Mitochondrial Diseases Definition for Version 2.0 CDE Recommendations

Primary mitochondrial diseases comprise clinically, genetically, and biochemically diverse disorders that are caused by genetic defects that primarily affect intrinsic mitochondrial functions including: oxidative-phosphorylation[1], mitochondrial protein synthesis[2], mitochondrial mRNA synthesis/processing[3], mitochondrial fission and fusion[4], mitochondrial protein quality control and degradation[5], iron-sulfur protein assembly[6], mitochondrial sulfide oxidation[7], mitochondrial nucleoside/nucleotide metabolism[8], mitochondrial DNA maintenance[9], pyruvate dehydrogenase complex[10], primary defects of mitochondrial protein importation[11], and ATP/ADP transport[12] (specific examples are listed in the Appendix).

Some diseases that affect mitochondrial functions are excluded because they are classified as other types of disorders or cause secondary mitochondrial dysfunction such as: defects of mitochondrial fatty acid oxidation, Krebs cycle disorders, urea cycle disorders of intra-mitochondrial enzymes, mitochondrial phospholipid metabolism, congenital disorders of glycosylation, exogenous mitochondrial toxins, and drug-induced mitochondrial dysfunction.

Appendix: Specific examples of primary mitochondrial diseases.

[1]Oxidative-phosphorylation
Complex I: *NDUFS1*, *NDUFS2*, *NDUFS3*, *NDUFS4*, *NDUFS6*, *NDUFS7*, *NDUFS8*, *NDUFV1*, *NDUFV2*, *NDUFA1*, *NDUFA2*, *NDUFA9*, *NDUFA10*, *NDUFA11*, *NDUFA12*, *NDUFA13*, *NDUFAF2*, *NDUFAF6* and *NDUFB11*
Complex II: *SDHA*, *SDHB*, *SDHC*, *SDHD* and *SDHAF1*
Complex III: *UQCRB*, BCS1L, *UQCRQ*, *UQCRC2*, *CYC1*, *TTC19*, *LYRM7*, *UQCC2* and *UQCC3*
Complex IV: *COA5*, *SURF1*, *COX10*, *COX14*, *COX15*, *COX20*, *COX6B1*, *ETHE1, FASTKD2*, *SCO1*, *SCO2*, *LRPPRC*, *TACO1* and *PET100*
Complex V: *ATPAF2*, *TMEM70*, *ATP5E, ATP5A1*, *USMGE5*
Coenzyme Q_{10} deficiency: *PDSS1*, *PDSS2*, *COQ2*, *COQ4*, *COQ5, COQ6*, COQ7, *COQ8A*, *COQ8B* and *COQ9*

[2]Mitochondrial protein synthesis

Aminoacyl-tRNA synthetases: *AARS2*, *DARS2*, *EARS2*, *RARS2*, *YARS2*, *FARS2*, *HARS2*, *LARS2*, *VARS2*, *TARS2*, *IARS2*, *CARS2*, *PARS2*, *NARS2*, *KARS*, *GARS*, *SARS2* and *MARS2*

tRNA modification: *MTO1*, *GTP3BP*, *TRMU*, *PUS1*, *MTFMT*, *TRIT1*, *TRNT1* and *TRMT5*

Mitoribosomal proteins: *MRPS16*, *MRPS22*, *MRPL3*, *MRP12* and *MRPL44*

Elongation factors: *TUFM*, *TSFM,* and *GFM1*

Release factors: *C12orf65*

[3]Mitochondrial mRNA synthesis/processing
LRPPRC, *TACO1*, *ELAC2*, *PNPT1*, *HSD17B10*, *MTPAP* and *PTCD1*

[4]Mitochondrial fission and fusion
OPA1, MFN2, MSTO1, and MICOS13

[5]mitochondrial protein quality control and degradation
FBXL4, *AFG3L2, LONP1,* and *SPG7*

[6]Iron-sulfur protein assembly
ISCU, *BOLA3*, *NFU1* and *IBA57*

[7]Mitochondrial sulfide oxidation
GFER

[8]Mitochondrial nucleoside/nucleotide metabolism
TYMP, *DGUOK*, *TK2*, *MGME1*, *SUCLG1*, *SUCLA2*, *GUK1, RRM1,* and *RRM2B*

[9]Mitochondrial DNA maintenance
C10orf2, *POLG*, *POLG2, DNA2, RNASEH1*, *TFAM, TOP3A, SSBP1, LIG3*

[10]Pyruvate dehydrogenase complex
PDHA1, PDHB, LIAS, PDP1, PDHX, DLAT

[11]Primary defects of mitochondrial protein importation
TIMM8A

[12]ATP/ADP transport
ANT1