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Mitochondrial Dynamic Changes in Health and Genetic Diseases

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Abstract

Mitochondria are highly specialized in function, but mitochondrial and, therefore, cellular integrity is maintained through their dynamic nature. Through the frequent processes of fusion and fission, mitochondria continuously change in shape and adjust function to meet cellular requirements. Abnormalities in fusion/fission dynamics generate cellular dysfunction that may lead to diseases. Mutations in the genes encoding mitochondrial fusion/fission proteins, such as MFN2 and OPA1, have been associated with an increasing number of genetic disorders, including Charcot-Marie-Tooth disease type 2A (CMT2A) and autosomal dominant optic atrophy (ADOA). In this review, we try to address the mitochondrial dynamic changes in several important genetic diseases, which will bring the new insight of clinical relevance of mitochondrial genetics.

Mitochondrial Fusion and Fission

Mitochondrial fusion and fission are fundamental biological processes that influence cell function and survival. At steady state, overall mitochondrial morphology and function is maintained through balanced rates of fusion and fission events (1, 2). Regulating fusion/fission may be involved in the inter-mitochondrial exchange of content and information, as well as promoting survival or eliminating damaged mitochondria (3–5). Mitochondrial fission facilitates mitochondrial distribution during cell division to achieve equal segregation into daughter cells and may help to segregate damaged sections of mitochondria and, thus, facilitate mitophagy (6). Fusion protects function by enabling mitochondria to combine their contents for protein complementation and mtDNA repair. Because the roles of mitochondrial fusion and fission are essential to cellular function, abnormalities such as loss of balanced fusion/fission rate can lead to apoptosis (5, 7). Among the proteins that control mitochondrial fission in mammalian cells are Drp1 (DNM1 in yeast) (8), as well as its receptors Fis1 (9) and Mff (10). Drp1, a large GTPase, exists in the cytoplasm and can form complexes that associate at organelle fission sites on the outer mitochondrial surface (11). When GTPase activity is inhibited with a dominant negative protein defective in GTP

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binding, elongated mitochondria develop in mammalian cells (12). Human Fis1 (hFis1) localizes to the outer surface of mitochondria, but not specifically to mitochondrial fission sites (13). Use of RNA interference (RNAi) to down-regulate mammalian Fis1 expression also induces mitochondrial elongation (14). Independently to Fis1, mitochondrial fission factor (Mff) knockdown released the Drp1 foci from the mitochondrial outer membrane accompanied by mitochondrial elongation, whereas Mff overexpression stimulated mitochondrial recruitment of Drp1 accompanied by mitochondrial fission (10). Mitochondrial fusion in mammalian cells is controlled by the large GTPases mitofusin (MFN) 1, MFN2, and OPA 1 (MGM1 in yeast) (15–17). Loss of any of these proteins leads to mitochondrial fragmentation (17–20). Although debate persists, there is some data supporting that another mitochondrial membrane located protein, OPA3, also contributes to the mitochondrial fusion/fission process (21). Recent evidence showed that downregulation of OPA3 led to mitochondrial elongation (22), while overexpressing OPA3 contributed to mitochondrial fragmentation (23).

Mitochondrial cycling and culling is crucial to maintaining cellular homeostasis and is conducted through mitochondrial fusion, fission, and mitophagy. The renewal and distribution of proteins, respiratory chain components, and mtDNA ensures the maintenance and production of healthy mitochondria in the cell (24). Fragmented mitochondria are often targeted to mitophagy while mitochondrial fission is thought to precede mitophagy, but it is not sufficient for mitophagy initiation. OPA1 overexpression and DRP1 silencing causes excessive fusion and decreases mitophagy (25). Furthermore, MFN2 knockdown inhibits mitophagy by reducing lipid transfer between mitochondria and autophagosomes (26).

Mitochondrial dynamic changes and human genetic diseases

Mitochondrial dysfunction has been found in numerous genetic diseases. Initially, mitochondrial dynamic changes were associated with a few rare inherited neurodegenerative disorders such as CMT2A and ADOA (1). However, expanding evidence suggests that mitochondrial dynamic dysfunction is involved in some common diseases as well, including Parkinson's disease and diabetes, affecting almost all organs.

Charcot-Marie-Tooth (CMT) Disease Type 2A (CMT2A)

CMT disease is the most common congenital neuromuscular disorder with a prevalence of 1/2500. CMT affects motor and sensory neurons (27). The three main forms of axonal CMTs have been categorized by genetic studies as dominant (CMT2), recessive (CMT4C or AR-CMT2) and X-linked recessive (CMTX). Among patients with axonal dominant forms (CMT2), up to 20% have subtype CMT2A, which is specifically caused by mutations in MFN2 (27). To date, about 60 mutations on the MFN2 gene have been reported in CMT2A patients, almost all of which are single point mutations in MFN2 coding regions leading to an amino acid substitution (27). Some of the clinical symptoms encountered by patients with CMT2A such as severe muscle atrophy are due to the expression of an MFN2 mutation (MFN2T105M), which causes severe abnormalities leading to massive motor axon degeneration (28). Remarkably, overexpression of MFN1 is capable of rescuing the defective mitochondrial fusion from MFN2 mutations because MFN1 and MFN2 wild-type physically

associate while the CMT2A mutant promotes mitochondrial fusion (1). MFN2 mutations have also been detected in a hereditary motor and sensory neuropathy type VI case with optic atrophy (29).

Autosomal dominant optic atrophy (ADOA)

ADOA type 1 is a neurological disease involving axons of the retinal ganglion cells (RGCs) that comprise the optic nerve. This leads to reduced visual acuity and possibility of blindness with an incidence ranging from 1/12000 to 1/500000. Approximately 60–70% of ADOA cases are autosomal dominant mutations caused by OPA1 mutations that cause to Kjer's disease (30). About 50% of these OPA1 mutations are predicted to truncate the protein and induce haplo-insufficiency due to frame-shift and nonsense mutations, stop codons, splicing errors, or deletions/insertions. The remaining mutated OPA1 proteins are due to missense mutations, which cause heterozygous amino acid substitutions with about 30% of these mutations being close to the GTPase domain (30). Zanna and colleagues have shown that ADOA-1 patients have a reduced rate of complex I-driven ATP synthesis (31). This study revealed a potential link between OPA1 mutations and defects in the respiratory chain by using co-immunoprecipitation to identify interactions between OPA1, AIF and respiratory complexes I, II and III. However, it remains controversial as these changes were not confirmed by other studies of different mutations in AODA patients. Muscle biopsies of AODA patients demonstrated neurogenic atrophy as well as abnormal morphology and distribution of mitochondria; however, they were not correlated with altered bioenergetics or increased susceptibility to pro-apoptotic stimuli (32). The OPA1-driven mitochondrial fusion in RGCs of ADOA1 patients with the deletion of the GTPase effector domain (OPA1 58) cannot adequately oppose fission, thus they are rendered more sensitive to apoptotic stimuli and optic nerve eventually degenerates (18). The wide range of mutations associated with ADOA likely accounts for both the broad spectrum of disease severity and differences in basic studies of mitochondrial function and apoptosis.

OPA3 mutations also cause ADOA and Cataract (ADOAC) and Type III 3-methylglutaconic aciduria. Two dominant missense mutations in OPA3 were identified in exon 2 as the c.277G>A transition and the c.313C>G transversion (33). Fibroblasts from ADOAC patients exhibited heightened apoptotic sensitivity, but did not develop abnormalities of the respiratory chain, mitochondrial membrane potential, or morphology. Type III 3-methylglutaconic aciduria or Costeff syndrome is caused by an autosomal recessive OPA3 mutation, and presents with early-onset bilateral optic atrophy, spasticity, extrapyramidal signs, as well as a cognitive deficit (34). Ryu et al. observed cells that overexpress OPA3 are more sensitive to apoptotic stimuli because increased OPA3 triggered mitochondrial fragmentation, leading to cell death via a FIS1/DRP1-independent pathway (23). Interestingly, others have found that the balance between mitochondrial fission and fusion becomes offset when OPA3 mutations in the hydrophobic region inhibit mitochondrial fragmentation and induces the overexpression of MFN1 (23). The function of OPA3 is not well understood, and more investigations are needed in this area.

Parkinson's disease (PD)

PD is a relatively prevalent, progressive neurodegenerative disorder characterized by loss of the nigrostriatal dopaminergic neurons leading mainly to movement-related symptoms. About 10% of PD cases are familial with a genetic basis. PD risk increases have been associated with genetic mutations in many proteins linked to the mitochondria, such as α -synuclein, DJ-1, parkin, PINK1, and LRRK2 (35). Moreover, risk of PD increases upon exposure to neurotoxins and other environmental factors including 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) via its active metabolite 1-methyl-4-phenylpyridinium ion (MPP⁺) (36). Emerging evidence suggests that the mitochondrial dysfunction is an essential component of PD pathogenesis and this is supported by genetic PD models precipitated by abnormal mitochondrial dynamics. This has been recently nicely reviewed by Yan et al. (37).

Autosomal dominant PD is triggered by point mutations in mitochondrial proteins, such as the A53T and E46K mutations in α -synuclein. Overexpressing human α -synuclein in mice resulted in the development of dysfunctional mitochondria and increased oxidative stress (38), whereas the overexpression of the A35T α -synuclein mutation in transgenic mice lead to abnormal α -synuclein accumulation in the mitochondria, which were markedly abnormal (39). Another study recently demonstrated that a probable role of α -synuclein is to block spontaneous membrane fusion, as α -synuclein overexpression results in mitochondrial fragmentation, independent of the fission and fusion machinery (40). A second, more recent study confirmed that DRP1-independent fragmentation was induced by α -synuclein overexpression (41). In contrast, others showed *in vivo* mitochondrial fragmentation due to A53T α -synuclein overexpression, which was concurrent with a drastic change in expression of DRP1/MFN1/MFN2 in neurons of both mito-CFP and A53T α -synuclein expressing transgenic mice (42). More work is needed to fully understand the function(s) of α -synuclein.

Autosomal recessive juvenile Parkinsonism develops secondary to mutations in either parkin or PINK1. Parkin and PINK1 have been widely investigated for their essential role in mitophagy. PINK1, a serine/threonine protein kinase located on the cytoplasmic side of the outer mitochondrial membrane, phosphorylates cytoplasmic parkin and causes its translocation to the mitochondria (43). The PINK1/parkin pathway encourages mitochondrial fission and/or impedes fusion by its negative regulation of MFN1/2 and OPA1 function, and/or the pathway's positive regulation of DRP1, as seen in *Drosophila* (44). The ubiquitination of MFN1/2, but not OPA1 or Fis1, was reported to be promoted by the PINK1/parkin pathway within an hour of H₂O₂ treatment in PD patient-derived fibroblast cells (45). Additionally, it has recently been demonstrated that wild-type parkin interacts with and ubiquitinates Drp1, but parkin with a pathogenic mutation or its knocked down inhibits Drp1 ubiquitination and degradation, which leads to an increased Drp1 resulting in mitochondrial fragmentation (46). Yu et al. discovered a decrease in mitochondrial size in primary neurons with PINK1 and parkin over-expression, in contrast to elongated mitochondria when they were silenced. Furthermore, it has been demonstrated in both *Drosophila* and a mammalian system that parkin-mediated ubiquitination and subsequent MFN2 degradation likely underlie suppressed mitochondrial fusion (47). Overall, these

studies strongly suggest that the PINK1/parkin pathway directly influences mitochondrial dynamics.

Autosomal recessive early onset Parkinsonism is caused by pathogenic mutations in DJ-1, a small 20 kDa protein with a crucial role in the cellular response to oxidative stress (48–50). Interestingly, it has been reported that fragmented mitochondria were found in human fibroblasts from DJ-1 E64D PD patients and in lymphoblasts derived from DJ-1 L166P or DJ-1 deletion mutation PD patients (51, 52). Moreover, extensive mitochondrial fragmentation as well as ultrastructural defects in M17 neuronal cells and primary cortical neurons are caused by the overexpression of several pathogenic DJ-1 mutants (52). In contrast, the overexpression of wild-type DJ-1 in neurons resulted in significantly elongated mitochondria, giving them an enhanced resistance to H₂O₂ and MPP⁺ (52). Mouse embryonic fibroblasts with DJ-1 knockout exhibit extensive mitochondrial fragmentation, which reduces mitochondrial connectivity, but overexpression of wild type human DJ-1, PINK1 or parkin restores mitochondrial dynamics (53). These studies confirmed the contribution of DJ-1 in regulating mitochondrial dynamics.

Mutations in the leucine-rich repeat kinase 2 (LRRK2), a large multi-domain protein kinase, are linked to autosomal dominant PD. LRRK2 co-localizes with mitochondria in order to directly interact with Drp1 for recruitment, which induces mitochondrial fragmentation and dysfunction, while its kinase activity may also increase cell vulnerability to stress. PD-associated LRRK2 mutants further aggravate these effects (54). After treatment with P110, a selective peptide inhibitor of Drp1, both LRRK2G2019S-expressing cells and PD patient fibroblasts carrying this specific mutant showed reduced mitochondrial fragmentation and damage (55). This suggests a possible new approach for treatment of PD through inhibition of Drp1-mediated increased mitochondrial fission.

In addition to the PD gene related mitochondrial disorder, other studies demonstrated that the neurotoxin, MPP⁺, induces a DRP1-dependent biphasic increase in mitochondrial fragmentation while simultaneously decreasing ATP levels in both SH-SY5Y neuroblastoma cells and primary rat dopaminergic midbrain neurons (46). Indeed, attenuation of mitochondrial fragmentation by DRP1 knockdown reduces the downstream events induced by MPP⁺, including ROS accumulation and ATP depletion.

Alzheimer's diseases (AD)

Familial AD (more than 2 persons in a family are affected) accounts for approximately 25% of all AD and, of those afflicted with familial AD, 95% is considered late onset (occurring after 65 years of age) and 5% is early onset (56). AD neurons have fewer mitochondria with an increased size, suggesting a potential incidence of abnormal mitochondrial dynamics in the AD brain (57).

An increasing number of reports are showing that the dynamic nature of the mitochondria is disturbed in AD brain. Supporting studies that reveal significant changes in protein levels such as decreased MFN1/2 and OPA1 affecting mitochondrial fusion, and decreased DRP1 and increased Fis1 disrupting fission in the AD brain (58–60). Although the total cellular

levels of DRP1 decrease, mitochondrial DRP1 used for mitochondrial fission as well as phosphorylated Ser616DRP1 (a posttranslational modification to facilitate mitochondrial translocation) are increased in AD brain (58).

S-nitrosylation of DRP1 facilitates mitochondrial fission by activating the GTPase activity of DRP1 and is also increased in AD brain (61). Furthermore, the interaction of Drp1 with amyloid beta (A β) lead to abnormal mitochondrial dynamics and damage to the synapse, resulting in AD disease progression (62). Interestingly, nitric oxide production enhanced by A β was reported to trigger mitochondrial fission and cause neuronal damage because it activated Drp1 GTPase activity via C644 nitrosylation (63), although the proposed process was challenged (64). The combination of the decreased fusion proteins and increased Fis1 in AD brain (62) in peripheral blood lymphocytes from AD (65) suggest that the increased mitochondrial fragmentation in AD likely contributes to mitochondrial dysfunction.

Huntington's diseases (HD)

HD, the devastating autosomal dominant neurodegenerative disorder, is caused by the abnormal triplet expansion of the CAG repeat in exon 1 of the HD gene. This mutated gene generates an elongated polyglutamine stretch in the protein product called mutant Htt that may directly bind the mitochondria (3). Studies have demonstrated the localization of mutant Htt to the outer mitochondrial membrane using both HD transgenic mice and HD striatal cells (STHdhQ111) (66). The discovery of Htt aggregates localized to the mitochondria (67) suggests that mitochondrial dysfunction contributes to HD. Apoptotic stimulation in cellular models of HD reveals the aggravation of mitochondrial cristae alterations characteristic of fragmented HD mitochondria (68). Studies on cellular models of HD as well as HD postmortem brain tissue have reported an increased expression of Drp1 and Fis1, and depressed expression of mitofusins and OPA1 (69–72). The direct interaction between mutant Htt and Drp1 stimulates DRP1 GTPase activity, leading both *in vivo* and *in vitro* to mitochondrial fragmentation. Thus, the critical mitochondrial fusion/fission balance is impaired and neuronal cell death ensues (71). However, this issue is not resolved, as others have reported increased vacuolization, abnormal cristae, and giant mitochondria in the skin fibroblasts and muscle tissues from HD patients (73). In sum, although controversial, the evidence supports a role for impaired mitochondrial fusion/fission in HD.

Diabetes

Mitochondria have an important function in insulin secretion and mutation in mitochondrial DNA leads to the known etiological subdivision of diabetes (74). Pancreatic β -cells require healthy mitochondrial function in order to properly regulate insulin secretion. The pancreatic islets of patients with type 2 diabetes have mitochondria that are both functionally and morphologically altered with decreased mitochondrial membrane potential, depressed ATP production, and many swollen mitochondria (75). Mitochondria from β -cells in the Zucker diabetic fatty rat model were reported as short and swollen, and reduced levels of both MFN2 mRNA and protein were confirmed (76). Islet beta cells exposed to hyperglycemic conditions resulted in a drastic increase in Drp1 expression. When Drp1 expression was induced, Drp1 wild-type cells from inducible beta cell line significantly promoted high

glucose-induced apoptosis, but this was not observed in the Drp1K38A (dominant negative Drp1 mutant) inducible beta cell line (77). The downregulation of Fis1 in β -cell mitochondria may significantly reduce high glucose-induced insulin secretion via decreased respiration (78). β -cells with overexpressed hFis1 or MFN1 contained smaller mitochondria and lower levels of cellular ATP, and therefore had impaired glucose-stimulated insulin secretion as well (79). Key proteins in mitochondrial dynamics such as OPA1, DRP1, and Fis1 were manipulated in order to test their role in β -cell mitochondrial morphology (80). In this case, increasing mitochondrial fusion proteins inhibited mitochondrial fragmentation, maintained mitochondrial dynamics, and blocked apoptosis. Mice β -cells lacking OPA1 develop hyperglycemia, which suggests that OPA1 is physiologically relevant in β -cells in order to maintain the electron transport chain (81). Mitochondria found in the skeletal muscle of both mice with genetic and diet-induced obesity were smaller and shorter with increased fission machinery. Mitochondrial fission inhibition led to improved muscle cell insulin signaling, as well as to better systemic insulin sensitivity in obese mice (82). Interestingly, after three hours of insulin treatment, OPA1 protein levels and mitochondrial membrane potential increased, mitochondrial fusion was improved, and both intracellular ATP levels and oxygen consumption in cardiomyocytes *in vitro* and *in vivo* were elevated (83). These observations suggest disruption of mitochondrial dynamics in diabetes may contribute to diabetic pathologies at a cellular and organ level.

Cardiomyopathy

In patients, especially children, with mitochondrial disease, cardiomyopathy was common (17% of patients) and was associated with increased mortality (84). However, studies are limited as to whether inherited cardiomyopathy is associated with changes in mitochondrial dynamics. In part this reflects the diversity of inherited cardiomyopathy. *In vivo* investigations suggest some degree of impaired cardiac function that ranges from moderate hypertrophy observed in MFN2 knockout mice to severe heart failure in the absence of both mitofusins (85, 86). An OPA1 aberrant expression mouse, modeling ADOA, has also been associated with late-onset cardiomyopathy in mouse models with a heterozygous null OPA1 mutation (87). The heterozygous mutation of OPA3 in exon 2, modeling ADOAC, lead to a dilated cardiomyopathy (88). These evidences suggested an important potential role for abnormalities of mitochondrial dynamics in inherited cardiomyopathy.

Mechanisms in Mitochondrial Dynamic Related Diseases

Mitochondrial fusion/fission plays critical roles in maintaining mitochondrial morphology, and has been strongly linked to mtDNA stability, antioxidant processes and apoptosis. In almost all the genetic diseases discussed above, loss of balanced mitochondrial dynamics may contribute to the phenotypes/syndromes.

mtDNA Loss and Mitochondrial Dynamics

Many mitochondrial disorders are accompanied by mtDNA mutation or deletion. Mitochondrial dynamic proteins have been linked to maintenance of the stability of mtDNA. The “ADOA plus” syndromes are associated with a subset of OPA1 missense mutations

(89). This syndrome usually involves not only vision loss, but also weakness in the muscles (ophthalmoplegia, ataxia), hearing loss, motor and sensory neuropathy, and muscle weakness (myopathy). A subset of OPA1 missense mutations have been correlated with the “ADOA plus” syndrome, as well as with stable tissues like skeletal muscle that have accumulated mtDNA deletions (89). The implication of MFN2 in mtDNA maintenance, replication, and repair is indirectly supported by the qualitative (multiple deletions) and quantitative (depletion) abnormalities of mtDNA in the skeletal muscle of mitofusin-deficient mice (90). OPA1 heterozygous mutation also caused significant mtDNA loss in a mouse modeling ADOA (87). High levels of mtDNA deletions in CMT2A patients have been confirmed, which suggests that MFN2 mutations affect mtDNA replication by altering mitochondrial oxidative phosphorylation (91). mtDNA is also affected by PD, while greater levels of mtDNA damage was detected in neural cells from patients carrying homozygous or heterozygous LRRK2 G2019S mutations (92). mtDNA deletions, as well as other alterations, can result from oxidative damage to nucleic acids in AD patients (93). In a clinic study with AD patients, markedly increased level of mtDNA deletions has been found (94).

Oxidative stress and Mitochondrial Dynamics

Mitochondrial fusion/fission balance is particularly susceptible to oxidative stress. For example, it has been shown that hydrogen peroxide at low levels elicits reversible mitochondrial swelling, fragmentation, and fine structural alterations by modulation of fission/fusion proteins (95). Mitochondrial depolarization, such as from a sustained cytosolic Ca²⁺ influx, triggers significant mitochondrial fragmentation, presumably secondary to phosphorylation of DRP1 (96). On the other hand, excessive mitochondrial fragmentation can enhance ROS production. For example, high-glucose-induced respiration escalation and ROS overproduction are secondary to mitochondrial fragmentation facilitated by excessive fission (97). Decreased antioxidant gene expression, reduced total antioxidant capacity, as well as accumulated ROS, has been found in the OPA1 mutant mouse heart (87). Defects in mitochondrial dynamics may cause damaged mitochondrial components to accumulate due to inefficient elimination through mitophagy coupled with fission (25). A direct adverse effect on the function of critical mitochondrial protein complexes is also implicated because mitochondrial fission may also be necessary for the proper assembly and function of mitochondrial ETC complexes (87). Thus, the balance of mitochondrial fission/fusion can be offset by oxidative stress, which would further amplify ROS generation.

Apoptosis and Mitochondrial Dynamics

It has been generally accepted that loss of balanced mitochondrial fusion/fission, especially in a favor of fission, results in apoptosis. Manipulating mitochondrial fusion or fission proteins has been widely used to investigate the relationship between mitochondrial dynamic changes and apoptosis (19, 20, 98–101). The well-known apoptotic pathways, including Bcl2, Bax, Bnip3 and Endogenous G, have all been reported to be involved in the mitochondrial dynamic related apoptosis (101–104). However, this still remains controversial. In some MFN1/2 or OPA1 mutation cases, especially in CMT2A and ADOA patients and genetic animal models, changes in apoptosis are not obvious (86, 105–108).

Summary

Mitochondria dynamic equilibrium plays a vital role in maintaining health through their regulation of mitochondrial function. Unbalanced mitochondrial fusion/fission has been identified in many mitochondria related genetic diseases, in which mtDNA deletion, apoptosis, and ROS accumulation lead to marked dysfunction. The growing investigation of the mitochondrial dynamic pathways will provide the new insights into therapeutic approaches to these genetic diseases.

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Table I

Genetic Abnormalities Associate with Mitochondrial Dynamic Genes

Abnormalities	Changes in Mitochondrial dynamic genes	Mitochondria changes	References
CMT2A	MFN2 mutations	Fragmented mitochondria	(26,27)
ADOA	OPA1/OPA3 mutations	Fragmented mitochondria	(29,30)
ADOAC	Opa3 mutations	Fragmented mitochondria	(33,34)
Parkinson's disease	Parkin/PINK1 mutations; Decreased OPA1, MFN2; Increased Drp1	Fragmented mitochondria	(40–42)
Alzheimer's diseases	Decreased OPA1, MFN2; Increased Fis1; Decreased total Drp1 but increased mitochondrial Drp1	Fragmented mitochondria	(57–65)
Huntington's diseases	Increased Drp1 and Fis1	Fragmented mitochondria in neuron cell, but giant mitochondria in muscle and skin cell	(68–71)
Diabetes	Decreased MFN2, OPA1; Increased Drp1, Fis1	Shorter, swollen mitochondria	(76–83)
Cardiomyopathy	Loss of MFN2 OPA1/OPA3 mutations;	Fragmented mitochondria	(84–88)