ND1* mutations can also cause excessive ROS production, thereby affecting the development of T2D. Patients with diabetes with the m.T4216C and m.C5178A mutations showed higher levels of ROS and decreased ATP production [58]. In conclusion, mtDNA mutations, such as *MT-ND1* mutations, participate in the occurrence and development of T2D mainly by affecting mitochondrial electron transfer, ATP, and ROS production. Although it has been proven that *MT-ND1* mutations can be contributing factors to the occurrence of T2D, further research is needed to reveal the extent to which *MT-ND1* mutations affect the course of the disease and how the mutations interact with other genetic or environmental factors to ultimately lead to the occurrence of T2D.

3.4. MT-ND1 mutations and other diseases

MT-ND1 mutations are also involved in the occurrence and progress of neurological disorders, cardiovascular diseases, hearing loss, cancer, and other diseases, providing new insights for the study of the pathology and treatment of these diseases. To date, *MT-ND1* mutations have been found to be involved in neurological disorders, including Leigh disease, Parkinson disease (PD), Alzheimer disease (AD), and Autism spectrum disorder (ASD). Different mutations in *MT-ND1* might result in a Leigh Disease phenotype through different pathogenic processes, such as m.3928G > C (p.V208L), which might affect the ubiquinone binding or catalytic efficiency of CI [60]. However, m.3955G > A interfered with the expression of MT-ND1 and the assembly of CI, leading to mitochondrial dysfunction [24]. In addition, *MT-ND1* mutations such as m.3397 A > G are associated with PD and AD [61], and missense mutations of *MT-ND1* might play important roles in the pathogenesis of ASD [62]. The mutation m.3946G > A/ND1 (p.E214K) was found in patients with west syndrome evolving to Lennox–Gastaut syndrome, which does not affect the expression of the *MT-ND1* gene but leads to a decrease in protein stability. Lower protein levels affect the assembly of CI and respirasomes, leading to an increase in ROS and possibly leading to the disease phenotype [25]. Intact mitochondrial function is crucial for the nervous system, and respiratory disorders caused by *MT-ND1* mutations are important for neurological disorders.

MT-ND1 mutations might also cause hearing impairment and cardiovascular diseases, such as cardiomyopathy and hypertension. Mutation m.3861 A > C/ND1 is associated with syndromic hearing loss [63]. Mutation m.3395 A > G/MT-ND1 leads to a decrease in the MT-ND1 protein level and a decrease in CI activity and level [64], and this mutation was also found in patients with hypertrophic

cardiomyopathy and severe bilateral hearing loss, which may have cumulative negative effects on cardiac function [65]. *MT-ND1* m.3337G > A might also cause cardiomyopathy [66]. Mutation m. 3839C > T Ser178Leu causes dramatic changes in the polarity of protein products, which might result in mitochondrial functional defects, and participates in the occurrence of congenital defects in tricuspid atresia, and is related to complex coronary heart disease [67]. The occurrence of hypertension is associated with m.3308T > C/MT-ND1 [68]. In addition, this mutation was also reported to be associated with diabetes [59] and MELAS [57].

MtDNA mutations in somatic cells have also been reported in cancer, possibly affecting the occurrence, progression, and prognosis of cancer. A previously reported mutation, m4216T > C/MT-ND1, related to T2D, was observed in the tumor tissue of patients with colorectal cancer [58], which was significantly different from normal tissue [69]. A strong correlation between *MT-ND1* mutations and postoperative recurrence of local renal cell carcinoma (RCC) was reported [70]. *MT-ND1* mutations in tumor tissue are likely related to the growth and proliferation of tumor cells, and it might become biomarkers for cancer.

In conclusion, *MT-ND1* mutations are associated with the occurrence and development of many diseases, including cardiovascular diseases, neurological disorders and other complicated diseases. Further understanding is needed as to how mutations in *MT-ND1*, as a widely expressed gene, affect these specific diseases. *MT-ND1* and its mutations might serve as indicators and treatment targets for the diagnosis and monitoring of these diseases in the future.

4. The application of *MT-ND1* mutations in disease diagnosis and treatment

Mitochondrial DNA is present in many copies and is easy to detect, and its content is related to the occurrence and development of diseases. Thus, the variation and content of *MT-ND1* can be used for disease diagnosis. High frequency *MT-ND1* mutations are found in patients with, for example, pancreatic cancer [9], thyroid cancer [71], and colorectal cancer [7]. Extracellular vesicles or the circulating cell-free *MT-ND1* content can be used as a tool to diagnose and detect cancer. *MT-ND1* mRNA might also serve as a biomarker for T2D, and it has been verified to be downregulated in patients with diabetic kidney diseases [72,73]. In addition, mutations in *MT-ND1* mutation-induced decreases in respiratory chain CI levels and/or enzyme activity are important genetic factors causing diseases such as LHON, MELAS, and T2D. The pathogenicity of *MT-ND1* mutations is threshold-dependent. Most tissues can tolerate a certain level of CI deficiency, while a few tissues and organs with high energy requirements lack sufficient compensatory mechanisms, and are thus easily affected by a decrease in CI enzyme activity. High levels of m.3460G > A/MT-ND1 mutations significantly affect the disease phenotype [74], and the observed decrease in CI activity in this mutant cell line does not exceed 80%, as complete inhibition is likely to be fatal [75]. The *MT-ND1* mutation might affect the function of CI and the ATP synthesis driven by CI; however, mitochondria can also compensate through the CII parallel pathway, as observed in experiments where the activity of CII is not affected by *MT-ND1* mutation [76]. To some extent, mitochondrial dysfunction can also be compensated for by an increase in the number of mitochondria. Therefore, studying the pathogenic thresholds of different *MT-ND1* mutations will contribute to the accurate diagnosis of diseases. In addition, the mutation levels of *MT-ND1* in different tissues of gene mutation carriers might vary, for example the *MT-ND1* mutation load could be different in different tissue samples such as blood, skeletal muscle, urine, and in different cell types [19,75,77]. This means that mutation level detection in a single tissue sample might make it difficult to predict the occurrence and development of the disease. Therefore, gene screening for patients with mtDNA genetic diseases based on *MT-ND1* mutations has limitations, but can still assist in diagnosing the disease. In clinical practice, detection of MT-ND1 protein levels and the mutation load could assist in the diagnosis of diseases such as colorectal cancer and LHON.

Treatment of LHON patients with mitochondrial mutations such as m.3460G > A/MT-ND1 with edbenquinone has been found to increase the proportion of patients with some degree of (maintained or restored) visual function [78]. Additionally, it is possible to treat related diseases by regulating the expression of *MT-ND1*. Using microRNAs (miRNAs) which can synergistically cooperate with Argonaut 2 protein (Ago 2) to upregulate *MT-ND1* expression in cardiac tissue has been shown to improve heart failure in mice [79,80]. Transfecting a human standard cDNA library to overexpress related genes can inhibit molecular defects caused by *MT-ND1* mutations, restore the activity of CI, and regulate the production of ROS to the normal range [26]. The efficacy of bilateral gene therapy injection against MT-ND4-induced LHON has been demonstrated [81], and MT-ND1 can also be expected to have the potential to ameliorate the disease through gene therapy injection. The difficulty in developing gene therapy for mtDNA lies in transporting DNA to mitochondria, and the current developed technology mainly focuses on ectopic expression of genes. Deficiency of *MT-ND1* leads to the loss of the protein product, thus, its ectopic expression can improve the disease phenotype. After transfection of cells with mixed mRNA located on the surface of mitochondria, the ectopic-expressed MT-ND1 protein compensates for the defective gene, resulting in the rescue of some defects in CI in the cells [82]. In addition, the phenotype of human LHON disease was simulated by injecting mitochondrial targeted Adeno-associated virus (MTS-AAV) fused with m.3460G > A/MT-ND1; and secondary injection of the wild-type ND1 carrier restored the activity of CI and the ATP synthesis rate [83]. Upregulation of normal *MT-ND1* expression or ectopic expression of *MT-ND1* has been shown to salvage respiratory chain CI defects caused by *MT-ND1* mutations and can be applied in the treatment of related diseases. A CRISPR-free RNA-free DDDA-derived cytosine base editor (DdCBE), reported in 2020, is able to precisely manipulate mtDNA to make specific base changes directly in mitochondrial DNA without damaging the mitochondrial genome. This also provides new insights into targeted manipulation of MT-ND1 delivery for the treatment of mitochondrial diseases [84].

The levels of MT-ND1 and its mutations are related to diseases and are easy to detect. Currently, applications in disease diagnosis have been proposed, but because our insufficient understanding of the pathogenic mechanism of mtDNA mutations in diseases, further research is required. Treatment to regulate MT-ND1 expression could effectively improve the disease phenotype. Targeting DNA delivery to mitochondria, researchers have developed technologies for the ectopic expression of *MT-ND1* using vectors such as targeted mixed mRNA or mitochondrial targeting related viruses [82,83]. This provides an effective solution for future treatment development.

5. Issues and prospects

MT-ND1 is one of the core subunits in the mitochondrial respiratory chain CI, and is necessary for the coupling of ubiquinone redox and proton pump in complex I. Understanding the function of the MT-ND1 subunit is significant to determine the structure and function of respiratory chain CI. However, there are three aspects that require further research and clarification: (1) It is currently understood that MT-ND1 is involved in the early assembly of CI, and an assembly model has been proposed; it constitutes important structural domains (ubiquinone binding domain and proton pump) on CI and thus influences the function of CI; however, further research is needed to provide a more detailed explanation of the long-distance coupling mechanism between ubiquinone reduction and the proton pump. (2) Studying the pathogenic mechanism of *MT-ND1* mutations and their impact on disease development and prognosis will provide new insights for the genetic diagnosis and treatment of diseases. However, at present, our understanding of mtDNA mutations is shallow. Various factors, such as nuclear modification genes, mitochondrial haplogroup, and heteroplasmy of mtDNA mutations all affect their pathogenicity, and the pathogenesis of their related diseases is very complex. For diseases affected by *MT-ND1* mutations, more research is needed to confirm the interaction between multiple factors and *MT-ND1* mutation, such as the heteroplasmy of mutations, the penetrance of diseases, and how similar mutations cause different disease phenotypes. (3) The correlation between the content and mutation level of MT-ND1 and the occurrence and development of diseases, mean that MT-ND1 expression and mutation level can be applied in disease diagnosis and treatment, including using the MT-ND1 mutation level to predict disease development, and its ectopic expression to compensate for gene defects, which has good prospects for the treatment of mitochondrial diseases.

No data was used for the research described in the article.

CRediT authorship contribution statement

Xi Lin: Writing – original draft, Conceptualization. **Yanhong Zhou:** Writing – review & editing. **Lei Xue:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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