Descriptions of 24 Nuclear Genes Related to Mitochondrial Disorders

**BCS1L**: The *BCS1L* gene encodes a mitochondrial inner membrane protein that acts as a chaperone for the insertion of the Rieske Fe/S subunit into complex III. Mutations in *BCS1L* have been associated with autosomal recessive Björnstad syndrome (sensorineural hearing loss and pili torti), GRACILE (growth retardation, aminoaciduria, cholestasis, iron overload, lactacidosis, and early death) syndrome, and fatal complex III deficiency in neonates presenting with encephalopathy, alone or with visceral involvement. In 12 Turkish patients presenting with neonatal complex III deficiency, *BCS1L* mutations were identified in four patients (8/24 alleles). In 5 patients with Björnstad syndrome, *BCS1L* mutations were identified on 10/10 alleles with 3 Norwegian patients harboring at least one R306H mutation, and in 14 patients with GRACILE syndrome, mutations were identified on 27/28 *BCS1L* alleles. Of the GRACILE patients, the 11 Finnish patients were homozygous for a S78G mutation and were found to have normal complex III activity while 3 British patients had deficiency of complex III.

**C10ORF2 (aka Twinkle/PEO1)**: The *C10ORF2* gene encodes the mitochondrial helicase and mutations in this gene cause loss of integrity of the mitochondrial genome, resulting in primarily the accumulation of multiple mtDNA deletions; however, depletion of mtDNA has also been reported. Disorders associated with *C10ORF2* mutations are predominantly autosomal dominant: chronic progressive external ophthalmoplegia (CPEO) of varying severity and SANDO (sensory ataxic neuropathy, dysarthria, and ophthalmoparesis). *C10ORF2* mutations that cause the autosomal recessive disorder have been associated with infantile onset spinocerebellar ataxia and early onset encephalopathy with liver involvement. The frequency of *C10ORF2* mutations in patients with autosomal dominant CPEO has been reported as ~7%-27%. The frequency of mutations was found to be higher in familial (~27%) compared to sporadic (~4%) cases of autosomal dominant CPEO.

**COQ2**: Coenzyme Q10 (CoQ10), or ubiquinone, is a mobile lipophilic electron carrier critical for electron transfer by the mitochondrial inner membrane respiratory chain from complex II and I to complex III. Intracellular synthesis is the major source of CoQ10, although a small proportion is acquired through diet. CoQ10 is synthesized in the mitochondrial inner membrane and CoQ2 catalyzes one of the final reactions of its biosynthesis. Primary CoQ10 deficiency is a rare, clinically heterogeneous autosomal recessive disorder with 5 major phenotypes: (1) an encephalomyopathic form with seizures and ataxia; (2) a multisystem infantile form with encephalopathy, cardiomyopathy and renal failure; (3) a predominantly cerebellar form with ataxia and cerebellar atrophy; (4) Leigh syndrome with growth retardation; and (5) an isolated myopathic form. Typical CoQ10 deficiency has relatively normal isolated complex I, II and III activity, but deficient I+III and II+III activity. COQ2 is one of the four genes (COQ2, PDSS1, PDSS2 and APTX) currently having reported mutations causing COQ10 deficiency. Mutations in COQ2 gene have been reported in patients with COQ10 deficiency and infantile-childhood encephalopathy & nephrotic syndrome. CoQ10 deficiency can be treated by supplement of CoQ10.

**COX10**: The *COX10* gene encodes a cytochrome c oxidase (COX) assembly protein, heme A:farnesyltransferase, involved in the mitochondrial heme biosynthetic pathway. The COX10 protein catalyzes the conversion of protoheme to heme O and is required for expression of functional COX. COX10 deficiency is an autosomal recessive disorder with a heterogeneous clinical picture that includes anemia, Leigh syndrome, sensorineural deafness, fatal infantile hypertrophic cardiomyopathy, tubulopathy and leukodystrophy. The disease progression is rapid with all patients dying within a few
months after the onset of symptoms. Other general features are hypotonia, elevated blood lactate and the presence of residual COX activity. In one study of 11 patients with decreased COX activity in cultured fibroblasts, one individual was homozygous for a mutation in the COX10 gene.

**COX15:** The COX15 gene encodes a membrane bound mitochondrial protein involved in the last part of the biosynthetic pathway of heme A, an essential step in the biogenesis of cytochrome c oxidase (COX). Studies in yeast indicate that the COX15 protein is part of a three component mono-oxygenase, catalyzing the hydroxylation of a methyl group of heme O, the precursor molecule of heme A. Mutations in COX15 have been described in 3 patients with autosomal recessive COX deficiency. The first patient presented soon after birth with muscle hypotonia, epilepsy, lactic acidosis and the development of a rapidly fatal hypertrophic cardiomyopathy. The second patient is reported to have had rapidly progressive Leigh syndrome and chronic gastrointestinal dysfunction, with death at 4 years of age. The third patient had a slow progressive clinical course with partial preservation of cognitive function and survival beyond adolescence. Sequencing of the COX15 gene in 6 patients with hypertrophic cardiomyopathy and COX deficiency identified mutations in a single patient.

**COX6B1:** The COX6B1 gene encodes one of the 10 nuclear encoded subunits that make up cytochrome c oxidase (COX). The COX6B1 protein connects the two COX monomers into the physiological dimeric form and is also believed to interact with cytochrome c. At this time, mutation of the COX6B1 gene has been identified in two brothers presenting with early-onset leukodystrophy, myopathy, growth retardation and COX deficiency. The two siblings were homozygous for an R19H (p.Arg19His) mutation.

**DGUOK:** The DGUOK gene encodes the deoxyguanosine kinase (dGK) enzyme that is involved in phosphorylation of mitochondrial deoxyribonucleotides. Mutations in the DGUOK gene are associated with mtDNA depletion and combined deficiencies of the mtDNA-encoded respiratory chain complexes. Patients with dGK deficiency typically present with liver dysfunction at birth or within a few months, with or without neurological impairment. Elevated serum tyrosine or phenylalanine may be present and may be identified on newborn screening. Neurological disease may also be apparent. Patients harboring null mutations usually have early onset liver failure and significant neurological disease, while those with missense mutations usually have isolated liver disease. The inheritance pattern is autosomal recessive and DGUOK mutations have been found on 18% of alleles from patients with mtDNA depletion, on 17% of alleles from patients with hepatocerebral disease and combined respiratory chain deficiencies, and on ~46% of alleles from patients with infantile hepatocerebralopathies and mtDNA depletion.

**DLD:** The DLD gene encodes the dihydrolipoamide dehydrogenase (E3) enzyme, which is a component of several multi-enzyme complexes: pyruvate dehydrogenase complex, α-ketoglutarate dehydrogenase complex, and branched-chain α-ketoacid dehydrogenase complex. E3 is also a component in the glycine cleavage system in mitochondria. The clinical picture of patients with deficiency of E3 ranges from a severe neonatal presentation with neurological deficits to a less severe childhood presentation with exertional fatigue between decompensation episodes. Patients may also present with severe liver failure. The inheritance pattern is autosomal recessive. In a study of seven unrelated Ashkenazi Jewish patients with E3 deficiency, DLD mutations were identified on all alleles (14/14). Other reports of DLD mutations in E3 deficient patients from varied ethnic backgrounds have consisted of single case studies; therefore, sensitivity of mutation analysis cannot be established.

**MPV17:** Mutations in the MPV17 gene are associated with an autosomal recessive form of hepatocerebral mitochondrial depletion syndrome whereby patients present with early-onset hepatopathy and later develop neurologic symptoms. The MPV17 gene encodes an inner membrane mitochondrial protein of unknown function. A p.R50Q mutation in MPV17 has been associated with a variant form of mitochondrial depletion syndrome in the Navajo population. MPV17 mutations were found on 2% of alleles in 50 patients identified with mitochondrial depletion.
**OPA1:** The **OPA1** gene codes for an inner mitochondrial membrane protein critical for mtDNA maintenance and oxidative phosphorylation. Mutations in **OPA1** are associated with autosomal dominant optic atrophy characterized by bilateral and symmetric optic nerve pallor associated with vision loss and color vision defects. More severe phenotypes have also been described in ~10% of **OPA1** mutation carriers and include sensorineural deafness, ptosis and myopathy.18 In a large study of 980 cases of suspected hereditary optic neuropathy, mutations in the **OPA1** gene were identified in 30%, with mutations found in 52% of familial cases and in 48% of apparently sporadic cases.18 Patients with **OPA1** mutations and multiple mtDNA deletions have also been described.19 Of 21 patients with multiple mtDNA deletions who did not have mutations in **POLG1, POLG2, SLC25A4 or PEO1** (other genes associated with multiple mtDNA deletions), approximately 14% harbored an **OPA1** mutation.19 Missense mutations, splicing mutations and small deletions are commonly seen.

**PDHA1:** The **PDHA1** gene is located on the X chromosome and encodes the E1α subunit of the pyruvate dehydrogenase complex (PDH). The PDH complex is located in the mitochondrial matrix and catalyzes the irreversible oxidative decarboxylation of pyruvate to acetyl-CoA. Defects in the PDH complex are an important cause of primary lactic acidosis, and clinical symptoms of patients with a PDH complex deficiency vary considerably, ranging from an intermittent ataxia to a progressive disease with mental retardation and neurological complications to an early neonatal presentation with severe lactic acidosis and early death. The majority (>80%) of PDH complex deficiencies result from mutation in the **PDHA1** gene.20 In a series of studies involving between 7 and 14 patients with PDH complex deficiency, a single **PDHA1** mutation was identified in all male and female patients.21, 22, 23 However, in a more recent study of 40 patients with biochemically demonstrated PDH complex deficiency or strong suspicion of PDH complex deficiency, a **PDHA1** mutation was identified in 20 individuals.62 Thirty-two patients from this cohort of 40 showed specific deficiency of the PDH-E1 component and of these 32 individuals a mutation in the **PDHA1** gene was identified in 17 (53%).62 Small numbers of patients with PDH complex deficiency with mutations in genes encoding the other PDH complex subunits (**PDHB, DLAT, DLD, PDHX, PDP1**) have been reported.20, 24

**POLG:** The **POLG** (aka **POLG1**) gene encodes the catalytic subunit of polymerase gamma (poly), the only polymerase known to be involved in replication of the mtDNA. Mutations in **POLG** are one of the most common causes of inherited mitochondrial disease in children and adults and are responsible for a heterogeneous group of disorders and phenotypes exhibiting both autosomal dominant and autosomal recessive inheritance including autosomal dominant and recessive chronic progressive external ophthalmoplegia (CPEO), Alpers syndrome (aka Alpers-Huttenlocher syndrome), childhood Myocerebrohepatopathy Spectrum Disorders (MCHS), mtDNA deletion disorders in the Ataxia Neuropathy Spectrum (ANS) including spinocerebella ataxia with epilepsy (SCAE) and mitochondrial recessive ataxia syndrome without ophthalmoplegia (MIRAS), and Myoclonus Epilepsy Myopathy Sensory Ataxia (MEMSA). Parkinsonism and premature ovarian failure has also been described in some families with autosomal dominant inheritance.25, 26 In two large studies, sequence analysis was performed to identify mutations in the **POLG** gene in 350 and 232 patients exhibiting a **POLG**-related phenotype.26, 27 Between 8%-9% of patients had an autosomal recessive **POLG**-related phenotype and had two known **POLG** mutations identified.26, 27 Several patients with a known autosomal dominant **POLG**-related phenotype had a single **POLG** mutation identified. In addition, approximately 4-7% of patients had a single **POLG** mutation identified but could not be classified as having an autosomal dominant or autosomal recessive **POLG**-related phenotype.26, 27 A separate report of 27 individuals with sporadic CPEO, found a **POLG** mutation in 7 (~26%) with two **POLG** mutations identified in 3 individuals and a single **POLG** mutation identified in the remaining 4.9 Recent evidence showed that certain mutations in **POLG** gene can lead to a range of clinical phenotypes which predispose to development of liver failure after exposure to vaproic acid (VPA).25, 61 Approximately 90% of mutations are missense.
**POLG2:** The POLG2 gene encodes a 55-kDa polymerase γ accessory subunit that functions as a DNA-binding factor increasing the affinity of polymerase γ to mtDNA. In 100 patients with sporadic or familial progressive external ophthalmoplegia (PEO) and histochemical evidence of mitochondrial disease, a POLG2 mutation, p.Gly451Glu (G451E), was found in a single patient.54 In a second study of 62 patients with multiple mtDNA deletions in muscle DNA, a 24 bp insertion (c.1207_1208ins24) was found in a single individual.55 Both individuals are reported to have autosomal dominant PEO.54, 55

**RRM2B:** The RRM2B gene encodes the p53-controlled ribonucleotide reductase subunit responsible for the de novo synthesis of deoxyribonucleoside 5’-diphosphates (dNTPs) essential for maintenance of mtDNA. Mutations in the RRM2B gene are associated with the most severe condition of mtDNA depletion in muscle tissue thus far described with most affected patients displaying a severe phenotype with lactic acidosis, profound mtDNA depletion and death prior to four months of age; however, two patients with a more benign course are still living at ages 2 and 3 years.28, 29 In nine patients with severe mtDNA depletion in muscle in whom mutations in other genes associated with mtDNA depletion (TK2, SUCLA2, DGUOK, POLG, SUCLG1 and MPV17) had been excluded, RRM2B mutations were identified on 6/18 alleles.29 Recently, a heterozygous truncating mutation in RRM2B gene causing autosomal-dominant progressive external ophthalmoplegia with multiple deletions has been reported (Am J Hum Genet, 2009, 85:290-295).

**SCO1:** The SCO1 gene encodes a protein that is believed to be involved in the transfer of copper to cytochrome c oxidase (COX).60 Mutations in SCO1 have been found in a family with isolated COX deficiency, early-onset hepatic failure and encephalopathy.60 Affected individuals were compound heterozygous for a 2bp deletion and a missense mutation (p.P174L).60 No SCO1 mutations were identified in an additional 18 patients with isolated COX deficiency and a similar clinical presentation.60

**SCO2:** The SCO2 gene encodes a metallochaperone involved in the delivery of copper to Complex IV (COX) of the respiratory chain. Mutations in SCO2 are associated with autosomal recessive decreased COX activity and early onset, fatal hypertrophic cardiomyopathy (HCM). In a study involving 26 patients with COX deficiency and various clinical phenotypes, single strand conformation polymorphism (SSCP) analysis identified SCO2 mutations in a single patient with HCM corresponding to ~16% of patients with an early-onset HCM phenotype having mutations in SCO2.30 A study including 9 unrelated patients with COX deficiency and HCM, identified SCO2 mutations in 4/18 alleles (~22%).31 Nearly all reported patients carry at least one copy of the common c.1541 G>A (E140K) mutation. Patients homozygous for E140K have a delayed onset of disease and a more prolonged survival, while patients with one copy of E140K in combination with a more deleterious mutation follow a severe clinical course, which sometimes mimicks Spinal Muscular Atrophy I (Werdnig-Hoffman disease)32. To date, a single patient with fatal infantile cardiomyopathy has been reported as homozygous for a mutation other than E140K in the SCO2 gene.33

**SLC25A4 (aka ANT1):** The SLC25A4 gene encodes the heart and skeletal muscle-specific isoform of the adenine nucleotide translocator (ANT1) that controls ATP and ADP shuttling at the mitochondrial inner membrane. Mutations in SLC25A4 are associated with autosomal dominant progressive external ophthalmoplegia (adPEO) characterized by adult-onset of symptoms, ptosis and occasionally limb weakness, sings of peripheral neuropathy, sensorineural hearing loss, major depression and endocrine dysfunction. Muscle biopsy commonly reveals multiple mtDNA deletions. SLC25A4 mutations are considered to be rare in patients with adPEO when compared with POLG and PEO1 mutations.34 A study of 27 patients with sporadic PEO, found a SLC25A4 mutation in a single patient (~4%), while a report of 67 patients with multiple DNA deletions with or without PEO, found a SLC25A4 mutation in 6 (~9%) which represents ~15% of the familial cases in the study population.9, 11 A single patient who presented with hypertrophic cardiomyopathy and mild myopathy with exercise intolerance and lactic acidosis but no ophthalmoplegia was found to be homozygous for a SLC25A4 mutation.34
**SUCLA2:** The SUCLA2 gene codes for the β subunit of the mitochondrial matrix enzyme succinyl-CoA synthase that catalyzes the formation of succinate and ATP from succinyl-CoA and ADP in the Krebs cycle. Mutations in the SUCLA2 gene cause SUCLA2-related mitochondrial DNA depletion syndrome, which is a very rare autosomal recessive condition characterized by onset of severe hypotonia in infancy, severe muscular atrophy with failure to achieve ambulation, progressive scoliosis or kyphosis, dystonia and/or hyperkinesias, epilepsy, growth retardation, sensorineural hearing loss and early lethality. Affected individuals have elevated levels of methylmalonic acid in urine and plasma, deficiency of respiratory complex I, III, and IV, with normal complex II activity, and mtDNA depletion. Sequence analysis of SUCLA2 is estimated to detect greater than 95% of mutations. A founder mutation, c.534+1 G>A, has been identified in the Faroese population where approximately 1 in 33 individuals is a carrier.

**SUCLG1:** The SUCLG1 gene codes for the α subunit of the mitochondrial matrix enzyme succinyl-CoA synthase that catalyzes the formation of succinate and ATP from succinyl-CoA and ADP in the Krebs cycle. At this time very few patients with mutations in the SUCLG1 gene have been described. A small consanguineous family where affected members are homozygous for a 2-bp deletion of SUCLG1 has been reported with severe, fatal lactic acidosis within the first few days of life, urinary excretion of methylmalonic acid, deficiency of respiratory chain complex I, III, and IV, and mtDNA depletion. Other individuals with mutations in SUCLG1 have been found with a milder phenotype that includes hypotonia, muscle atrophy, dystonia, “Leigh-like” syndrome, mtDNA depletion in muscle and a short life span of up to 21 years. Liver impairment is frequently reported in SUCLG1 patients and the combination of lactic acidemia, mild methylmalonic aciduria, acyl-carnitine ester abnormalities and combined respiratory complex deficiency has been established as characteristic markers. MtDNA depletion is not a constant finding. Because reports of SUCLG1 mutations have consisted of studies with very few patients, the sensitivity of mutation analysis cannot be established at this time.

**SURF1:** The SURF1 gene encodes a factor believed to be involved in the assembly of Complex IV (COX) of the respiratory chain. Mutations in SURF1 most often result in autosomal recessive Leigh syndrome and severe COX deficiency. Leigh syndrome is a progressive and often fatal neurological disorder characterized by bilaterally symmetrical necrotic lesions in the brain stem and basal ganglia. SURF1 mutations have rarely been associated with villous atrophy, leukodystrophy and dysmorphic facial features. Mutations in the SURF1 gene have been identified in 26%-75% of patients with Leigh syndrome associated with COX deficiency.

**TACO1:** A homozygous single-base-pair insertion of the TACO1 gene was identified in a family with late-onset Leigh syndrome and isolated cytochrome c oxidase (COX) deficiency. The TACO1 gene is believed to code for a mitochondrial translational activator necessary for the efficient translation of COX.

**TIMM8A (aka DDPI):** TIMM8A is a gene located on the X chromosome that encodes the mitochondrial import inner membrane translocase subunit Tim8 that acts in a complex together with the Tim13 protein in a chaperone-like manner to facilitate the import of nuclear-encoded precursor proteins into the mitochondrial inner membrane. Mutations in TIMM8A cause deafness-dystonia-optic neuropathy (DDON) syndrome (aka Mohr-Tranebjaerg syndrome) a rare neurodegenerative disease with early-onset deafness, dystonia and other neurological abnormalities including cortical blindness, spasticity, dementia and mental retardation. DDON may also occur as a contiguous gene deletion syndrome, which also includes X-linked agammaglobulinemia caused by disruption of the BTK gene that is telomeric to TIMM8A. Females may have mild hearing impairment and focal dystonia. Only a small number of individuals with DDON syndrome have been reported; therefore, the sensitivity of mutation analysis in the TIMM8A gene has not been established.
**TK2:** The TK2 gene encodes thymidine kinase 2, a deoxyribonucleoside kinase that participates in the salvage pathway of deoxyribonucleoside synthesis in the mitochondria. Mutations in this gene cause an autosomal recessive progressive, myopathic form of mtDNA depletion syndrome with patients exhibiting severe infantile myopathy with motor regression and early death. Affected patients have also been reported with brain involvement, ptosis, ophthalmoplegia, nephropathy, optic neuropathy, spinal muscular atrophy type 3-like presentation, rigid spine syndrome and a milder myopathic phenotype without motor regression and with longer survival.\(^{43, 44}\) In patients with myopathic forms of mtDNA depletion syndrome, mutations in the TK2 gene have been identified on 11%-16% of TK2 alleles.\(^{45, 46}\) In patients with mtDNA depletion syndrome not specified as having the myopathic form, TK2 mutations have been found on 2%-9% of alleles.\(^{13, 46}\)

**TYMP (aka ECGF1 or TP):** The TYMP gene encodes the thymidine phosphorylase (TP) enzyme that catalyzes the reversible phosphorolysis of thymidine and is likely to have an important role in nucleoside metabolism by regulating the availability of thymidine for DNA synthesis. Mutations in the TYMP gene cause mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) an autosomal recessive disorder characterized by severe gastrointestinal dysmotility, cachexia (loss of body mass that cannot be reversed nutritionally), ptosis and/or ophthalmoparesis, peripheral neuropathy and leukoencephalopathy. Skeletal muscle biopsies of affected patients reveal abnormalities of mtDNA and mitochondrial respiratory chain enzymes, and the activity of the TP enzyme is decreased in leukocytes. In patients diagnosed with MNGIE either by strict clinical criteria or by reduced TP enzyme activity, mutations in the TYMP gene have been identified on greater than 98% of alleles.\(^{47, 48, 49}\)

**References:**