**Part 1 – Clinical Description**

1. **\***Primary Clinical Diagnosis of Mitochondrial Disease (Choose one):1

|  |  |
| --- | --- |
| 1: Alpers syndrome: | Present Absent \*Age at symptom onset: |
| 2: Cardiomyopathy: | Present Absent \*Age at symptom onset: |
| 3: Chronic progressive external ophthalmoplegia (CPEO): | Present Absent \*Age at symptom onset: |
| 4: Chronic progressive external ophthalmoplegia (CPEO "plus"): | Present Absent \*Age at symptom onset: |
| 5: Maternally Inherited Diabetes and Deafness (MIDD): | Present Absent \*Age at symptom onset: |
| 6: Kearns-Sayre syndrome (KSS): | Present Absent \*Age at symptom onset: |
| 7: Leber hereditary optic neuropathy (LHON): | Present Absent \*Age at symptom onset: |
| 8: Leigh syndrome: | Present Absent \*Age at symptom onset: |
| 9: Maternal-inherited deafness: | Present Absent \*Age at symptom onset: |
| 10: MELAS: | Present Absent \*Age at symptom onset: |
| 11: MNGIE: | Present Absent \*Age at symptom onset: |
| 12: Multi-systemic syndrome: | Present Absent \*Age at symptom onset: |
| 13: MERRF: | Present Absent \*Age at symptom onset: |
| 14: Myopathy: | Present Absent \*Age at symptom onset: |
| 15: Neuropathy, ataxia and retinitis pigmentosa (NARP): | Present Absent \*Age at symptom onset: |
| 16: Pearson syndrome: | Present Absent \*Age at symptom onset: |
| 17: Reversible infantile myopathy with cytochrome c oxidase deficiency: | Present Absent \*Age at symptom onset: |
| 18: Ataxia Neuropathy syndrome: | Present Absent \*Age at symptom onset: |
| 19: Other POLG related disorders: | Present Absent \*Age at symptom onset: |
| 20. Aminoglycoside-induced deafness: | Present Absent \*Age at symptom onset: |
| 21: Barth syndrome: | Present Absent \*Age at symptom onset: |
| 22: Encephalomyopathy: | Present Absent \*Age at symptom onset: |
| 23: Hepatocerebral syndrome: | Present Absent \*Age at symptom onset: |
| 24: Leukoencephalopathy: | Present Absent \*Age at symptom onset: |
| 25: Encephalopathy: | Present Absent \*Age at symptom onset: |
| 26: Other clinical syndrome/symptom, specify: | Present Absent \*Age at symptom onset: |

1. Signs Supportive of PMD Diagnosis:

|  |  |
| --- | --- |
| Bilateral basal ganglia lesions: | Present Absent N/A |
| Lactate peak on MRI: | Present Absent N/A |
| Metabolic stroke: | Present Absent N/A |
| Elevated tissue lactate: | Present Absent N/A |
| Elevated blood alanine: | Present Absent N/A |
| Elevated CPK: | Present Absent N/A |
| Elevated GDF-15: | Present Absent N/A |
| Elevated tissue ragged-red fibers: | Present Absent N/A |
| Tissue COX deficient stain: | Present Absent N/A |
| Tissue SDH positive stain: | Present Absent N/A |
| Abnormal mitochondria in electron microscope: | Present Absent N/A |
| Abnormal OXPHOS function: | Present Absent N/A |
| Other, specify: | Present Absent N/A |

**Part II – Genetics Summary**

1. Was genetic testing performed?  Yes  No

If YES, please answer questions below:

* 1. What year was the genetic testing performed?
  2. Indicate the source(s) of the genetic test results: (Choose all that apply)

Geneticist

Genetic counselor

Neurologist

Medical records

Other general practitioner

Other specialty physician

Other, specify:

* 1. Was the participant informed of the test results?  Yes  No
     1. If YES, who informed them of the results?

Geneticist

Genetic Counselor

Metabolic specialist

Neurologist

Self (results from Direct-to-Consumer test)

Other, specify:

* 1. Known Variant/s in participant’s DNA:1  Present  Absent  Unknown
     1. If present or absent, describe:1

1. Has the participant had a sample drawn for DNA banking?  Yes  No  Unknown

If YES,

* 1. Specify the type of sample drawn:

Blood draw

Buccal smear (cheek swab)

Saliva

Urine sediment

Muscle tissue

Other, specify:

* 1. Specify the study for which the sample was initially taken:
  2. Specify where the sample is banked, if known:
  3. Did the participant sign a consent form at the time the sample was taken?

Yes  No  Unknown

* 1. Does the consent form for this sample allow for sharing of the sample?  Yes  No
  2. Has the participant given a sample of blood to a repository?  Yes  No

If YES,

* + 1. Name of repository:
    2. Sample ID:
    3. Repository contact:
    4. Type of tissue collected:
    5. GUID:

1. Has the participant registered for organ donation? Yes No
   1. If YES, name of repository:
2. Is a sample available from a family member? Yes No

If YES,

* 1. Name of repository:
  2. Sample ID:
  3. Repository contact:
  4. Type of tissue collected:
  5. GUID:

**Part III – Study Description**

1. Study type(s) (Choose all that apply):2

Longitudinal

Case-control

Case set

Control set

Parent-offspring trios

Cohort

Clinical trial

Other, specify:

1. Is aggregate-level data appropriate for General Research Use? 2 Y  N
2. Please check all data types expected for this study: 2
   1. General

Individual Phenotype

Individual Genotype

Individual Sequencing

Supporting Documents

Transcriptomic

Proteomic/Metabolomic

RNA seq

Images

* 1. Sample Types

Germline

Tumor/Normal

DNA

RNA

Mitochondria

Microbiome

From Repository

Other tissue, specify:

* 1. Array Data

SNP Array

Expression Array

Methylation Array

* 1. Genotypes

Array derived genotypes

CNV calls from microarray

CNV calls derived from Sequencing

Genotype calls derived from Sequence

Somatic SNV (MAF)

Array CGH CNVs

* 1. Sequencing

Whole Genome

Whole Exome

Targeted Genome

Targeted Exome

Whole Transcriptome

Targeted Transcriptome

Epigenomic Marks

Sanger

16S rRNA

* 1. Analysis

Association/Linkage results

Array-derived expression

Bulk RNA Seq derived expression

Array-derived methylation

**Part IV – Genotype Platform Information**

1. Name and version: 2
2. Vendor: 2
3. # Probes: 2
4. URL: 2
5. Description (optional): 2

**Part V – Variant/Mutation Analysis**

1. \*\*Lab name:
2. \*\*Date report issued:
3. \*\*Variant analysis results available on this participant:  Yes  No

(IF NO, Stop completing form)

1. \*\*Variant analysis performed on the participant:  Yes  No
2. If NO, was variant analysis performed on a family member?  Yes  No
3. If NO, provide explanation:
4. \*\*Variant analysis results:
5. Variant(s) detected:

Homozygous

Compound Heterozygous

Heterozygous

Hemizygous

Digenic (variants in more than one gene)

No pathogenic variant detected

1. Are there additional variants in other genes of unknown significance?  Yes  No

If YES, indicate:

1. Are there additional genes sequenced with no variants detected?  Yes  No

If YES, indicate:

1. \*\*What type of testing was performed?
   1. mtDNA panel testing
      1. What tissue?

Blood

Saliva

Buccal smear

Urine sediment

Muscle

Liver

Other, please specify:

* + 1. What genes?
  1. mtDNA genome deletion/duplication analysis
     1. What tissue?

Blood

Saliva

Buccal smear

Urine sediment

Muscle

Liver

Other, please specify:

* + 1. What genes?
  1. Karyotype
     1. What tissue?

Blood

Amnio

Skin

Other, please specify:

1. \*\*Allele specific information
2. Allele #1
3. Gene Name:
4. Variant Class:

Reduced Number of Copies

Increased Number of Copies

Missense

Nonsense

Splice

Pseudoexon

Potential (variant of unknown significance)

Subexonic Insertion/Deletion

Other, specify:

1. \*\*For Exonic Deletions/ Duplications:
   * 1. Was the copy number directly tested for all exons?  Yes  No  Unknown
     2. Are the limits of the copy number completely defined?  Yes  No  Unknown
        1. First Exon affected:
        2. Last Exon affected:
        3. Whole gene affected?  Yes  No  Unknown
        4. Predicted reading frame:  In  Out  Unknown
        5. Are known gene promoters affected:  Yes  No Unknown
2. \*\*For Missense/nonsense variant or Pseudoexons:
   * 1. Was the entire coding region sequenced:  Yes  No
     2. Targeted variant analysis only:  Yes  No
        1. If YES, type of analysis:  Hot-spot  Known familial variant  Other, specify:
     3. Missense/nonsense variant location (Choose one)
        1. Exon (Point Variant):
        2. Intron:
        3. Other, specify:
     4. Missense/nonsense variant subclass information:
        1. Insertion Deletion:  Insertion  Deletion  Insertion/Deletion
        2. Nonsense Type:  UAA  UAG  UGA  Not applicable
3. \*\*mRNA analysis
   * 1. mRNA analysis performed:  Yes  No  Unknown
        1. If YES, were implications confirmed:  Yes  No
4. \*\*Variant Information (HGVS Nomenclature)
   * 1. cDNA: (if relevant, data to be entered by site)
     2. mRNA: (if relevant, data to be entered by site)
     3. Protein: (if relevant, data to be entered by site)
5. \*\*Allele Specific Information
6. Allele #2
7. Was a second disease allele identified?  Yes  No (Skip to question 24)
8. Is allele #2 identical to allele #1 (Homozygous only):  Yes (Skip to question 24)  No

If NO, repeat filling out allele specific information for Allele #2.

1. \*\*For Mitochondrial DNA variant:
   1. Quantitative analyses (Heteroplasmy assessment)

Evaluation method

Restriction PCR

Deep sequencing

Allele specific PCR

qPCR (deletions, depletion)

Southern blot

Other, specify:

Heteroplasmy level

Blood

Muscle

Urinary sediment

Buccal cells

Saliva

Other, specify:

1. Please fill out the tables and associated questions. One row in the table should be filled out for each individual variant.
   1. \*Table 1: Genetic Testing Results for nuclear DNA

| Gene\*\* | DNA change[[1]](#footnote-1) | Tissue\*\* | Test Methodology\*\* | Region Tested: Coverage\*\* | Clinical Category\*\* | References |
| --- | --- | --- | --- | --- | --- | --- |
| Data to be filled in by site | Data to be filled in by site | Blood  Amniocytes  Skin  Other, specify: | Data to be filled in by site | Data to be filled in by site | Definite pathogenic  Likely pathogenic  Variant of uncertain significance  Likely benign  Definitely benign | Data to be filled in by site |

* 1. \*Table 2: Genetic Testing Results for mtDNA

| Gene\*\* | DNA changei | Tissue\*\* | Heteroplasmy Levels\*\* | Test Methodology\*\* | Region Tested: Coverage\*\* | Clinical Category\*\* | References |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Data to be filled in by site | Data to be filled in by site | Blood  Urine  Muscle  Buccal  Other, specify: | Data to be filled in by site | Data to be filled in by site | Data to be filled in by site | Definite pathogenic  Likely pathogenic  Variant of uncertain significance  Likely benign  Definitely benign | Data to be filled in by site |

1. \*\*Basis for the evaluation of the clinical category:

Previously reported

Familial segregation

Prevision software (name of the software)

Experimental validation

Functional complementation in cultured cells

Other, specify:

1. For Mitochondrial DNA variant:
2. \*\*Basis for the clinical evaluation of the clinical category:

Previously reported

Familial segregation

Tissular segregation

Prevision software (name of the software)

\*\*Experimental validation

Transfer into cybrid cells

Single muscle fiber

Recorder Signature: Date:

## General Instructions

This form contains data elements collecting information on the genetic etiology of participants with primary mitochondrial disease (PMD). The focus is on variables related to sample processing and genetic testing results while also capturing some information on variables related to phenotype in both the clinical and research setting.

Important note: Some of the data elements included on this CRF Module are classified as Core (i.e., strongly recommended for all mitochondrial disease clinical studies to collect) or Supplemental – Highly Recommended (i.e., essential information for specified conditions, study types, or designs), as indicated by asterisks below, and should be collected if genetics studies are performed.

\*Element is classified as Core

\*\*Element is classified as Supplemental – Highly Recommended

The remaining data elements are Supplemental (i.e., non-Core) and should only be collected if the research team considers them appropriate for their study.

Please see the Data Dictionary for element classifications.

## Specific Instructions

Please see the Data Dictionary for definitions for each of the data elements included in this CRF Module.

* Date – Date/time should be recorded to the level of granularity known (e.g., year, year and month, complete date plus hours and minutes, etc.) and in an unambiguous format acceptable to the study database like DD-MMM-YYYY. When date/time data are prepared for aggregation or sharing, they should be converted to the format specified by [ISO 8601](https://www.iso.org/iso-8601-date-and-time-format.html); YYYY-MM-DD T:hh:mm:ss.

References

1Question and permissible values from [Coriell Institute for Medical Research](https://www.coriell.org/1/About-Us/Legal-Notice) used and modified with permission.

2Question and permissible values from dbGaP/database of Genotypes and Phenotypes/ National Center for Biotechnology Information, National Library of Medicine (NCBI/NLM) <https://www.ncbi.nlm.nih.gov/gap> used and modified with permission.

1. i Note: The mtDNA genome is rather small, completely sequenced and numbered. According to current recommendations variants in the mitochondrial DNA should be described in relation to the full mitochondrial DNA sequence, i.e., for human the Homo sapiens mitochondrion, complete genome(GenBank [NC\_012920.1](http://www.ncbi.nlm.nih.gov/nuccore/NC_012920)). Descriptions should be preceded by "m.", like m.8993T>C ([*see Recommendations*](http://www.hgvs.org/mutnomen/recs.html#prefix)). The mtDNA encodes a range of different proteins. To prevent confusion, changes at protein level should be described including a reference to the protein changed, like ATP6:p.Leu156Pro (GenBank [YP\_003024031.1](http://www.ncbi.nlm.nih.gov/protein/251831112), ATP synthase 6). (*HGVS recommendations)* [↑](#footnote-ref-1)