## Biomarker Testing

1. Was a biomarker analysis done?

[ ]  Yes

[ ]  No

If yes, please answer questions below:

1. Sample/method used to assess the biomarker:

[ ]  Blood (serum/plasma)

[ ]  Urine

[ ]  CSF

[ ]  Fibroblasts

[ ]  Leukocytes

[ ]  Neutrophils

[ ]  Monocytes

[ ]  Platelets (high OXPHOS)

[ ]  Lymphocytes

[ ]  Lymphoblasts (EBV)

[ ]  Muscle biochemistry

[ ]  Muscle histology

[ ]  Myotubes

[ ]  Liver histology

[ ]  Liver biochemistry

[ ]  Genetic

1. Which biomarker(s) were assessed from the specimen's blood (serum/plasma) sample?

[ ]  Lactate

[ ]  Pyruvate

[ ]  Lactate/pyruvate ratio

[ ]  Leukocyte coenzyme Q10

[ ]  Amino acids (emphasis on alanine, alanine/ lysine ratio, alanine//phenylalanine + lysine ratio, citrulline)

[ ]  Carnitine levels

[ ]  Acylcarnitines

[ ]  CPK

[ ]  Creatine

[ ]  Free glutathione (fGSH), oxidized disulfide (GSSG), fGSH/GSSG ratio

[ ]  Plasma carbonyl content

[ ]  Fibroblast growth factor 21 (FGF21)

[ ]  Metabolic profiling

[ ]  Hepatic enzymes (AST, ALT, GGT)

[ ]  Ammonia

[ ]  Thymidine

[ ]  Deoxyuridine

Lactate accumulation level:

[ ]  Increase in lactate

[ ]  Normal lactate

[ ]  Decrease in lactate

1. Pyruvate accumulation level:

[ ]  Increase in pyruvate

[ ]  Normal pyruvate

[ ]  Decrease in pyruvate

1. Lactate/pyruvate ratio level:

[ ]  Increase in L: P ratio

[ ]  Normal L: P ratio

[ ]  Decrease in L: P ratio

1. Which biomarker(s) were assessed from the specimen's urine sample?

[ ]  Organic acids

[ ]  3-methylglutaconic acid

[ ]  Amino acids

[ ]  lactate/creatinine

1. Which biomarker(s) were assessed from the specimen's cerebrospinal fluid (CSF) sample?

[ ]  Lactate

[ ]  Pyruvate

[ ]  Lactate/pyruvate ratio

[ ]  Amino acids (alanine, alanine/lysine ratio, alanine/phenylalanine + lysine ratio)

[ ]  Cell count

[ ]  Protein

[ ]  Glucose (with simultaneous blood glucose)

1. Which biomarker(s) were assessed from the specimen's fibroblasts sample?

[ ]  High resolution respirometry

[ ]  OXPHOS enzymology

[ ]  Lactate/pyruvate ratio

[ ]  Pyruvate dehydrogenase enzymology

[ ]  Pyruvate dehydrogenase subunit western blot

[ ]  Pyruvate dehydrogenase immunohistochemistry

[ ]  ATP synthesis

[ ]  Fibroblast OXPHOS subunit immunohistochemistry

[ ]  OXPHOS subunit western blot

[ ]  Blue native gel electrophoresis (OXPHOS)

[ ]  Clear native gel OXPHOS immunoblot

[ ]  Clear native gel OXPHOS enzymology

[ ]  Coenzyme Q10

1. Which biomarker(s) were assessed from the specimen's leukocytes sample?

[ ]  Intracellular free glutathione (fGSH), oxidized disulfide (GSSG), fGSH/GSSG ratio

[ ]  Intracellular coenzyme Q10

[ ]  Pyruvate dehydrogenase enzymology

[ ]  Thymidine phosphorylase enzymology

[ ]  Coenzyme Q10 level

[ ]  mtDNA deletion/duplication

[ ]  mtDNA copy number

1. Which biomarker(s) were assessed from the specimen's neutrophils sample?

[ ]  OXPHOS enzymology

[ ]  High resolution respirometry

[ ]  Coenzyme Q10

[ ]  Intracellular glutathione

1. Which biomarker(s) were assessed from the specimen's monocytes sample?

[ ]  Intracellular free glutathione (fGSH), oxidized disulfide (GSSG), fGSH/GSSG ratio

[ ]  Pyruvate dehydrogenase enzymology

[ ]  Thymidine phosphorylase enzymology

[ ]  OXPHOS enzymology

[ ]  High resolution respirometry

[ ]  Coenzyme Q10

[ ]  Intracellular glutathione

1. Which biomarker(s) were assessed from the specimen's platelets (high OXPHOS) sample?

[ ]  OXPHOS enzymology

[ ]  High resolution respirometry

[ ]  Coenzyme Q10

[ ]  Peripheral-type benzodiazepine receptor binding kinetics

1. Which biomarker(s) were assessed from the specimen's lymphocytes sample?

[ ]  OXPHOS enzymology

[ ]  High resolution respirometry

[ ]  Coenzyme Q10

[ ]  Intracellular glutathione

[ ]  DNA strand breaks by comet assay (cultured cells)

[ ]  Micronucleus assay followed by fluorescence in situ hybridization

[ ]  Pyruvate dehydrogenase

1. Which biomarker(s) were assessed the specimen's lymphoblast sample?

[ ]  ATP synthesis

[ ]  High resolution respirometry

## PLACEHOLDER

1. Which biomarker(s) were assessed from the specimen's muscle biochemistry?

[ ]  OXPHOS enzymology

[ ]  High resolution respirometry

[ ]  mtDNA copy number

[ ]  mtDNA deletion/duplication

[ ]  Pyruvate dehydrogenase enzymology

[ ]  Pyruvate dehydrogenase subunit western blot

[ ]  Coenzyme Q10

[ ]  Glutathione content

[ ]  OXPHOS subunit western blot

[ ]  Blue native gel electrophoresis

[ ]  Clear native gel immunoblot

[ ]  Clear native gel enzymology

[ ]  Human mitochondrial transcription factor A (hmtTFA or Tfam)

[ ]  mtDNA absence sensitive factor (midas)

[ ]  Biogenesis regulator peroxisome proliferator-activated recerptor-gamma-coactivator-1alpha (PGC-1alpha)

[ ]  8-oxoguanine DNA glycolase-1 (OCG-1)

[ ]  Manganese superoxide dismutase (MnSOD)

[ ]  AIF

[ ]  Bcl-2

[ ]  Aconitase enzymology

1. Which biomarker(s) were assessed from the specimen's muscle histology?

[ ]  Gomori trichrome

[ ]  Succinate dehydrogenase (SDH)

[ ]  Cytochrome C Oxidase (COX) (Complex IV)

[ ]  Combined SDH + COX

[ ]  Fibroblast growth factor 21 (FGF21)

[ ]  OXPHOS subunit immunohistochemistry

[ ]  Humanin immunohistochemistry

1. Which biomarker(s) were assessed from the specimen's myotubes?

[ ]  Metabolic profiling

[ ]  High resolution respirometry

1. Which biomarker(s) were assessed from the specimen's genetics?

[ ]  Cellular energetics gene sequencing (NDS) (nDNA + mtDNA)

[ ]  mtDNA sequencing

[ ]  Exome sequencing (NGS) (nDNA)

[ ]  mtDNA deletion/duplication (leukocytes)

[ ]  mtDNA deletion/duplication (muscle)

[ ]  mtDNA copy number (leukocytes)

[ ]  mtDNA copy number (muscle)

[ ]  Mitochondrial haplotype

[ ]  Mitochondrial gene expression profiling

## References

1. Taivassalo, T., et al., *The spectrum of exercise tolerance in mitochondrial myopathies: a study of 40 patients.* Brain, 2003. 126(Pt 2): p. 413-23.

2. Siciliano, G., et al., *Effects of aerobic training on lactate and catecholaminergic exercise responses in mitochondrial myopathies.* Neuromuscul Disord, 2000. 10(1): p. 40-5.

3. Taivassalo, T., et al., *Effects of aerobic training in patients with mitochondrial myopathies.* Neurology, 1998. 50(4): p. 1055-60.

4. Taivassalo, T., et al., *Combined aerobic training and dichloroacetate improve exercise capacity and indices of aerobic metabolism in muscle cytochrome oxidase deficiency.* Neurology, 1996. 47(2): p. 529-34.

5. Tarnopolsky, M.A. and S. Raha, *Mitochondrial myopathies: diagnosis, exercise intolerance, and treatment options.* Med Sci Sports Exerc, 2005. 37(12): p. 2086-93.

6. Tarnopolsky, M., *Exercise testing as a diagnostic entity in mitochondrial myopathies.* Mitochondrion, 2004. 4(5-6): p. 529-42.

7. Suomalainen, A., *Biomarkers for mitochondrial respiratory chain disorders.* J Inherit Metab Dis, 2011. 34(2): p. 277-82.

8. Haas, R.H., et al., *Mitochondrial disease: a practical approach for primary care physicians.* Pediatrics, 2007. 120(6): p. 1326-33.

9. Mancuso, M., et al., *Diagnostic approach to mitochondrial disorders: the need for a reliable biomarker.* Curr Mol Med, 2009. 9(9): p. 1095-107.

10. Davis, R.L., et al., *Fibroblast growth factor 21 is a sensitive biomarker of mitochondrial disease.* Neurology, 2013. 81(21): p. 1819-26.

11. Atkuri, K.R., et al., *Inherited disorders affecting mitochondrial function are associated with glutathione deficiency and hypocitrullinemia.* Proc Natl Acad Sci U S A, 2009. 106(10): p. 3941-5.

12. Longo, N., C. Amat di San Filippo, and M. Pasquali, *Disorders of carnitine transport and the carnitine cycle.* Am J Med Genet C Semin Med Genet, 2006. 142C(2): p. 77-85.

13. Shaham, O., et al., *A plasma signature of human mitochondrial disease revealed through metabolic profiling of spent media from cultured muscle cells.* Proc Natl Acad Sci U S A, 2010. 107(4): p. 1571-5.

14. Frye, R.E., et al., *Redox metabolism abnormalities in autistic children associated with mitochondrial disease.* Transl Psychiatry, 2013. 3: p. e273.

15. Ribas, V., C. Garcia-Ruiz, and J.C. Fernandez-Checa, *Glutathione and mitochondria.* Front Pharmacol, 2014. 5: p. 151.

16. Chau, M.D., et al., *Fibroblast growth factor 21 regulates energy metabolism by activating the AMPK-SIRT1-PGC-1alpha pathway.* Proc Natl Acad Sci U S A, 2010. 107(28): p. 12553-8.

17. Gavrilova, R. and R. Horvath, *Fibroblast growth factor 21, a biomarker for mitochondrial muscle disease.* Neurology, 2013. 81(21): p. 1808-9.

18. Liang, C., K. Ahmad, and C.M. Sue, *The broadening spectrum of mitochondrial disease: Shifts in the diagnostic paradigm.* Biochim Biophys Acta, 2014. 1840(4): p. 1360-1367.

19. Su, S.L., et al., *FGF21 in ataxia patients with spinocerebellar atrophy and mitochondrial disease.* Clin Chim Acta, 2012. 414: p. 225-7.

20. Suomalainen, A., *Fibroblast growth factor 21: a novel biomarker for human muscle-manifesting mitochondrial disorders.* Expert Opin Med Diagn, 2013. 7(4): p. 313-7.

21. Suomalainen, A., et al., *FGF-21 as a biomarker for muscle-manifesting mitochondrial respiratory chain deficiencies: a diagnostic study.* Lancet Neurol, 2011. 10(9): p. 806-18.

22. Turnbull, D., *A new biomarker for mitochondrial disease.* Lancet Neurol, 2011. 10(9): p. 777-8.

23. Tyynismaa, H., et al., *Mitochondrial myopathy induces a starvation-like response.* Hum Mol Genet, 2010. 19(20): p. 3948-58.

24. Valentino, M.L., et al., *Thymidine and deoxyuridine accumulate in tissues of patients with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE).* FEBS Lett, 2007. 581(18): p. 3410-4.

25. Lara, M.C., et al., *Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): biochemical features and therapeutic approaches.* Biosci Rep, 2007. 27(1-3): p. 151-63.

26. Barshop, B.A., *Metabolomic approaches to mitochondrial disease: correlation of urine organic acids.* Mitochondrion, 2004. 4(5-6): p. 521-7.

27. Wortmann, S., et al., *Association of 3-methylglutaconic aciduria with sensori-neural deafness, encephalopathy, and Leigh-like syndrome (MEGDEL association) in four patients with a disorder of the oxidative phosphorylation.* Mol Genet Metab, 2006. 88(1): p. 47-52.

28. Wortmann, S.B., et al., *Biochemical and genetic analysis of 3-methylglutaconic aciduria type IV: a diagnostic strategy.* Brain, 2009. 132(Pt 1): p. 136-46.

29. Benoist, J.F., et al., *Cerebrospinal fluid lactate and pyruvate concentrations and their ratio in children: age-related reference intervals.* Clin Chem, 2003. 49(3): p. 487-94.

30. Leen, W.G., et al., *Cerebrospinal fluid analysis in the workup of GLUT1 deficiency syndrome: a systematic review.* JAMA Neurol, 2013. 70(11): p. 1440-4.

31. Cameron, J.M., et al., *Respiratory chain analysis of skin fibroblasts in mitochondrial disease.* Mitochondrion, 2004. 4(5-6): p. 387-94.

32. van den Heuvel, L.P., J.A. Smeitink, and R.J. Rodenburg, *Biochemical examination of fibroblasts in the diagnosis and research of oxidative phosphorylation (OXPHOS) defects.* Mitochondrion, 2004. 4(5-6): p. 395-401.

33. Cameron, J.M., et al., *Deficiency of pyruvate dehydrogenase caused by novel and known mutations in the E1alpha subunit.* Am J Med Genet A, 2004. 131(1): p. 59-66.

34. Schwab, M.A., et al., *Optimized spectrophotometric assay for the completely activated pyruvate dehydrogenase complex in fibroblasts.* Clin Chem, 2005. 51(1): p. 151-60.

35. Capaldi, R.A., et al., *Immunological approaches to the characterization and diagnosis of mitochondrial disease.* Mitochondrion, 2004. 4(5-6): p. 417-26.

36. Shepherd, R.K., et al., *Measurement of ATP production in mitochondrial disorders.* J Inherit Metab Dis, 2006. 29(1): p. 86-91.

37. de Paepe, B., et al., *Diagnostic value of immunostaining in cultured skin fibroblasts from patients with oxidative phosphorylation defects.* Pediatr Res, 2006. 59(1): p. 2-6.

38. Calvaruso, M.A., J. Smeitink, and L. Nijtmans, *Electrophoresis techniques to investigate defects in oxidative phosphorylation.* Methods, 2008. 46(4): p. 281-7.

39. Carrozzo, R., et al., *Subcomplexes of human ATP synthase mark mitochondrial biosynthesis disorders.* Ann Neurol, 2006. 59(2): p. 265-75.

40. DiMauro, S., C.M. Quinzii, and M. Hirano, *Mutations in coenzyme Q10 biosynthetic genes.* J Clin Invest, 2007. 117(3): p. 587-9.

41. Lopez, L.C., et al., *Leigh syndrome with nephropathy and CoQ10 deficiency due to decaprenyl diphosphate synthase subunit 2 (PDSS2) mutations.* Am J Hum Genet, 2006. 79(6): p. 1125-9.

42. Mollet, J., et al., *Prenyldiphosphate synthase, subunit 1 (PDSS1) and OH-benzoate polyprenyltransferase (COQ2) mutations in ubiquinone deficiency and oxidative phosphorylation disorders.* J Clin Invest, 2007. 117(3): p. 765-72.

43. Quinzii, C., et al., *A mutation in para-hydroxybenzoate-polyprenyl transferase (COQ2) causes primary coenzyme Q10 deficiency.* Am J Hum Genet, 2006. 78(2): p. 345-9.

44. Cordero, M.D., et al., *Mitochondrial dysfunction and mitophagy activation in blood mononuclear cells of fibromyalgia patients: implications in the pathogenesis of the disease.* Arthritis Res Ther, 2010. 12(1): p. R17.

45. Duncan, A.J., et al., *Determination of coenzyme Q10 status in blood mononuclear cells, skeletal muscle, and plasma by HPLC with di-propoxy-coenzyme Q10 as an internal standard.* Clin Chem, 2005. 51(12): p. 2380-2.

46. Kramer, P.A., et al., *A review of the mitochondrial and glycolytic metabolism in human platelets and leukocytes: Implications for their use as bioenergetic biomarkers.* Redox Biol, 2014. 2: p. 206-210.

47. Hroudova, J., et al., *Mitochondrial respiration in blood platelets of depressive patients.* Mitochondrion, 2013. 13(6): p. 795-800.

48. Martini, C., et al., *Peripheral benzodiazepine binding sites in platelets of patients affected by mitochondrial diseases and large scale mitochondrial DNA rearrangements.* Mol Med, 2002. 8(12): p. 841-6.

49. Tomasetti, M., et al., *Coenzyme Q10 enrichment decreases oxidative DNA damage in human lymphocytes.* Free Radic Biol Med, 1999. 27(9-10): p. 1027-32.

50. Migliore, L., et al., *Evaluation of cytogenetic and DNA damage in mitochondrial disease patients: effects of coenzyme Q10 therapy.* Mutagenesis, 2004. 19(1): p. 43-9.

51. Naccarati, A., et al., *Cytogenetic damage in peripheral lymphocytes of mitochondrial disease patients.* Neurol Sci, 2000. 21(5 Suppl): p. S963-5.

52. Vallance, H.D., J.R. Toone, and D.A. Applegarth, *Measurement of pyruvate dehydrogenase complex (PDHC) in interleukin-2 (IL-2) stimulated lymphocytes.* J Inherit Metab Dis, 1994. 17(5): p. 627-8.

53. Fouque, F., et al., *Differential effect of DCA treatment on the pyruvate dehydrogenase complex in patients with severe PDHC deficiency.* Pediatr Res, 2003. 53(5): p. 793-9.

54. Van Bergen, N.J., et al., *Oxidative phosphorylation measurement in cell lines and tissues.* Mitochondrion, 2014.

55. Adeva, M., et al., *Enzymes involved in l-lactate metabolism in humans.* Mitochondrion, 2013. 13(6): p. 615-29.

56. Hargreaves, I.P., et al., *Glutathione deficiency in patients with mitochondrial disease: implications for pathogenesis and treatment.* J Inherit Metab Dis, 2005. 28(1): p. 81-8.

57. Comi, G.P., et al., *Cytochrome c oxidase subunit I microdeletion in a patient with motor neuron disease.* Ann Neurol, 1998. 43(1): p. 110-6.

58. Andringa, K., A. King, and S. Bailey, *Blue native-gel electrophoresis proteomics.* Methods Mol Biol, 2009. 519: p. 241-58.

59. Tuppen, H.A., et al., *Mutations in the mitochondrial tRNA Ser(AGY) gene are associated with deafness, retinal degeneration, myopathy and epilepsy.* Eur J Hum Genet, 2012. 20(8): p. 897-904.

60. Assouline, Z., et al., *A constant and similar assembly defect of mitochondrial respiratory chain complex I allows rapid identification of NDUFS4 mutations in patients with Leigh syndrome.* Biochim Biophys Acta, 2012. 1822(6): p. 1062-9.

61. Pitceathly, R.D., et al., *Kearns-Sayre syndrome caused by defective R1/p53R2 assembly.* J Med Genet, 2011. 48(9): p. 610-7.

62. Gerards, M., et al., *Defective complex I assembly due to C20orf7 mutations as a new cause of Leigh syndrome.* J Med Genet, 2010. 47(8): p. 507-12.

63. Wittig, I. and H. Schagger, *Features and applications of blue-native and clear-native electrophoresis.* Proteomics, 2008. 8(19): p. 3974-90.

64. Wittig, I. and H. Schagger, *Advantages and limitations of clear-native PAGE.* Proteomics, 2005. 5(17): p. 4338-46.

65. Wumaier, Z., et al., *Chapter 8 Two-dimensional native electrophoresis for fluorescent and functional assays of mitochondrial complexes.* Methods Enzymol, 2009. 456: p. 153-68.

66. Wittig, I., et al., *Functional assays in high-resolution clear native gels to quantify mitochondrial complexes in human biopsies and cell lines.* Electrophoresis, 2007. 28(21): p. 3811-20.

67. Wittig, I., M. Karas, and H. Schagger, *High resolution clear native electrophoresis for in-gel functional assays and fluorescence studies of membrane protein complexes.* Mol Cell Proteomics, 2007. 6(7): p. 1215-25.

68. Siciliano, G., et al., *Abnormal levels of human mitochondrial transcription factor A in skeletal muscle in mitochondrial encephalomyopathies.* Neurol Sci, 2000. 21(5 Suppl): p. S985-7.

69. Nakashima-Kamimura, N., et al., *MIDAS/GPP34, a nuclear gene product, regulates total mitochondrial mass in response to mitochondrial dysfunction.* J Cell Sci, 2005. 118(Pt 22): p. 5357-67.

70. Adhihetty, P.J., et al., *The effect of training on the expression of mitochondrial biogenesis- and apoptosis-related proteins in skeletal muscle of patients with mtDNA defects.* Am J Physiol Endocrinol Metab, 2007. 293(3): p. E672-80.

71. Filosto, M., et al., *Neuropathology of mitochondrial diseases.* Biosci Rep, 2007. 27(1-3): p. 23-30.

72. Ross, J.M., *Visualization of mitochondrial respiratory function using cytochrome c oxidase/succinate dehydrogenase (COX/SDH) double-labeling histochemistry.* J Vis Exp, 2011(57): p. e3266.

73. De Paepe, B., et al., *Immunohistochemical analysis of the oxidative phosphorylation complexes in skeletal muscle from patients with mitochondrial DNA encoded tRNA gene defects.* J Clin Pathol, 2009. 62(2): p. 172-6.

74. Kin, T., et al., *Humanin expression in skeletal muscles of patients with chronic progressive external ophthalmoplegia.* J Hum Genet, 2006. 51(6): p. 555-8.

75. DaRe, J.T., et al., *Targeted exome sequencing for mitochondrial disorders reveals high genetic heterogeneity.* BMC Med Genet, 2013. 14: p. 118.

76. Dames, S., et al., *The development of next-generation sequencing assays for the mitochondrial genome and 108 nuclear genes associated with mitochondrial disorders.* J Mol Diagn, 2013. 15(4): p. 526-34.

77. Amstutz, U., et al., *Sequence capture and next-generation resequencing of multiple tagged nucleic acid samples for mutation screening of urea cycle disorders.* Clin Chem, 2011. 57(1): p. 102-11.

78. McMillan, H.J., et al., *Compound heterozygous mutations in glycyl-tRNA synthetase are a proposed cause of systemic mitochondrial disease.* BMC Med Genet, 2014. 15(1): p. 36.

79. Lieber, D.S., et al., *Next generation sequencing with copy number variant detection expands the phenotypic spectrum of HSD17B4-deficiency.* BMC Med Genet, 2014. 15(1): p. 30.

80. Prasad, R., et al., *Thioredoxin reductase 2 (TXNRD2) mutation associated with familial glucocorticoid deficiency (FGD).* J Clin Endocrinol Metab, 2014: p. jc20133844.

81. Poduri, A., et al., *SLC25A22 is a novel gene for migrating partial seizures in infancy.* Ann Neurol, 2013. 74(6): p. 873-82.

82. Falk, M.J., et al., *AGC1 Deficiency Causes Infantile Epilepsy, Abnormal Myelination, and Reduced N-Acetylaspartate.* JIMD Rep, 2014.

83. Farhan, S.M., et al., *Exome sequencing identifies NFS1 deficiency in a novel Fe-S cluster disease, infantile mitochondrial complex II/III deficiency.* Mol Genet Genomic Med, 2014. 2(1): p. 73-80.

84. Ohtake, A., et al., *Diagnosis and molecular basis of mitochondrial respiratory chain disorders: Exome sequencing for disease gene identification.* Biochim Biophys Acta, 2014. 1840(4): p. 1355-9.

85. Haack, T.B., et al., *Phenotypic spectrum of eleven patients and five novel MTFMT mutations identified by exome sequencing and candidate gene screening.* Mol Genet Metab, 2014. 111(3): p. 342-52.

86. Monies, D.M., et al., *Clinical and pathological heterogeneity of a congenital disorder of glycosylation manifesting as a myasthenic/myopathic syndrome.* Neuromuscul Disord, 2014. 24(4): p. 353-9.

87. Nakajima, J., et al., *A novel homozygous YARS2 mutation causes severe myopathy, lactic acidosis, and sideroblastic anemia 2.* J Hum Genet, 2014.

88. Spiegel, R., et al., *Delineation of C12orf65-related phenotypes: a genotype-phenotype relationship.* Eur J Hum Genet, 2014.

89. Boczonadi, V. and R. Horvath, *Mitochondria: impaired mitochondrial translation in human disease.* Int J Biochem Cell Biol, 2014. 48: p. 77-84.

90. Platt, J., R. Cox, and G.M. Enns, *Points to Consider in the Clinical Use of NGS Panels for Mitochondrial Disease: An Analysis of Gene Inclusion and Consent Forms.* J Genet Couns, 2014.

91. Morino, H., et al., *Exome sequencing reveals a novel TTC19 mutation in an autosomal recessive spinocerebellar ataxia patient.* BMC Neurol, 2014. 14: p. 5.

92. Soreze, Y., et al., *Mutations in human lipoyltransferase gene LIPT1 cause a Leigh disease with secondary deficiency for pyruvate and alpha-ketoglutarate dehydrogenase.* Orphanet J Rare Dis, 2013. 8: p. 192.

93. Logan, C.V., et al., *Loss-of-function mutations in MICU1 cause a brain and muscle disorder linked to primary alterations in mitochondrial calcium signaling.* Nat Genet, 2014. 46(2): p. 188-93.

94. Hong, Y.B., et al., *A compound heterozygous mutation in HADHB gene causes an axonal Charcot-Marie-tooth disease.* BMC Med Genet, 2013. 14: p. 125.

95. Girotto, G., et al., *Linkage study and exome sequencing identify a BDP1 mutation associated with hereditary hearing loss.* PLoS One, 2013. 8(12): p. e80323.

96. Ashraf, S., et al., *ADCK4 mutations promote steroid-resistant nephrotic syndrome through CoQ10 biosynthesis disruption.* J Clin Invest, 2013. 123(12): p. 5179-89.

97. Rosenthal, E.A., et al., *Joint linkage and association analysis with exome sequence data implicates SLC25A40 in hypertriglyceridemia.* Am J Hum Genet, 2013. 93(6): p. 1035-45.

98. Davit-Spraul, A., et al., *Secondary Mitochondrial Respiratory Chain Defect Can Delay Accurate PFIC2 Diagnosis.* JIMD Rep, 2013.

99. Tucci, A., et al., *Novel C12orf65 mutations in patients with axonal neuropathy and optic atrophy.* J Neurol Neurosurg Psychiatry, 2013.

100. Saisawat, P., et al., *Whole-exome resequencing reveals recessive mutations in TRAP1 in individuals with CAKUT and VACTERL association.* Kidney Int, 2013.

101. Carroll, C.J., V. Brilhante, and A. Suomalainen, *Next-generation sequencing for mitochondrial disorders.* Br J Pharmacol, 2014. 171(8): p. 1837-53.

102. Neveling, K., et al., *A post-hoc comparison of the utility of sanger sequencing and exome sequencing for the diagnosis of heterogeneous diseases.* Hum Mutat, 2013. 34(12): p. 1721-6.

103. Hildick-Smith, G.J., et al., *Macrocytic anemia and mitochondriopathy resulting from a defect in sideroflexin 4.* Am J Hum Genet, 2013. 93(5): p. 906-14.

104. Pitceathly, R.D., et al., *COX10 mutations resulting in complex multisystem mitochondrial disease that remains stable into adulthood.* JAMA Neurol, 2013. 70(12): p. 1556-61.

105. Imagawa, E., et al., *A hemizygous GYG2 mutation and Leigh syndrome: a possible link?* Hum Genet, 2014. 133(2): p. 225-34.

106. Gai, X., et al., *Mutations in FBXL4, encoding a mitochondrial protein, cause early-onset mitochondrial encephalomyopathy.* Am J Hum Genet, 2013. 93(3): p. 482-95.

107. Bonnen, P.E., et al., *Mutations in FBXL4 cause mitochondrial encephalopathy and a disorder of mitochondrial DNA maintenance.* Am J Hum Genet, 2013. 93(3): p. 471-81.

108. Craigen, W.J., et al., *Exome sequencing of a patient with suspected mitochondrial disease reveals a likely multigenic etiology.* BMC Med Genet, 2013. 14: p. 83.

109. Sarig, O., et al., *Infantile mitochondrial hepatopathy is a cardinal feature of MEGDEL syndrome (3-methylglutaconic aciduria type IV with sensorineural deafness, encephalopathy and Leigh-like syndrome) caused by novel mutations in SERAC1.* Am J Med Genet A, 2013. 161(9): p. 2204-15.

110. Proverbio, M.C., et al., *Whole genome SNP genotyping and exome sequencing reveal novel genetic variants and putative causative genes in congenital hyperinsulinism.* PLoS One, 2013. 8(7): p. e68740.

111. DiMauro, S., et al., *The clinical maze of mitochondrial neurology.* Nat Rev Neurol, 2013. 9(8): p. 429-44.

112. Persico, A.M. and V. Napolioni, *Autism genetics.* Behav Brain Res, 2013. 251: p. 95-112.

113. Pitceathly, R.D., et al., *NDUFA4 mutations underlie dysfunction of a cytochrome c oxidase subunit linked to human neurological disease.* Cell Rep, 2013. 3(6): p. 1795-805.

114. Haddad, D.M., et al., *Mutations in the intellectual disability gene Ube2a cause neuronal dysfunction and impair parkin-dependent mitophagy.* Mol Cell, 2013. 50(6): p. 831-43.

115. Tran-Viet, K.N., et al., *Mutations in SCO2 are associated with autosomal-dominant high-grade myopia.* Am J Hum Genet, 2013. 92(5): p. 820-6.

116. Dinwiddie, D.L., et al., *Diagnosis of mitochondrial disorders by concomitant next-generation sequencing of the exome and mitochondrial genome.* Genomics, 2013. 102(3): p. 148-56.

117. Jonckheere, A.I., et al., *A complex V ATP5A1 defect causes fatal neonatal mitochondrial encephalopathy.* Brain, 2013. 136(Pt 5): p. 1544-54.

118. Lieber, D.S., et al., *Targeted exome sequencing of suspected mitochondrial disorders.* Neurology, 2013. 80(19): p. 1762-70.

119. Nota, B., et al., *Deficiency in SLC25A1, encoding the mitochondrial citrate carrier, causes combined D-2- and L-2-hydroxyglutaric aciduria.* Am J Hum Genet, 2013. 92(4): p. 627-31.

120. Gonzalez, M., et al., *Mutations in phospholipase DDHD2 cause autosomal recessive hereditary spastic paraplegia (SPG54).* Eur J Hum Genet, 2013. 21(11): p. 1214-8.

121. Kevelam, S.H., et al., *Exome sequencing reveals mutated SLC19A3 in patients with an early-infantile, lethal encephalopathy.* Brain, 2013. 136(Pt 5): p. 1534-43.

122. Auranen, M., et al., *Dominant GDAP1 founder mutation is a common cause of axonal Charcot-Marie-Tooth disease in Finland.* Neurogenetics, 2013. 14(2): p. 123-32.

123. Marina, A.D., et al., *NDUFS8-related Complex I Deficiency Extends Phenotype from "PEO Plus" to Leigh Syndrome.* JIMD Rep, 2013. 10: p. 17-22.

124. Gerards, M., et al., *Exome sequencing reveals a novel Moroccan founder mutation in SLC19A3 as a new cause of early-childhood fatal Leigh syndrome.* Brain, 2013. 136(Pt 3): p. 882-90.

125. Edvardson, S., et al., *Agenesis of corpus callosum and optic nerve hypoplasia due to mutations in SLC25A1 encoding the mitochondrial citrate transporter.* J Med Genet, 2013. 50(4): p. 240-5.

126. Prasad, C., et al., *Exome sequencing reveals a homozygous mutation in TWINKLE as the cause of multisystemic failure including renal tubulopathy in three siblings.* Mol Genet Metab, 2013. 108(3): p. 190-4.

127. Sambuughin, N., et al., *Exome sequencing reveals SCO2 mutations in a family presented with fatal infantile hyperthermia.* J Hum Genet, 2013. 58(4): p. 226-8.

128. Kennerson, M.L., et al., *A new locus for X-linked dominant Charcot-Marie-Tooth disease (CMTX6) is caused by mutations in the pyruvate dehydrogenase kinase isoenzyme 3 (PDK3) gene.* Hum Mol Genet, 2013. 22(7): p. 1404-16.

129. Miyake, N., et al., *Mitochondrial complex III deficiency caused by a homozygous UQCRC2 mutation presenting with neonatal-onset recurrent metabolic decompensation.* Hum Mutat, 2013. 34(3): p. 446-52.

130. Lee, H.J., et al., *Two novel mutations of GARS in Korean families with distal hereditary motor neuropathy type V.* J Peripher Nerv Syst, 2012. 17(4): p. 418-21.

131. Falk, M.J., et al., *Mitochondrial disease genetic diagnostics: optimized whole-exome analysis for all MitoCarta nuclear genes and the mitochondrial genome.* Discov Med, 2012. 14(79): p. 389-99.

132. McCormick, E., E. Place, and M.J. Falk, *Molecular genetic testing for mitochondrial disease: from one generation to the next.* Neurotherapeutics, 2013. 10(2): p. 251-61.

133. Siriwardena, K., et al., *Mitochondrial citrate synthase crystals: novel finding in Sengers syndrome caused by acylglycerol kinase (AGK) mutations.* Mol Genet Metab, 2013. 108(1): p. 40-50.

134. Lindberg, J., et al., *The mitochondrial and autosomal mutation landscapes of prostate cancer.* Eur Urol, 2013. 63(4): p. 702-8.

135. Rinaldi, C., et al., *Cowchock syndrome is associated with a mutation in apoptosis-inducing factor.* Am J Hum Genet, 2012. 91(6): p. 1095-102.

136. Keogh, M.J. and P.F. Chinnery, *Next generation sequencing for neurological diseases: new hope or new hype?* Clin Neurol Neurosurg, 2013. 115(7): p. 948-53.

137. Janer, A., et al., *An RMND1 Mutation causes encephalopathy associated with multiple oxidative phosphorylation complex deficiencies and a mitochondrial translation defect.* Am J Hum Genet, 2012. 91(4): p. 737-43.

138. Lamperti, C., et al., *A novel homozygous mutation in SUCLA2 gene identified by exome sequencing.* Mol Genet Metab, 2012. 107(3): p. 403-8.

139. Garone, C., et al., *MPV17 Mutations Causing Adult-Onset Multisystemic Disorder With Multiple Mitochondrial DNA Deletions.* Arch Neurol, 2012. 69(12): p. 1648-51.

140. Eschenbacher, W.H., et al., *Two rare human mitofusin 2 mutations alter mitochondrial dynamics and induce retinal and cardiac pathology in Drosophila.* PLoS One, 2012. 7(9): p. e44296.

141. Elo, J.M., et al., *Mitochondrial phenylalanyl-tRNA synthetase mutations underlie fatal infantile Alpers encephalopathy.* Hum Mol Genet, 2012. 21(20): p. 4521-9.

142. Li, X., H. Zou, and W.T. Brown, *Genes associated with autism spectrum disorder.* Brain Res Bull, 2012. 88(6): p. 543-52.

143. Zhao, Q., et al., *Rare inborn errors associated with chronic hepatitis B virus infection.* Hepatology, 2012. 56(5): p. 1661-70.

144. Casey, J.P., et al., *Identification of a mutation in LARS as a novel cause of infantile hepatopathy.* Mol Genet Metab, 2012. 106(3): p. 351-8.

145. Haack, T.B., et al., *Homozygous missense mutation in BOLA3 causes multiple mitochondrial dysfunctions syndrome in two siblings.* J Inherit Metab Dis, 2013. 36(1): p. 55-62.

146. Sailer, A. and H. Houlden, *Recent advances in the genetics of cerebellar ataxias.* Curr Neurol Neurosci Rep, 2012. 12(3): p. 227-36.

147. Horvath, R., et al., *A new phenotype of brain iron accumulation with dystonia, optic atrophy, and peripheral neuropathy.* Mov Disord, 2012. 27(6): p. 789-93.

148. Haack, T.B., et al., *Molecular diagnosis in mitochondrial complex I deficiency using exome sequencing.* J Med Genet, 2012. 49(4): p. 277-83.

149. Shamseldin, H.E., et al., *Genomic analysis of mitochondrial diseases in a consanguineous population reveals novel candidate disease genes.* J Med Genet, 2012. 49(4): p. 234-41.

150. Steenweg, M.E., et al., *Leukoencephalopathy with thalamus and brainstem involvement and high lactate 'LTBL' caused by EARS2 mutations.* Brain, 2012. 135(Pt 5): p. 1387-94.

151. Spiegel, R., et al., *Infantile cerebellar-retinal degeneration associated with a mutation in mitochondrial aconitase, ACO2.* Am J Hum Genet, 2012. 90(3): p. 518-23.

152. Dundar, H., et al., *Identification of a novel Twinkle mutation in a family with infantile onset spinocerebellar ataxia by whole exome sequencing.* Pediatr Neurol, 2012. 46(3): p. 172-7.

153. Calvo, S.E., et al., *Molecular diagnosis of infantile mitochondrial disease with targeted next-generation sequencing.* Sci Transl Med, 2012. 4(118): p. 118ra10.

154. Lieber, D.S., et al., *Atypical case of Wolfram syndrome revealed through targeted exome sequencing in a patient with suspected mitochondrial disease.* BMC Med Genet, 2012. 13: p. 3.

155. Pierson, T.M., et al., *Whole-exome sequencing identifies homozygous AFG3L2 mutations in a spastic ataxia-neuropathy syndrome linked to mitochondrial m-AAA proteases.* PLoS Genet, 2011. 7(10): p. e1002325.

156. Berger, I., et al., *Early prenatal ventriculomegaly due to an AIFM1 mutation identified by linkage analysis and whole exome sequencing.* Mol Genet Metab, 2011. 104(4): p. 517-20.

157. Takata, A., et al., *Exome sequencing identifies a novel missense variant in RRM2B associated with autosomal recessive progressive external ophthalmoplegia.* Genome Biol, 2011. 12(9): p. R92.

158. Tyynismaa, H., et al., *Thymidine kinase 2 mutations in autosomal recessive progressive external ophthalmoplegia with multiple mitochondrial DNA deletions.* Hum Mol Genet, 2012. 21(1): p. 66-75.

159. Marti-Masso, J.F., et al., *Exome sequencing identifies GCDH (glutaryl-CoA dehydrogenase) mutations as a cause of a progressive form of early-onset generalized dystonia.* Hum Genet, 2012. 131(3): p. 435-42.

160. Gotz, A., et al., *Exome sequencing identifies mitochondrial alanyl-tRNA synthetase mutations in infantile mitochondrial cardiomyopathy.* Am J Hum Genet, 2011. 88(5): p. 635-42.

161. Sundaram, S.K., et al., *Exome sequencing of a pedigree with Tourette syndrome or chronic tic disorder.* Ann Neurol, 2011. 69(5): p. 901-4.

162. Glazov, E.A., et al., *Whole-exome re-sequencing in a family quartet identifies POP1 mutations as the cause of a novel skeletal dysplasia.* PLoS Genet, 2011. 7(3): p. e1002027.

163. Bai, R.K. and L.J. Wong, *Simultaneous detection and quantification of mitochondrial DNA deletion(s), depletion, and over-replication in patients with mitochondrial disease.* J Mol Diagn, 2005. 7(5): p. 613-22.

164. Liu, C.S., et al., *Alteration in the copy number of mitochondrial DNA in leukocytes of patients with mitochondrial encephalomyopathies.* Acta Neurol Scand, 2006. 113(5): p. 334-41.

165. de Mendoza, C., et al., *Could mitochondrial DNA quantitation be a surrogate marker for drug mitochondrial toxicity?* AIDS Rev, 2004. 6(3): p. 169-80.

166. Ridge, P.G., et al., *Mitochondrial haplotypes associated with biomarkers for Alzheimer's disease.* PLoS One, 2013. 8(9): p. e74158.

167. Hagen, C.M., et al., *Mitochondrial haplogroups modify the risk of developing hypertrophic cardiomyopathy in a Danish population.* PLoS One, 2013. 8(8): p. e71904.

168. Crimi, M., et al., *Skeletal muscle gene expression profiling in mitochondrial disorders.* FASEB J, 2005. 19(7): p. 866-8.

169. He, S.L., et al., *Mitochondrial-related gene expression profiles suggest an important role of PGC-1alpha in the compensatory mechanism of endemic dilated cardiomyopathy.* Exp Cell Res, 2013. 319(17): p. 2604-16.

170. Zhang, Z., et al., *Primary respiratory chain disease causes tissue-specific dysregulation of the global transcriptome and nutrient-sensing signaling network.* PLoS One, 2013. 8(7): p. e69282.

171. Herrmann, P.C. and E.C. Herrmann, *Mitochondrial proteome: toward the detection and profiling of disease associated alterations.* Methods Mol Biol, 2012. 823: p. 265-77.