Mitochondrial Disorders

Subjects: Neurosciences

Contributor: Parthena F. Foltopoulou, Androulla N. Miliotou, Alexandra Ingendoh-Tsakmakidis, Asterios S. Tsiftsoglou, Ioannis S. Vizirianakis, Ioannis S. Pappas, Lefkothea C. Papadopoulou

Mitochondrial disorders represent a heterogeneous group of genetic disorders with variations in severity and clinical outcomes, mostly characterized by respiratory chain dysfunction and abnormal mitochondrial function. More specifically, mutations in the human *synthesis of cytochrome c oxidase 2* (*SCO2*) gene, encoding the mitochondrial inner membrane Sco2 cytochrome *c* oxidase (COX) assembly protein, have been implicated in the mitochondrial disorder fatal infantile cardioencephalomyopathy with COX deficiency.

Keywords: Sco2 ; COX deficiency ; mitochondria ; mitochondrial disorders ; encephalomyopathies ; cardiac hypertrophy

1. Mitochondria: Characteristics and Function

It has been over 150 years since the discovery of the mitochondrion, the double-membrane intracellular organelle with critical roles in multiple cellular and metabolic pathways [1][2]. Still, the interest for medicinal applications targeting deficiency of their function has mostly been undertaken for the last three (3) decades.

These essential semi-autonomous organelles consist of two membranes, i.e., the outer (OMM) and the inner (IMM) mitochondrial membrane, separated by a small intermembrane soluble space (IMS). The two membranes have different architecture and permeability properties, where the OMM allows the passage of small proteins and ions, while the IMM is more restricted towards permeabilization. The IMM folds over many times and creates layered structures called cristae, which extend into the interior soluble compartment (the matrix) of the organelle [3][4]. The main function of mitochondria in eukaryotic cells is the production of chemical energy through the oxidative phosphorylation (OXPHOS) pathway [5][6]. This metabolic energy-generating pathway is embedded in the inner mitochondrial membrane and under normal physiological conditions produces more than 90% of the cellular energy. Moreover, in the matrix, metabolic pathways such as the β-oxidation of fatty acids, the tricarboxylic acid cycle (TCA or citric acid cycle or Krebs cycle), as well the urea cycle take place. Other cellular processes in which mitochondria are implicated include the initiation of apoptosis (programmed cell death) [7][8], calcium homeostasis [9], heme and iron–sulfur cluster biosynthesis [10], amino acid and lipid metabolism [11], and generation of reactive oxygen species (ROS) [12][13].

Mitochondria are highly dynamic organelles with their own set of DNA, called mitochondrial DNA (mtDNA), of which each mitochondrion in humans can have two to ten copies of circular DNA. It is widely believed that these organelles were once primitive bacteria with their own DNA that were swallowed up by larger cells more than a billion years ago. As these bacteria and their host cells evolved, they developed a co-dependent relationship [14]. Through evolution, many of the mitochondrial genes either were lost or transferred to nucleus [15]; thus, the mitochondrial proteome is derived from both mitochondrial and nuclear DNA (nDNA). mtDNA is a highly compact, circular, double-stranded, haploid DNA strand molecule of 16,569 base pairs (bp) in humans, lacking introns and containing 37 genes that encode 13 structural subunits of the OXPHOS system (complexes I, III, IV, and V) and 22 tRNAs necessary for intramitochondrial protein synthesis and the small (12S) and large (16S) ribosomal RNAs (rRNAs) [16]. The organization of the mammalian mitochondrial genome is highly conserved [17], while only 3% of the mtDNA (the D-loop area of the 1.1 kilobases (kb) in humans) is a non-coding region and contains elements crucial for its replication and transcription [18]. The mitochondrial DNA is replicated, transcribed, and translated within the matrix space, with a modified mitochondrial genetic code differing from the universal one in four codons [19], and it is maternally inherited [20].

The number of mitochondria in cells varies between organisms, tissues, and cell types and depends mainly on their metabolic needs. These numbers range per cell from a single large mitochondrion to thousands of organelles. In humans, erythrocytes (mature red blood cells) are the only cells that lack mitochondria, while organs with high demands for energy production, such as heart, muscle, liver, kidney, and to a certain extent the brain, can have hundreds or thousands of these organelles in each cell.

2. Oxidative Phosphorylation Pathway

The OXPHOS pathway, i.e., the electron transport-linked phosphorylation, is a metabolic pathway responsible for producing chemical energy in the form of adenosine trisphosphate (ATP). This pathway consists of five multi-subunits protein complexes and two mobile electron carriers (coenzyme Q (CoQ) and cytochrome *c*). OXPHOS generates an electrochemical transmembrane gradient through the first four multi-protein complexes (I–IV), which consist the mitochondrial respiratory chain (MRC) that fuels ATP synthesis through the last complex (V) of OXPHOS, the ATP synthase complex [5]. In this pathway, the two electron donors (the reduced nicotinamide dinucleotide (NADH) and the reduced flavin adenine dinucleotide (FADH2)), which are products of the glycolysis, the β-oxidation of fatty acids, and the TCA cycle, start passing along electrons during oxidation to complex I (ubiquinone oxidoreductase-NADH) or complex II (succinate dehydrogenase), respectively, and then to electron carrier coenzyme Q or ubiquinone. Reduced ubiquinol transfers electrons to complex III (ubiquinol: cytochrome *c* oxidoreductase) and, more specifically, to cytochrome c_1. Then, the second soluble electron carrier, cytochrome *c*, transfers the electrons to complex IV (cytochrome *c* oxidase or COX), which catalyzes molecular oxygen (O_2) to water (H_2O) at the final stage. The downstream transport of electrons results in a proton gradient as protons are pumped into the intermembrane space, thus providing the energy to ATP synthase (complex V) to convert adenosine diphosphate (ADP) and inorganic phosphate (Pi) into ATP.

While the complexes I, III, IV, and V are under dual genomic control since their structural proteins are encoded from both genomes, complex II's structural proteins are encoded only by the nDNA. Additionally, numerous ancillary proteins called assembly factors (all being encoded by the nDNA) are necessary for the biogenesis and assembly of the five multi-subunits complexes of OXPHOS.

3. The Mitochondrial Machinery for Protein Import and Assembly

Although mitochondria have their own DNA, less than 1% (13 structural subunits of OXPHOS) of the roughly 1500 mitochondrial proteins are produced in the matrix. The vast majority of the mitochondrial proteome is encoded by the nDNA (spread across most chromosomes) and expressed as protein precursors (preproteins) in the cytosol. The mitochondrial preproteins either carry a cleavable mitochondrial targeting signal (MTS) peptide in their sequence or various internal targeting signals, which in both cases guide them to the mitochondria. The MTS peptide (predicted by the Mitoprot logistic program: https://ihg.helmholtz-muenchen.de/ihg/mitoprot.html, accessed on 1 November 1996) or leader peptide (L) is typically a 15–50 amino acid (aa) peptide, mostly in the N-terminus of the protein precursors, with some exceptions found in C-terminus [21]. Cytosolic chaperones facilitate the transfer of the preproteins to the general entry gate of mitochondria, the translocase of the outer membrane (TOM) complex. Nearly all mitochondrial preproteins are imported via the TOM complex, and they are subsequently sorted into one of the mitochondrial sub-compartments using the mitochondrial protein import-sorting machinery. Depending on the final destination of mitochondrial proteins, Pfanner's group [22] suggests five major protein import pathways. The majority of matrix proteins and inner-membrane proteins, which are synthesized with N- (or C-) terminal cleavable MTS peptides (pre-sequences), utilize the classical import pathway (or pre-sequence pathway) consisting of the TOM complex, the translocase of the inner membrane (TIM23), and the pre-sequence translocase-associated motor (PAM). Once these preproteins enter into the matrix, the mitochondrial processing peptidase (MPP) [23] cleaves off the MTS peptides. Pre-proteins with internal targeting signals utilize the other four (4) described pathways, with the final destination defining which of the pathways will be employed. Components of these pathways are the small TIM chaperones of the intermembrane space, the carrier translocase of the intermembrane space, the translocase of the inner membrane (TIM22), the sorting assembly machinery (SAM), the mitochondrial intermembrane space import and assembly (MIA), translocase of the inner membrane (TIM), and the mitochondrial import complex (MIM). Ongoing research will probably reveal additional import routes and complexity given that the pathways responsible for several precursor proteins remain still un-identified.

4. Mitochondrial Genetic Disorders

While mitochondrial disorders represent a heterogeneous group of rare inherited genetic disorders with varying severity and clinical outcomes, they are generally characterized by respiratory chain dysfunction and abnormal mitochondrial function. The overall estimated prevalence of these disorders is one to three cases per 20,000 individuals [24], with lifelong symptoms that can appear from very early (newborn) to later in life. Unsurprisingly, mitochondrial disorders often affect organs with high metabolic needs such as muscles, heart, liver, kidneys, central nervous system (CNS), peripheral nervous system (PNS), as well sensory organs (eyes and ears) [13][25]. It has been reported that some mitochondrial disorders can affect only a single organ (as in Leber hereditary optic neuropathy (LHON) [26] and in mitochondrial non-syndromic hearing loss and deafness), but often, these disorders cause multi-system dysfunction.

Primary mitochondrial disorders (PMDs) are genetic disorders caused by pathogenic variants in either mitochondrial or nuclear genes coding for mitochondrial respiratory chain and related proteins. The first time that mitochondrial disorder was reported was in 1962 [27] in a patient with severe hypermetabolism, while in 1988, the first mutations in mtDNA were associated with human disease [26][28]. Since then, pathogenic variants in more than 400 genes of both mitochondrial and nuclear origin have been reported in primary mitochondrial disorders.

Mitochondrial dysfunction has also been observed in numerous neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), and Friedreich's ataxia (FRDA); in age-related disorders; in metabolic disorders; as well in traumatic brain injury, ischemic stroke, and in a wide spectrum of human cancers [6][15][29].

4.1. Mitochondrial Disorders Attributed to Genes Encoded by mtDNA

The mtDNA is highly polymorphic among individuals (~50–60 neutral polymorphisms between two individuals). The lack of protective histones and limited repair mechanisms make the mitochondrial genome highly susceptible to oxidative damage [30][31], with an estimated mutation rate 10–20 times higher than that of nDNA [32]. Mutations in mtDNA include: (a) large-scale rearrangements (single deletions or duplications) that are always heteroplasmic and (b) point mutations (either homo- or heteroplasmic). In the latter, pathogenic point mtDNA mutations frequently coexist with wild-type (w/t) mtDNA (a phenomenon termed heteroplasmy), with higher levels of mutation accumulating in post-mitotic tissues such as skeletal muscle, heart, and the central nervous system [33]. In these cases, individuals develop symptoms/clinical phenotype when the mutated mtDNA exceeds a threshold level (usually 60–90%) compared to normal [34]. Interestingly, family members may have different levels of mutated mtDNA, and even individuals may experience different levels of mutated mtDNA in different organs and tissues [35].

- Large-scale rearrangements are associated with:
  - Sporadic progressive external ophthalmoplegia (PEO) [36];
  - Kearns–Sayre syndrome (KSS) [36];
  - Pearson's syndrome [37];
  - Leigh syndrome (LS) (rarely) [38][39]
- Homoplasmic point mutations are associated with:
  - Leber hereditary optic neuropathy (LHON) [26]
- Heteroplasmic point mutations are associated with:
  - Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) [40];
  - Myoclonic epilepsy with ragged red fibers (MERRF) [41];
  - Neurogenic weakness ataxia and retinitis pigmentosa (NARP) [42];
  - Leigh syndrome (LS) [38][39]

4.2. Mitochondrial Disorders Attributed to Genes Encoded by nDNA

Mitochondrial disorders can also be caused by mutations in nDNA, specifically in genes that encode either (a) structural proteins of the core subunits of the mitochondrial respiratory chain (complex I–IV) and ATP synthase complex V [43] or (b) no-structural proteins [44]. The second category includes: (i) assembly factors of the respiratory complexes; (ii) proteins responsible for the transcription and translation of mtDNA; (iii) proteins involved in mtDNA replication and maintenance of its integrity and abundance; (iv) proteins necessary for mitochondrial import; (v) proteins involved in iron homeostasis as well as in coenzyme Q10 biogenesis; and (vi) proteins involved in mitochondrial metabolism.

5. Cytochrome c Oxidase (COX) Deficiency

COX, the terminal enzyme of mitochondrial respiratory chain, is a 14-subunit holoenzyme that catalyzes the electron transfer from reduced cytochrome *c* to molecular oxygen in order to produce water and thus facilitates the generation of

the proton gradient across the inner mitochondrial membrane that is used to synthesize ATP [45][46]. This electron transfer occurs through COX's redox centers, two heme A moieties (*a* and a_3), and two copper centers (Cu_A and Cu_B) [47][48].

Three of the COX's subunits are encoded by the mtDNA (MT-CO1, MT-CO2, and MT-CO3), and form the catalytic core of the holoenzyme, while the remaining eleven (COX4, COX5A, COX5B, COX6A, COX6B, COX6C, COX7A, COX7B, COX7C, COX8, and NDUFA4/COXFA4 [46][49]) are encoded by nDNA. Interestingly, some of the nuclear encoded subunits of COX (4, 6A, 6B, 7A, 7B, and 8A) appear with different isoforms that are tissue-, developmental-, and species-specific isoforms [50]. The heme *a* and the heme a_3-Cu_B binuclear centers are associated with MT-CO1, whereas MT-CO2 contains the Cu_A center [51]. Additional, around 30 nDNA-encoded ancillary factors, including copper chaperones, also called COX-assembly proteins, are involved in the biogenesis and assembly of COX holoenzyme. To date, mutations in the subunits encoded by both genomes have been associated with disorder (*MT-CO1* [52], *MT-CO2* [53], *MT-CO3* [54], *COX4I1* [55], *COX4I2* [56], *COX5A* [57], *COX6A1* [56][58], *COX6A2* [56][59], *COX6B1* [60], *COX7A1* [56], *COX7A2* [56], *COX7B* [61], *COX8A* [62], and *NDUFA4* or *COXFA4* [63]), while the majority of isolated COX deficiencies are caused by mutations in COX assembly factors. Specifically, disorder-causing mutations were found in genes such as *SURF1* (the first identified nuclear gene encoding a factor involved in the biogenesis of COX and being mutated in the neurodegenerative Leigh's syndrome with COX deficiency) [64][65]; *SCO2/SCO1* (involved in mitochondrial copper pathway) [66][67]; *COX10* and *COX15* (involved in heme A biosynthesis) [68][69][70]; *COX14* (or *C12ORF62*; involved in COX assembly) [71]; *COX20* (or *FAM36A*; involved in MT-CO2 stabilization) [72]; *COA3* (*CCDC56* or *MITRAC12;* involved in *MT-CO1* maturation) [73]; *PET100* (involved in COX biogenesis) [74]; *PET117* (involved in the assembly of MT-CO2) [75]; *COA5* (*C2ORF64)* [76]; *COA6* [77]; *COA7* [78]; *COA8* (previously known as *APOPT1*) [79]; *FASTKD2* [80]; *LRPPRC*; and *TACO1* (essential for COX expression) [81][82].

6. *Synthesis of Cytochrome C Oxidase 2*

The *synthesis of cytochrome c oxidase 2* (*SCO2*) gene is located on chromosome 22 (22q13.33), and it encodes a precursor mitochondrial protein of 266aa. This precursor protein (full length) harbors a mitochondrial targeting sequence (MTS or L) on its N-terminus (1-41aa) that facilitates its transportation to mitochondria and, more specifically, to the inner mitochondria membrane. Sco2 protein acts as assembly factor of COX (complex IV) and is involved in the biogenesis of COX subunit II (MT-CO2), an essential core subunit of complex IV [83]. Sco2 contains a highly conserved copper-binding motif (CXXXC), and acting as metallochaperone, it participates in transport of copper to the Cu(A) site of MT-CO2 along with Sco1 homolog protein and Coa6, downstream of Cox17 [84][85][86][87][88][89]. In addition, Sco2 acts as a thiol-disulfide oxidoreductase to regulate the redox state of the cysteines in Sco1 [90]. Sco2 protein is also involved in mitochondrial redox signaling [91] and the p53 regulatory pathway in mitochondria [92][93].

Mutations in *SCO2* are often reported in cases of COX deficiency and have been associated with severe phenotypes and different clinical outcomes, such as myopathies, cardiac hypertrophy, neuropathies, and Leigh syndrome [66][94][95][96][97][98][99][100][101][102][103][104][105][106][107][108][109][110][111][112][113][114][115][116][117][118][119][120][121]. Initially, mutations in *SCO2* were found in three unrelated infants with fatal cardioencephalomyopathy and COX deficiency [66]. To date, nearly 100 patients with pathogenic variations in the *SCO2* gene have been reported (**Table 1**). A recurrent p.Glu140Lys (E140K) mutation has been described in at least one allele in the majority of the patients, raising the possibility of a hot-spot mutation. Patients homozygous for the E140K mutation have a delayed onset of disorder and longer survival compared with patients compound heterozygous for the E140K mutation [122]. Characterization of the E140K mutation in Sco2 protein from researcher's group [84] revealed decreased affinity to copper when compared to the w/t Sco2 protein.

Table 1. Reported Sco2 mutations and associated pathologies.

***SCO2* Genotype**	**Clinical Outcome**	**Affected Individual(s)**	**References ***
Q53X/E140K	**Fatal infantile cardioencephalomyopathy with COX deficiency, neurological symptoms with lactic/metabolic acidosis, respiratory difficulties**	**6**	**Papadopoulou L.C. et al., 1999 [66]; Tay S.K.H. et al., 2004 [110]; Vesela K. et al., 2004 [113]; Pronicki M. et al., 2010 [103]; Pronicka E. et al., 2013 [102]**
E140K/S225F	**Fatal infantile cardioencephalomyopathy with COX deficiency**	**1**	**Papadopoulou L.C. et al., 1999 [66]**

SCO2 Genotype	Clinical Outcome	Affected Individual(s)	References *
E140K/R171W	Fatal hypertrophic cardiomyopathy (HCMP), seizures, muscle hypotonia (MH), respiratory insufficiency	1	Jaksch M. et al., 2000 [97]
R90X/E140K	Fatal hypertrophic cardiomyopathy (HCMP), seizures, muscle hypotonia (MH), respiratory insufficiency	2	Jaksch M. et al., 2000 [97]
E140K/E140K	Delayed infantile onset of cardiomyopathy and neuropathy, laryngeal inspiratory stridor, infantile SMA-like/Leigh-like picture	39	Jaksch M. et al., 2001 [122]; Vesela K. et al., 2004 [113]; Bohm M. et al., 2006 [118]; Pronicki M. et al., 2010 [103]; Pronicka E. et al., 2013 [102]
10 bp duplication (1302–1311)/E140K	Prominent spinal cord involvement mimicking spinal muscular atrophy (Werdnig–Hoffmann disease)	1	Salviati L. et al., 2002 [106]
E140K/L151P	Hypertrophic cardiomyopathy and encephalomyopathy	1	Sacconi S. et al., 2003 [105]
C133S/E140K	Neonatal hypotonia with a spinal muscular atrophy (SMA) type 1 phenotype	1	Tarnopolsky M.A. et al., 2004 [109]
1518delA/E140K	Cytochrome *c* oxidase deficiency and a Werdnig–Hoffmann disease phenotype	2	Bohm M. et al., 2006 [118]; Vesela K. et al., 2008 [114];
Hemizygosity 16 bp deletion within the intron_E140K	Early onset rapidly progressive, fatal cardiomyopathy	1	Leary S.C. et al., 2006 [100]
E140K/V160G	Cytochrome *c* oxidase deficiency, fatal infantile cardioencephalomyopathy	1	Knuf M. et al., 2007 [99]
W36X/E140K	Fatal infantile cardioencephalomyopathy	2	Verdijk R.M. et al., 2008 [112]
G193S/G193S	Fatal infantile cardioencephalomyopathy	1	Mobley B.C. et al., 2009 [101]
E140K/M177T	Classical SMA or SMA-like picture, laryngeal inspiratory stridor, milder encephalopathic	4	Pronicki M. et al., 2010 [103]; Pronicka E. et al., 2013 [102]
E140K/w/t	Respiratory failure, artificial ventilation, hypotony, high-grade myopia	4	Pronicki M. et al. 2010 [103]; Tran-Viet K.N. et al. 2013 [111]
19 bp insertion at position 17 (17INS19bp)/ E140K	Failure to thrive, muscular hypotonia, hypertrophic cardiomyopathy, and lactic acidemia, totally absent of COX activity	1	Joost K. et al., 2010 [98]
12 bp deletion (c.1519_1530del)/ E140K	Cardioencephalomyopathy, stridor, neuropathy	1	Gurgel-Giannetti J. et al., 2013 [96]
Q53X/w/t	High-grade myopia	7	Tran-Viet K.N. et al., 2013 [111]
R114H/w/t	High-grade myopia	1	Tran-Viet K.N. et al. 2013 [111]
p82delK/E140K	Progressive encephalopathy, cardiomegaly, spinal muscular atrophy, COX deficiency	1	Pronicka E. et al., 2013 [102]
W75R/E140K	Neonatal cardiomyopathy, muscle weakness	1	Pronicka E. et al., 2013 [102]
E140K/T241X	Neonatal cardiomyopathy, muscle weakness, Leigh disease	1	Pronicka E. et al., 2013 [102]

SCO2 Genotype	Clinical Outcome	Affected Individual(s)	References *
V160A/P233T	Fatal hyperthermia and metabolic acidosis	1	Sambuughin N. et al., 2013 [107]
A259V/w/t	High-grade myopia	1	Tran-Viet K.N. et al., 2013 [111]
D223N/87 kb deletion on chr.22	Severe hypotonic syndrome, failure to thrive, divergent strabismus and ataxia, regression of psychomotor development	1	Vondrackova A. et al., 2014 [115]
R112W/w/t	Early-onset high myopia	1	Jiang D. et al., 2014 [119]
R120W/w/t	Early-onset high myopia	1	Jiang D. et al., 2014 [119]
A97V/w/t	Extreme myopia	1	Wakazono T. et al., 2016 [117]
D135G/R171Q	Early-onset axonal Charcot–Marie–Tooth disease associated with cellular copper deficiency	1	Rebelo A.P. et al., 2018 [104]
E140K/P169T	Early-onset axonal Charcot–Marie–Tooth disease associated with cellular copper deficiency	1	Rebelo A.P. et al., 2018 [104]
D173V/w/t	Non-syndromic high myopia	1	Cai X.B. et al., 2019 [120]
A201P/w/t	Non-syndromic high myopia	1	Cai X.B. et al., 2019 [120]
I221V/w/t	Non-syndromic high myopia	1	Cai X.B. et al., 2019 [120]
R255W/R255W	Cerebellar ataxia, progressive peripheral axonal neuropathy and long survival	2	Barcia G. et al., 2019 [94]
p82delK/w/t	Non-syndromic high myopia	1	Zheng Y.H et al., 2021 [121]
R60Q/G193S	Adult cerebellar ataxia, axonal neuropathy, and sensory impairments	1	Rucheton B. et al., 2021 [116]
G121R/G121R	Early-onset axonal Charcot–Marie–Tooth disease	2	Gangfuß A. et al., 2022 [95]

***** Sco2 mutants are shown in chronological order based on their first report.

Homozygous deletion of *SCO2* mice (knock-out mice $SCO2^{KO/KO}$) is embryonic-lethal [123]. Heterozygous *SCO2* knock-out/knock-in ($SCO2^{KO/KI}$) mice carrying a *SCO2* knock-out (KO) allele and a *SCO2* knock-in (KI) allele with the missense mutation E129K (corresponding to the E140K mutation found in almost all human *SCO2*-mutated patients) and homozygous *SCO2* knock-in mice ($SCO2^{KI/KI}$) carrying the missense mutation E129K in both alleles have been shown to be viable and fertile despite the muscle weakness and reduction in COX activity [123]. Additionally, heterozygous $SCO2^{KO/KI}$ mice have increased fat mass associated with reduced β-oxidation and increased adipogenesis markers, reduced insulin receptor beta (IR-β levels in adipose tissue), reduced muscle glucose transporter 4 (Glut4) levels, and an impaired response to the insulin-tolerance test consistent with insulin resistance [124]. Even though these mice models do not recapitulate human disorder, they are still a valuable preclinical tool for testing new therapeutic approaches for COX deficiencies.

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