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iPSC models of mitochondrial diseases

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ABSTRACT

Mitochondrial diseases are historically difficult to study. They cause multi-systemic defects with prevalent impairment of hard-to-access tissues such as the brain and the heart. Furthermore, they suffer from a paucity of conventional model systems, especially because of the challenges associated with mitochondrial DNA (mtDNA) engineering. Consequently, most mitochondrial diseases are currently untreatable. Human induced pluripotent stem cells (iPSCs) represent a promising approach for developing human model systems and assessing therapeutic avenues in a patient- and tissue-specific context. iPSCs are being increasingly used to investigate mitochondrial diseases, either for dissecting mutation-specific defects within two-dimensional (2D) or three-dimensional (3D) progenies or for unveiling the impact of potential treatment options. Here, we review how iPSC-derived 2D cells and 3D organoid models have been applied to the study of mitochondrial diseases caused by either nuclear or mtDNA defects. We anticipate that the field of iPSC-driven modeling of mitochondrial diseases will continue to grow, likely leading to the development of innovative platforms for treatment discovery and toxicity that could benefit the patient community suffering from these debilitating disorders with highly unmet medical needs.

1. Mitochondrial diseases and their challenges

Primary mitochondrial diseases are the most common group of inherited metabolic disorders, and they can be caused by mutations in either nuclear DNA or mitochondrial DNA (mtDNA) (Cree et al., 2009; Gorman et al., 2016; Vafai and Mootha, 2012). As mitochondria are the main responsible for ATP production in the cell, all these mutations can lead to bioenergetic defects. Mitochondrial diseases are multi-systemic, because cells from all kinds of tissues rely on ATP production to function properly. However, tissues with especially high energy demands, such as the brain, the heart, and skeletal muscles, are worst affected (Carelli and Chan, 2014; Ng and Turnbull, 2016; Pfeffer et al., 2013).

Mitochondrial diseases are highly heterogenous and usually have an unclear genotype-phenotype correlation, which hamper the investigation of pathomechanisms and the identification of effective treatments. Currently, the majority of drug options available to mitochondrial patients focus on mitigating the symptoms and increasing the life expectancy, but do not correct the root cause of the disease, i.e. the genetic disturbance (Bottani et al., 2020; Russell et al., 2020; Weissig, 2020).

Drug discovery is especially challenging for mitochondrial diseases because there are insufficient pre-clinical model systems (Inak et al., 2017; Tolle et al., 2023). Most mitochondrial diseases are species-specific, leading to limitations in animal models (Kovářová et al., 2016; Stewart, 2021; Tyynismaa and Suomalainen, 2009). For instance, mice with a knock-out for the gene *SURF1*, an assembly factor of complex IV whose mutations cause the severe mitochondrial disease Leigh syndrome (Tiranti et al., 1998), failed to develop pathological features, and even showed increased life-span compared to wild-type animals (Dell'agnello et al., 2007). Moreover, introducing disease-specific mtDNA defects into animal models has been hindered by the difficulty associated with mtDNA manipulation (Silva-Pinheiro and Minczuk, 2022).

1.1. Induced pluripotent stem cells (iPSCs)

In 2007, the group of Shinya Yamanaka successfully generated human induced pluripotent stem cells (iPSCs) by inducing the expression of embryonic stem cells (ESCs)-associated transcription factors OCT4, SOX2, KLF4, and c-MYC into dermal fibroblasts via retroviral transduction (Takahashi et al., 2007). iPSCs showed ESC-like features

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with respect to morphology, proliferation, gene expression, telomerase activity, and differentiation potential (Takahashi et al., 2007). Overall, somatic cells reprogrammed into iPSCs appear remarkably similar to ESCs, as they self-renew indefinitely and can differentiate into virtually any cell type of the three germ layers (ectoderm, endoderm and mesoderm). Since the first discovery in 2007, several viral and non-viral reprogramming methods have been established to force the expression in somatic cells of transcription factors that are normally present in ESCs.

Indeed, iPSCs have now become a commonly utilized model for studying diseases (Liu et al., 2020; Rowe and Daley, 2019; Shi et al., 2017). By using human iPSCs, the human genomic background is preserved, which is important for studying human diseases as most of them are species-specific. Studies show that only around 5 % of animal-tested therapeutic interventions obtain regulatory approval for human applications (Ineichen et al., 2024). Therefore, iPSCs already largely contribute to the application of 3R (replace, reduce, refine) principle in scientific research (Retter et al., 2024). The main advantage of iPSCs is that they allow researchers to study specialized cell types that can be directly generated from individual patients, thus enabling them to assess the contribution of defined mutations on the functionality of specific tissues in a personalized manner. In this context, iPSCs are also promising for the application in regenerative medicine, as they can be differentiated in any cell type, thereby serving as a source for cell replacement therapies (Aboul-Soud et al., 2021). At the same time, using patient-specific differentiated iPSCs increases safety of autologous transplants without risk of immunorejection (Aboul-Soud et al., 2021). These features imply that iPSC-based studies, either as cell replacement or as a platform for drug screening, might lead to personalized therapeutic suggestions.

iPSCs and their derived two-dimensional (2D) cell types may still hold limitations for modeling complex three-dimensional (3D) human tissues. Like other 2D cell cultures, iPSC cultures are not as physiologically relevant as 3D tissues, as they lack complex cell-to-cell and cell-to-extracellular matrix interactions, as well as the variety of different cell type organization of human tissues. In accordance, also mitochondrial dynamics show differences between in vitro 2D cells and in vivo models (Han et al., 2023; Rodger et al., 2017). To overcome this issue, iPSCs can now be differentiated in 3D to build so-called organoids which are complexly organized cellular structures that are capable of recapitulating key features of actual human tissues and organs (Lancaster et al., 2013; Rossi et al., 2018). Other limitations of iPSCs include the variability in reprogramming efficiency and the inter-individual genetic variation between the generated iPSC lines. To overcome this latter limitation, researchers developed so-called chimeroids, a multi-donor human brain cortical organoid model formed by pooling iPSCs derived from different donors (Antón-Bolaños et al., 2024). This model system could be useful for high-throughput investigation of inter-individual variation in processes of brain development and disease (Antón-Bolaños et al., 2024). Challenges in modeling late-onset disease phenotypes with iPSCs are more difficult to be addressed, despite attempts using telomerase shortening or genome editing (Vera et al., 2016). For aging-related defects, by-passing iPSCs and using direct reprogramming approaches currently appear as the most promising strategy (Pitrez et al., 2024).

In this review article, we provide a summary of how iPSCs and their 2D and 3D differentiated progenies have been used to model human diseases primarily impairing mitochondrial function.

1.2. iPSCs and mitochondria

To model mitochondrial diseases with iPSCs, it is important to understand how cellular reprogramming can impact mitochondria and their DNA. In humans, mitochondrial DNA (mtDNA) comprises 37 genes (Anderson et al., 1981). 13 of these genes express mRNAs to encode proteins of the mitochondrial respiratory chain (MRC), which is responsible for generating ATP in the presence of oxygen through oxidative phosphorylation (OXPHOS). The remaining 24 genes encode for 22 rRNAs and 2 tRNAs that are important for translating mitochondrial mRNA into proteins. Mitochondria are involved in a plethora of cellular functions (Picard and Shirihai, 2022) and form an interconnected network whose shape is regulated by mitochondrial fusion and fission processes (Campello and Scorrano, 2010).

As each mitochondrion contains several mtDNA molecules and each cell comprises various amounts of mitochondria, the total mtDNA copy number differs from cell to cell and tissue to tissue (Filograna et al., 2021). This multi-copy nature of mtDNA results in some genetic peculiarities. Mutations in mtDNA can in fact occur within a distinct percentage of mtDNA molecules, a phenomenon known as heteroplasmy. A mutation can also be present in all mtDNA molecules in a state defined as homoplasmy. The level of heteroplasmy has implications on the impact of specific mutations on mitochondrial and cellular function, thereby influencing the overall disease phenotype (Bannwarth et al., 2013). Moreover, as mitochondria are solely inherited by the mother during fertilization, mtDNA diseases follow a pattern of inheritance that is non-mendelian (Stewart and Chinnery, 2015).

Within iPSCs, mitochondria appear as peri-nuclear and less fused than in their parental somatic cells, and with less defined cristae (Armstrong et al., 2010; Prigione et al., 2010). Since cristae are the site of OXPHOS production, their reduction is suggestive of a diminished reliance on mitochondrial-based ATP production. Accordingly, iPSCs mostly rely on glycolysis for energy generation (Folmes et al., 2011; Prigione et al., 2010). Upon differentiation, iPSCs switch to OXPHOS and increase their mtDNA content (Prigione et al., 2010; Varum et al., 2011). Altogether, mitochondria appear to modify their status in a plastic manner that varies in concert with the specific cell fate identity (Lisowski et al., 2018).

The number of mtDNA copies is typically reduced in iPSCs compared to their parental cells (Prigione et al., 2010; Sercel et al., 2021). In parallel to this, the level of mtDNA heteroplasmy can vary among iPSC lines derived from the same somatic cells (Kang et al., 2016; Palombo et al., 2021; Perales-Clemente et al., 2016; Prigione et al., 2011; Wei et al., 2021). This phenomenon might be due to a bottleneck effect reminiscent of the one occurring during embryonic development, where upon mtDNA replication in response to a drastic reduction, mitochondrial segregation might occur (Stewart and Chinnery, 2015), thereby resulting in cells carrying variable ratios of wild-type and mutant mtDNA (Prigione et al., 2010; Sercel et al., 2021). Such features may have implications for iPSC-based modeling, as de novo mtDNA mutations might arise upon induction of pluripotency while other mtDNA variants may be lost (Carelli et al., 2022; Kelly et al., 2013; Prigione et al., 2011). Hence, the derived iPSC lines might not mirror exactly the parental cells with respect to mtDNA profile, a situation that could potentially complicate disease-related interpretations. For these reasons, mtDNA monitoring has been suggested to be included in the quality control analysis of all newly derived iPSC lines (Carelli et al., 2022; Hämäläinen, 2016; Rossi et al., 2022).

In the context of mtDNA diseases, changes of heteroplasmy levels during reprogramming can have both negative and positive implications. The negative aspects relate to the potential loss of pathogenic mutations and the consequent need for screening several iPSC clones and for continuous mtDNA monitoring also within differentiated progenies. The positive implications refer to the possibility of generating from the same patient cells iPSC lines carrying high mutation levels and also iPSC lines that are mutation-free. These latter lines can function as isogenic control iPSCs, and therefore represent an important asset for disease modeling (Tolle et al., 2023). In fact, due to the inherent heterogeneity of individual iPSCs, isogenic iPSC lines, which share the same genetic background and differ only in the presence of a specific mutation, have become essential for investigating disease phenotypes associated with specific gene defects (Ben Jehuda et al., 2018). For nuclear mutations, the generation of isogenic iPSC lines can be accomplished

using CRISPR/Cas9 knock-in gene editing, by either correcting the mutation in patient-derived iPSCs or by introducing the mutation in healthy iPSCs (Hockemeyer and Jaenisch, 2016). Both options are valid and allow unveiling the direct consequences of defined nuclear defects.

Unfortunately, the derivation of isogenic iPSC lines for mtDNA mutations remains challenging. The mechanisms driving the changes in mtDNA profile during reprogramming are unknown (Sercel et al., 2021; Tolle et al., 2023), and thus the loss of pathogenic mtDNA mutations appears random and difficult to control. Furthermore, the active manipulation of mtDNA is notoriously difficult (Silva-Pinheiro and Minczuk, 2022). In fact, the polyploid nature of mtDNA, the presence of a double mitochondrial membrane, as well as the lack of efficient DNA recombination hinder the engineering of mtDNA by classical methods like CRISPR/Cas9 (Gammage et al., 2018; Jinek et al., 2012). Novel mtDNA base editing approaches have been recently developed based on CRISPR-free DddA-derived cytosine base editor (DdCBE) (Mok et al., 2020; Silva-Pinheiro et al., 2023). DdCBE-related approaches are starting to be applied also in iPSCs (Chen et al., 2023b), which will likely lead to key technological advances for iPSC-based modeling of mitochondrial diseases (Tolle et al., 2023).

Overall, given the current challenges associated with the development of mitochondrial disease models, iPSCs appear to represent a promising system for investigating the underlying mutation-specific and tissue-specific disease mechanisms and for establishing innovative cellular platforms for treatment identification (Inak et al., 2017; McKnight et al., 2021).

In the following sections, we review how iPSCs have been used in the past years to model primary mitochondrial disorders caused by either nuclear or mitochondrial defects.

1.3. iPSC models for nuclear DNA disorders

Different mitochondrial diseases arise as a consequence of mutations in nuclear genes encoding for MRC components or for proteins involved in mitochondria-related processes (Koopman et al., 2012). As mentioned above, all tissues can be in principle affected by mitochondrial diseases, but neuronal and cardiac/skeletal systems are typically more strongly impacted. Here, we first describe iPSC models for diseases mainly impacting neuronal cells, and afterwards those for diseases mainly affecting cardiac and skeletal cells. Lastly, we report on other systems affected by mitochondrial diseases that have been modeled with iPSCs. The published disease-specific iPSC lines and their respective findings are reported in Table 1.

Leigh Syndrome (LS, OMIM #256000) is a severe pediatric mitochondrial disease causing encephalomyopathy and intellectual and physiological regression, eventually leading to early death in most cases (Baertling et al., 2014; Lim et al., 2022). More than 100 gene defects have been identified as a cause of LS (Rahman, 2023). Among the most common nuclear mutations causing LS, there are complex I genes (e.g. *NDUFS4*, encoding for NADH dehydrogenase [ubiquinone] iron–sulphur protein 4) and the complex IV assembly factor *SURF1* (Tiranti et al., 1998). *SURF1* mutations were investigated with iPSCs using isogenic pairs that carried the mutations in either a healthy or patient-specific background (Inak et al., 2021). Cerebral organoids with *SURF1* mutations differentiated from those iPSC isogenic pairs showed a compromised neuronal morphogenesis that emerged at the level of neural progenitor cells (NPCs), which retain a glycolytic proliferative state and failed to commit to the neuronal fate as seen by impaired neurite outgrowth (Inak et al., 2021). Neuronal morphogenesis could be restored by *SURF1* gene augmentation or by induction of the mitochondrial biogenesis master regulator PGC1A via bezafibrate treatment, which supported the metabolic programming of mutant NPCs (Inak et al., 2021). Azole compounds have been suggested to be beneficial for *SURF1* mutations by promoting neuronal morphogenesis in 2D neurons and 3D midbrain organoids (Menacho et al., 2024). NPCs carrying *NDUFS4* mutations showed similar defects with reduced neurite outgrowth and decreased mitochondrial membrane potential (MMP) (Inak et al., 2021). *NDUFS4* knock-out in iPSCs led to increased neuronal apoptosis in iPSC-derived neurons and cardiomyocytes that could be attenuated by nicotinamide riboside supplementation, leading to normalization of MMP and reduction of excessive reactive oxygen species (ROS) production (Yoon et al., 2022). Introduction of *NDUFS4* mutations by CRIPSR/Cas9 in healthy iPSCs was used to study neurodevelopmental defects in cortical brain organoids, which manifested elevated proinflammatory pathways, as LS neurons appeared more susceptible to glutamate excitotoxicity (Daneshgar et al., 2022). LS-associated mutations in the complex I nuclear gene *NDUFV1* (NADH Dehydrogenase [Ubiquinone] Flavoprotein 1) were investigated using iPSC-derived NPCs and neurons, which showed decreased ATP production and MMP, and increased ROS levels (Sequiera et al., 2022). Similar defects were observed in NPCs and neurons derived from a patient with the ultrarare Leigh-like syndrome harboring *ECHS1* mutations (Sequiera et al., 2022). Drug screenings in *ECHS1* mutant NPCs identified drugs capable of decreasing ROS, restore MMP, and improve mitochondrial respiration in LS neural cells, among others ubiquinol and α-lipoic acid (Sequiera et al., 2022). LS iPSC-derived neuroepithelial stem cells carrying a mutation in the gene *PMPCB*, a subunit of mitochondrial processing protease (MPP), displayed accumulation of the processing intermediate of frataxin (Vögtle et al., 2018). This accumulation could be caused by the block of its second processing step by the MPP, making frataxin a possible early marker for MPP dysfunction (Vögtle et al., 2018). Hence, iPSC models of LS highlighted a neurodevelopmental component of this disease that could be ameliorated using various drug-based or genetic strategies.

Charcot Marie Tooth (CMT, e.g. OMIM #609260) disease is an inherited neuropathy that can be caused by different gene defects (Baets et al., 2014). CMT iPSC-derived motor neurons carrying mutations in the gene *MFN2,* which encodes for mitofusin 2 protein that regulates mitochondrial fusion, showed selective mitochondrial depletion, apoptosis resistance, and increased mitophagy (Rizzo et al., 2016), as well as electrophysiological abnormalities, including reduced action potential threshold and abnormal channel current properties (Saporta et al., 2015). Neurite network alterations were also observed in *MFN2* mutant CMT neurons, with progressive deficits in mitochondrial morphology and mitochondrial and lysosomal trafficking, as well as altered profiles of mitochondrial expression and bioenergetics that appeared more evident in motor neurons than in sensory neurons (Van Lent et al., 2021). Inhibition of dual leucine kinase, an upstream metabolite in the c-Jun N-terminal kinase stress-responsive pathway, reverted the disease phenotypes in *MFN2* mutant neurons (Van Lent et al., 2021). iPSC-derived motor neurons from CMT patients with mutations in ganglioside induced differentiation associated protein 1 (*GDAP1*) exhibited decreased cell viability due to lipid dysfunction and oxidative stress as well as mitochondrial cristae defects (Miressi et al., 2021). Treatment with amlexanox, an inhibitor of the nonsense-mediated mRNA degradation system, induced a restoration of the mitochondrial morphology in *GDAP1* mutant neuronal cells (Benslimane et al., 2023). In the X-linked dominant CMT disease (OMIM # 300905), mutations in pyruvate dehydrogenase kinase 3 (*PDK3*) caused bioenergetic defects and mitochondrial abnormalities in iPSC-derived motor neurons, including reduced velocity of trafficking mitochondria in the affected axons, which could be reversed upon exposure to a PDK inhibitor (Perez-Siles et al., 2020). Altogether, CMT modeling with iPSCs identified specific defects in defined neuronal populations and unveiled potential treatment avenues.

The gene optic atrophy 1 (*OPA1*) encodes for a GTPase at the inner mitochondrial membrane involved in regulating mitochondrial fusion, stability, and energy output (Lenaers et al., 2021). *OPA1* mutations can cause dominant optic atrophy (DOA, OMIM #165500), a disease associated with central vision loss and degeneration of retinal ganglion cells (RGCs) that can be associated with additional neurological defects in DOA+ syndrome (OMIM #125250) (Lenaers et al., 2021). iPSCs derived

Table 1
iPSC models for nuclear DNA disorders leading to mitochondrial diseases. Compound heterozygotes are marked with "&". iPSCs are all patient-derived, except for when stated differently. NPCs: neural progenitor cells, RGCs: retinal ganglion cells, RPE: retinal pigment epithelium.

Disease	Gene and mutation	iPSC model	Outcome	Reference
Alpers syndrome	***POLG*** c.2243G > C; c.2243G > C & c.1399G > A	iPSCs, iPSC-derived neural stem cells	iPSCs: reduced ATP production. Neural stem cells: decreased ATP production, ROS excess and mtDNA depletion.	Liang et al., 2020
		iPSC-derived dopaminergic neurons	mtDNA depletion, loss of complex I and mitochondrial membrane potential, ROS overproduction and cellular senescence. Amelioration of mitochondrial dysfunction and reduced oxidative stress by treatment with N-acetylcysteine amide.	Liang et al., 2021
	POLG c.1399G > A	iPSC-derived hepatocyte-like cells	Mitochondrial permeability transition pore opening-dependent apoptosis at valproic acid exposure, rescued by cyclosporine A	Li et al., 2015a
Auditory neuropathy (AN)	***AIFM1*** c.1265G > A	iPSC-derived neurons	Increase of ADP/ATP ratio and ROS levels, mitochondrial calcium overload, caspase-independent apoptosis. Improvement of physiological state by gene correction.	Qiu et al., 2023
Autosomal recessive spinocerebellar ataxia (ARCA)	***PITRM1*** exon 3/4 frameshift deletion	Mutation-induced iPSC-derived cortical neurons and cerebral organoids	Neurons: induction of mitochondrial unfolded protein response, enhanced mitochondrial clearance. Cerebral organoids: accumulation of protein aggregates, tau pathology, neuronal cell death.	Pérez et al., 2021
Barth Syndrome (BTHS)	***TAZ*** c.590G > T, c.111G > C, c.170G > T	iPSCs	Impairment in remodeling cardiolipin, decrease in basal oxygen consumption rate and maximal respiratory capacity.	Dudek et al., 2013
	TAZ c.517delG, c.328T > C	iPSC-derived cardiomyocytes	Metabolic, structural and functional abnormalities, e.g. in sarcomere assembly and myocardial contraction.	Wang et al., 2014
	TAZ c.590 G > T	iPSC-derived cardiomyocytes	Structural changes in respiratory chain supercomplexes, loss of succinate dehydrogenase.	Dudek et al., 2016
		iPSC-derived cardiomyocytes	Reduction in HIF-1α protein level under hypoxic conditions.	Chowdhury et al., 2018
	TAZ c.517delG	iPSC-derived cardiomyocytes	High glucose uptake, increased glycolytic lactate production and decreased palmitate uptake. Increase of mitochondrial and cellular ROS.	Fatica et al., 2019
		iPSC-derived cardiomyocytes	Rescue of aberrant Ca^{2+} handling and improvement of contractile function by genome editing.	Liu et al., 2021
Charcot Marie Tooth disease type 2 A (CMT2 A)	***MFN2*** c.1090C > T	iPSC-derived spinal cord motor neurons	Reduced action potential threshold and abnormal channel current properties.	Saporta et al., 2015
	MFN2 c.1188C >T	iPSC-derived motor neurons	Selective mitochondrial depletion, apoptosis resistance, increased mitophagy.	Rizzo et al., 2016
	MFN2 c.281G > A	iPSC-derived motor and sensory neurons	Motor neurons: neurite network alterations, extracellular electrophysiological abnormalities, deficits in mitochondrial and lysosomal trafficking and mitochondrial morphology, mitochondrial expression bioenergetic profile alterations. Rescue by dual leucine kinase inhibition. Sensory neurons: less effects.	Van Lent et al., 2021
Charcot Marie Tooth disease type 2H (CMT2H)	***GDAP1*** c.581C > G	iPSC-derived motor neurons	Decrease of cell viability due to lipid dysfunction and oxidative stress, mitochondrial cristae defects.	Miressi et al., 2021
		iPSC-derived neuronal cells	Restoration of mitochondrial cristae defects by treatment with amlexanox.	Benslimane et al., 2023
Charcot-Marie-Tooth disease X-linked dominant 6 (CMTX6)	***PDK3*** c.473G > A	iPSC-derived motor neurons	Energy metabolism defects, reduced velocity of trafficking mitochondria in the affected axons. Rescue of functional deficits by treatment with a PDK inhibitor.	Perez-Siles et al., 2020
Coenzyme Q10 deficiency	***COQ2*** c.1159C > T & c.1178T > C	iPSC-derived neurons	Functional deficiencies in mitochondrial respiration and the antioxidative system, rescued by gene correction.	Nakamoto et al., 2018
	COQ4 c.483G > C	iPSCs, iPSC-derived skeletal muscle cells, neurons	iPSCs: CoQ10 deficiency, metabolic dysfunction, respiration defects. Skeletal muscle: respiration defects. Neurons: unaffected.	Romero-Moya et al., 2017
Dilated cardiomyopathy with ataxia syndrome (DCMA)	***DNAJC19*** c.130 - 1G > C	iPSC-derived cardiomyocytes	Highly fragmented and abnormally shaped mitochondria, rescued by treatment with SS-31.	Rohani et al., 2020
Dominant optic atrophy (DOA)	***OPA1*** c.2496 + 1G > T	iPSC-derived RGCs	Increased apoptosis, inability to efficiently differentiate into RGCs. Promotion of differentiation by addition of neural induction medium, Noggin or estrogen.	Chen et al., 2016
	OPA1 c.33-34ins9	iPSC-derived dopaminergic neurons	Late defect in oxidative phosphorylation, reduced complex I levels and activity without a significant change in the ultrastructure of mitochondria.	Jonikas et al., 2018
	OPA1 c.2873_2876delTTAG	iPSC-derived NPCs	Control of nuclear DNA methylation and expression of key transcription factors needed for proper neural cell specification by OPA1.	Caglayan et al., 2020
	OPA1 c.2708_2711delTTAG	iPSC-derived RGCs	Impaired mitochondrial bioenergetic output and DNA maintenance.	Sladen et al., 2022

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Table 1 (*continued*)

Disease	Gene and mutation	iPSC model	Outcome	Reference
Dominant optic atrophy plus syndrome (DOA+)	***OPA1*** c.1334G > A	iPSCs	Restoration of mitochondrial network, basal respiration, and ATP production by gene editing.	Sladen et al., 2021
		iPSC-derived RGCs	Impaired mitochondrial bioenergetic output and DNA maintenance. iPSCs: no disease phenotype.	Sladen et al., 2022
		iPSCs, iPSC-derived neurons and cardiomyocytes	Neurons and cardiomyocytes: decreased mitochondrial membrane potential, progressive mitochondrial degeneration.	Hick et al., 2013
		iPSC-derived NPCs and neurons	NPCs: No altered susceptibility to cell death, normal mitochondrial function, differentiation into functional neurons.	Bird et al., 2014
		iPSC-derived cardiomyocytes	Disorganized mitochondrial network and mtDNA depletion upon iron-overload.	Lee et al., 2014
Friedreich's ataxia (FA)	***FXN*** GAA·TTC triplet repeat hyperexpansions in the 1st intron	iPSC-derived neurons	Increased *FXN* expression and epigenetic changes by treatment with HDACi 109/RG2833.	Soragni et al., 2014
		iPSC-derived RPE cells	Normal OXPHOS activity and phagocytosis.	Crombie et al., 2015
		iPSC-derived neurons	Alleviation of intracellular ATP levels by zinc finger nuclease-mediated gene correction.	Li et al., 2015b
		iPSC-derived neurons	Higher expression of mitochondrial superoxide dismutase, increased ROS and sensitivity to oxidants. Protection from oxidative stress-mediated cell death by treatment with HDAC.	Codazzi et al., 2016
		iPSC-derived cardiomyocytes	Suppression of ROS and iron-induced mitochondrial stress by iron chelator deferiprone.	Lee et al., 2016
		iPSC-derived cardiomyocytes	Deficiency in calcium handling. Prevention of increased variation in beating rates by nifedipine.	Crombie et al., 2017
		iPSC-derived cardiomyocytes	Correction of the transcriptional profile by genome editing.	Li et al., 2019
		iPSC-derived ventricular cardiac tissue	Electrophysiological defects including action potential duration prolongation and maximum capture frequency reduction. Rescue of contractility defects and *FXN* protein levels by lentiviral transduction.	Wong et al., 2019
		iPSC-derived β cells and sensory neurons	Decreased *FXN* expression, basal respiration, ATP production, and maximal respiratory capacity, enhanced oxidative stress. Induction of *FXN* expression, reduced oxidative stress, and improved mitochondrial function by GLP-1 analogues.	Igoillo-Esteve et al., 2020
		iPSC-derived dorsal root ganglia organoids	Impaired survival rates, less axonal mitochondria with smaller size, and more circular morphology. Rescue of disease phenotype upon *FXN* intron 1 removal.	Mazzara et al., 2020
		iPSC-derived neurons and cardiomyocytes	Neurons: affected expression of glycolytic pathway genes. Cardiomyocytes: affected expression of extracellular matrix pathway genes. Rescue of expression levels upon frataxin supplementation.	Angulo et al., 2023
		FXN knock-down iPSC-derived cardiomyocytes	Decreased basal respiration, maximal respiration and ATP production, type I interferon response due to mtDNA release.	Cotticelli et al., 2023
		iPSC-derived proprioceptors-enriched neuronal cultures	Impairment of cytoskeleton organization at the growth cone, neurite extension and synaptic plasticity, altered spiking profile.	Dionisi et al., 2023
	ATAD3A c.1064G > A	iPSC-derived neurons	Altered dynamics of the mitochondrial network, increased lysosomal mass.	Cooper et al., 2017
	ZFYVE26 c.2554 - 1 G > A & c.3417_3418insTA ***AP5Z1*** (c.1732 C > T)	iPSC-derived telencephalic glutamatergic and midbrain dopaminergic neurons	Reduction in mitochondrial length density within axons, decreased mitochondrial membrane potential. Rescue of mitochondrial morphology defects by inhibitors of the mitochondrial fission GTPase DRP1.	Denton et al., 2018
	SPAST IVS9 + 1G > A	iPSC-derived cortical neurons	Decrease in total neurite length and branching point numbers. Increase of neurite length by inhibition of microRNA 33a.	Nakazeki et al., 2019
Hereditary spastic paraplegia (HSP)	***ATL1*** c.1024C > T	iPSC-derived forebrain neurons	Impaired axonal growth, decreased mitochondrial motility. Rescue of axon growth defects by microtubule-binding agents.	Zhu et al., 2014
		iPSC-derived telencephalic glutamatergic neurons	Reduced mitochondrial length and aspect ratio, reduction in the percentage of motile mitochondria.	Mou et al., 2020
		iPSC-derived cortical neurons	Shorter and less complex neurites. Rescue of neuritic impairments, reduction of cell death and amelioration of membranous inclusions by tideglusib.	Pozner et al., 2018
	SPG11 c.3036C > A & c.5798delC; c.267G > A & c.1457-2 A > G	NPCs and cerebral organoids	NPCs: increased rate of asymmetric divisions causing premature neurogenesis. Organoids: smaller, larger ventricles, thinner germinal wall. Rescue of size and premature neurogenesis by tideglusib.	Pérez-Brangulí et al., 2019
		iPSC-derived motor neurons	Longer and thinner mitochondrial morphology within neurites, impaired mitochondrial membrane potential.	Güner et al., 2021

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Table 1 (*continued*)

Disease	Gene and mutation	iPSC model	Outcome	Reference
	SPG11 c.3965delG & c.5769_5770dupT	iPSC-derived cortical projection neurons	Rescue of mitochondrial morphology, motility and membrane potential as well as axonal and neuronal degeneration in long-term cultures by mitochondrial fission GTPase DRP1 inhibitor.	Chen et al., 2022
	SPG7 c.1449+1G > A, c.1529C > T; c.415C > T, c.941 T > A; chr16:g.89623293 A > G, c.2182-2 A > G, c.1529C > T	iPSC-derived NPCs and cortical neurons	NPCs: increased mitochondrial size and reduced membrane potential. Neurons: increased mitochondrial size, reduced membrane potential, reduced neurite complexity and length. Rescue of mitochondrial and neurite morphological defects and mitochondrial membrane potential by Bz-423.	Wali et al., 2023
Hypertrophic cardiomyopathy	***SCO2*** c.577G > A, c.418G > A & c.17ins19	iPSC-derived cardiomyocytes	Decreased number of cristae, inordinate mitochondrial size increase with age, attenuated response to the inotropic interventions and caffeine.	Hallas et al., 2018
	MYBPC3 c.1800delA	iPSC-derived cardiomyocytes	Impaired mitochondrial bioenergetics and altered excitation-contraction coupling in combination with *MYH7* mutation.	Escribá et al., 2023
Leigh-like Syndrome	***ECHS1*** c.518C > T & c.849_852delAAAG	iPSC-derived fibroblasts, NPCs, mature neurons and cardiomyocytes	All cell types: decreased ATP production and mitochondrial membrane potential, increased ROS production. Neurons and cardiomyocytes: increased lactate levels. Fibroblasts and NPCs: retarded growth.	Sequiera et al., 2022
	PMPCB c.1265T > C	iPSC-derived neuroepithelial stem cells	Reduced *PMPCB* levels, accumulation of the processing intermediate of frataxin.	Vögtle et al., 2018
	NDUFS4 c.462delA, c.316C > T	iPSC-derived NPCs	Reduction of mitochondrial membrane potential and neurite outgrowth.	Inak et al., 2021
	NDUFS4 knock-out	iPSC-derived neurons and cardiomyocytes	Neurons: increased apoptosis, attenuated by nicotinamide riboside supplementation. Cardiomyocytes: lower mitochondrial membrane potential and higher levels of cellular ROS.	Yoon et al., 2022
	NDUFS4 c.20C>G knock-in	iPSC-derived neurons and cortical brain organoids	Neurons: higher susceptibility to glutamate excitotoxicity. Organoids: elevated proinflammatory pathways.	Daneshgar et al., 2022
Leigh Syndrome (LS)	***NDUFV1*** c.529dupT & c.640G > A	iPSC-derived fibroblasts, NPCs, mature neurons and cardiomyocytes	All cell types: decreased ATP production and mitochondrial membrane potential, increased ROS production. Neurons and cardiomyocytes: increased lactate levels. Fibroblasts and NPCs: retarded growth.	Sequiera et al., 2022
	SURF1 c.530T > G, c.769G > A	iPSC-derived NPCs and cerebral organoids	NPCs: retention of glycolytic proliferative state. Organoids: compromised neuronal morphogenesis. Enhancement of metabolic programming of NPCs leading to restored neuronal morphogenesis by *SURF1* gene augmentation and PGC1A induction via bezafibrate treatment.	Inak et al., 2021
	SURF1 c.769G > A	iPSC-derived neurons and midbrain organoids	Neurons: defects in neuromorphogenesis. Midbrain organoids: increased lactate release, altered calcium activity and aberrant neurite organization. Lowered lactate release and improved neurogenesis and neurite organization by azole compounds Talarozole and Sertaconazole.	Menacho et al., 2024
Leukoencephalo-pathy with brainstem and spinal cord involvement and lactate elevation (LBSL)	***DARS2*** c.753G > T & c.228-20delTTinsC; c.473A > T & c.829G > A; c.265C > T & c.492 + 2 T > C; c.228-20delTTinsC; c.228-20delTTinsC & c.492 + 2 T > C; c.228-17C>G & c.492+2T>C	iPSC-derived neurons and cerebral organoids	Neurons: growth defects. Organoids: dysregulated expression of genes that encode RNA binding proteins and spliceosomal proteins.	Guang et al., 2023
mtDNA depletion syndrome (MTDPS)	***DGUOK*** c.763_766dupGATT; c.4G > T & c.142+1G > A & c.591G > A	iPSC-derived hepatocyte organoids and hepatocyte-like cells	Hepatocytes: decreased mtDNA level and ATP production. Hepatocytes and orgnaoids: higher sensitivity to iron overload-induced ferroptosis, rescued by N-Acetylcysteine.	Guo et al., 2021
	DGUOK p.Trp166Ter & p. His167LeufsTer213	iPSC-derived hepatocyte-like cells	Decreased mtDNA level and basal and maximal respiration. Improved mitochondrial function and ATP production by nicotinamide adenine dinucleotide.	Jing et al., 2018
	RRM2B knock-out	iPSC-derived hepatocyte-like cells	Decreased mtDNA level and basal and maximal respiration. Improved mitochondrial function and ATP production by nicotinamide adenine dinucleotide.	Jing et al., 2018
	FBXL4 c.993insA	iPSC-derived NPCs and cortical neurons	Excessive mitophagy.	Chen et al., 2023c
Pompe disease	***GAA*** c.1822C > T & c.2662G > T	iPSC-derived cardiomyocytes	Decreased number of mitochondria and expression of mitochondrial complexes, impaired respiratory function, ATP production and fusion and autophagy of mitochondria, elevated ROS levels.	Huang et al., 2023

(*continued on next page*)

Table 1 (*continued*)

Disease	Gene and mutation	iPSC model	Outcome	Reference
Progressive external ophthalmoplegia (PEO)	***POLG*** p.Q811R	iPSC-derived midbrain spheroids	Astrocytes with decreased rate of uncoupled mitochondrial respiration and mitochondrial spare capacity.	Chumarina et al., 2019
Sudden infant death syndrome	***HADHA*** knockout	iPSC-derived cardiomyocytes	Defective calcium dynamics and repolarization kinetics, reduced fatty acid beta oxidation and mitochondrial proton gradient, disrupted cristae structure and defective cardiolipin remodeling.	Miklas et al., 2019
very long-chain acyl-CoA dehydrogenase deficiency (VLCADD)	***ACADVL*** (c.104delC; c.848T > C & c.1141_1143delGAG)	iPSC-derived cardiomyocytes	Shorter action potentials, more delayed afterdepolarizations (DADs) and higher intracellular calcium concentrations. Prolongation of action potential duration and reduced DADs and calcium concentrations by etomoxir.	Knottnerus et al., 2020
	ACADVL (c.848T > C & c.1141_1143delGAG)	iPSC-derived cardiomyocytes	Shorter action potentials, more delayed afterdepolarizations. No improvement by carnitine supplementation.	Verkerk et al., 2020

from patients suffering from DOA appeared more apoptotic than control iPSCs and exhibited impaired capacity to differentiate into RGCs (Chen et al., 2016). The addition of neural induction medium, Noggin or estrogen improved RGC differentiation from DOA iPSCs, suggesting that extracellular metabolism and signaling could play a role in disease manifestation (Chen et al., 2016). Dopaminergic neurons from DOA patient-derived iPSCs showed defective OXPHOS due to reduced complex I levels and activity without overt ultrastructural mitochondrial modifications (Jonikas et al., 2018). In addition, *OPA1* mutations significantly altered the expression profile of iPSC-derived NPCs, hindering their differentiation capacity towards GABAergic neurons (Caglayan et al., 2020). iPSC-derived RGCs from patients with DOA as well as DOA+ showed impaired mitochondrial homeostasis and reduced bioenergetic output with compromised mtDNA maintenance (Sladen et al., 2022). CRISPR/Cas9 correction of iPSCs from DOA+ patients restored mitochondrial homeostasis by re-establishing the mitochondrial network and bioenergetics (Sladen et al., 2021). Hence, iPSC models of DOA highlighted alterations in the differentiation capacity that paralleled metabolic defects. Treatment options have not been extensively studied in these models, but the identification of the disease defects should facilitate future drug assessments.

Hereditary spastic paraplegia (HSP, e.g. OMIM #182600 and #182601), is a heterogenous disorder that can be caused by mutations in around 70 genes and lead to progressive degeneration of corticospinal motor neuron axons resulting to spastic weakness of the lower limbs (Tesson et al., 2015). iPSC studies have focused on different kinds of iPSC-derived neuronal subtypes. Cooper et al. generated neurons from HSP patients with a mutation in the gene *ATAD3 A* (ATPase family AAA-domain containing protein 3 A encoding for a mitochondrial inner membrane ATPase) and identified altered dynamics of the mitochondrial network and increased lysosomal mass (Cooper et al., 2017). HSP iPSC-derived telencephalic glutamatergic and midbrain dopaminergic neurons carrying mutations in the genes *ZFYVE26* and *AP5Z1*, which mainly have *endo*-lysosomal functions, showed significantly reduced neurite branching capacity (Denton et al., 2018). Likewise, decreased total neurite length was seen in cortical neurons from HSP patients with *SPAST* mutation, encoding the microtubule-severing protein SPASTIN (Nakazeki et al., 2019), and in neurons from other HSP patients (Pozner et al., 2018; Wali et al., 2023). Impaired axonal growth was also seen in HSP iPSC-derived forebrain neurons with an *ATL1* mutation (encoding the atlastin-1 GTPase) (Zhu et al., 2014). Mitochondria of HSP patient-derived neurons were also less motile (Güner et al., 2021; Mou et al., 2020; Zhu et al., 2014). Alterations of mitochondrial morphology manifested in mitochondrial fragmentation in telencephalic HSP glutamergic neurons carrying defects in genes *ATL1*, *ZFYVE26*, and *AP5Z1* (Denton et al., 2018; Mou et al., 2020) but in mitochondrial fusion within HSP NPCs and cortical neurons (Güner et al., 2021; Wali et al., 2023). MMP was found to be reduced in neurons with several HSP mutations (Chen et al., 2022; Denton et al., 2018; Güner et al., 2021; Wali et al., 2023). HSP NPCs also displayed an increased rate of asymmetric divisions, leading to proliferation defects and premature neurogenesis (Pérez-Brangulí et al., 2019). Accordingly, HSP cerebral organoids appeared smaller than control organoids and exhibited larger ventricles as well as a thinner germinal wall (Pérez-Brangulí et al., 2019). Different drugs could rescue the disease phenotypes in HSP patient iPSC-derived neurons. Neurite length could be ameliorated by inhibition of microRNA 33a through locked nucleic acid-anti-miR (Nakazeki et al., 2019), by microtubule-binding agents (Zhu et al., 2014), as well as by the mitochondria permeability pore regulator Bz-423 (Wali et al., 2023). The latter also restored mitochondrial morphology defects and membrane potential in HSP neurons (Wali et al., 2023). Similarly, inhibitors of the mitochondrial fission GTPase DRP1 rescued mitochondrial morphology defects in HSP cortical neurons (Denton et al., 2018), as well as mitochondrial motility and membrane potential, thereby preventing axonal and neuronal degeneration in long-term cultures (Chen et al., 2022). In these HSP neurons, GSK3 inhibitors like tideglusib were able to restore neuritic impairments, reduce cell death, and ameliorate membranous inclusions (Pozner et al., 2018). Tideglusib treatment also rescued premature neurogenesis and the overall size in HSP cerebral organoids (Pérez-Brangulí et al., 2019). Taken together, iPSC models of HSP successfully unveiled pathogenetic mechanisms and various treatment strategies targeting different pathways related to neuronal morphogenesis and mitochondrial function.

Mutations in the gene *PITRM1*, encoding for a mitochondrial peptidase that digests the mitochondrial-targeting sequences of proteins imported into the mitochondria, can be responsible for autosomal recessive spinocerebellar ataxia (ARCA, OMIM #619405) (Synofzik et al., 2019). The group of Michela Deleidi generated cortical neurons and cerebral organoids from iPSCs with a CRISPR/Cas9-induced frameshift deletion in exon 3 and 4 of the *PITRM1* gene (Pérez et al., 2021). *PITRM1* knockout led to mitochondrial unfolded protein response and enhanced mitochondrial clearance in differentiated neurons, which then developed features reminiscent of Alzheimer's disease, including the accumulation of protein aggregates, tau pathology, and neuronal cell death (Pérez et al., 2021).

The disorder Coenzyme Q10 deficiency (e.g. OMIM #607426 and 616276) can originate from mutations in genes *COQ2* or *COQ4*, encoding for coenzymes Q2 and Q4 involved in the biosynthesis of the antioxidant coenzyme Q10 (Trevisson et al., 2011). *COQ2* mutant neurons showed functional deficiencies in mitochondrial respiration and antioxidant system that could be rescued through CRISPR/Cas9-mediated gene corrections (Nakamoto et al., 2018). iPSCs from *COQ4* mutant patients revealed coenzyme Q10 deficiency and metabolic dysfunction as well as respiration defects that were present in skeletal muscle cells differentiated from iPSCs (Romero-Moya et al., 2017). Conversely, neurons derived from the same patient iPSCs appeared unaffected (Romero-Moya et al., 2017).

Other rare neurodevelopmental disorders were also investigated with iPSCs. Leukoencephalopathy with Brainstem and Spinal cord involvement and Lactate elevation (LBSL, OMIM #611105) is caused by

mutations in *DARS2* encoding the mitochondrial aspartyl-tRNA synthetase and therefore plays an important role in the mitochondrial translation machinery (Li et al., 2021). Cerebral organoids generated from iPSCs of seven LBSL patients showed dysregulated expression of genes that encode RNA binding proteins and spliceosomal proteins (Guang et al., 2023). In LBSL iPSC-derived neurons, growth defects were revealed (Guang et al., 2023). Auditory neuropathy (AN, e.g. OMIM # 619832) is characterized by impaired hearing and comprehension of speech caused by dysfunction in the inner hair cells, ribbon synapses, spiral ganglion neurons or the auditory nerve (Kaga, 2016). It can be caused by mutations in the *TMEM43* gene, whose corresponding protein is important for inner ear homeostasis (Jang et al., 2021). In addition, the *AIFM1* gene can be affected, which encodes for the protein apoptosis-inducing factor (AIF) that might contribute to cell survival by promoting biogenesis and maintenance of the mitochondrial OXPHOS system (Wischhof et al., 2022). iPSC-derived neurons derived from AN patients harboring *AIFM1* mutation displayed inhibited mitochondrial import of MRC subunits (Qiu et al., 2023). Consequently, ADP/ATP ratio as well as ROS levels were abnormally increased in AN neurons, and mitochondrial calcium overload and caspase-independent apoptosis occurred. Gene correction by CRISPR/Cas9 improved the physiological state of the neurons as it lowered the ADP/ATP ratio (Qiu et al., 2023). These studies collectively highlight how iPSC models can be used to unveil mechanistic details in the neuropathology of rare neurodevelopmental diseases affecting mitochondrial function.

Friedreich's ataxia (FA, OMIM #229300) is an inherited neurodegenerative disease associated with hypertrophic cardiomyopathy (Cook and Giunti, 2017). It is caused by GAA·TTC triplet repeat hyperexpansions in the first intron of the frataxin (*FXN*) gene. The protein frataxin is involved in the mitochondrial assembly of iron-sulphur (Fe—S) clusters and therefore interacts with respiratory complexes I, II and III (Doni et al., 2023). Hick et al. generated iPSCs from FA patients and differentiated them into neurons and cardiomyocytes (Hick et al., 2013). Whereas undifferentiated FA iPSCs showed no biochemical defect, impaired mitochondrial function was detected in FA neurons and cardiomyocytes, which showed decreased MMP and progressive mitochondrial degeneration (Hick et al., 2013). FA neurons displayed higher expression of mitochondrial superoxide dismutase, increased ROS, and lower reduced glutathione levels, indicating higher sensitivity to prooxidant molecules (Codazzi et al., 2016). FA iPSC-derived proprioceptors-enriched neuronal cultures exhibited aberrant cytoskeleton organization at the growth cone, leading to defective neurite extension and synaptic plasticity, as well as alterations in the spiking profile (Dionisi et al., 2023). FA patient-derived cardiomyocytes also showed deficiencies in calcium handling (Crombie et al., 2017) and mtDNA depletion, together with a disorganized mitochondrial network indicative of an iron-overloaded condition (Lee et al., 2014). A *FXN* knockdown model of iPSC-derived FA cardiomyocytes highlighted severe bioenergetic dysfunction with decreased basal respiration, maximal respiration, and ATP production, coupled with a type I interferon response partly caused by release of mtDNA into the cytosol (Cotticelli et al., 2023). Human engineered 3D cardiac tissue models developed electrophysiological defects including action potential duration prolongation and maximum capture frequency reduction (Wong et al., 2019). Dorsal root ganglia organoids derived from FA iPSCs displayed impaired survival rates and their axons contained reduced number of mitochondria with fragmented appearance (Mazzara et al., 2020). Conversely, other studies with FA patient-derived iPSCs detected normal mitochondrial function in NPCs and preserved differentiation capacity into functional neurons (Bird et al., 2014), as well as normal OXPHOS activity and phagocytosis of retinal pigment epithelium cells (Crombie et al., 2015). Hence, more work is needed to fully understand the impact of FA defects in differentiated cells. With respect to therapeutic strategies, Soragni et al. identified the HDAC inhibitor 109 (RG2833) with the ability to increase the level of FXN in FA neurons and to trigger favorable epigenetic changes in the *FXN* gene (Soragni et al., 2014). Additionally, treatment with benzamide HDAC inhibitor 109 downregulated superoxide dismutase 2 levels and related ROS levels, thereby protecting cardiomyocyte cells from oxidative stress-mediated cell death (Codazzi et al., 2016). In cardiomyocytes, the iron chelator deferiprone modulated iron-induced mitochondrial stress and suppressed ROS synthesis (Lee et al., 2016), while treatment with L-type Ca^{2+} channel inhibitor nifedipine prevented abnormal beat rate variabilities (Crombie et al., 2017). Supplementation with frataxin restored the expression of glycolytic pathway genes in neurons and extracellular matrix pathway genes in FA cardiomyocytes (Angulo et al., 2023). The GLP-1 analogue exenatide induced frataxin expression in iPSC-derived sensory neurons and β-cells, that additionally led to reduced oxidative stress and improved mitochondrial function in FA neurons (Igoillo-Esteve et al., 2020). Zinc finger nuclease-mediated correction of the mutation in the *FXN* gene led to an alleviation of ATP levels in FA patient-derived neurons (Li et al., 2015b), and to a correction of the transcriptional profile in cardiomyocytes (Li et al., 2019). In 3D cardiac models, forced expression of *FXN* by lentiviral transduction rescued their contractility defects (Wong et al., 2019), and in 3D dorsal root ganglia organoids, removal of the entire *FXN* intron had a rescuing effect as seen by improvement in mitochondrial size, number, and morphology (Mazzara et al., 2020). Hence, iPSC models of FA demonstrated how the disease impacts cardiac and neuronal cells and were successfully used as platforms for testing therapeutics.

Barth Syndrome (BTHS, OMIM #302060) is a severe mitochondrial cardiomyopathy induced by mutations in the gene *TAZ* encoding for taffazin, an acyltransferase that acetylates the mitochondrial inner membrane phospholipid cardiolipin (Houtkooper et al., 2009). Dudek et al. found that iPSCs from BTHS patients were able to recapitulate features of the patient phenotypes (Dudek et al., 2013). iPSCs were deficient in remodeling cardiolipin and showed decreased basal oxygen consumption rate and maximal respiratory capacity (Dudek et al., 2013). Other groups found that BTHS iPSC-derived cardiomyocytes displayed metabolic, structural, and functional abnormalities, for example in sarcomere assembly and myocardial contraction (Wang et al., 2014). Severe structural mitochondrial changes in MRC assembly could be observed, together with the loss of succinate dehydrogenase (Dudek et al., 2016) and decreased HIF-1a signaling in hypoxic conditions (Chowdhury et al., 2018). Metabolic alterations reflected by high glucose uptake, increase in glycolytic lactate production, and decrease in palmitate uptake were also found in BTHS cardiomyocytes (Fatica et al., 2019). Additionally, higher levels of ROS could be detected (Liu et al., 2021). Genome correction of the *TAZ* gene in BTHS patient-derived iPSCs normalized calcium handling in cardiomyocytes, thereby leading to improved contractile function (Liu et al., 2021). Overall, iPSCs were used to generate multiple BTHS models that will hopefully lead to the identification of potential rescuing strategies.

Several other cardiac-related disorders have been investigated using iPSCs. Very long-chain acyl-CoA dehydrogenase deficiency (VLCADD, OMIM #201475) is a mitochondrial long-chain fatty acid oxidation disorder associated with cardiac arrhythmias that is caused by mutations in the *ACADVL* gene, which encodes the protein very long-chain acyl-CoA dehydrogenase (Knottnerus et al., 2018). VLCADD iPSC-derived cardiomyocytes displayed shorter action potentials, delayed depolarizations, and higher calcium concentrations compared to control cardiomyocytes (Knottnerus et al., 2020; Verkerk et al., 2020). Furthermore, patient cardiomyocytes accumulated potentially toxic intermediates of fatty acid oxidation. Etomoxir and in part resveratrol, but not carnitine supplementation, could attenuate these disease phenotypes (Knottnerus et al., 2020; Verkerk et al., 2020). Dilated cardiomyopathy with ataxia syndrome (DCMA) is caused by mutations in the gene *DNAJC19* encoding for a mitochondrial import inner membrane translocase subunit (Davey et al., 2006). DCMA patient iPSC-derived cardiomyocytes displayed highly fragmented and abnormally shaped mitochondria (Rohani et al., 2020). The mitochondrially-targeted peptide SS-31 could reverse these abnormalities and is therefore a promising

therapeutic strategy for this disease (Rohani et al., 2020). Mitochondrial-related nuclear mutations can also lead to hypertrophic cardiomyopathy, a complex cardiovascular disease often leading to severe heart failure (Mosqueira et al., 2018). iPSC-derived cardiomyocytes from patients with *SCO2* mutations, causing cytochrome *c* oxidase deficiencies, showed major mitochondrial ultrastructural abnormalities including decreased number of cristae (Hallas et al., 2018). On a functional level, *SCO2* mutant cardiomyocytes displayed attenuated response to inotropic interventions and caffeine (Hallas et al., 2018). *MYBPC3* mutations, encoding myosin-binding protein C, led to impaired mitochondrial bioenergetics, and altered excitation-contraction coupling (Escribá et al., 2023).

iPSC-derived cardiomyocytes were also used to study other nuclear defects. Cardiac impairment and sudden infant death syndrome (SIDS, OMIM #272120) can be associated to fatty acid oxidation defects due to mutations in hydratase subunit A (*HADHA*). This gene is part of the trifunctional protein, which plays a major role in the in beta-oxidation of long chain fatty acids for ATP production in mitochondria (Taylor et al., 2012). Miklas et al. knocked out *HADHA* in iPSCs by CRIPSR/Cas and observed that the generated cardiomyocytes developed defective calcium dynamics, reduced mitochondrial proton gradient, and disrupted cristae structure, coupled with defective cardiolipin remodeling and repolarization kinetics resulting in a pro-arrhythmic state (Miklas et al., 2019). Pompe disease (OMIM #232300) is a glycogen storage disease causing life-threatening cardiac and skeletal muscle myopathy due to mutations in the gene *GAA* encoding for acid alpha-glucosidase, which hydrolyses glycogen to glucose in lysosomes (Hers, 1963; van der Ploeg and Reuser, 2008). iPSC-derived cardiomyocytes from Pompe disease patients displayed fewer mitochondria and impaired respiratory function and ATP production (Huang et al., 2023). Additionally, they manifested elevated levels of intracellular ROS caused by depolarized mitochondria, impaired mitochondrial fusion, and abnormal mitophagy, resulting in reduced expression of MRC complexes (Huang et al., 2023). Hence, iPSCs can help to address how different nuclear mutations might lead to specific impairment of defined tissues, potentially hinting to new targets of interventions.

Mitochondrial Neurogastrointestinal Encephalomyopathy (MNGIE, OMIM #603041) is caused by mutations in the gene *TYMP*, encoding for thymidine phosphorylase. Mutations result in accumulation of triphosphates which in turn imbalance the mitochondrial deoxyribonucleoside triphosphate pools, resulting in deletions, point mutations and depletion of mtDNA (Hirano et al., 2004; Nishigaki et al., 2003). MNGIE patients suffer from gastrointestinal dysmotility, sensorimotor peripheral neuropathy, severe muscle weakness, and progressive leukoencephalopathy (Hirano et al., 2004). Pacitti and Bax developed a cerebral organoid model from MNGIE patient-derived iPSCs that displayed a defect in *TYMP* expression, which represents an important patient disease phenotype (Pacitti and Bax, 2018). However, organoid stainings did not reveal alterations in neural cell populations so far, supporting previous hypotheses that white matter lesions seen in patients with leukoencephalopathy may not be the result of intrinsic molecular derangements but could rather stem from an increased permeability of the blood brain barrier (BBB) (Szigeti et al., 2004). To conclude, iPSC models like the cerebral organoid model could potentially help to elucidate the involvement of the central nervous system (CNS) in MNGIE.

Mitochondrial DNA depletion syndrome (MTDPS, e.g. OMIM #251880) comprises a group of heterogenous genetic diseases characterized by reduction of mtDNA content mostly associated with neurological defects leading to death by liver failure (El-Hattab and Scaglia, 2013). Several forms of MTDPS have been modeled with iPSCs. Mutations in the nuclear gene encoding the catalytic subunit of the mtDNA polymerase gamma (POLG) can cause Alpers syndrome (OMIM #203700), an early-onset encephalopathy (Naviaux and Nguyen, 2004). Whereas undifferentiated iPSCs from Alpers patients only showed a partial disease phenotype with reduced ATP production, differentiated neural stem cells (NSCs) developed a biochemical phenotype that resembled that of post-mortem patient brain tissue, characterized by decreased ATP production, excessive ROS production, and mtDNA depletion (Hong et al., 2024; Liang et al., 2020), in addition to a downregulated NADH pathway (Hong et al., 2024). These findings were confirmed in iPSC-derived dopaminergic neurons that displayed mtDNA depletion in addition to reduced MMP and complex, ROS overproduction, and cellular senescence (Liang et al., 2020). Treatment with *N*-acetylcysteine amide ameliorated mitochondrial dysfunction and reduced oxidative stress (Liang et al., 2021). Cortical organoids from Alpers syndrome patient showed cortical neuronal loss, mtDNA depletion and complex I deficiency (Hong et al., 2024). In accordance with downregulated NADH pathway *POLG* mutant NSCs, treatment with NAD+ precursor nicotinamide riboside ameliorated the mitochondrial defects in *POLG* mutant cortical organoids (Hong et al., 2024). Alpers syndrome is associated with an increased risk of hepatotoxicity following valproic acid therapy, which is commonly used in patients (Nanau and Neuman, 2013). The effect of valproic acid was therefore assessed on iPSC-derived hepatocyte-like cells carrying different *POLG* mutations (Li et al., 2015a). In hepatocyte-like cells from Alpers iPSCs, valproic acid led to significantly increased apoptosis through the opening of the mitochondrial permeability transition pore (mPTP), and this effect could be prevented by applying the mPTP inhibitor cyclosporine A (Li et al., 2015a). *POLG* mutations can also cause progressive external ophthalmoplegia (PEO, OMIM #157640) (Filosto et al., 2003). iPSC-derived midbrain spheroids derived from PEO patients contained astrocytes but not neurons like in the case of control spheroids, and showed decreased rate of uncoupled mitochondrial respiration and mitochondrial spare capacity (Chumarina et al., 2019). Hepatocyte-like cells were generated also from MTDPS patient iPSCs carrying mutations in the gene *DGUOK* encoding the mitochondrial kinase responsible for the phosphorylation of purine deoxyribonucleosides, as well as from iPSCs engineered to knock-out the gene *RRM2B* encoding for ribonucleoside-diphosphate reductase subunit M2B (Jing et al., 2018). Hepatocyte-like cells for both mutations recapitulated MTDPS-specific phenotypes, including decreased mtDNA levels and reduced basal and maximal respiration (Jing et al., 2018). Supplementation with nicotinamide adenine dinucleotide improved mitochondrial function and ATP production (Jing et al., 2018). *DGUOK*-mutated hepatocyte-like cells also displayed decreased mtDNA levels along with mitochondrial dysfunction, reduced ATP production and ROS enhancement, as well as higher sensitivity to iron overload-induced ferroptosis, which could be confirmed in hepatocyte organoids and rescued using *N*-acetylcysteine (Guo et al., 2021). iPSC-derived NPCs and cortical neurons from MTDPS patients carrying a mutation in the gene *FBXL4* (F-Box And Leucine-Rich Repeat Protein 4) which encodes a protein involved in mtDNA maintenance (Gai et al., 2013), were also investigated and found to exhibit excessive mitophagy (Chen et al., 2023c). Hence, iPSC studies are helping to decode some of the complexity of multi-systemic disease such as MTDPS: they were able to identify defects in neuronal commitment and highlighted therapeutic options for ameliorating disease phenotypes and common complications related to drugs currently used in patients.

Taken together, several iPSC models of nuclear mutations causative of mitochondrial disorders have been generated in the past few years, encompassing both patient-derived and genetically-engineered lines. The obtained models mainly focused on neuronal or cardiac defects, recapitulating disease-associated features. In addition to unveiling mechanisms related to disease development, iPSC models were used to assess various treatment strategies, highlighting their importance as innovative drug discovery platforms.

1.4. iPSC models for mitochondrial DNA disorders

Mitochondrial diseases caused by mtDNA defects can be due to single point mutations in mRNA genes encoding for individual MRC components or in tRNA genes leading to impairment of mitochondrial protein

translation (Cree et al., 2009; Russell et al., 2020; Wallace, 1999). Gene defects can also be represented by mtDNA deletions that can be small or relatively large. All these genetic alterations can result in multi-systemic syndromes that strongly impair energy-demanding tissues such as the nervous and cardiac system. Since challenges related to mtDNA editing hinder the development of engineered lines, most of the iPSC works so far focused on patient-derived lines (McKnight et al., 2021; Tolle et al., 2023). Published disease-specific iPSCs and their respective findings are reported in Table 2.

Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes (MELAS, OMIM #540000) is the most common progressive and devastating multisystemic mtDNA disease (Pavlakis et al., 1984). A frequently recurring mutation is the m.3243 A > G in the *MT-TL1* gene, encoding the mitochondrial tRNA-Leucine 1 (Goto et al., 1990; Nesbitt et al., 2013). iPSCs reprogrammed from MELAS patients displayed high variability in heteroplasmy levels, and even mutation-free isogenic iPSC lines could be obtained starting from MELAS patient fibroblasts (Kodaira et al., 2015; Perales-Clemente et al., 2016). The mutation could also be purged by extended iPSC passaging, resulting in isogenic iPSC subclones with various degrees of disease-causing genotypes (Folmes et al., 2013). High heteroplasmy levels in the parent cells were associated with reduced reprogramming efficiency but did not affect the maintenance of the obtained iPSCs (Yokota et al., 2015), despite their impaired complex I activity (Kodaira et al., 2015; Yokota et al., 2017; Yokota et al., 2015). MELAS iPSCs with high heteroplasmy exhibited increased autophagy as well as OXPHOS defects indicating a greater reliance on glycolysis (Lin et al., 2019). MELAS iPSC-derived NPCs also showed diminished mitochondrial metabolism (Ma et al., 2015). Upon further differentiation, the disease phenotype became even more enhanced, hindering effective differentiation. High heteroplasmy MELAS mutations induced neuronal cell death (Yokota et al., 2017), defective neuronal maturation (Kobayashi et al., 2021), and inhibited lineage commitment to cardiomyocytes (Ma et al., 2015; Yokota et al., 2017). Accordingly, spinal cord MELAS organoids displayed defects in mitochondrial respiration as well as elevated Notch signaling resulting in delayed neuronal differentiation (Winanto et al., 2020). Ryytty and colleagues succeeded in differentiating patient iPSCs to cardiomyocytes, but these cells manifested impaired mitochondrial respiration that was dependent on the mutation load (Ryytty et al., 2022). iPSC-derived retinal pigment epithelial cells showed a heteroplasmy-dependent impairment of mitochondrial bioenergetics (Bhattacharya et al., 2022) and abnormal mitochondria and melanosomes (Chichagova et al., 2017). Pro-atherogenic and pro-inflammatory properties were found in MELAS iPSC-derived endothelial cells (Pek et al., 2019). MELAS iPSCs with high heteroplasmy m.5541C > T mutation in the gene *MT-TW*, encoding for the mitochondrial tRNA-tryptophan, also showed a significant loss of terminally differentiated neurons, but not their stem and progenitor cells, and no effect on skeletal muscle cells (Hatakeyama et al., 2015). MELAS iPSC-derived neurons with high heteroplasmy for m.3243 A > G developed respiratory chain deficiency patterns, especially in complex I, similar to those occurring in MELAS patients (Hämäläinen et al., 2013). MELAS iPSC-derived neurons with high heteroplasmy for m.3243 A > G could be directly compared to isogenic neurons with low heteroplasmy (Klein Gunnewiek et al., 2020). High heteroplasmy neurons exhibited mitochondrial dysfunction and delayed neural maturation, as seen by reduced dendritic complexity, fewer excitatory synapses, reduced network activity, and decreased synchronous network bursting (Klein Gunnewiek et al., 2020). These alterations were significantly counteracted by treating the high heteroplasmy MELAS neurons with the antioxidant sonlicromanol (Klein Gunnewiek et al., 2021). The phosphofructokinase-1 inhibitor Tryptolinamide recovered the defective differentiation phenotypes into MELAS neurons and cardiomyocytes (Kobayashi et al., 2021). Furthermore, Yang et al. successfully eliminated the m.3243 A > G mutation in patient iPSCs by mitoTALENS, suggesting a potential therapeutic approach for the treatment of this mitochondrial disease (Yang et al., 2018). A similar effect could be achieved in iPSCs from MELAS patients with a m.13513G > A mutation in the complex I gene *MT-ND5*, where iPSCs showed TALEN-mediated decrease in heteroplasmy leading to functional improvements (Yahata et al., 2017). These studies collectively demonstrated how MELAS-associated mutations affect tissue development and highlighted different genetic-based or drug-based treatments.

Maternally inherited Leigh Syndrome (MILS) encompasses those cases of Leigh syndrome that are caused by mtDNA mutations (Ciafaloni et al., 1993). The most frequently occurring defects involve high heteroplasmic or homoplasmic defects in the gene *MT-ATP6*, encoding for a subunit of complex V, the ATP synthase (Del Dotto et al., 2024). *MT-ATP6* mutations occurring at lower heteroplasmy instead cause neuropathy, ataxia, retinitis pigmentosa, and ptosis (NARP, OMIM #551500) which usually causes less severe symptomatology and develops later in adulthood (Holt et al., 1990). iPSC-derived NPCs carrying homoplasmic mutation m.9185 T > C in the *MT-ATP6* gene exhibited defective ATP production and abnormally elevated MMP, which in turn caused altered calcium homeostasis (Lorenz et al., 2017). This MMP defect was used to carry out a compound screening that identified phosphodiesterase 5 (PDE5) inhibitor avanafil as a potential treatment strategy, given its ability to rescue calcium alterations in MILS NPCs and dopaminergic neurons carrying homoplasmic mutation m.9185 T > C (Lorenz et al., 2017). Undifferentiated iPSCs with the same mutation showed bioenergetic defects, including reduced maximal respiration and spare reserve capacity, but their ATP production was not significantly altered, while differentiated iPSCs showed more severe bioenergetic impairment, including lower ATP content (Meshrkey et al., 2023). iPSCs and derived NPCs as well as neurons carrying the homoplasmic *MT-ATP6* mutation m.8993 T > G showed decreased basal oxygen consumption rate and increased ROS levels (Zheng et al., 2016). m.8993 T > G mutant neurons also exhibited mitochondrial ATP synthesis defects and degenerative phenotypes (Zheng et al., 2016). Upon rapamycin treatment, a significant rescue was visible, as MILS neurons became more resilient against glutamate toxicity (Zheng et al., 2016). iPSC-derived cerebral organoids were also employed for MILS modeling and were found to develop defects in neural epithelial bud generation, overall size, and cortical architecture (Romero-Morales et al., 2022). Ma and colleagues investigated the effect of homoplasmic m.8993 T > G mutation on iPSC-derived fibroblasts and skeletal muscle cells, which exhibited aberrant metabolic profiles that could be rescued by replacing the mutant mtDNA using somatic cell nuclear transfer (Ma et al., 2015). The *MT-ATP6* mutation m.9154C > T, which leads to a truncated protein, impaired neurogenesis and bioenergetics in iPSC-derived motor neurons, with a heteroplasmy threshold at 49 % seen as necessary to cause defects (Kenvin et al., 2022). Heteroplasmic mutations in *MT-ND3* and *MT-ND5* genes, encoding subunits of the complex I mitochondrial NADH dehydrogenase, were also investigated using patient iPSCs. *MT-ND5* mutation m.12706 T > C led to reduced maximal respiration and spare reserve capacity in iPSC-derived cardiomyocytes, which showed abnormal beating capacity (Meshrkey et al., 2023). Cardiomyocytes from iPSCs with *MT-ND5* mutation m.13513G > A could only be generated for heteroplasmy lower than 30 %, and even then, they appeared to be dysfunctional (Galera-Monge et al., 2019). iPSCs carrying the *MT-ND5* mutation m.13513G > A with 45 % heteroplasmy displayed a diminished basal respiration (Galera-Monge et al., 2020). Neurons generated from those iPSCs, containing 20 % heteroplasmy at NSC level, showed compromised OXPHOS function and diminished calcium buffering capacity (Galera-Monge et al., 2020). Finally, Meshrkey and colleagues analyzed five different patient-derived iPSC lines carrying heteroplasmic mutations in genes *MT-ND3, MT-ND5*, or *MT-ATP6* at the undifferentiated state, and observed altered MMP and reduction in mitochondrial content (Meshrkey et al., 2021). Overall, iPSC models of MILS unveiled bioenergetic defects in differentiated cardiac and neural cells that were associated with calcium abnormalities and impaired development. No isogenic iPSCs could be successfully derived for MILS, either because the starting somatic cells were

Table 2
iPSC models for mitochondrial DNA disorders leading to mitochondrial diseases. iPSCs are all patient-derived, except for when stated differently. NPCs: neural progenitor cells, RGCs: retinal ganglion cells.

Disease	Gene and mutation	iPSC model	Outcome	Reference
Hypertrophic cardiomyopathy (HCM)	***MT-RNR2*** m.2336T > C	iPSC-derived cardiomyocytes	Mitochondrial dysfunctions and ultrastructure defects caused by decreased 16S rRNA stability and reduced levels of mitochondrial proteins. Lower basal oxygen consumption rates.	Li et al., 2018
	MT-TI m.4300A > G	iPSCs	Efficient gene correction with limited off-target editing by DdCBE, restoration of mitochondrial function.	Chen et al., 2023b
Kearns–Sayre Syndrome (KSS)	**Large mtDNA deletions** 5 kB deletion, 7.3 kB deletion	Mutation-free iPSCs, iPSC-derived cardiomyocytes, fibroblasts and NPCs	iPSCs: Normal differentiation potential towards cardiomyocytes, fibroblasts and NPCs without any mtDNA deletions Differentiated cells: Normal ATP production, ROS generation, lactate accumulation and mitochondrial membrane potential.	Lester Sequiera et al., 2021
Leber's Hereditary Optic Neuropathy (LHON)	***MT-ND1*** m.3460G > A	iPSC-derived neurons	Increased autophagy and mitophagy.	Danese et al., 2022
	MT-ND1 m.4160T > C	iPSC-derived RGCs	Increased cell death, rescued by mitochondrial replacement with wildtype mtDNA.	Wong et al., 2017
	MT-ND6 m.14484T > C *(double-mutation)*	iPSCs	Only modest decrease in reprogramming efficiency, normal expression of genes associated with mitochondrial biogenesis, fusion and glycine production.	Hung et al., 2016
		iPSCs	Only modest decrease in reprogramming efficiency, normal expression of genes associated with mitochondrial biogenesis, fusion and glycine production.	Hung et al., 2016
		iPSCs-derived RGCs	Enhanced mitochondrial biogenesis, decreased basal respiration, neurite outgrowth and catalase expression.	Wu et al., 2018
		iPSC-derived RGCs	Decreased expression levels of AMPA subunits and associated scaffold proteins.	Yang et al., 2019
	MT-ND4 m.11778G > A	iPSC-derived RGCs	Increased ROS production and retrograde mitochondria, decreased stationary mitochondria. Rescue of mitochondrial movement by N-acetyl-L-cysteine.	Yang et al., 2020
		iPSC-derived neurons	Increased autophagy and mitophagy.	Danese et al., 2022
		iPSC-derived RGCs	Greater defects in development, morphology and function with additional X-linked *PRICKLE3* mutation (c.157C > T).	Nie et al., 2023
		iPSC-derived RGC-like cells	Greater defects in neuronal differentiation, morphology including reduced area of soma, numbers of neurites and shortened length of axons, and electrophysiological properties with additional nuclear *YARS2* mutation (c.572G > T).	Chen et al., 2023a
	MT-ND3 m.10158T > C	iPSCs	Decreased mitochondrial membrane potential, decrease in total mitochondria.	Meshrkey et al., 2021
		iPSC-derived cardiomyocytes	Generation of dysfunctional cardiomyocytes upon under 30 % mutation load, over 30 % no cardiomyocyte generation.at all.	Galera-Monge et al., 2019
	MT-ND5 m.13513G > A	iPSCs, iPSC-derived neurons	iPSCs: diminished basal respiration. Neurons: Compromised OXPHOS function and diminished calcium buffering capacity.	Galera-Monge et al., 2020
	MT-ND5 m.12706T > C	iPSCs	Decreased mitochondrial membrane potential, decrease in total mitochondria.	Meshrkey et al., 2021
		iPSCs, iPSC-derived cardiomyocytes	iPSCs: reduced maximal respiration and spare reserve capacity. Cardiomyocytes: higher abnormal beat.	Meshrkey et al., 2023
		iPSC-derived NPCs	Defective ATP production, abnormally high mitochondrial membrane potential and altered calcium homeostasis, rescued by PDE-5 inhibitor Avanafil.	Lorenz et al., 2017
Maternally Inherited Leigh Syndrome (MILS)	***MT-ATP6*** m.9185T > C	iPSCs	Decreased mitochondrial membrane potential, decrease in total mitochondria.	Meshrkey et al., 2021
		iPSCs	Reduced maximal respiration and spare reserve capacity, slightly elevated ATP content.	Meshrkey et al., 2023
		iPSC-derived fibroblasts and skeletal muscle cells	Fibroblasts: diminished metabolic profiles, rescued by replacement of mutant mtDNA by somatic cell nuclear transfer. Skeletal muscle cells: lower ATP turnover.	Ma et al., 2015
	MT-ATP6 m.8993T > G	iPSCs, iPSC-derived NPCs and neurons	All cell types: decreased basal oxygen consumption rate, increased ROS level. Neurons: mitochondrial ATP synthesis deficiency and degenerative phenotype, rescue by rapamycin treatment.	Zheng et al., 2016
		iPSC-derived cerebral organoids	Defects in neural epithelial bud generation, size and cortical architecture.	Romero-Morales et al., 2022
		iPSCs	Decreased mitochondrial membrane potential, increase in total mitochondria.	Meshrkey et al., 2021
		iPSCs	Reduced maximal respiration, in part lower ATP content and spare reserve capacity.	Meshrkey et al., 2023
	MT-ATP6 m.9154C > T	iPSC-derived motor neurons	Multiple threshold effects in cellular reprogramming, neurogenesis and metabolism. Increase in mitochondrial respiration and proton leakage at 49 % heteroplasmy.	Kenvin et al., 2022

(*continued on next page*)

Table 2 (*continued*)

Disease	Gene and mutation	iPSC model	Outcome	Reference
		iPSC-derived neurons	Respiratory chain deficiency patterns, especially in complex I.	Hämäläinen et al., 2013
		iPSC, NPCs, cardiomyocytes	iPSCs and NPCs: lower OCR (oxygen consumption rate), decreased OCR/ECAR (extracellular acidification rate) ratio. Cardiomyocytes: compromised differentiation.	Ma et al., 2015
		iPSCs	Wide variety of heteroplasmy levels, impaired complex I activity upon high heteroplasmy levels.	Kodaira et al., 2015
		iPSCs	Decreased reprogramming efficiency and complex I activity upon high heteroplasmy, but no effect on maintenance of the pluripotent state.	Yokota et al., 2015
		iPSCs	Inter- and intra-person variability in heteroplasmy level.	Perales-Clemente et al., 2016
		iPSC-derived retinal pigment epithelial cells	Functional and structural defects like abnormal mitochondria and melanosomes.	Chichagova et al., 2017
		iPSCs, iPSC-derived neurons and cardiomyocytes	iPSCs: impaired complex I activity and basal respiration. Neurons: induced cell death. Cardiomyocytes: inhibited lineage commitment.	Yokota et al., 2017
Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes (MELAS)	***MT-TL1*** m.3243A > G	iPSCs	Successful elimination of the m.3243A > G mutation by mitoTALENS.	Yang et al., 2018
		iPSC-derived endothelial cells	Pro-atherogenic and pro-inflammatory properties.	Pek et al., 2019
		iPSCs	Increase of autophagy and activation of mitophagy.	Lin et al., 2019
		iPSC-derived iNeurons	Mitochondrial dysfunction, delayed neural maturation, reduced dendritic complexity, fewer excitatory synapses, reduced network activity and decreased synchronous network bursting.	Klein Gunnewiek et al., 2020
		iPSC-derived spinal cord organoids	Defects in mitochondrial respiration, elevated Notch signaling resulting in delayed neuronal differentiation.	Winanto et al., 2020
		iPSC-derived neurons	Alleviation of mitochondrial dysfunction in high heteroplasmy MELAS neurons upon treatment with the antioxidant sonlicromanol.	Klein Gunnewiek et al., 2021
		iPSC-derived neurons and cardiomyocytes	Defects in maturation, recovery by tryptolinamide treatment.	Kobayashi et al., 2021
		iPSC-derived cardiomyocytes	Impaired mitochondrial respiration depending on the mutation load.	Ryytty et al., 2022
		iPSC-derived retinal pigment epithelial cells	Heteroplasmy-dependent impairment of mitochondrial bioenergetics.	Bhattacharya et al., 2022
	MT-TW m.5541C > T	iPSC-derived neurons and skeletal muscle cells	Neurons: significant loss upon terminal differentiation. Skeletal muscle cells: no effect.	Hatakeyama et al., 2015
	MT-ND5 m.13513G > A	iPSCs	Purge of mutant mtDNA by extended stem cell passaging, resulting in subclones with various disease genotypes.	Folmes et al., 2013
		iPSCs	TALEN-mediated decrease in heteroplasmy.	Yahata et al., 2017
Myoclonic Epilepsy and Ragged-Red Fibers (MERRF)	***MT-TK*** m.8344A > G	iPSCs, iPSC-derived cardiomyocytes and NPCs	iPSCs: reduced oxygen consumption and growth, elevated ROS production, fragmented mitochondrial morphology. Cardiomyocytes and NPCs: increased ROS levels, altered antioxidant gene expression and fragmented mitochondria.	Chou et al., 2016
		iPSCs	Successful generation of patient-derived iPSCs with high and low heteroplasmy.	Chou et al., 2018
		iPSC-derived inner ear hair cells	Increased ROS levels and MnSOD and CAT gene expression.	Chen et al., 2018
Pearson Marrow– Pancreas syndrome (PMPS)	**Large scale mtDNA deletions** m.8469_13447 del, m. 6897_13411 del	iPSCs	Aberrant mitochondrial ultrastructure, defective oxidative phosphorylation, decreased mitochondrial ATP, respiratory complex IV activity and oxygen consumption.	Hernández-Ainsa et al., 2022
	Large scale mtDNA deletion m.10949_13449 del	Patient-derived iPSCs differentiated into hematopoietic progenitors	Differences in growth, mitochondrial function, and hematopoietic phenotype between low and high mutation load cells.	Cherry et al., 2013
Sensorineural hearing loss	***MT-RNR1*** m.1555A>G	iPSC-derived otic epithelial progenitor cells and inner ear hair cell-like cells	Otic epithelial cells: Increased apoptosis with additional nuclear *TRMU* mutation (c.28G > T). Inner ear hair cell-like cells: Greater defects in development, morphology and functions of hair cell-like cells with additional nuclear *TRMU* mutation (c.28G > T).	Chen and Guan, 2022

homoplasmic for the mutation, or because of other unknown factors preventing the straightforward elimination of the mutations during reprogramming. Nonetheless, possible new treatment strategies were suggested thanks to these models.

Leber's Hereditary Optic Neuropathy (LHON, OMIM #535000) commonly affects retinal ganglion cells (RGCs) which undergo degeneration causing patients to suffer from subacute optic nerve atrophy and severe loss of central vision (Yu-Wai-Man et al., 2002). The most frequent genetic causes of LHON include homoplasmic mutations in mtDNA genes encoding for NADH dehydrogenase (ND) subunits of complex I, namely *MT-ND1*, *MT-ND4* and *MT-ND6* (Wallace et al., 1988). Most studies have been conducted with iPSCs-derived RGCs from patients harboring homoplasmic *MT-ND4* mutation m.11778G > A. RGCs carrying this mutation displayed defective neurite outgrowth, enhanced mitochondrial biogenesis, as well as decreased basal respiration and expression of the antioxidant enzyme catalase (Wu et al., 2018). Furthermore, RGCs manifested a decrease in protein expression levels of the subunits of the AMPA receptor, and their associated scaffold proteins, which indicates the importance of AMPA receptors to the disease phenotype (Yang et al., 2019). RGCs also exhibited increased ROS

production and defective mitochondria motility (Yang et al., 2020). Hung and colleagues reprogrammed fibroblasts from patients carrying homoplasmic mutations (m.11778G > A in *MT-ND4* as well as m.4160 T > C (*MT-ND1*) and m.14484 T > C (*MT-ND6)* double-mutation) and found that the mutations exerted only a modest decrease in reprogramming efficiency (Hung et al., 2016). However, the mutations caused more severe defects in differentiated RGCs (Wong et al., 2017). LHON RGCs exhibited increased cell death that could be rescued when iPSCs underwent mitochondrial replacement with wildtype mtDNA before being differentiated into RGCs (Wong et al., 2017). The expression of the mitochondrial anchoring protein KIF5A was decreased in LHON RGCs, and upon its increase following treatment with antioxidant *N*-acetyl-L-cysteine, the defective mitochondrial movement could be restored (Yang et al., 2020). RGCs carrying *MT-ND4* defects in combination with nuclear mutations in genes *PRICKLE3* (c.157C > T) or *YARS2* (c.572G > T) showed even greater defects, with impact on RGC development, morphology, and function (Chen et al., 2023a; Nie et al., 2023). Lastly, iPSC-derived neurons carrying the homoplasmic mutation m.11778G > A in *MT-ND4* or m.3460G > A in *MT-ND1* also experience defects, including an aberrant increase in autophagy and mitophagy (Danese et al., 2022). Overall, these studies indicate that LHON mutations caused specific defects to RGCs, but that also other neuronal types might be affected, opening the way to therapeutic assessments.

Myoclonic Epilepsy and Ragged-Red Fibers (MERRF, OMIM #545000) disease is a maternally inherited encephalomyopathy, predominantly caused by a m.8344 A > G mutation in the gene *MT-TK* encoding for the mitochondrial tRNA-Lys (Shoffner and Wallace, 1992). As the heteroplasmy level is crucial for the severity of the disease, Chou et al. generated patient-derived iPSCs with high and low heteroplasmy, laying the foundation for the investigation of different disease phenotypes (Chou et al., 2018). MERRF patient-derived iPSCs with 50–70 % heteroplasmy for m.8344 A > G mutation showed reduced oxygen consumption, elevated ROS production, and fragmented mitochondria (Chou et al., 2016). Upon differentiation into cardiomyocytes or NPCs, ROS levels further increased together with altered antioxidant gene expression, and mitochondria underwent additional fragmentation (Chou et al., 2016). As MERRF is also characterized by sensorineural hearing loss, inner ear hair cells were differentiated from MERRF iPSCs and were found to exhibit elevated ROS levels as well as increased antioxidant expression (Chen et al., 2018). Hence, only limited studies demonstrated successful derivation of iPSC models of MERRF, indicating that additional efforts are needed to shine lights on the underlying disease mechanisms and to identify possible interventional targets.

Large mtDNA deletions can cause syndromes like Kearns-Sayre Syndrome (KSS, OMIM #530000), a multisystem disorder with slow progression, and Pearson Marrow-Pancreas syndrome (PMPS, OMIM #557000), also a multisystemic disease characterized by refractory sideroblastic anemia (Broomfield et al., 2015; Goldstein and Falk, 1993; Harding and Hammans, 1992; Pitceathly et al., 2012). iPSC from PMPS patients with different large-scale mtDNA deletions showed aberrant mitochondrial ultrastructure as well as defective OXPHOS, indicated by decreased mitochondrial ATP, respiratory complex IV activity and overall oxygen consumption (Hernández-Ainsa et al., 2022). In KSS, deletions are typically found in muscle tissue but are nearly absent in peripheral blood mononuclear cells (PBMCs) (Holt et al., 1988). Leveraging on this feature, Lester Sequiera and colleagues reprogrammed deletion-free PBMCs from KSS patients and further differentiated them into cardiomyocytes, fibroblasts, and NPCs (Lester Sequiera et al., 2021). As these differentiated cells did not carry mtDNA defects but still retained the same isogenic background, the authors suggested these cells as potential cell therapy options for KSS patients (Lester Sequiera et al., 2021). Additional iPSC works are needed to investigate in more detail how mtDNA deletions affect the functionality of various differentiated cell types.

In addition to the nuclear defects mentioned in the previous session, hypertrophic cardiomyopathy (HCM) can also arise as a consequence of mutations in mtDNA genes encoding for mitochondrial rRNA and tRNA (Song et al., 2011). iPSC-derived cardiomyocytes from patients carrying homoplasmic m.2336 T > C mutation in the mitochondrial 16S RNA gene (*MT-RNR2*) showed defects in mitochondrial function and ultrastructure due to reduced stability of the 16S rRNA and consequently lower levels of mitochondrial proteins (Li et al., 2018). Patient-derived iPSCs with homoplasmic m.4300 A > G mutation in the gene *MT-TI* encoding the mitochondrial tRNA for isoleucine, displayed lower basal oxygen consumption rates (Chen et al., 2023b). Furthermore, this group could efficiently correct the A > G mutation back to G > A by applying mtDNA base editing with DdCBE, which could restore mitochondrial function with limited off-target effects (Chen et al., 2023b). Hence, iPSC models of HCM demonstrated how mtDNA defects causing protein translation impairment can impact cardiac function, and the use of DdCBE editing on these mutations may open the way to gene therapy applications.

Lastly, another disease associated with a defect in mitochondrial rRNA is sensorineural hearing loss, such as the case for m.1555 A > G mutation in the gene *MT-RNR1*, encoding for mitochondrial 12S rRNA (Fischel-Ghodsian, 1999). Chen and Guan generated iPSCs from a family in which members carrying m.1555 A > G mutation in the gene *MT-RNR1* were asymptomatic, while members carrying the same mutation in combination with a nuclear mutation in the gene *TRMU* (c.28G > T, encoding for the mitochondrial tRNA-modifying enzyme tRNA mitochondrial 2-thiouridylase) had sensorineural hearing loss (Chen and Guan, 2022). iPSC-derived otic epithelial progenitor cells and subsequent inner ear hair cell-like cells recapitulated this clinical phenotype, as the combinatory mutations led to increased apoptosis in otic epithelial cells, and greater defects in development, morphology, and electrophysiological properties in inner ear hair cell-like cells (Chen and Guan, 2022). Further studies are warranted to address the mechanisms leading to mtDNA-related sensorineural hearing loss.

Taken together, studies using iPSCs for modeling diseases due to mtDNA defects are steadily increasing. Despite the challenges in mtDNA engineering, it has been possible to derive isogenic iPSC lines with low or absent mtDNA defects by taking advantage of reprogramming associated reconfigurations of the mtDNA profile. However, this approach was not equally successful for all types of mtDNA defects, potentially indicating that some mutations are more amenable to being eliminated than others. Limited gene-based and drug-based treatments have been identified with iPSC models of mtDNA defects, but the establishment of iPSC-driven platforms has the potential to increase the discovery of treatments in the near future.

2. Conclusion

We have described how iPSC-driven approaches have been harnessed for mitochondrial disease research. Besides primary mitochondrial diseases discussed here, mitochondrial dysfunction can also contribute to other diseases, including neuropsychiatric and neurological disorders such as bipolar disorder, schizophrenia, Alzheimer's disease, Huntington's disease, and Parkinson's disease (Ni et al., 2022; Norat et al., 2020). Several iPSC models of these disorders have been generated and employed to investigate the impact of mitochondrial dysfunction on the disease mechanisms. For example, in a bipolar disorder model, iPSC-derived neurons displayed increased mitochondrial membrane potential and reduced size of mitochondria, whereas iPSC-derived neurons from schizophrenia patients showed lower ATP levels and transport chain activity (Perrottelli et al., 2024). iPSC-derived neurons to study Alzheimer's diseases manifested in defective mitophagy and mitochondrial abnormalities, and dopaminergic neurons from Parkinson's disease patients displayed among others altered mitochondrial morphology and decreased mitochondrial membrane potential (Barak et al., 2022; Bose et al., 2022). iPSC-derived brain organoids highlighted defects in the mitochondrial protein CHCHD2 in the early dysregulation caused by Huntington's disease (Lisowski et al., 2024).

Understanding the role played by mitochondrial defects in driving human pathologies might therefore have implications not only for rare mitochondrial diseases but also for other common disorders in the population.

We can divide iPSC-based modeling in two components: i) the cell line development, ii) the differentiation into 2D or 3D systems for downstream applications (Fig. 1). The key element of the first component is the derivation of isogenic lines that differ only for the presence or absence of a defined gene defect. These lines allow researchers to determine the specific effect of genetic mutations within a defined genomic background. There are two strategies to obtain such lines, either by introducing a mutation into healthy iPSCs or by correcting a mutation in patient-derived iPSCs (Hockemeyer and Jaenisch, 2016). For mitochondrial diseases, this process is complicated by the fact that mtDNA cannot be easily manipulated. We could simplify this process by stating that nuclear defects can be targeted using CRISPR/Cas9 editing and mtDNA defects by DdCBE-based editing (Fig. 1). In reality however, there are several kinds of gene engineering approaches for nuclear mutations (Park et al., 2023; van der Oost and Patinios, 2023), while DdCBE and other similar types of mtDNA base editing can only effectively target some mtDNA point mutations, while other mtDNA point mutations and large-scale mtDNA deletions are harder to be targeted (Tolle et al., 2023). In addition to active editing, mtDNA changes may occur during iPSC derivation, leading to the generation of isogenic lines. However, as mentioned above, this approach is not yet understood and cannot be effectively harnessed. The second component of iPSC-based modeling is the derivation of actual cell types and tissues to dissect how mutations can lead to the clinical features observed in patients, and to identify strategies to counteract such defects (Fig. 1). This second component is essential for enabling the translation of findings in vitro to practical medical applications. For mitochondrial diseases, several cell types have been derived and analyzed, but the major focus has been on neuronal and cardiac cells (Tables 1–2). We have described above how these cell types in 2D and 3D have been used in the context of specific mutations and diseases.

We anticipate that continuous advances in gene and stem cell

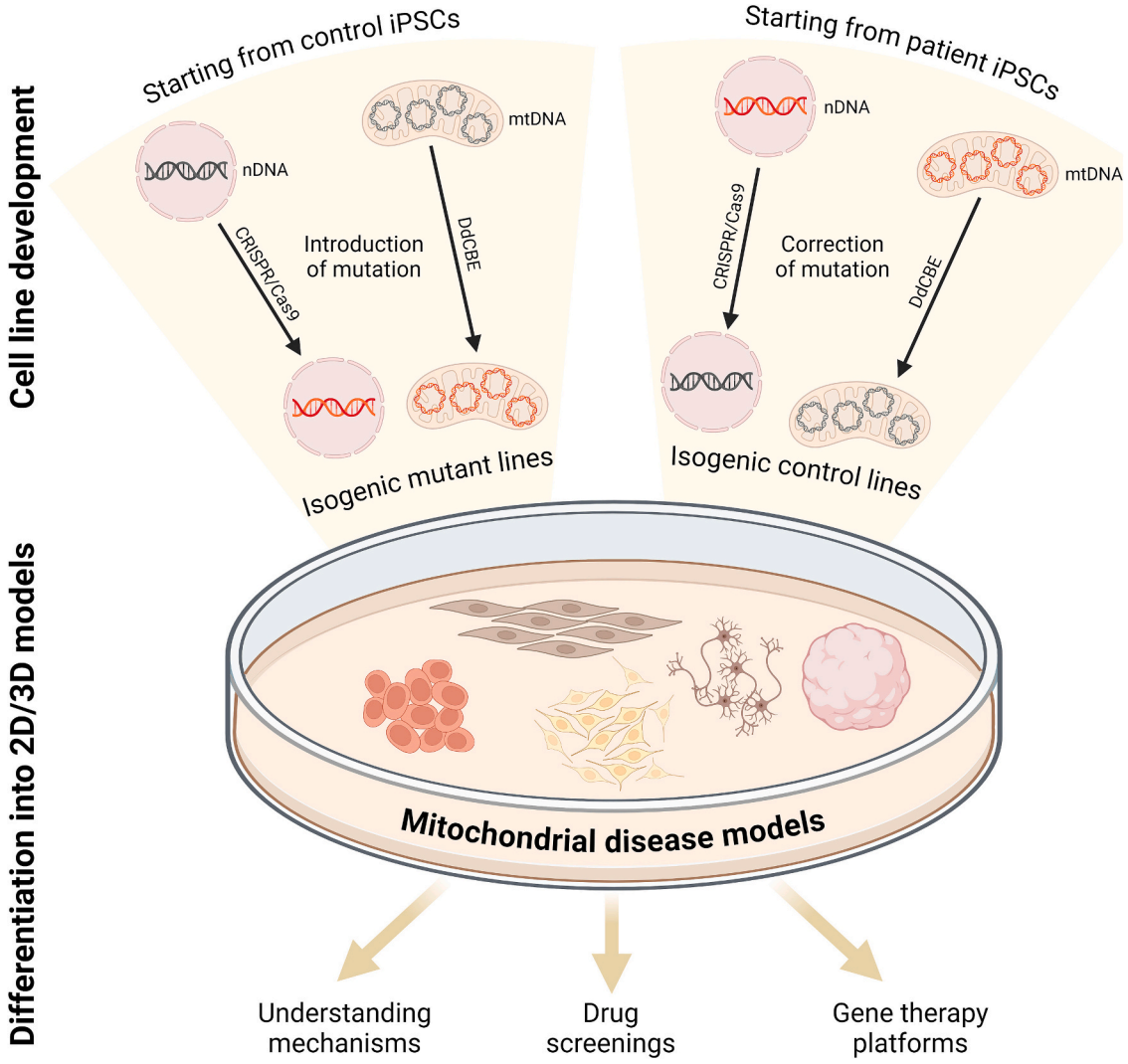

Fig. 1. Current strategies for using iPSCs to establish models of mitochondrial diseases. Cartoon simplifying the two components of iPSC-based modeling of mitochondrial diseases: i) cell line development, ii) differentiation towards defined cell types and tissues for understanding the disease mechanisms and assessing treatments. Each component requires quality control assessments and different sets of expertise. For mitochondrial diseases, the first component is complicated by the fact that the causative genetic defects can affect the nuclear or the mitochondrial genome. Hence, gene engineering approaches need to be tailored for these defects. Several editing tools may be used to tackle this issue. Here, we simplify the processes by indicating CRISPR/Cas9 editing for nuclear defects and DdCBE editing for mtDNA mutations. See text for additional details. Red-colored nuclear or mitochondrial DNAs indicate DNAs carrying disease-causing mutations. CRISPR: clustered regularly interspaced short palindromic repeats; Cas9: CRISPR-associated protein 9; DdCBE: double-stranded DNA deaminase toxin A (DddA)-derived cytosine base editor; mtDNA: mitochondrial DNA; nDNA: nuclear DNA. (Figure created with Biorender). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

technologies will lead to further refinement in these two components of iPSC-based modeling, leading to improved models with higher chances of enabling a critical understanding of the causative processes of mitochondrial diseases that can transform the field through the identification of disease-modifying therapeutics.

CRediT authorship contribution statement

Sonja Heiduschka: Writing – original draft. **Alessandro Prigione:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbd.2025.106822.

Data availability

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

References

Aboul-Soud, M.A.M., Alzahrani, A.J., Mahmoud, A., 2021. Induced pluripotent stem cells (iPSCs)—roles in regenerative therapies, Disease Modelling and Drug Screening. Cells 10, 2319. https://doi.org/10.3390/cells10092319.

Anderson, S., Bankier, A.T., Barrell, B.G., de Bruijn, M.H., Coulson, A.R., Drouin, J., Eperon, I.C., Nierlich, D.P., Roe, B.A., Sanger, F., Schreier, P.H., Smith, A.J., Staden, R., Young, I.G., 1981. Sequence and organization of the human mitochondrial genome. Nature 290, 457–465. https://doi.org/10.1038/290457a0.

Angulo, M.B., Bertalovitz, A., Argenziano, M.A., Yang, J., Patel, A., Zesiewicz, T., McDonald, T.V., 2023. Frataxin deficiency alters gene expression in Friedreich ataxia derived IPSC-neurons and cardiomyocytes. Mol. Genet. Genomic Med. 11, e2093. https://doi.org/10.1002/mgg3.2093.

Antón-Bolaños, N., Faravelli, I., Faits, T., Andreadis, S., Kastli, R., Trattaro, S., Adiconis, X., Wei, A., Sampath Kumar, A., Di Bella, D.J., Tegtmeyer, M., Nehme, R., Levin, J.Z., Regev, A., Arlotta, P., 2024. Brain Chimeroids reveal individual susceptibility to neurotoxic triggers. Nature 631, 142–149. https://doi.org/10.1038/s41586-024-07578-8.

Armstrong, L., Tilgner, K., Saretzki, G., Atkinson, S.P., Stojkovic, M., Moreno, R., Przyborski, S., Lako, M., 2010. Human induced pluripotent stem cell lines show stress defense mechanisms and mitochondrial regulation similar to those of human embryonic stem cells. Stem Cells Dayt. Ohio 28, 661–673. https://doi.org/10.1002/stem.307.

Baertling, F., Rodenburg, R.J., Schaper, J., Smeitink, J.A., Koopman, W.J.H., Mayatepek, E., Morava, E., Distelmaier, F., 2014. A guide to diagnosis and treatment of Leigh syndrome. J. Neurol. Neurosurg. Psychiatry 85, 257–265. https://doi.org/10.1136/jnnp-2012-304426.

Baets, J., De Jonghe, P., Timmerman, V., 2014. Recent advances in Charcot-Marie-tooth disease. Curr. Opin. Neurol. 27, 532–540. https://doi.org/10.1097/WCO.0000000000000131.

Bannwarth, S., Procaccio, V., Lebre, A.S., Jardel, C., Chaussenot, A., Hoarau, C., Maoulida, H., Charrier, N., Gai, X., Xie, H.M., Ferre, M., Fragaki, K., Hardy, G., Mousson de Camaret, B., Marlin, S., Dhaenens, C.M., Slama, A., Rocher, C., Paul Bonnefont, J., Rötig, A., Aoutil, N., Gilleron, M., Desquiret-Dumas, V., Reynier, P., Ceresuela, J., Jonard, L., Devos, A., Espil-Taris, C., Martinez, D., Gaignard, P., Le Quan Sang, K.-H., Amati-Bonneau, P., Falk, M.J., Florentz, C., Chabrol, B., Durand-Zaleski, I., Paquis-Flucklinger, V., 2013. Prevalence of rare mitochondrial DNA mutations in mitochondrial disorders. J. Med. Genet. 50, 704–714. https://doi.org/10.1136/jmedgenet-2013-101604.

Barak, M., Fedorova, V., Pospisilova, V., Raska, J., Vochyanova, S., Sedmik, J., Hribkova, H., Klimova, H., Vanova, T., Bohaciakova, D., 2022. Human iPSC-derived neural models for studying Alzheimer's disease: from neural stem cells to cerebral organoids. Stem Cell Rev. Rep. 18, 792. https://doi.org/10.1007/s12015-021-10254-3.

Ben Jehuda, R., Shemer, Y., Binah, O., 2018. Genome editing in induced pluripotent stem cells using CRISPR/Cas9. Stem Cell Rev. Rep. 14, 323–336. https://doi.org/10.1007/s12015-018-9811-3.

Benslimane, N., Miressi, F., Loret, C., Richard, L., Nizou, A., Pyromali, I., Faye, P.-A., Favreau, F., Lejeune, F., Lia, A.-S., 2023. Amlexanox: Readthrough induction and nonsense-mediated mRNA decay inhibition in a Charcot-Marie-tooth model of hiPSCs-derived neuronal cells harboring a nonsense mutation in GDAP1 gene. Pharm. Basel Switz. 16, 1034. https://doi.org/10.3390/ph16071034.

Bhattacharya, S., Yin, J., Huo, W., Chaum, E., 2022. Modeling of mitochondrial bioenergetics and autophagy impairment in MELAS-mutant iPSC-derived retinal pigment epithelial cells. Stem Cell Res Ther 13, 260. https://doi.org/10.1186/s13287-022-02937-6.

Bird, M.J., Needham, K., Frazier, A.E., van Rooijen, J., Leung, J., Hough, S., Denham, M., Thornton, M.E., Parish, C.L., Nayagam, B.A., Pera, M., Thorburn, D.R., Thompson, L. H., Dottori, M., 2014. Functional characterization of Friedreich ataxia iPS-derived neuronal progenitors and their integration in the adult brain. PLoS One 9, e101718. https://doi.org/10.1371/journal.pone.0101718.

Bose, A., Petsko, G.A., Studer, L., 2022. Induced pluripotent stem cells: a tool for modeling Parkinson's disease. Trends Neurosci. 45, 608–620. https://doi.org/10.1016/j.tins.2022.05.001.

Bottani, E., Lamperti, C., Prigione, A., Tiranti, V., Persico, N., Brunetti, D., 2020. Therapeutic approaches to treat mitochondrial diseases: "one-size-fits-all" and "precision medicine" strategies. Pharmaceutics 12, 1083. https://doi.org/10.3390/pharmaceutics12111083.

Broomfield, A., Sweeney, M.G., Woodward, C.E., Fratter, C., Morris, A.M., Leonard, J.V., Abulhoul, L., Grunewald, S., Clayton, P.T., Hanna, M.G., Poulton, J., Rahman, S., 2015. Paediatric single mitochondrial DNA deletion disorders: an overlapping spectrum of disease. J. Inherit. Metab. Dis. 38, 445–457. https://doi.org/10.1007/s10545-014-9778-4.

Caglayan, S., Hashim, A., Cieslar-Pobuda, A., Jensen, V., Behringer, S., Talug, B., Chu, D. T., Pecquet, C., Rogne, M., Brech, A., Brorson, S.H., Nagelhus, E.A., Hannibal, L., Boschi, A., Taskén, K., Staerk, J., 2020. Optic Atrophy 1 Controls Human Neuronal Development by Preventing Aberrant Nuclear DNA Methylation. iScience 23, 101154. https://doi.org/10.1016/j.isci.2020.101154.

Campello, S., Scorrano, L., 2010. Mitochondrial shape changes: orchestrating cell pathophysiology. EMBO Rep. 11, 678–684. https://doi.org/10.1038/embor.2010.115.

Carelli, V., Chan, D.C., 2014. Mitochondrial DNA: impacting central and peripheral nervous systems. Neuron 84, 1126–1142. https://doi.org/10.1016/j.neuron.2014.11.022.

Carelli, V., Hirano, M., Enríquez, J.A., Chinnery, P.F., 2022. Implications of mitochondrial DNA mutations in human induced pluripotent stem cells. Nat. Rev. Genet. 23, 69–70. https://doi.org/10.1038/s41576-021-00430-z.

Chen, C., Guan, M.-X., 2022. Genetic correction of TRMU allele restored the mitochondrial dysfunction-induced deficiencies in iPSCs-derived hair cells of hearing-impaired patients. Hum. Mol. Genet. 31, 3068–3082. https://doi.org/10.1093/hmg/ddac096.

Chen, J., Riazifar, H., Guan, M.-X., Huang, T., 2016. Modeling autosomal dominant optic atrophy using induced pluripotent stem cells and identifying potential therapeutic targets. Stem Cell Res Ther 7, 2. https://doi.org/10.1186/s13287-015-0264-1.

Chen, Y.-C., Tsai, C.-L., Wei, Y.-H., Wu, Y.-T., Hsu, W.-T., Lin, H.-C., Hsu, Y.-C., 2018. ATOH1/RFX1/RFX3 transcription factors facilitate the differentiation and characterisation of inner ear hair cell-like cells from patient-specific induced pluripotent stem cells harbouring A8344G mutation of mitochondrial DNA. Cell Death Dis. 9, 437. https://doi.org/10.1038/s41419-018-0488-y.

Chen, Z., Chai, E., Mou, Y., Roda, R.H., Blackstone, C., Li, X.-J., 2022. Inhibiting mitochondrial fission rescues degeneration in hereditary spastic paraplegia neurons. Brain J. Neurol. 145, 4016–4031. https://doi.org/10.1093/brain/awab488.

Chen, J.-R., Chen, C., Chen, J., Ji, Y., Lian, Y., Zhang, J., Yu, J., Li, X.-Y., Qu, J., Guan, M.-X., 2023a. Nuclear modifier YARS2 allele correction restored retinal ganglion cells-

specific deficiencies in Leber's hereditary optic neuropathy. Hum. Mol. Genet. 32, 1539–1551. https://doi.org/10.1093/hmg/ddad001.
Chen, X., Chen, M., Zhu, Y., Sun, H., Wang, Y., Xie, Y., Ji, L., Wang, C., Hu, Z., Guo, X., Xu, Z., Zhang, J., Yang, S., Liang, D., Shen, B., 2023b. Correction of a homoplasmic mitochondrial tRNA mutation in patient-derived iPSCs via a mitochondrial base editor. Commun. Biol. 6, 1116. https://doi.org/10.1038/s42003-023-05500-y.
Chen, Y., Jiao, D., Liu, Y., Xu, X., Wang, Y., Luo, X., Saiyin, H., Li, Y., Gao, K., Chen, Yucai, Zhao, S.-M., Ma, L., Wang, C., 2023c. FBXL4 mutations cause excessive mitophagy via BNIP3/BNIP3L accumulation leading to mitochondrial DNA depletion syndrome. Cell Death Differ. 30, 2351–2363. https://doi.org/10.1038/s41418-023-01205-1.
Cherry, A.B., Gagne, K.E., McLoughlin, E.M., Baccei, A., Gorman, B., Hartung, O., Miller, J.D., Zhang, J., Zon, R.L., Ince, T.A., Neufeld, E.J., Lerou, P.H., Fleming, M.D., Daley, G.Q., Agarwal, S., 2013. Induced pluripotent stem cells with a mitochondrial DNA deletion. Stem Cells 31 (7), 1287–1297. https://doi.org/10.1002/stem.1354.
Chichagova, V., Hallam, D., Collin, J., Buskin, A., Saretzki, G., Armstrong, L., Yu-Wai-Man, P., Lako, M., Steel, D.H., 2017. Human iPSC disease modelling reveals functional and structural defects in retinal pigment epithelial cells harbouring the m.3243A>G mitochondrial DNA mutation. Sci. Rep. 7, 12320. https://doi.org/10.1038/s41598-017-12396-2.
Chou, S.-J., Tseng, W.-L., Chen, C.-T., Lai, Y.-F., Chien, C.-S., Chang, Y.-L., Lee, H.-C., Wei, Y.-H., Chiou, S.-H., 2016. Impaired ROS scavenging system in human induced pluripotent stem cells generated from patients with MERRF syndrome. Sci. Rep. 6, 23661. https://doi.org/10.1038/srep23661.
Chou, S.-J., Ko, Y.-L., Yang, Y.-H., Yarmishyn, A.A., Wu, Y.-T., Chen, C.-T., Lee, H.-C., Wei, Y.-H., Chiou, S.-H., 2018. Generation of two isogenic human induced pluripotent stem cell lines from a 15 year-old female patient with MERRF syndrome and A8344G mutation of mitochondrial DNA. Stem Cell Res. 30, 201–205. https://doi.org/10.1016/j.scr.2018.05.011.
Chowdhury, A., Aich, A., Jain, G., Wozny, K., Lüchtenborg, C., Hartmann, M., Bernhard, O., Balleininger, M., Alfar, E.A., Zieseniss, A., Toischer, K., Guan, K., Rizzoli, S.O., Brügger, B., Fischer, A., Katschinski, D.M., Rehling, P., Dudek, J., 2018. Defective mitochondrial Cardiolipin remodeling dampens HIF-1α expression in hypoxia. Cell Rep. 25, 561–570.e6. https://doi.org/10.1016/j.celrep.2018.09.057.
Chumarina, M., Russ, K., Azevedo, C., Heuer, A., Pihl, M., Collin, A., Frostner, E.Å., Elmer, E., Hyttel, P., Cappelletti, G., Zini, M., Goldwurm, S., Roybon, L., 2019. Cellular alterations identified in pluripotent stem cell-derived midbrain spheroids generated from a female patient with progressive external ophthalmoplegia and parkinsonism who carries a novel variation (p.Q811R) in the POLG1 gene. Acta Neuropathol. Commun. 7, 208. https://doi.org/10.1186/s40478-019-0863-7.
Ciafaloni, E., Santorelli, F.M., Shanske, S., Deonna, T., Roulet, E., Janzer, C., Pescia, G., DiMauro, S., 1993. Maternally inherited Leigh syndrome. J. Pediatr. 122, 419–422. https://doi.org/10.1016/s0022-3476(05)83431-6.
Codazzi, F., Hu, A., Rai, M., Donatello, S., Salerno Scarzella, F., Mangiameli, E., Pelizzoni, I., Grohovaz, F., Pandolfo, M., 2016. Friedreich ataxia-induced pluripotent stem cell-derived neurons show a cellular phenotype that is corrected by a benzamide HDAC inhibitor. Hum. Mol. Genet. 25, 4847–4855. https://doi.org/10.1093/hmg/ddw308.
Cook, A., Giunti, P., 2017. Friedreich's ataxia: clinical features, pathogenesis and management. Br. Med. Bull. 124, 19–30. https://doi.org/10.1093/bmb/ldx034.
Cooper, H.M., Yang, Y., Ylikallio, E., Khairullin, R., Woldegebriel, R., Lin, K.-L., Euro, L., Palin, E., Wolf, A., Trokovic, R., Isohanni, P., Kaakkola, S., Auranen, M., Lönnqvist, T., Wanrooij, S., Tyynismaa, H., 2017. ATPase-deficient mitochondrial inner membrane protein ATAD3A disturbs mitochondrial dynamics in dominant hereditary spastic paraplegia. Hum. Mol. Genet. 26, 1432–1443. https://doi.org/10.1093/hmg/ddx042.
Cotticelli, M.G., Xia, S., Truitt, R., Doliba, N.M., Rozo, A.V., Tobias, J.W., Lee, T., Chen, J., Napierala, J.S., Napierala, M., Yang, W., Wilson, R.B., 2023. Acute frataxin knockdown in induced pluripotent stem cell-derived cardiomyocytes activates a type I interferon response. Dis. Model. Mech. 16, dmm049497. https://doi.org/10.1242/dmm.049497.
Cree, L.M., Samuels, D.C., Chinnery, P.F., 2009. The inheritance of pathogenic mitochondrial DNA mutations. Biochim. Biophys. Acta 1792, 1097–1102. https://doi.org/10.1016/j.bbadis.2009.03.002.
Crombie, D.E., Van Bergen, N., Davidson, K.C., Anjomani Virmouni, S., Mckelvie, P.A., Chrysostomou, V., Conquest, A., Corben, L.A., Pook, M.A., Kulkarni, T., Trounce, I. A., Pera, M.F., Delatycki, M.B., Pébay, A., 2015. Characterization of the retinal pigment epithelium in Friedreich ataxia. Biochem. Biophys. Rep. 4, 141–147. https://doi.org/10.1016/j.bbrep.2015.09.003.
Crombie, D.E., Curl, C.L., Raaijmakers, A.J., Sivakumaran, P., Kulkarni, T., Wong, R.C., Minami, I., Evans-Galea, M.V., Lim, S.Y., Delbridge, L., Corben, L.A., Dottori, M., Nakatsuji, N., Trounce, I.A., Hewitt, A.W., Delatycki, M.B., Pera, M.F., Pébay, A., 2017. Friedreich's ataxia induced pluripotent stem cell-derived cardiomyocytes display electrophysiological abnormalities and calcium handling deficiency. Aging 9, 1440–1452. https://doi.org/10.18632/aging.101247.
Danese, A., Patergnani, S., Maresca, A., Peron, C., Raimondi, A., Caporali, L., Marchi, S., La Morgia, C., Del Dotto, V., Zanna, C., Iannielli, A., Segnali, A., Di Meo, I., Cavaliere, A., Lebiedzinska-Arciszewska, M., Wieckowski, M.R., Martinuzzi, A., Moraes-Filho, M.N., Salomao, S.R., Berezovsky, A., Belfort, R., Buser, C., Ross-Cisneros, F.N., Sadun, A.A., Tacchetti, C., Broccoli, V., Giorgi, C., Tiranti, V., Carelli, V., Pinton, P., 2022. Pathological mitophagy disrupts mitochondrial homeostasis in Leber's hereditary optic neuropathy. Cell Rep. 40, 111124. https://doi.org/10.1016/j.celrep.2022.111124.
Daneshgar, N., Leidinger, M.R., Le, S., Hefti, M., Prigione, A., Dai, D.-F., 2022. Activated microglia and neuroinflammation as a pathogenic mechanism in Leigh syndrome. Front. Neurosci. 16, 1068498. https://doi.org/10.3389/fnins.2022.1068498.
Davey, K.M., Parboosingh, J.S., McLeod, D.R., Chan, A., Casey, R., Ferreira, P., Snyder, F. F., Bridge, P.J., Bernier, F.P., 2006. Mutation of DNAJC19, a human homologue of yeast inner mitochondrial membrane co-chaperones, causes DCMA syndrome, a novel autosomal recessive Barth syndrome-like condition. J. Med. Genet. 43, 385–393. https://doi.org/10.1136/jmg.2005.036657.
Del Dotto, V., Musiani, F., Baracca, A., Solaini, G., 2024. Variants in human ATP synthase mitochondrial genes: biochemical dysfunctions, associated diseases, and therapies. Int. J. Mol. Sci. 25, 2239. https://doi.org/10.3390/ijms25042239.
Dell'agnello, C., Leo, S., Agostino, A., Szabadkai, G., Tiveron, C., Zulian, A., Prelle, A., Roubertoux, P., Rizzuto, R., Zeviani, M., 2007. Increased longevity and refractoriness to ca(2+)-dependent neurodegeneration in Surf1 knockout mice. Hum. Mol. Genet. 16, 431–444. https://doi.org/10.1093/hmg/ddl477.
Denton, K., Mou, Y., Xu, C.-C., Shah, D., Chang, J., Blackstone, C., Li, X.-J., 2018. Impaired mitochondrial dynamics underlie axonal defects in hereditary spastic paraplegias. Hum. Mol. Genet. 27, 2517–2530. https://doi.org/10.1093/hmg/ddy156.
Dionisi, C., Chazalon, M., Rai, M., Keime, C., Imbault, V., Communi, D., Puccio, H., Schiffmann, S.N., Pandolfo, M., 2023. Proprioceptors-enriched neuronal cultures from induced pluripotent stem cells from Friedreich ataxia patients show altered transcriptomic and proteomic profiles, abnormal neurite extension, and impaired electrophysiological properties. Brain Commun. 5, fcad007. https://doi.org/10.1093/braincomms/fcad007.
Doni, D., Cavion, F., Bortolus, M., Baschiera, E., Muccioli, S., Tombesi, G., d'Ettorre, F., Ottaviani, D., Marchesan, E., Leanza, L., Greggio, E., Ziviani, E., Russo, A., Bellin, M., Sartori, G., Carbonera, D., Salviati, L., Costantini, P., 2023. Human frataxin, the Friedreich ataxia deficient protein, interacts with mitochondrial respiratory chain. Cell Death Dis. 14, 805. https://doi.org/10.1038/s41419-023-06320-y.
Dudek, J., Cheng, I.-F., Balleininger, M., Vaz, F.M., Streckfuss-Bömeke, K., Hübscher, D., Vukotic, M., Wanders, R.J.A., Rehling, P., Guan, K., 2013. Cardiolipin deficiency affects respiratory chain function and organization in an induced pluripotent stem cell model of Barth syndrome. Stem Cell Res. 11, 806–819. https://doi.org/10.1016/j.scr.2013.05.005.
Dudek, J., Cheng, I.-F., Chowdhury, A., Wozny, K., Balleininger, M., Reinhold, R., Grunau, S., Callegari, S., Toischer, K., Wanders, R.J., Hasenfuß, G., Brügger, B., Guan, K., Rehling, P., 2016. Cardiac-specific succinate dehydrogenase deficiency in Barth syndrome. EMBO Mol. Med. 8, 139–154. https://doi.org/10.15252/emmm.201505644.
El-Hattab, A.W., Scaglia, F., 2013. Mitochondrial DNA depletion syndromes: review and updates of genetic basis, manifestations, and therapeutic options. Neurother. J. Am. Soc. Exp. Neurother. 10, 186–198. https://doi.org/10.1007/s13311-013-0177-6.
Escribá, R., Larrañaga-Moreira, J.M., Richaud-Patin, Y., Pourchet, L., Lazis, I., Jiménez-Delgado, S., Morillas-García, A., Ortiz-Genga, M., Ochoa, J.P., Carreras, D., Pérez, G. J., de la Pompa, J.L., Brugada, R., Monserrat, L., Barriales-Villa, R., Raya, A., 2023. iPSC-based modeling of variable clinical presentation in hypertrophic cardiomyopathy. Circ. Res. 133, 108–119. https://doi.org/10.1161/CIRCRESAHA.122.321951.
Fatica, E.M., DeLeonibus, G.A., House, A., Kodger, J.V., Pearce, R.W., Shah, R.R., Levi, L., Sandlers, Y., 2019. Barth syndrome: exploring cardiac metabolism with induced pluripotent stem cell-derived cardiomyocytes. Metabolites 9, 306. https://doi.org/10.3390/metabo9120306.
Filograna, R., Mennuni, M., Alsina, D., Larsson, N.-G., 2021. Mitochondrial DNA copy number in human disease: the more the better? FEBS Lett. 595, 976–1002. https://doi.org/10.1002/1873-3468.14021.
Filosto, M., Mancuso, M., Nishigaki, Y., Pancrudo, J., Harati, Y., Gooch, C., Mankodi, A., Bayne, L., Bonilla, E., Shanske, S., Hirano, M., DiMauro, S., 2003. Clinical and genetic heterogeneity in progressive external ophthalmoplegia due to mutations in polymerase gamma. Arch. Neurol. 60, 1279–1284. https://doi.org/10.1001/archneur.60.9.1279.
Fischel-Ghodsian, N., 1999. Mitochondrial deafness mutations reviewed. Hum. Mutat. 13, 261–270. https://doi.org/10.1002/(SICI)1098-1004(1999)13:4<261::AID-HUMU1>3.0.CO;2-W.
Folmes, C.D.L., Nelson, T.J., Martinez-Fernandez, A., Arrell, D.K., Lindor, J.Z., Dzeja, P. P., Ikeda, Y., Perez-Terzic, C., Terzic, A., 2011. Somatic oxidative bioenergetics transitions into pluripotency-dependent glycolysis to facilitate nuclear reprogramming. Cell Metab. 14, 264–271. https://doi.org/10.1016/j.cmet.2011.06.011.
Folmes, C.D.L., Martinez-Fernandez, A., Perales-Clemente, E., Li, X., McDonald, A., Oglesbee, D., Hrstka, S.C., Perez-Terzic, C., Terzic, A., Nelson, T.J., 2013. Disease-causing mitochondrial heteroplasmy segregated within induced pluripotent stem cell clones derived from a patient with MELAS. Stem Cells Dayt. Ohio 31, 1298–1308. https://doi.org/10.1002/stem.1389.
Gai, X., Ghezzi, D., Johnson, M.A., Biagosch, C.A., Shamseldin, H.E., Haack, T.B., Reyes, A., Tsukikawa, M., Sheldon, C.A., Srinivasan, S., Gorza, M., Kremer, L.S., Wieland, T., Strom, T.M., Polyak, E., Place, E., Consugar, M., Ostrovsky, J., Vidoni, S., Robinson, A.J., Wong, L.-J., Sondheimer, N., Salih, M.A., Al-Jishi, E., Raab, C.P., Bean, C., Furlan, F., Parini, R., Lamperti, C., Mayr, J.A., Konstantopoulou, V., Huemer, M., Pierce, E.A., Meitinger, T., Freisinger, P., Sperl, W., Prokisch, H., Alkuraya, F.S., Falk, M.J., Zeviani, M., 2013. Mutations in FBXL4, encoding a mitochondrial protein, cause early-onset mitochondrial Encephalomyopathy. Am. J. Hum. Genet. 93, 482–495. https://doi.org/10.1016/j.ajhg.2013.07.016.
Galera-Monge, T., Zurita-Díaz, F., Garesse, R., Gallardo, M.E., 2019. The mutation m.13513G>a impairs cardiac function, favoring a neuroectoderm commitment, in a mutant-load dependent way. J. Cell. Physiol. 234, 19511–19522. https://doi.org/10.1002/jcp.28549.

Galera-Monge, T., Zurita-Díaz, F., Canals, I., Hansen, M.G., Rufián-Vázquez, L., Ehinger, J.K., Elmér, E., Martin, M.A., Garesse, R., Ahlenius, H., Gallardo, M.E., 2020. Mitochondrial dysfunction and calcium dysregulation in Leigh syndrome induced pluripotent stem cell derived neurons. Int. J. Mol. Sci. 21, 3191. https://doi.org/10.3390/ijms21093191.

Gammage, P.A., Moraes, C.T., Minczuk, M., 2018. Mitochondrial genome engineering: The revolution may not be CRISPR-Ized. Trends Genet. TIG 34, 101–110. https://doi.org/10.1016/j.tig.2017.11.001.

Goldstein, A., Falk, M.J., 1993. Single large-scale mitochondrial DNA deletion syndromes. In: Adam, M.P., Feldman, J., Mirzaa, G.M., Pagon, R.A., Wallace, S.E., Bean, L.J., Gripp, K.W., Amemiya, A. (Eds.), GeneReviews®. University of Washington, Seattle, Seattle (WA).

Gorman, G.S., Chinnery, P.F., DiMauro, S., Hirano, M., Koga, Y., McFarland, R., Suomalainen, A., Thorburn, D.R., Zeviani, M., Turnbull, D.M., 2016. Mitochondrial diseases. Nat. Rev. Dis. Primers 2, 1–22. https://doi.org/10.1038/nrdp.2016.80.

Goto, Y., Nonaka, I., Horai, S., 1990. A mutation in the tRNA(Leu)(UUR) gene associated with the MELAS subgroup of mitochondrial encephalomyopathies. Nature 348, 651–653. https://doi.org/10.1038/348651a0.

Guang, S., O'Brien, B.M., Fine, A.S., Ying, M., Fatemi, A., Nemeth, C.L., 2023. Mutations in DARS2 result in global dysregulation of mRNA metabolism and splicing. Sci. Rep. 13, 13042. https://doi.org/10.1038/s41598-023-40107-7.

Güner, F., Pozner, T., Krach, F., Prots, I., Loskarn, S., Schlötzer-Schrehardt, U., Winkler, J., Winner, B., Regensburger, M., 2021. Axon-specific mitochondrial pathology in SPG11 Alpha Motor neurons. Front. Neurosci. 15, 680572. https://doi.org/10.3389/fnins.2021.680572.

Guo, J., Duan, L., He, X., Li, S., Wu, Y., Xiang, G., Bao, F., Yang, L., Shi, H., Gao, M., Zheng, L., Hu, H., Liu, X., 2021. A combined model of human iPSC-derived liver organoids and hepatocytes reveals Ferroptosis in DGUOK mutant mtDNA depletion syndrome. Adv. Sci. Weinh. Baden-Wurtt. Ger. 8, 2004680. https://doi.org/10.1002/advs.202004680.

Hallas, T., Eisen, B., Shemer, Y., Ben Jehuda, R., Mekies, L.N., Naor, S., Schick, R., Eliyahu, S., Reiter, I., Vlodavsky, E., Katz, Y.S., Õunap, K., Lorber, A., Rodenburg, R., Mandel, H., Gherghiceanu, M., Binah, O., 2018. Investigating the cardiac pathology of SCO2-mediated hypertrophic cardiomyopathy using patients induced pluripotent stem cell-derived cardiomyocytes. J. Cell. Mol. Med. 22, 913–925. https://doi.org/10.1111/jcmm.13392.

Hämäläinen, R.H., 2016. Mitochondrial DNA mutations in iPS cells: mtDNA integrity as standard iPSC selection criteria? EMBO J. 35, 1960–1962. https://doi.org/10.15252/embj.201695185.

Hämäläinen, R.H., Manninen, T., Koivumäki, H., Kislin, M., Otonkoski, T., Suomalainen, A., 2013. Tissue- and cell-type-specific manifestations of heteroplasmic mtDNA 3243A>G mutation in human induced pluripotent stem cell-derived disease model. Proc. Natl. Acad. Sci. USA 110, E3622–E3630. https://doi.org/10.1073/pnas.1311660110.

Han, R., Liu, Y., Li, S., Li, X.-J., Yang, W., 2023. PINK1-PRKN mediated mitophagy: differences between in vitro and in vivo models. Autophagy 19, 1396–1405. https://doi.org/10.1080/15548627.2022.2139080.

Harding, A.E., Hammans, S.R., 1992. Deletions of the mitochondrial genome. J. Inherit. Metab. Dis. 15, 480–486. https://doi.org/10.1007/BF01799606.

Hatakeyama, H., Katayama, A., Komaki, H., Nishino, I., Goto, Y.-I., 2015. Molecular pathomechanisms and cell-type-specific disease phenotypes of MELAS caused by mutant mitochondrial tRNA(Trp). Acta Neuropathol. Commun. 3, 52. https://doi.org/10.1186/s40478-015-0227-x.

Hernández-Ainsa, C., López-Gallardo, E., García-Jiménez, M.C., Climent-Alcalá, F.J., Rodríguez-Vigil, C., Fernández, García, de Villalta, M., Artuch, R., Montoya, J., Ruiz-Pesini, E., Emperador, S., 2022. Development and characterization of cell models harbouring mtDNA deletions for in vitro study of Pearson syndrome. Dis. Model. Mech. 15, dmm049083. https://doi.org/10.1242/dmm.049083.

Hers, H.G., 1963. Alpha-glucosidase deficiency in generalized glycogenstorage disease (Pompe's disease). Biochem. J. 86, 11–16. https://doi.org/10.1042/bj0860011.

Hick, A., Wattenhofer-Donzé, M., Chintawar, S., Tropel, P., Simard, J.P., Vaucamps, N., Gall, D., Lambot, L., André, C., Reutenauer, L., Rai, M., Teletin, M., Messaddeq, N., Schiffmann, S.N., Viville, S., Pearson, C.E., Pandolfo, M., Puccio, H., 2013. Neurons and cardiomyocytes derived from induced pluripotent stem cells as a model for mitochondrial defects in Friedreich's ataxia. Dis. Model. Mech. 6, 608–621. https://doi.org/10.1242/dmm.010900.

Hirano, M., Nishigaki, Y., Martí, R., 2004. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): a disease of two genomes. Neurologist 10, 8–17. https://doi.org/10.1097/01.nrl.0000106919.06469.04.

Hockemeyer, D., Jaenisch, R., 2016. Induced pluripotent stem cells meet genome editing. Cell Stem Cell 18, 573–586. https://doi.org/10.1016/j.stem.2016.04.013.

Holt, I.J., Harding, A.E., Morgan-Hughes, J.A., 1988. Deletions of muscle mitochondrial DNA in patients with mitochondrial myopathies. Nature 331, 717–719. https://doi.org/10.1038/331717a0.

Holt, I.J., Harding, A.E., Petty, R.K., Morgan-Hughes, J.A., 1990. A new mitochondrial disease associated with mitochondrial DNA heteroplasmy. Am. J. Hum. Genet. 46, 428–433.

Hong, Y., Zhang, Z., Yangzom, T., Chen, A., Lundberg, B.C., Fang, E.F., Siller, R., Sullivan, G.J., Zeman, J., Tzoulis, C., Bindoff, L.A., Liang, K.X., 2024. The NAD+ precursor nicotinamide riboside rescues mitochondrial defects and neuronal loss in iPSC derived cortical organoid of Alpers' disease. Int. J. Biol. Sci. 20, 1194–1217. https://doi.org/10.7150/ijbs.91624.

Houtkooper, R.H., Turkenburg, M., Poll-The, B.T., Karall, D., Pérez-Cerdá, C., Morrone, A., Malvagia, S., Wanders, R.J., Kulik, W., Vaz, F.M., 2009. The enigmatic role of tafazzin in cardiolipin metabolism. Biochim. Biophys. Acta BBA – Biomembr. Includes Special Section: Cardiolipin 1788, 2003–2014. https://doi.org/10.1016/j.bbamem.2009.07.009.

Huang, W., Zhou, R., Jiang, C., Wang, J., Zhou, Y., Xu, X., Wang, T., Li, A., Zhang, Y., 2023. Mitochondrial dysfunction is associated with hypertrophic cardiomyopathy in Pompe disease-specific induced pluripotent stem cell-derived cardiomyocytes. Cell Prolif. e13573. https://doi.org/10.1111/cpr.13573.

Hung, S.S.C., Van Bergen, N.J., Jackson, S., Liang, H., Mackey, D.A., Hernández, D., Lim, S.Y., Hewitt, A.W., Trounce, I., Pébay, A., Wong, R.C.B., 2016. Study of mitochondrial respiratory defects on reprogramming to human induced pluripotent stem cells. Aging 8, 945–957. https://doi.org/10.18632/aging.100950.

Igoillo-Esteve, M., Oliveira, A.F., Cosentino, C., Fantuzzi, F., Demarez, C., Toivonen, S., Hu, A., Chintawar, S., Lopes, M., Pachera, N., Cai, Y., Abdulkarim, B., Rai, M., Marselli, L., Marchetti, P., Tariq, M., Jonas, J.-C., Boscolo, M., Pandolfo, M., Eizirik, D.L., Cnop, M., 2020. Exenatide induces frataxin expression and improves mitochondrial function in Friedreich ataxia. JCI Insight 5 (e134221), 134221. https://doi.org/10.1172/jci.insight.134221.

Inak, G., Lorenz, C., Lisowski, P., Zink, A., Mlody, B., Prigione, A., 2017. Concise review: induced pluripotent stem cell-based drug discovery for mitochondrial disease. Stem Cells Dayt. Ohio 35, 1655–1662. https://doi.org/10.1002/stem.2637.

Inak, G., Rybak-Wolf, A., Lisowski, P., Pentimalli, T.M., Jüttner, R., Glažar, P., Uppal, K., Bottani, E., Brunetti, D., Secker, C., Zink, A., Meierhofer, D., Henke, M.-T., Dey, M., Ciptasari, U., Mlody, B., Hahn, T., Berruezo-Llacuna, M., Karaiskos, N., Di Virgilio, M., Mayr, J.A., Wortmann, S.B., Priller, J., Gotthardt, M., Jones, D.P., Mayatepek, E., Stenzel, W., Diecke, S., Kühn, R., Wanker, E.E., Rajewsky, N., Schuelke, M., Prigione, A., 2021. Defective metabolic programming impairs early neuronal morphogenesis in neural cultures and an organoid model of Leigh syndrome. Nat. Commun. 12, 1929. https://doi.org/10.1038/s41467-021-22117-z.

Ineichen, B.V., Furrer, E., Grüninger, S.L., Zürrer, W.E., Macleod, M.R., 2024. Analysis of animal-to-human translation shows that only 5% of animal-tested therapeutic interventions obtain regulatory approval for human applications. PLoS Biol. 22, e3002667. https://doi.org/10.1371/journal.pbio.3002667.

Jang, M.W., Kim, T.Y., Sharma, K., Kwon, J., Yi, E., Lee, C.J., 2021. A deafness associated protein TMEM43 interacts with KCNK3 (TASK-1) two-pore domain K+ (K2P) channel in the cochlea. Exp. Neurobiol. 30, 319–328. https://doi.org/10.5607/en21028.

Jinek, M., Chylinski, K., Fonfara, I., Hauer, M., Doudna, J.A., Charpentier, E., 2012. A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. Science 337, 816–821. https://doi.org/10.1126/science.1225829.

Jing, R., Corbett, J.L., Cai, J., Beeson, G.C., Beeson, C.C., Chan, S.S., Dimmock, D.P., Lazcares, L., Geurts, A.M., Lemasters, J.J., Duncan, S.A., 2018. A screen using iPSC-derived hepatocytes reveals NAD+ as a potential treatment for mtDNA depletion syndrome. Cell Rep. 25, 1469–1484.e5. https://doi.org/10.1016/j.celrep.2018.10.036.

Jonikas, M., Madill, M., Mathy, A., Zekoll, T., Zois, C.E., Wigfield, S., Kurzawa-Akanbi, M., Browne, C., Sims, D., Chinnery, P.F., Cowley, S.A., Tofaris, G.K., 2018. Stem cell modeling of mitochondrial parkinsonism reveals key functions of OPA1. Ann. Neurol. 83, 915–925. https://doi.org/10.1002/ana.25221.

Kaga, K., 2016. Auditory nerve disease and auditory neuropathy spectrum disorders. Auris Nasus Larynx 43, 10–20. https://doi.org/10.1016/j.anl.2015.06.008.

Kang, E., Wang, X., Tippner-Hedges, R., Ma, H., Folmes, C.D.L., Gutierrez, N.M., Lee, Y., Van Dyken, C., Ahmed, R., Li, Y., Koski, A., Hayama, T., Luo, S., Harding, C.O., Amato, P., Jensen, J., Battaglia, D., Lee, D., Wu, D., Terzic, A., Wolf, D.P., Huang, T., Mitalipov, S., 2016. Age-related accumulation of somatic mitochondrial DNA mutations in adult-derived human iPSCs. Cell Stem Cell 18, 625–636. https://doi.org/10.1016/j.stem.2016.02.005.

Kelly, R.D.W., Rodda, A.E., Dickinson, A., Mahmud, A., Nefzger, C.M., Lee, W., Forsythe, J.S., Polo, J.M., Trounce, I.A., McKenzie, M., Nisbet, D.R., St John, J.C., 2013. Mitochondrial DNA haplotypes define gene expression patterns in pluripotent and differentiating embryonic stem cells. Stem Cells Dayt. Ohio 31, 703–716. https://doi.org/10.1002/stem.1313.

Kenvin, S., Torregrosa-Muñumer, R., Reidelbach, M., Pennonen, J., Turkia, J.J., Rannila, E., Kvist, J., Sainio, M.T., Huber, N., Herukka, S.-K., Haapasalo, A., Auranen, M., Trokovic, R., Sharma, V., Ylikallio, E., Tyynismaa, H., 2022. Threshold of heteroplasmic truncating MT-ATP6 mutation in reprogramming, notch hyperactivation and motor neuron metabolism. Hum. Mol. Genet. 31, 958–974. https://doi.org/10.1093/hmg/ddab299.

Klein Gunnewiek, T.M., Van Hugte, E.J.H., Frega, M., Guardia, G.S., Foreman, K., Panneman, D., Mossink, B., Linda, K., Keller, J.M., Schubert, D., Cassiman, D., Rodenburg, R., Vidal Folch, N., Oglesbee, D., Perales-Clemente, E., Nelson, T.J., Morava, E., Nadif Kasri, N., Kozicz, T., 2020. M.3243A > G-induced mitochondrial dysfunction impairs human neuronal development and reduces neuronal network activity and synchronicity. Cell Rep. 31, 107538. https://doi.org/10.1016/j.celrep.2020.107538.

Klein Gunnewiek, T.M., Verboven, A.H.A., Pelgrim, I., Hogeweg, M., Schoenmaker, C., Renkema, H., Beyrath, J., Smeitink, J., de Vries, B.B.A., Hoen, P.-B.A.C.'.T., Kozicz, T., Nadif Kasri, N., 2021. Sonlicromanol improves neuronal network dysfunction and transcriptome changes linked to m.3243A>G heteroplasmy in iPSC-derived neurons. Stem Cell Rep. 16, 2197–2212. https://doi.org/10.1016/j.stemcr.2021.07.002.

Knottnerus, S.J.G., Bleeker, J.C., Wüst, R.C.I., Ferdinandusse, S., IJlst, L., Wijburg, F.A., Wanders, R.J.A., Visser, G., Houtkooper, R.H., 2018. Disorders of mitochondrial long-chain fatty acid oxidation and the carnitine shuttle. Rev. Endocr. Metab. Disord. 19, 93–106. https://doi.org/10.1007/s11154-018-9448-1.

Knottnerus, S.J.G., Mengarelli, I., Wüst, R.C.I., Baartscheer, A., Bleeker, J.C., Coronel, R., Ferdinandusse, S., Guan, K., IJlst, L., Li, W., Luo, X., Portero, V.M., Ulbricht, Y., Visser, G., Wanders, R.J.A., Wijburg, F.A., Verkerk, A.O., Houtkooper, R.H.,

Bezzina, C.R., 2020. Electrophysiological abnormalities in VLCAD deficient hiPSC-cardiomyocytes can be improved by lowering accumulation of fatty acid oxidation intermediates. Int. J. Mol. Sci. 21, 2589. https://doi.org/10.3390/ijms21072589.
Kobayashi, H., Hatakeyama, H., Nishimura, H., Yokota, M., Suzuki, S., Tomabechi, Y., Shirouzu, M., Osada, H., Mimaki, M., Goto, Y., Yoshida, M., 2021. Chemical reversal of abnormalities in cells carrying mitochondrial DNA mutations. Nat. Chem. Biol. 17, 335–343. https://doi.org/10.1038/s41589-020-00676-4.
Kodaira, M., Hatakeyama, H., Yuasa, S., Seki, T., Egashira, T., Tohyama, S., Kuroda, Y., Tanaka, A., Okata, S., Hashimoto, H., Kusumoto, D., Kunitomi, A., Takei, M., Kashimura, S., Suzuki, T., Yozu, G., Shimojima, M., Motoda, C., Hayashiji, N., Saito, Y., Goto, Y.-I., Fukuda, K., 2015. Impaired respiratory function in MELAS-induced pluripotent stem cells with high heteroplasmy levels. FEBS Open Bio 5, 219–225. https://doi.org/10.1016/j.fob.2015.03.008.
Koopman, W.J.H., Willems, P.H.G.M., Smeitink, J.A.M., 2012. Monogenic mitochondrial disorders. N. Engl. J. Med. 366, 1132–1141. https://doi.org/10.1056/NEJMra1012478.
Kovářová, N., Pecina, P., Nůsková, H., Vrbacký, M., Zeviani, M., Mráček, T., Viscomi, C., Houštěk, J., 2016. Tissue- and species-specific differences in cytochrome c oxidase assembly induced by SURF1 defects. Biochim. Biophys. Acta 1862, 705–715. https://doi.org/10.1016/j.bbadis.2016.01.007.
Lancaster, M.A., Renner, M., Martin, C.-A., Wenzel, D., Bicknell, L.S., Hurles, M.E., Homfray, T., Penninger, J.M., Jackson, A.P., Knoblich, J.A., 2013. Cerebral organoids model human brain development and microcephaly. Nature 501, 373–379. https://doi.org/10.1038/nature12517.
Lee, Y.-K., Ho, P.W.-L., Schick, R., Lau, Y.-M., Lai, W.-H., Zhou, T., Li, Y., Ng, K.-M., Ho, S.-L., Esteban, M.A., Binah, O., Tse, H.-F., Siu, C.-W., 2014. Modeling of Friedreich ataxia-related iron overloading cardiomyopathy using patient-specific-induced pluripotent stem cells. Pflugers Arch. 466, 1831–1844. https://doi.org/10.1007/s00424-013-1414-x.
Lee, Y.-K., Lau, Y.-M., Ng, K.-M., Lai, W.-H., Ho, S.-L., Tse, H.-F., Siu, C.-W., Ho, P.W.-L., 2016. Efficient attenuation of Friedreich's ataxia (FRDA) cardiomyopathy by modulation of iron homeostasis-human induced pluripotent stem cell (hiPSC) as a drug screening platform for FRDA. Int. J. Cardiol. 203, 964–971. https://doi.org/10.1016/j.ijcard.2015.11.101.
Lenaers, G., Neutzner, A., Le Dantec, Y., Jüschke, C., Xiao, T., Decembrini, S., Swirski, S., Kieninger, S., Agca, C., Kim, U.S., Reynier, P., Yu-Wai-Man, P., Neidhardt, J., Wissinger, B., 2021. Dominant optic atrophy: culprit mitochondria in the optic nerve. Prog. Retin. Eye Res. 83, 100935. https://doi.org/10.1016/j.preteyeres.2020.100935.
Lester Sequiera, G., Srivastava, A., Alagarsamy, K.N., Rockman-Greenberg, C., Dhingra, S., 2021. Generation and evaluation of isogenic iPSC as a source of cell replacement therapies in patients with Kearns Sayre syndrome. Cells 10, 568. https://doi.org/10.3390/cells10030568.
Li, S., Guo, J., Ying, Z., Chen, S., Yang, L., Chen, K., Long, Q., Qin, D., Pei, D., Liu, X., 2015a. Valproic acid-induced hepatotoxicity in Alpers syndrome is associated with mitochondrial permeability transition pore opening-dependent apoptotic sensitivity in an induced pluripotent stem cell model. Hepatol. Baltim. Md 61, 1730–1739. https://doi.org/10.1002/hep.27712.
Li, Y., Polak, U., Bhalla, A.D., Rozwadowska, N., Butler, J.S., Lynch, D.R., Dent, S.Y.R., Napierala, M., 2015b. Excision of expanded GAA repeats alleviates the molecular phenotype of Friedreich's Ataxia. Mol. Ther. J. Am. Soc. Gene Ther. 23, 1055–1065. https://doi.org/10.1038/mt.2015.41.
Li, S., Pan, H., Tan, C., Sun, Y., Song, Y., Zhang, X., Yang, W., Wang, X., Li, D., Dai, Y., Ma, Q., Xu, C., Zhu, X., Kang, L., Fu, Y., Xu, X., Shu, J., Zhou, N., Han, F., Qin, D., Huang, W., Liu, Z., Yan, Q., 2018. Mitochondrial dysfunctions contribute to hypertrophic cardiomyopathy in patient iPSC-derived cardiomyocytes with MT-RNR2 mutation. Stem Cell Rep. 10, 808–821. https://doi.org/10.1016/j.stemcr.2018.01.013.
Li, J., Rozwadowska, N., Clark, A., Fil, D., Napierala, J.S., Napierala, M., 2019. Excision of the expanded GAA repeats corrects cardiomyopathy phenotypes of iPSC-derived Friedreich's ataxia cardiomyocytes. Stem Cell Res. 40, 101529. https://doi.org/10.1016/j.scr.2019.101529.
Li, J., Lee, N., Chen, P., Lee, G.H., Wu, R., 2021. Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation: a novel DARS2 mutation and intra-familial heterogeneity. Mov. Disord. Clin. Pract. 8, 1116–1122. https://doi.org/10.1002/mdc3.13281.
Liang, K.X., Kristiansen, C.K., Mostafavi, S., Vatne, G.H., Zantingh, G.A., Kianian, A., Tzoulis, C., Høyland, L.E., Ziegler, M., Perez, R.M., Furriol, J., Zhang, Z., Balafkan, N., Hong, Y., Siller, R., Sullivan, G.J., Bindoff, L.A., 2020. Disease-specific phenotypes in iPSC-derived neural stem cells with POLG mutations. EMBO Mol. Med. 12, e12146. https://doi.org/10.15252/emmm.202012146.
Liang, K.X., Vatne, G.H., Kristiansen, C.K., Ievglevskyi, O., Kondratskaya, E., Glover, J.C., Chen, A., Sullivan, G.J., Bindoff, L.A., 2021. N-acetylcysteine amide ameliorates mitochondrial dysfunction and reduces oxidative stress in hiPSC-derived dopaminergic neurons with POLG mutation. Exp. Neurol. 337, 113536. https://doi.org/10.1016/j.expneurol.2020.113536.
Lim, A.Z., Ng, Y.S., Blain, A., Jiminez-Moreno, C., Alston, C.L., Nesbitt, V., Simmons, L., Santra, S., Wassmer, E., Blakely, E.L., Turnbull, D.M., Taylor, R.W., Gorman, G.S., McFarland, R., 2022. Natural history of Leigh syndrome: a study of disease burden and progression. Ann. Neurol. 91, 117–130. https://doi.org/10.1002/ana.26260.
Lin, D.-S., Huang, Y.-W., Ho, C.-S., Hung, P.-L., Hsu, M.-H., Wang, T.-J., Wu, T.-Y., Lee, T.-H., Huang, Z.-D., Chang, P.-C., Chiang, M.-F., 2019. Oxidative insults and mitochondrial DNA mutation promote enhanced autophagy and Mitophagy compromising cell viability in pluripotent cell model of mitochondrial disease. Cells 8, 65. https://doi.org/10.3390/cells8010065.
Lisowski, P., Kannan, P., Mlody, B., Prigione, A., 2018. Mitochondria and the dynamic control of stem cell homeostasis. EMBO Rep. 19, e45432. https://doi.org/10.15252/embr.201745432.
Lisowski, P., Lickfett, S., Rybak-Wolf, A., Menacho, C., Le, S., Pentimalli, T.M., Notopoulou, S., Dykstra, W., Oehler, D., Lopez-Calcerrada, S., Mlody, B., Otto, M., Wu, H., Richter, Y., Roth, P., Anand, R., Kulka, L.A.M., Meierhofer, D., Glazar, P., Legnini, I., Telugu, N.S., Hahn, T., Neuendorf, N., Miller, D.C., Boeddrich, A., Polzin, A., Mayatepek, E., Diecke, S., Olzscha, H., Kirstein, J., Ugalde, C., Petrakis, S., Cambridge, S., Rajewsky, N., Kuehn, R., Wanker, E.E., Priller, J., Metzger, J.J., Prigione, A., 2024. Mutant huntingtin impairs neurodevelopment in human brain organoids through CHCHD2-mediated neurometabolic failure. Nat. Commun. https://doi.org/10.1038/s41467-024-51216-w.
Liu, G., David, B.T., Trawczynski, M., Fessler, R.G., 2020. Advances in pluripotent stem cells: history, mechanisms, technologies, and applications. Stem Cell Rev. Rep. 16, 3–32. https://doi.org/10.1007/s12015-019-09935-x.
Liu, X., Wang, S., Guo, X., Li, Y., Ogurlu, R., Lu, F., Prondzynski, M., de la Serna Buzon, S., Ma, Q., Zhang, D., Wang, G., Cotton, J., Guo, Y., Xiao, L., Milan, D.J., Xu, Y., Schlame, M., Bezzerides, V.J., Pu, W.T., 2021. Increased reactive oxygen species-mediated Ca2+/calmodulin-dependent protein kinase II activation contributes to calcium handling abnormalities and impaired contraction in Barth syndrome. Circulation 143, 1894–1911. https://doi.org/10.1161/CIRCULATIONAHA.120.048698.
Lorenz, C., Lesimple, P., Bukowiecki, R., Zink, A., Inak, G., Mlody, B., Singh, M., Semtner, M., Mah, N., Auré, K., Leong, M., Zabiegalov, O., Lyras, E.-M., Pfiffer, V., Fauler, B., Eichhorst, J., Wiesner, B., Huebner, N., Priller, J., Mielke, T., Meierhofer, D., Izsvák, Z., Meier, J.C., Bouillaud, F., Adjaye, J., Schuelke, M., Wanker, E.E., Lombès, A., Prigione, A., 2017. Human iPSC-derived neural progenitors are an effective drug discovery model for neurological mtDNA disorders. Cell Stem Cell 20, 659–674.e9. https://doi.org/10.1016/j.stem.2016.12.013.
Ma, H., Folmes, C.D.L., Wu, J., Morey, R., Mora-Castilla, S., Ocampo, A., Ma, L., Poulton, J., Wang, X., Ahmed, R., Kang, E., Lee, Y., Hayama, T., Li, Y., Van Dyken, C., Gutierrez, N.M., Tippner-Hedges, R., Koski, A., Mitalipov, N., Amato, P., Wolf, D.P., Huang, T., Terzic, A., Laurent, L.C., Izpisua Belmonte, J.C., Mitalipov, S., 2015. Metabolic rescue in pluripotent cells from patients with mtDNA disease. Nature 524, 234–238. https://doi.org/10.1038/nature14546.
Mazzara, P.G., Muggeo, S., Luoni, M., Massimino, L., Zaghi, M., Valverde, P.T.-T., Brusco, S., Marzi, M.J., Palma, C., Colasante, G., Iannielli, A., Paulis, M., Cordiglieri, C., Giannelli, S.G., Podini, P., Gellera, C., Taroni, F., Nicassio, F., Rasponi, M., Broccoli, V., 2020. Frataxin gene editing rescues Friedreich's ataxia pathology in dorsal root ganglia organoid-derived sensory neurons. Nat. Commun. 11, 4178. https://doi.org/10.1038/s41467-020-17954-3.
McKnight, C.L., Low, Y.C., Elliott, D.A., Thorburn, D.R., Frazier, A.E., 2021. Modelling mitochondrial disease in human pluripotent stem cells: what have we learned? Int. J. Mol. Sci. 22, 7730. https://doi.org/10.3390/ijms22147730.
Menacho, C., Okawa, S., Álvarez-Merz, I., Wittich, A., Muñoz-Oreja, M., Lisowski, P., Pentimalli, T.M., Rybak-Wolf, A., Inak, G., Zakin, S., Thevandavakkam, M., Petersilie, L., Zaliani, A., Mlody, B., Seibt, A., Donnelly, J., Woleben, K., Fernandez-Checa, J., Herebian, D., Mayatepek, E., Rajewsky, N., Spinazzola, A., Schuelke, M., Perlstein, E., Rossi, A., Distelmaier, F., Holt, I.J., Pless, O., Rose, C.R., Sol, A.D., Prigione, A., 2024. Deep learning-driven neuromorphogenesis screenings identify repurposable drugs for mitochondrial disease. https://doi.org/10.1101/2024.07.08.602501.
Meshrkey, F., Cabrera Ayuso, A., Rao, R.R., Iyer, S., 2021. Quantitative analysis of mitochondrial morphologies in human induced pluripotent stem cells for Leigh syndrome. Stem Cell Res. 57, 102572. https://doi.org/10.1016/j.scr.2021.102572.
Meshrkey, F., Scheulin, K.M., Littlejohn, C.M., Stabach, J., Saikia, B., Thorat, V., Huang, Y., LaFramboise, T., Lesnefsky, E.J., Rao, R.R., West, F.D., Iyer, S., 2023. Induced pluripotent stem cells derived from patients carrying mitochondrial mutations exhibit altered bioenergetics and aberrant differentiation potential. Stem Cell Res Ther 14, 320. https://doi.org/10.1186/s13287-023-03546-7.
Miklas, J.W., Clark, E., Levy, S., Detraux, D., Leonard, A., Beussman, K., Showalter, M.R., Smith, A.T., Hofsteen, P., Yang, X., Macadangdang, J., Manninen, T., Raftery, D., Madan, A., Suomalainen, A., Kim, D.-H., Murry, C.E., Fiehn, O., Sniadecki, N.J., Wang, Y., Ruohola-Baker, H., 2019. TFPa/HADHA is required for fatty acid beta-oxidation and cardiolipin re-modeling in human cardiomyocytes. Nat. Commun. 10, 4671. https://doi.org/10.1038/s41467-019-12482-1.
Miressi, F., Benslimane, N., Favreau, F., Rassat, M., Richard, L., Bourthoumieu, S., Laroche, C., Magy, L., Magdelaine, C., Sturtz, F., Lia, A.-S., Faye, P.-A., 2021. GDAP1 involvement in mitochondrial function and oxidative stress, investigated in a Charcot-Marie-tooth model of hiPSCs-derived motor neurons. Biomedicines 9, 945. https://doi.org/10.3390/biomedicines9080945.
Mok, B.Y., de Moraes, M.H., Zeng, J., Bosch, D.E., Kotrys, A.V., Raguram, A., Hsu, F., Radey, M.C., Peterson, S.B., Mootha, V.K., Mougous, J.D., Liu, D.R., 2020. A bacterial cytidine deaminase toxin enables CRISPR-free mitochondrial base editing. Nature 583, 631–637. https://doi.org/10.1038/s41586-020-2477-4.
Mosqueira, D., Mannhardt, I., Bhagwan, J.R., Lis-Slimak, K., Katili, P., Scott, E., Hassan, M., Prondzynski, M., Harmer, S.C., Tinker, A., Smith, J.G.W., Carrier, L., Williams, P.M., Gaffney, D., Eschenhagen, T., Hansen, A., Denning, C., 2018. CRISPR/Cas9 editing in human pluripotent stem cell-cardiomyocytes highlights arrhythmias, hypocontractility, and energy depletion as potential therapeutic targets for hypertrophic cardiomyopathy. Eur. Heart J. 39, 3879–3892. https://doi.org/10.1093/eurheartj/ehy249.
Mou, Y., Mukte, S., Chai, E., Dein, J., Li, X.-J., 2020. Analyzing mitochondrial transport and morphology in human induced pluripotent stem cell-derived neurons in hereditary spastic paraplegia. J. Vis. Exp. JoVE. https://doi.org/10.3791/60548.

Nakamoto, F.K., Okamoto, S., Mitsui, J., Sone, T., Ishikawa, M., Yamamoto, Y., Kanegae, Y., Nakatake, Y., Imaizumi, K., Ishiura, H., Tsuji, S., Okano, H., 2018. The pathogenesis linked to coenzyme Q10 insufficiency in iPSC-derived neurons from patients with multiple-system atrophy. Sci. Rep. 8, 14215. https://doi.org/10.1038/s41598-018-32573-1.

Nakazeki, F., Tsuge, I., Horie, T., Imamura, K., Tsukita, K., Hotta, A., Baba, O., Kuwabara, Y., Nishino, T., Nakao, T., Nishiga, M., Nishi, H., Nakashima, Y., Ide, Y., Koyama, S., Kimura, M., Tsuji, S., Naitoh, M., Suzuki, S., Izumi, Y., Kawarai, T., Kaji, R., Kimura, T., Inoue, H., Ono, K., 2019. MiR-33a is a therapeutic target in SPG4-related hereditary spastic paraplegia human neurons. Clin. Sci. Lond. Engl. 1979 (133), 583–595. https://doi.org/10.1042/CS20180980.

Nanau, R.M., Neuman, M.G., 2013. Adverse drug reactions induced by valproic acid. Clin. Biochem. 46, 1323–1338. https://doi.org/10.1016/j.clinbiochem.2013.06.012.

Naviaux, R.K., Nguyen, K.V., 2004. POLG mutations associated with Alpers' syndrome and mitochondrial DNA depletion. Ann. Neurol. 55, 706–712. https://doi.org/10.1002/ana.20079.

Nesbitt, V., Pitceathly, R.D.S., Turnbull, D.M., Taylor, R.W., Sweeney, M.G., Mudanohwo, E.E., Rahman, S., Hanna, M.G., McFarland, R., 2013. The UK MRC Mitochondrial Disease Patient Cohort Study: clinical phenotypes associated with the m.3243A>G mutation–implications for diagnosis and management. J. Neurol. Neurosurg. Psychiatry 84, 936–938. https://doi.org/10.1136/jnnp-2012-303528.

Ng, Y.S., Turnbull, D.M., 2016. Mitochondrial disease: genetics and management. J. Neurol. 263, 179–191. https://doi.org/10.1007/s00415-015-7884-3.

Ni, P., Ma, Y., Chung, S., 2022. Mitochondrial dysfunction in psychiatric disorders. Schizophr. Res. S0920-9964 (22), 00333–00334. https://doi.org/10.1016/j.schres.2022.08.027.

Nie, Z., Wang, C., Chen, J., Ji, Y., Zhang, H., Zhao, F., Zhou, X., Guan, M.-X., 2023. Abnormal morphology and function in retinal ganglion cells derived from patients-specific iPSCs generated from individuals with Leber's hereditary optic neuropathy. Hum. Mol. Genet. 32, 231–243. https://doi.org/10.1093/hmg/ddac190.

Nishigaki, Y., Martí, R., Copeland, W.C., Hirano, M., 2003. Site-specific somatic mitochondrial DNA point mutations in patients with thymidine phosphorylase deficiency. J. Clin. Invest. 111, 1913–1921. https://doi.org/10.1172/JCI17828.

Norat, P., Soldozy, S., Sokolowski, J.D., Gorick, C.M., Kumar, J.S., Chae, Y., Yağmurlu, K., Prada, F., Walker, M., Levitt, M.R., Price, R.J., Tvrdik, P., Kalani, M.Y. S., 2020. Mitochondrial dysfunction in neurological disorders: exploring mitochondrial transplantation. Npj Regen. Med. 5, 1–9. https://doi.org/10.1038/s41536-020-00107-x.

Pacitti, D., Bax, B.E., 2018. The development of an in vitro cerebral organoid model for investigating the pathomolecular mechanisms associated with the central nervous system involvement in mitochondrial Neurogastrointestinal Encephalomyopathy (MNGIE). Nucleosides Nucleotides Nucleic Acids 37, 603–617. https://doi.org/10.1080/15257770.2018.1492139.

Palombo, F., Peron, C., Caporali, L., Iannielli, A., Maresca, A., Di Meo, I., Fiorini, C., Segnali, A., Sciacca, F.L., Rizzo, A., Levi, S., Suomalainen, A., Prigione, A., Broccoli, V., Carelli, V., Tiranti, V., 2021. The relevance of mitochondrial DNA variants fluctuation during reprogramming and neuronal differentiation of human iPSCs. Stem Cell Rep. 16, 1953–1967. https://doi.org/10.1016/j.stemcr.2021.06.016.

Park, J.-C., Park, M.J., Lee, S.-Y., Kim, D., Kim, K.-T., Jang, H.-K., Cha, H.-J., 2023. Gene editing with 'pencil' rather than 'scissors' in human pluripotent stem cells. Stem Cell Res Ther 14, 164. https://doi.org/10.1186/s13287-023-03394-5.

Pavlakis, S.G., Phillips, P.C., DiMauro, S., De Vivo, D.C., Rowland, L.P., 1984. Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes: a distinctive clinical syndrome. Ann. Neurol. 16, 481–488. https://doi.org/10.1002/ana.410160409.

Pek, N.M.Q., Phua, Q.H., Ho, B.X., Pang, J.K.S., Hor, J.-H., An, O., Yang, H.H., Yu, Y., Fan, Y., Ng, S.-Y., Soh, B.-S., 2019. Mitochondrial 3243A>G mutation confers pro-atherogenic and pro-inflammatory properties in MELAS iPS derived endothelial cells. Cell Death Dis. 10, 802. https://doi.org/10.1038/s41419-019-2036-9.

Perales-Clemente, E., Cook, A.N., Evans, J.M., Roellinger, S., Secreto, F., Emmanuele, V., Oglesbee, D., Mootha, V.K., Hirano, M., Schon, E.A., Terzic, A., Nelson, T.J., 2016. Natural underlying mtDNA heteroplasmy as a potential source of intra-person hiPSC variability. EMBO J. 35, 1979–1990. https://doi.org/10.15252/embj.201694892.

Pérez, M.J., Ivanyuk, D., Panagiotakopoulou, V., Di Napoli, G., Kalb, S., Brunetti, D., Al-Shaana, R., Kaeser, S.A., Fraschka, S.A.-K., Jucker, M., Zeviani, M., Viscomi, C., Deleidi, M., 2021. Loss of function of the mitochondrial peptidase PITRM1 induces proteotoxic stress and Alzheimer's disease-like pathology in human cerebral organoids. Mol. Psychiatry 26, 5733–5750. https://doi.org/10.1038/s41380-020-0807-4.

Pérez-Brangulí, F., Buchsbaum, I.Y., Pozner, T., Regensburger, M., Fan, W., Schray, A., Börstler, T., Mishra, H., Gräf, D., Kohl, Z., Winkler, J., Berninger, B., Cappello, S., Winner, B., 2019. Human SPG11 cerebral organoids reveal cortical neurogenesis impairment. Hum. Mol. Genet. 28, 961–971. https://doi.org/10.1093/hmg/ddy397.

Perez-Siles, G., Cutrupi, A., Ellis, M., Screnci, R., Mao, D., Uesugi, M., Yiu, E.M., Ryan, M. M., Choi, B.O., Nicholson, G., Kennerson, M.L., 2020. Energy metabolism and mitochondrial defects in X-linked Charcot-Marie-tooth (CMTX6) iPSC-derived motor neurons with the p.R158H PDK3 mutation. Sci. Rep. 10, 9262. https://doi.org/10.1038/s41598-020-66266-5.

Perrottelli, A., Marzocchi, F.F., Caporusso, E., Giordano, G.M., Giuliani, L., Melillo, A., Pezzella, P., Bucci, P., Mucci, A., Galderisi, S., 2024. Advances in the understanding of the pathophysiology of schizophrenia and bipolar disorder through induced pluripotent stem cell models. J. Psychiatry Neurosci. JPN 49, E109. https://doi.org/10.1503/jpn.230112.

Pfeffer, G., Horvath, R., Klopstock, T., Mootha, V.K., Suomalainen, A., Koene, S., Hirano, M., Zeviani, M., Bindoff, L.A., Yu-Wai-Man, P., Hanna, M., Carelli, V., McFarland, R., Majamaa, K., Turnbull, D.M., Smeitink, J., Chinnery, P.F., 2013. New treatments for mitochondrial disease-no time to drop our standards. Nat. Rev. Neurol. 9, 474–481. https://doi.org/10.1038/nrneurol.2013.129.

Picard, M., Shirihai, O.S., 2022. Mitochondrial signal transduction. Cell Metab. 34, 1620–1653. https://doi.org/10.1016/j.cmet.2022.10.008.

Pitceathly, R.D.S., Rahman, S., Hanna, M.G., 2012. Single deletions in mitochondrial DNA–molecular mechanisms and disease phenotypes in clinical practice. Neuromuscul. Disord. NMD 22, 577–586. https://doi.org/10.1016/j.nmd.2012.03.009.

Pitrez, P.R., Monteiro, L.M., Borgogno, O., Nissan, X., Mertens, J., Ferreira, L., 2024. Cellular reprogramming as a tool to model human aging in a dish. Nat. Commun. 15, 1816. https://doi.org/10.1038/s41467-024-46004-5.

Pozner, T., Schray, A., Regensburger, M., Lie, D.C., Schlötzer-Schrehardt, U., Winkler, J., Turan, S., Winner, B., 2018. Tideglusib rescues neurite pathology of SPG11 iPSC derived cortical neurons. Front. Neurosci. 12, 914. https://doi.org/10.3389/fnins.2018.00914.

Prigione, A., Fauler, B., Lurz, R., Lehrach, H., Adjaye, J., 2010. The senescence-related mitochondrial/oxidative stress pathway is repressed in human induced pluripotent stem cells. Stem Cells Dayt. Ohio 28, 721–733. https://doi.org/10.1002/stem.404.

Prigione, A., Lichtner, B., Kuhl, H., Struys, E.A., Wamelink, M., Lehrach, H., Ralser, M., Timmermann, B., Adjaye, J., 2011. Human induced pluripotent stem cells harbor homoplasmic and heteroplasmic mitochondrial DNA mutations while maintaining human embryonic stem cell-like metabolic reprogramming. Stem Cells Dayt. Ohio 29, 1338–1348. https://doi.org/10.1002/stem.683.

Qiu, Y., Wang, H., Fan, M., Pan, H., Guan, J., Jiang, Y., Jia, Z., Wu, K., Zhou, H., Zhuang, Q., Lei, Z., Ding, X., Cai, H., Dong, Y., Yan, L., Lin, A., Fu, Y., Zhang, D., Yan, Q., Wang, Q., 2023. Impaired AIF-CHCHD4 interaction and mitochondrial calcium overload contribute to auditory neuropathy spectrum disorder in patient-iPSC-derived neurons with AIFM1 variant. Cell Death Dis. 14, 375. https://doi.org/10.1038/s41419-023-05899-6.

Rahman, S., 2023. Leigh syndrome. Handb. Clin. Neurol. 194, 43–63. https://doi.org/10.1016/B978-0-12-821751-1.00015-4.

Retter, I., Behm, L., Grohmann, L., Schmelz, K., Rosowski, J., Hippenstiel, S., 2024. 3R centres contributions to change animal experimentation. EMBO Rep. 25, 4105–4109. https://doi.org/10.1038/s44319-024-00262-y.

Rizzo, F., Ronchi, D., Salani, S., Nizzardo, M., Fortunato, F., Bordoni, A., Stuppia, G., Del Bo, R., Piga, D., Fato, R., Bresolin, N., Comi, G.P., Corti, S., 2016. Selective mitochondrial depletion, apoptosis resistance, and increased mitophagy in human Charcot-Marie-tooth 2A motor neurons. Hum. Mol. Genet. 25, 4266–4281. https://doi.org/10.1093/hmg/ddw258.

Rodger, C.E., McWilliams, T.G., Ganley, I.G., 2017. Mammalian mitophagy – from in vitro molecules to in vivo models. FEBS J. 285, 1185. https://doi.org/10.1111/febs.14336.

Rohani, L., Machiraju, P., Sabouny, R., Meng, G., Liu, S., Zhao, T., Iqbal, F., Wang, X., Ravandi, A., Wu, J.C., Khan, A., Shutt, T., Rancourt, D., Greenway, S.C., 2020. Reversible mitochondrial fragmentation in iPSC-derived cardiomyocytes from children with DCMA, a mitochondrial cardiomyopathy. Can. J. Cardiol. 36, 554–563. https://doi.org/10.1016/j.cjca.2019.09.021.

Romero-Morales, A.I., Robertson, G.L., Rastogi, A., Rasmussen, M.L., Temuri, H., McElroy, G.S., Chakrabarty, R.P., Hsu, L., Almonacid, P.M., Millis, B.A., Chandel, N. S., Cartailler, J.-P., Gama, V., 2022. Human iPSC-derived cerebral organoids model features of Leigh syndrome and reveal abnormal corticogenesis. Dev. Camb. Engl. 149, dev199914. https://doi.org/10.1242/dev.199914.

Romero-Moya, D., Castaño, J., Santos-Ocaña, C., Navas, P., Menendez, P., 2017. Generation, genome edition and characterization of iPSC lines from a patient with coenzyme Q10 deficiency harboring a heterozygous mutation in COQ4 gene. Stem Cell Res. 24, 144–147. https://doi.org/10.1016/j.scr.2016.09.007.

Rossi, G., Manfrin, A., Lutolf, M.P., 2018. Progress and potential in organoid research. Nat. Rev. Genet. 19, 671–687. https://doi.org/10.1038/s41576-018-0051-9.

Rossi, A., Lickfett, S., Martins, S., Prigione, A., 2022. A call for consensus guidelines on monitoring the integrity of nuclear and mitochondrial genomes in human pluripotent stem cells. Stem Cell Rep. 17, 707–710. https://doi.org/10.1016/j.stemcr.2022.01.019.

Rowe, R.G., Daley, G.Q., 2019. Induced pluripotent stem cells in disease modelling and drug discovery. Nat. Rev. Genet. 20, 377–388. https://doi.org/10.1038/s41576-019-0100-z.

Russell, O.M., Gorman, G.S., Lightowlers, R.N., Turnbull, D.M., 2020. Mitochondrial diseases: Hope for the future. Cell 181, 168–188. https://doi.org/10.1016/j.cell.2020.02.051.

Ryytty, S., Modi, S.R., Naumenko, N., Shakirzyanova, A., Rahman, M.O., Vaara, M., Suomalainen, A., Tavi, P., Hämäläinen, R.H., 2022. Varied responses to a high m.3243A>G mutation load and respiratory chain dysfunction in patient-derived cardiomyocytes. Cells 11, 2593. https://doi.org/10.3390/cells11162593.

Saporta, M.A., Dang, V., Volfson, D., Zou, B., Xie, X.S., Adebola, A., Liem, R.K., Shy, M., Dimos, J.T., 2015. Axonal Charcot-Marie-tooth disease patient-derived motor neurons demonstrate disease-specific phenotypes including abnormal electrophysiological properties. Exp. Neurol. 263, 190–199. https://doi.org/10.1016/j.expneurol.2014.10.005.

Sequiera, G.L., Srivastava, A., Sareen, N., Yan, W., Alagarsamy, K.N., Verma, E., Aghanoori, M.R., Aliani, M., Kumar, A., Fernyhough, P., Rockman-Greenberg, C., Dhingra, S., 2022. Development of iPSC-based clinical trial selection platform for patients with ultrarare diseases. Sci. Adv. 8, eabl4370. https://doi.org/10.1126/sciadv.abl4370.

Sercel, A.J., Carlson, N.M., Patananan, A.N., Teitell, M.A., 2021. Mitochondrial DNA dynamics in reprogramming to pluripotency. Trends Cell Biol. 31, 311–323. https://doi.org/10.1016/j.tcb.2020.12.009.
Shi, Y., Inoue, H., Wu, J.C., Yamanaka, S., 2017. Induced pluripotent stem cell technology: a decade of progress. Nat. Rev. Drug Discov. 16, 115–130. https://doi.org/10.1038/nrd.2016.245.
Shoffner, J.M., Wallace, D.C., 1992. Mitochondrial genetics: principles and practice. Am. J. Hum. Genet. 51, 1179–1186.
Silva-Pinheiro, P., Minczuk, M., 2022. The potential of mitochondrial genome engineering. Nat. Rev. Genet. 23, 199–214. https://doi.org/10.1038/s41576-021-00432-x.
Silva-Pinheiro, P., Mutti, C.D., Van Haute, L., Powell, C.A., Nash, P.A., Turner, K., Minczuk, M., 2023. A library of base editors for the precise ablation of all protein-coding genes in the mouse mitochondrial genome. Nat. Biomed. Eng. 7, 692–703. https://doi.org/10.1038/s41551-022-00968-1.
Sladen, P.E., Perdigão, P.R.L., Salsbury, G., Novoselova, T., van der Spuy, J., Chapple, J. P., Yu-Wai-Man, P., Cheetham, M.E., 2021. CRISPR-Cas9 correction of OPA1 c.1334G>a: p.R445H restores mitochondrial homeostasis in dominant optic atrophy patient-derived iPSCs. Mol. Ther. Nucleic Acids 26, 432–443. https://doi.org/10.1016/j.omtn.2021.08.015.
Sladen, P.E., Jovanovic, K., Guarascio, R., Ottaviani, D., Salsbury, G., Novoselova, T., Chapple, J.P., Yu-Wai-Man, P., Cheetham, M.E., 2022. Modelling autosomal dominant optic atrophy associated with OPA1 variants in iPSC-derived retinal ganglion cells. Hum. Mol. Genet. 31, 3478–3493. https://doi.org/10.1093/hmg/ddac128.
Song, Y.R., Liu, Z., Gu, S.L., Qian, L.J., Yan, Q.F., 2011. [advances in the molecular pathogenesis of hypertrophic cardiomyopathy]. Yi Chuan Hered. Zhongguo Yi Chuan Xue Hui Bian Ji 33, 549–557. https://doi.org/10.3724/SP.J.1005.2011.00549.
Soragni, E., Miao, W., Iudicello, M., Jacoby, D., De Mercanti, S., Clerico, M., Longo, F., Piga, A., Ku, S., Campau, E., Du, J., Penalver, P., Rai, M., Madara, J.C., Nazor, K., O'Connor, M., Maximov, A., Loring, J.F., Pandolfo, M., Durelli, L., Gottesfeld, J.M., Rusche, J.R., 2014. Epigenetic therapy for Friedreich ataxia. Ann. Neurol. 76, 489–508. https://doi.org/10.1002/ana.24260.
Stewart, J.B., 2021. Current progress with mammalian models of mitochondrial DNA disease. J. Inherit. Metab. Dis. 44, 325–342. https://doi.org/10.1002/jimd.12324.
Stewart, J.B., Chinnery, P.F., 2015. The dynamics of mitochondrial DNA heteroplasmy: implications for human health and disease. Nat. Rev. Genet. 16, 530–542. https://doi.org/10.1038/nrg3966.
Synofzik, M., Puccio, H., Mochel, F., Schöls, L., 2019. Autosomal recessive cerebellar ataxias: paving the way toward targeted molecular therapies. Neuron 101, 560–583. https://doi.org/10.1016/j.neuron.2019.01.049.
Szigeti, K., Sule, N., Adesina, A.M., Armstrong, D.L., Saifi, G.M., Bonilla, E., Hirano, M., Lupski, J.R., 2004. Increased blood-brain barrier permeability with thymidine phosphorylase deficiency. Ann. Neurol. 56, 881–886. https://doi.org/10.1002/ana.20302.
Takahashi, K., Tanabe, K., Ohnuki, M., Narita, M., Ichisaka, T., Tomoda, K., Yamanaka, S., 2007. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 131, 861–872. https://doi.org/10.1016/j.cell.2007.11.019.
Taylor, W.A., Mejia, E.M., Mitchell, R.W., Choy, P.C., Sparagna, G.C., Hatch, G.M., 2012. Human trifunctional protein alpha links Cardiolipin remodeling to Beta-oxidation. PLoS One 7, e48628. https://doi.org/10.1371/journal.pone.0048628.
Tesson, C., Koht, J., Stevanin, G., 2015. Delving into the complexity of hereditary spastic paraplegias: how unexpected phenotypes and inheritance modes are revolutionizing their nosology. Hum. Genet. 134, 511–538. https://doi.org/10.1007/s00439-015-1536-7.
Tiranti, V., Hoertnagel, K., Carrozzo, R., Galimberti, C., Munaro, M., Granatiero, M., Zelante, L., Gasparini, P., Marzella, R., Rocchi, M., Bayona-Bafaluy, M.P., Enriquez, J.A., Uziel, G., Bertini, E., Dionisi-Vici, C., Franco, B., Meitinger, T., Zeviani, M., 1998. Mutations of SURF-1 in Leigh disease associated with cytochrome c oxidase deficiency. Am. J. Hum. Genet. 63, 1609–1621. https://doi.org/10.1086/302150.
Tolle, I., Tiranti, V., Prigione, A., 2023. Modeling mitochondrial DNA diseases: from base editing to pluripotent stem-cell-derived organoids. EMBO Rep. 24, e55678. https://doi.org/10.15252/embr.202255678.
Trevisson, E., Dimauro, S., Navas, P., Salviati, L., 2011. Coenzyme Q deficiency in muscle. Curr. Opin. Neurol. 24, 449–456. https://doi.org/10.1097/WCO.0b013e32834ab528.
Tyynismaa, H., Suomalainen, A., 2009. Mouse models of mitochondrial DNA defects and their relevance for human disease. EMBO Rep. 10, 137–143. https://doi.org/10.1038/embor.2008.242.
Vafai, S.B., Mootha, V.K., 2012. Mitochondrial disorders as windows into an ancient organelle. Nature 491, 374–383. https://doi.org/10.1038/nature11707.
van der Oost, J., Patinios, C., 2023. The genome editing revolution. Trends Biotechnol. 40th anniversary 41, 396–409. https://doi.org/10.1016/j.tibtech.2022.12.022. Special issue:
van der Ploeg, A.T., Reuser, A.J.J., 2008. Pompe's disease. Lancet Lond. Engl. 372, 1342–1353. https://doi.org/10.1016/S0140-6736(08)61555-X.
Van Lent, J., Verstraelen, P., Asselbergh, B., Adriaenssens, E., Mateiu, L., Verbist, C., De Winter, V., Eggermont, K., Van Den Bosch, L., De Vos, W.H., Timmerman, V., 2021. Induced pluripotent stem cell-derived motor neurons of CMT type 2 patients reveal progressive mitochondrial dysfunction. Brain J. Neurol. 144, 2471–2485. https://doi.org/10.1093/brain/awab226.
Varum, S., Rodrigues, A.S., Moura, M.B., Momcilovic, O., Easley, C.A., Ramalho-Santos, J., Van Houten, B., Schatten, G., 2011. Energy metabolism in human pluripotent stem cells and their differentiated counterparts. PLoS One 6, e20914. https://doi.org/10.1371/journal.pone.0020914.
Vera, E., Bosco, N., Studer, L., 2016. Generating late-onset human iPSC-based disease models by inducing neuronal age-related phenotypes through telomerase manipulation. Cell Rep. 17, 1184–1192. https://doi.org/10.1016/j.celrep.2016.09.062.
Verkerk, A.O., Knottnerus, S.J.G., Portero, V., Bleeker, J.C., Ferdinandusse, S., Guan, K., IJlst, L., Visser, G., Wanders, R.J.A., Wijburg, F.A., Bezzina, C.R., Mengarelli, I., Houtkooper, R.H., 2020. Electrophysiological abnormalities in VLCAD deficient hiPSC-cardiomyocytes do not improve with carnitine supplementation. Front. Pharmacol. 11, 616834. https://doi.org/10.3389/fphar.2020.616834.
Vögtle, F.-N., Brändl, B., Larson, A., Pendziwiat, M., Friederich, M.W., White, S.M., Basinger, A., Kücükköse, C., Muhle, H., Jähn, J.A., Keminer, O., Helbig, K.L., Delto, C.F., Myketin, L., Mossmann, D., Burger, N., Miyake, N., Burnett, A., van Baalen, A., Lovell, M.A., Matsumoto, N., Walsh, M., Yu, H.-C., Shinde, D.N., Stephani, U., Van Hove, J.L.K., Müller, F.-J., Helbig, I., 2018. Mutations in PMPCB encoding the catalytic subunit of the mitochondrial Presequence protease cause neurodegeneration in early childhood. Am. J. Hum. Genet. 102, 557–573. https://doi.org/10.1016/j.ajhg.2018.02.014.
Wali, G., Li, Y., Liyanage, E., Kumar, K.R., Day, M.L., Sue, C.M., 2023. Pharmacological rescue of mitochondrial and neuronal defects in SPG7 hereditary spastic paraplegia patient neurons using high throughput assays. Front. Neurosci. 17, 1231584. https://doi.org/10.3389/fnins.2023.1231584.
Wallace, D.C., 1999. Mitochondrial diseases in man and mouse. Science 283, 1482–1488. https://doi.org/10.1126/science.283.5407.1482.
Wallace, D.C., Singh, G., Lott, M.T., Hodge, J.A., Schurr, T.G., Lezza, A.M., Elsas, L.J., Nikoskelainen, E.K., 1988. Mitochondrial DNA mutation associated with Leber's hereditary optic neuropathy. Science 242, 1427–1430. https://doi.org/10.1126/science.3201231.
Wang, G., McCain, M.L., Yang, L., He, A., Pasqualini, F.S., Agarwal, A., Yuan, H., Jiang, D., Zhang, D., Zangi, L., Geva, J., Roberts, A.E., Ma, Q., Ding, J., Chen, J., Wang, D.-Z., Li, K., Wang, J., Wanders, R.J.A., Kulik, W., Vaz, F.M., Laflamme, M.A., Murry, C.E., Chien, K.R., Kelley, R.I., Church, G.M., Parker, K.K., Pu, W.T., 2014. Modeling the mitochondrial cardiomyopathy of Barth syndrome with induced pluripotent stem cell and heart-on-chip technologies. Nat. Med. 20, 616–623. https://doi.org/10.1038/nm.3545.
Wei, W., Gaffney, D.J., Chinnery, P.F., 2021. Cell reprogramming shapes the mitochondrial DNA landscape. Nat. Commun. 12, 5241. https://doi.org/10.1038/s41467-021-25482-x.
Weissig, V., 2020. Drug development for the therapy of mitochondrial diseases. Trends Mol. Med. 26, 40–57. https://doi.org/10.1016/j.molmed.2019.09.002.
Winanto, Khong Z.J., Soh, B.-S., Fan, Y., Ng, S.-Y., 2020. Organoid cultures of MELAS neural cells reveal hyperactive notch signaling that impacts neurodevelopment. Cell Death Dis. 11, 182. https://doi.org/10.1038/s41419-020-2383-6.
Wischhof, L., Scifo, E., Ehninger, D., Bano, D., 2022. AIFM1 beyond cell death: An overview of this OXPHOS-inducing factor in mitochondrial diseases. EBioMedicine 83, 104231. https://doi.org/10.1016/j.ebiom.2022.104231.
Wong, R.C.B., Lim, S.Y., Hung, S.S.C., Jackson, S., Khan, S., Van Bergen, N.J., De Smit, E., Liang, H.H., Kearns, L.S., Clarke, L., Mackey, D.A., Hewitt, A.W., Trounce, I.A., Pébay, A., 2017. Mitochondrial replacement in an iPSC model of Leber's hereditary optic neuropathy. Aging 9, 1341–1350. https://doi.org/10.18632/aging.101231.
Wong, A.O.-T., Wong, G., Shen, M., Chow, M.Z.-Y., Tse, W.W., Gurung, B., Mak, S.Y., Lieu, D.K., Costa, K.D., Chan, C.W., Martelli, A., Nabhan, J.F., Li, R.A., 2019. Correlation between frataxin expression and contractility revealed by in vitro Friedreich's ataxia cardiac tissue models engineered from human pluripotent stem cells. Stem Cell Res Ther 10, 203. https://doi.org/10.1186/s13287-019-1305-y.
Wu, Y.-R., Wang, A.-G., Chen, Y.-T., Yarmishyn, A.A., Buddhakosai, W., Yang, T.-C., Hwang, D.-K., Yang, Y.-P., Shen, C.-N., Lee, H.-C., Chiou, S.-H., Peng, C.-H., Chen, S.-J., 2018. Bioactivity and gene expression profiles of hiPSC-generated retinal ganglion cells in MT-ND4 mutated Leber's hereditary optic neuropathy. Exp. Cell Res. 363, 299–309. https://doi.org/10.1016/j.yexcr.2018.01.020.
Yahata, N., Matsumoto, Y., Omi, M., Yamamoto, N., Hata, R., 2017. TALEN-mediated shift of mitochondrial DNA heteroplasmy in MELAS-iPSCs with m.13513G>a mutation. Sci. Rep. 7, 15557. https://doi.org/10.1038/s41598-017-15871-y.
Yang, Y., Wu, H., Kang, X., Liang, Y., Lan, T., Li, T., Tan, T., Peng, J., Zhang, Q., An, G., Liu, Y., Yu, Q., Ma, Z., Lian, Y., Soh, B.S., Chen, Q., Liu, P., Chen, Y., Sun, X., Li, R., Zhen, X., Liu, P., Yu, Y., Li, X., Fan, Y., 2018. Targeted elimination of mutant mitochondrial DNA in MELAS-iPSCs by mitoTALENs. Protein Cell 9, 283–297. https://doi.org/10.1007/s13238-017-0499-y.
Yang, Y.-P., Nguyen, P.N.N., Lin, T.-C., Yarmishyn, A.A., Chen, W.-S., Hwang, D.-K., Chiou, G.-Y., Lin, T.-W., Chien, C.-S., Tsai, C.-Y., Chiou, S.-H., Chen, S.-J., Peng, C.-H., Hsu, C.-C., 2019. Glutamate stimulation dysregulates AMPA receptors-induced signal transduction pathway in Leber's inherited optic neuropathy patient-specific hiPSC-derived retinal ganglion cells. Cells 8, 625. https://doi.org/10.3390/cells8060625.
Yang, T.-C., Yarmishyn, A.A., Yang, Y.-P., Lu, P.-C., Chou, S.-J., Wang, M.-L., Lin, T.-C., Hwang, D.-K., Chou, Y.-B., Chen, S.-J., Yu, W.-K., Wang, A.-G., Hsu, C.-C., Chiou, S.-H., 2020. Mitochondrial transport mediates survival of retinal ganglion cells in affected LHON patients. Hum. Mol. Genet. 29, 1454–1464. https://doi.org/10.1093/hmg/ddaa063.
Yokota, M., Hatakeyama, H., Okabe, S., Ono, Y., Goto, Y., 2015. Mitochondrial respiratory dysfunction caused by a heteroplasmic mitochondrial DNA mutation blocks cellular reprogramming. Hum. Mol. Genet. 24, 4698–4709. https://doi.org/10.1093/hmg/ddv201.

Yokota, M., Hatakeyama, H., Ono, Y., Kanazawa, M., Goto, Y.-I., 2017. Mitochondrial respiratory dysfunction disturbs neuronal and cardiac lineage commitment of human iPSCs. Cell Death Dis. 8, e2551. https://doi.org/10.1038/cddis.2016.484.

Yoon, J.-Y., Daneshgar, N., Chu, Y., Chen, B., Hefti, M., Vikram, A., Irani, K., Song, L.-S., Brenner, C., Abel, E.D., London, B., Dai, D.-F., 2022. Metabolic rescue ameliorates mitochondrial encephalo-cardiomyopathy in murine and human iPSC models of Leigh syndrome. Clin. Transl. Med. 12, e954. https://doi.org/10.1002/ctm2.954.

Yu-Wai-Man, P., Turnbull, D.M., Chinnery, P.F., 2002. Leber hereditary optic neuropathy. J. Med. Genet. 39, 162–169. https://doi.org/10.1136/jmg.39.3.162.

Zheng, X., Boyer, L., Jin, M., Kim, Y., Fan, W., Bardy, C., Berggren, T., Evans, R.M., Gage, F.H., Hunter, T., 2016. Alleviation of neuronal energy deficiency by mTOR inhibition as a treatment for mitochondria-related neurodegeneration. eLife 5, e13378. https://doi.org/10.7554/eLife.13378.

Zhu, P.-P., Denton, K.R., Pierson, T.M., Li, X.-J., Blackstone, C., 2014. Pharmacologic rescue of axon growth defects in a human iPSC model of hereditary spastic paraplegia SPG3A. Hum. Mol. Genet. 23, 5638–5648. https://doi.org/10.1093/hmg/ddu280.