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CoQ₁₀ deficiencies and MNGIE: Two Treatable Mitochondrial Disorders

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Abstract

Background—Although causative mutations have been identified for numerous mitochondrial disorders, few disease-modifying treatments are available. Two examples of treatable mitochondrial disorders are coenzyme Q₁₀ (CoQ₁₀ or ubiquinone) deficiency and mitochondrial neurogastrointestinal encephalomyopathy (MNGIE).

Scope of Review—Here, we describe clinical and molecular features of CoQ₁₀ deficiencies and MNGIE and explain how understanding their pathomechanisms have led to rationale therapies. Primary CoQ₁₀ deficiencies, due to mutations in genes required for ubiquinone biosynthesis, and secondary deficiencies, caused by genetic defects not directly related to CoQ₁₀ biosynthesis, often improve with CoQ₁₀ supplementation. *In vitro* and *in vivo* studies of CoQ₁₀ deficiencies have revealed biochemical alterations that may account for phenotypic differences among patients and variable responses to therapy. In contrast to the heterogeneous CoQ₁₀ deficiencies, MNGIE is a single autosomal recessive disease due to mutations in the *TYMP* gene encoding thymidine phosphorylase (TP). In MNGIE, loss of TP activity causes toxic accumulations of the nucleosides thymidine and deoxyuridine that are incorporated by the mitochondrial pyrimidine salvage pathway and cause deoxynucleoside triphosphate pool imbalances, which, in turn cause mtDNA instability. Allogeneic hematopoietic stem cell transplantation to restore TP activity and eliminate toxic metabolites is a promising therapy for MNGIE.

Conclusions—CoQ₁₀ deficiencies and MNGIE demonstrate the feasibility of treating specific mitochondrial disorders through replacement of deficient metabolites or via elimination of excessive toxic molecules.

General Significance—Studies of CoQ₁₀ deficiencies and MNGIE illustrate how understanding the pathogenic mechanisms of mitochondrial diseases can lead to meaningful therapies.

Coenzyme Q₁₀

An essential component of the mitochondrial respiratory chain, coenzyme Q₁₀ (CoQ₁₀) shuttles electrons from complexes I and II and from electron transferring flavoprotein dehydrogenase (ETF-DH) to complex III (Figure 1)[1]. In addition, CoQ₁₀ is a potent

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antioxidant, and is a cofactor of dihydro-orotate dehydrogenase a critical enzyme for *de novo* pyrimidine biosynthesis.

A lipophilic molecule, CoQ₁₀ is composed of a redox-active benzoquinone and a hydrocarbon tail comprised of 10 isoprenyl units. The reduced form is ubiquinol while the oxidized form is ubiquinone. CoQ₁₀ is synthesized within mitochondria through a complex pathway that is incompletely characterized in humans (Figure 1) [2]. The benzoquinone ring is derived from the amino acids phenylalanine and tyrosine while the decaprenyl side-chain is generated from acetyl-CoA via the mevalonate pathway. After condensation of para-hydroxybenzoate with the decaprenyl tail, the ring undergoes decarboxylation, hydroxylation, and methylation modifications to produce CoQ₁₀.

Screening for CoQ₁₀ Deficiency

The gold standard test for diagnosing CoQ₁₀ deficiency is high performance liquid chromatography (HPLC) measurement of ubiquinone in a skeletal muscle biopsy [3]. CoQ₁₀ levels reduced more than 2 standard deviations below control mean values are considered deficient [4]. Decreased activities of CoQ₁₀ dependent enzymes (e.g. NADH-cytochrome *c* reductase [complexes I+III] or succinate cytochrome *c* reductase [complex II+III]) strongly support the diagnosis of CoQ₁₀ deficiency; however, cases of mild CoQ₁₀ deficiency have shown normal activities of complexes I+III, II+III, or both. Plasma CoQ₁₀ level is dependent on concentration of lipoproteins, which act as carriers of CoQ₁₀ in the circulation and on dietary intake; therefore, plasma concentrations of CoQ₁₀ are not reliable for the diagnosis of CoQ₁₀ deficiency. Measurements of CoQ₁₀ level in blood mononuclear cells (MNCs) has detected deficiency in a small number of patients; however, correlations with muscle CoQ₁₀ measurements in a larger group of patients will be necessary to assess clinical utility of MNC ubiquinone levels. Cultured lymphoblastoid cell lines and primary fibroblasts have revealed CoQ₁₀ deficiency in most, but not all patients with ubiquinone deficiency in muscle [5–9]. Primary CoQ₁₀ deficiencies (due to defects of ubiquinone biosynthesis) cannot be distinguished from secondary deficiencies based on CoQ₁₀ levels.

Primary CoQ₁₀ Deficiencies

The first patients with CoQ₁₀ deficiency were reported in 1989 by Ogasahara and colleagues who described a pair of sisters, ages 12 and 14 years-old, with a mitochondrial disorder characterized by encephalopathy (mental retardation and seizures) and myopathy evident as elevated serum creatine kinase, and recurrent myoglobinuria [5]. Muscle biopsies showed ragged-red fibers, reduced biochemical activities of complexes I+III and II+III, and marked CoQ₁₀ deficiencies. Both patients improved markedly with CoQ₁₀ supplementation. Although 3 additional patients with similar encephalopathies and CoQ₁₀ deficiency have been reported [5, 10–12], causative molecular genetic defect has only been identified in one patient who has mutations in the *ADCK3* (*CABC1*) gene, which encodes a kinase, which is thought to modulate ubiquinone biosynthesis [7, 10, 13].

An infantile multisystemic presentation of CoQ₁₀ deficiency has been associated with mutations in four genes required for ubiquinone biosynthesis. The syndrome typically manifests as a combination of encephalopathy and kidney disease that is usually a steroid-resistant nephrotic syndrome. This condition was originally reported by Rötig and colleagues, who described 3 siblings who initially manifested neurological signs including nystagmus, optic atrophy, sensorineural hearing loss, ataxia, dystonia, and weakness with progressive nephropathy that was fatal in one and treated with renal transplant in the other [14]. The two living siblings improved with CoQ₁₀ supplementation. In 2006, we described the first defect of CoQ₁₀ biosynthesis in two siblings who shared a homozygous missense mutation in the *COQ2* gene, which encodes para-hydroxybenzoate-polyprenyl transferase

[9]. The older sibling had steroid-resistant nephrotic syndrome that required renal transplantation and then a severe encephalopathy [15]. After a muscle biopsy at age 33 months revealed ubiquinone deficiency, treatment with high-dose CoQ₁₀ led to neurological improvements. The younger sister, at age 12 months, developed nephrotic syndrome, which improved with CoQ₁₀ supplementation [16, 17]. *COQ2* mutations have been reported in four additional patients; a pair of siblings with fatal neonatal multisystemic disease, including nephrotic disease [18] and two other unrelated patients had early-onset glomerulopathy; one had only steroid-resistant nephrotic syndrome that improved with CoQ₁₀ therapy while the other progressed to end-stage renal disease and epileptic encephalopathy leading to death at age 6 months [16].

Mutations in *PDSS1* and *PDSS2*, genes encoding the two subunits of polyprenyl diphosphate synthase that produces the decaprenyl tail of CoQ₁₀, have been also identified as causes of the infantile-onset form of CoQ₁₀ deficiency. In an infant who presented with neonatal hypotonia and subsequently developed nephrotic syndrome and Leigh syndrome, we identified compound heterozygous mutations in *PDSS2* [8]. Despite CoQ₁₀ supplementation from age 3 months, the disease progressed to death at 8 months. In a consanguineous family, two siblings had CoQ₁₀ deficiency due to a homozygous *PDSS1* mutation manifesting as a complex multisystemic disease with early onset deafness, encephaloneuropathy, obesity, livedo reticularis and cardiac valvulopathy [18].

Duncan and colleagues reported mutations in *COQ9* in a newborn with generalized limb hypertonia, reduced truncal tone, lactic acidosis, renal tubulopathy and cardiomyopathy [6]. Despite CoQ₁₀ supplementation, he developed seizures and dystonia and died at age 2 years. In 2011, mutations in *COQ6* have been identified in 11 patients from 5 different kindreds, with a phenotype similar to that observed in patients with mutations in *COQ2* or *PDSS2* [19]. All had nephrotic syndrome with onset in the first years of life, associated with sensorineural hearing loss in most cases, and some also had CNS involvement with seizures or ataxia.

In 2001, Musumeci and colleagues described six patients with the most common phenotype associated with CoQ₁₀ deficiency – juvenile-onset cerebellar ataxia and atrophy variably associated with peripheral neuropathy, seizures, mental retardation, muscle weakness, and hypogonadism [20]. In a follow-up study of 135 patients with genetically undefined cerebellar ataxia, 13 (~10%) had CoQ₁₀ deficiency. *ADCK3* mutations have been reported in 12 patients (8 families) with juvenile-onset cerebellar ataxia and atrophy making this gene the most frequent cause of primary CoQ₁₀ deficiency [7, 13, 21]. CoQ₁₀ supplementation has been associated with mild subjective improvement in patients with *ADCK3* mutations.

Secondary CoQ₁₀ deficiencies

Of 6 patients with cerebellar ataxia and CoQ₁₀ deficiency reported by Musumeci and colleagues, three had *APTX* gene mutations known to cause ataxia oculomotor apraxia 1 (AOA1). *APTX* encodes aprataxin, a protein involved in single- and double-strand DNA break repair and localized to nuclei and mitochondria [22]. Low levels of CoQ₁₀ were subsequently found in muscle and fibroblasts of some patients with typical AOA1 [23]. However in other AOA1 patients, CoQ₁₀ levels may be normal or even elevated. Clear genotype-phenotype correlations have yet to be established, and the mechanism of CoQ₁₀ deficiency in this disorder remains unknown.

Mutations in the *ETFDH* gene (encoding the electron transfer flavoprotein dehydrogenase) were identified in patients who had been initially reported as having the isolated myopathy phenotype of CoQ₁₀ deficiency [24]. Biochemical investigations showed increased CK and lactate levels, with low carnitine and a characteristic acylcarnitine profile on tandem mass

spectrometry suggestive of multiple acyl-CoA dehydrogenase deficiency (MADD) [25]. Muscle biopsies exhibited mild to severe vacuolar changes, increased lipid content, ragged-red fibres, focal or diffuse SDH deficiency, COX-negative fibres, combined complex I/II+III deficiency, and decreased level of CoQ₁₀ in muscle (50% of normal). The mechanism of CoQ₁₀ deficiency in MADD remains unknown and it does not appear to be a universal feature of this disorder, since some patients have been demonstrated to have normal CoQ₁₀ levels [26, 27].

Secondary CoQ₁₀ deficiency has also been reported in a number of patients with primary mtDNA mutations. For example, levels of CoQ₁₀ in muscle from 25 patients with mitochondrial encephalopathies, mostly due to mtDNA mutations, were significantly lower than controls [28] while a multicenter study of 76 patients with heterogeneous mitochondrial diseases detected CoQ₁₀ deficiency in 28 (37%) of which nine had pathogenic mtDNA mutations [29]. Cultured skin fibroblasts from patients with MELAS had secondary CoQ₁₀ deficiency that triggered autophagy [30]. However the significance of CoQ₁₀ deficiency in these patients remain unclear.

Cell Culture Models of CoQ₁₀ Deficiency

In vitro models have revealed insights into the pathogenesis of CoQ₁₀ deficiency. Initial studies in cultured fibroblasts from two siblings with infantile-onset CoQ₁₀ deficiency showed mild respiratory chain defects, but did not detect elevated superoxide anions, lipid peroxidation, or apoptosis-mediated cell death [31]. Lopez-Martin and colleagues showed that *COQ2* mutant fibroblasts require uridine to sustain growth and proposed that deficiency of CoQ₁₀ impaired *de novo* pyrimidine biosynthesis because of the dependence of dihydro-orotate dehydrogenase on ubiquinone [32]. In the same two cell lines plus two other cells lines from patients with genetically undefined CoQ₁₀ deficiency, Rodriguez-Hernandez and colleagues noted increased autophagy of mitochondria [33].

We initially observed that *PDSS2* mutant fibroblasts have 12% residual CoQ₁₀ and markedly reduced ATP synthesis, but do not show increased reactive oxygen species (ROS) or oxidative stress, while *COQ2* mutant fibroblasts with 30% CoQ₁₀ content have mild defects of ATP synthesis and significantly increased ROS production as well as oxidation of lipids and proteins and cell death [34]. We have extended the studies to other patient cell lines with variable degrees of CoQ₁₀ deficiency due to different mutations in *COQ2*, *ADCK3*, and *COQ9*, and have observed similar correlations between levels of CoQ₁₀ and cellular phenotype: 10–15% or >60% residual CoQ₁₀ levels are not associated with significant ROS production whereas 30–50% residual CoQ₁₀ content is associated with maximal ROS production and cell death [35]. Thus, *in vitro*, severe deficiency of CoQ₁₀ causes bioenergetic defects, while moderate deficiency produces ROS, oxidative damage, and cell death.

Our *in vitro* therapeutic studies of patients' fibroblasts with mutations in *COQ9*, *COQ2* and *PDSS2* have revealed that the prolonged pharmacokinetics (>24 hours) of CoQ₁₀ required to reach the mitochondrial respiratory chain critically affects restoration of energy status of human CoQ₁₀ deficient cells [36]. Additionally, we demonstrated that short tail ubiquinone analogues cannot substitute CoQ₁₀ in the mitochondrial respiratory chain of human CoQ₁₀ deficient fibroblasts, thus revealing the importance of the decaprenyl tail most likely through interactions with complex I [37, 38]. In contrast, oxidative stress and cell death were attenuated by the administration of lipophilic (idebenone and CoQ₂) and hydrophilic (vitamin C) antioxidants.

Mouse Model of CoQ Deficiency

In the early 1970s, a spontaneous mutation (*kd*) in mouse colony was noted to cause autosomal recessive kidney disease [39]. Homozygous *kd/kd* mice appear healthy for at least the first 8 weeks of life, but histological examination of the kidneys at about 12 weeks reveals a mononuclear cell infiltrate and tubular dilation. Over time the entire kidney is involved and the mice die of renal failure [40]. The mutation responsible for the *kd/kd* phenotype was identified as a V117M amino acid substitution in *Pdss2* – murine homolog of human *PDSS2* [41, 42]. Although young homozygous *Pdss2^{kd/kd}* mice have a normal content of CoQ₉ (the predominant ubiquinone in rodents) and CoQ₁₀ in kidney, they fail to elevate levels of CoQ₉ and CoQ₁₀ in kidneys as wild-type mice do at about age 40 days. The onset of proteinuria and kidney disease ensues several weeks after the normal increase in CoQ₉ and CoQ₁₀ fails to occur [42]. Conditional knockout mice showed that proteinuria and kidney disease could be recapitulated when *Pdss2* was deleted in podocytes (*Podocin/cre, Pdss2^{loxP/loxP}*) but not when targeted to renal tubular epithelium, monocytes or hepatocytes [41].

Treatment of CoQ10 Deficiencies

Supplementation with oral CoQ₁₀ (10–30 mg/kg/day in children and 1,200–3,000 mg/day in adults) has been effective in patients with *COQ2* mutations, especially for the neurological and renal manifestations of this disorder. In contrast, poor responses to CoQ₁₀ supplementation have been observed in patients with *PDSS2* and *COQ9* mutations.

Response to treatment is also variable in patients with secondary CoQ₁₀ deficiency syndromes. In patients with myopathy due to *ETFDH* mutations, riboflavin supplementation was generally followed by clinical improvement and normalisation of CK and lactate levels with further positive effects in few patients additional supplementation with CoQ₁₀ [24]. In three siblings with cerebellar ataxia due to a homozygous stop codon mutation in *APTX* and secondary CoQ₁₀ deficiency in muscle, high-dose CoQ₁₀ supplementation (up to 3,000 mg daily) was associated with improved ambulation in all and resolution of seizures in the affected sister [43].

The reasons for the disparate responses to CoQ₁₀ are not known. A likely contributing factor is the poor bioavailability of CoQ₁₀; less than 5% of oral CoQ₁₀ reaches plasma in humans and rodent studies have demonstrated low uptake of CoQ by tissues with little or no detectable uptake by brain except in aged rats [1, 44–46]. Thus, the blood-brain barrier appears to impair central nervous system uptake of CoQ₁₀. Hence, tissue involvement may influence response to CoQ₁₀ supplementation as illustrated by the ubiquinone-responsive CoQ₁₀ deficient patients with *COQ2* mutations who manifested nephrotic syndrome and in one case had stroke-like episodes suggesting involvement of vascular structures, which is likely to be amenable to CoQ₁₀ supplementation [9, 15–17]. In contrast brain tissue was clearly affected in the CoQ₁₀-refractory patients with Leigh syndrome due to *PDSS2* mutations and refractory seizures caused by *COQ9* deficiency [6, 8]. Furthermore, because CoQ is highly lipophilic, exogenously administered CoQ will be integrated into plasma and other cellular membranes before reaching the inner mitochondrial membrane. This notion is supported by cell culture studies [36]. Because of the poor bioavailability and delayed mitochondrial uptake of ubiquinone, early rather than late supplementation is likely to successfully treat CoQ₁₀ deficiency.

Mitochondrial Neurogastrointestinal Encephalomyopathy (MNGIE)

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE; OMIM 603041) is a rare autosomal recessive disease caused by mutations in the *TYMP* gene encoding thymidine

phosphorylase (TP; E.C. 2.4.2.4). Seventeen years ago, we described MNGIE as a clinically distinct disorder characterized by extraocular muscle weakness causing ptosis and ophthalmoplegia, peripheral neuropathy, gastrointestinal dysmotility causing severe cachexia, leukoencephalopathy, and mitochondrial abnormalities including multiple deletions of mitochondrial DNA (mtDNA) in skeletal muscle[47]. Because of the prominent gastrointestinal dysfunction and cachexia, patients are often misdiagnosed with anorexia nervosa, inflammatory bowel disease, or celiac disease[48]. The disease is relentlessly progressive and fatal with an average age-at-onset of 19-years-old and an average age-at-death of 37-years-old[48–50]. We mapped the disease locus to chromosome 22q13.32-*tel*, identified the causative gene[51, 52], characterized the molecular pathogenesis[53–59], and generated a mouse model[60].

***TYMP* mutations cause severe TP deficiency**

Since our 1999 report describing *TYMP* mutations as the cause of MNGIE[52], we have received more than 1000 blood samples to screen for TP deficiency. To date, we have identified 102 MNGIE patients from 79 families with a spectrum of 54 *TYMP* mutations. In addition, 36 molecularly confirmed patients have been reported by others[59, 61–77]. The 138 MNGIE patients are of diverse ethnic origins and males and females are equally affected.

To confirm the pathogenicity of the TP gene mutations, we used a fixed-time spectrophotometric assay to measure TP activity in buffy coat based on techniques developed in the 1950s[52, 53, 58, 78–80]. Our TP assay measures thymine produced by cell extracts incubated at 37 °C for one hour in the presence of excess thymidine[53]. The assay is highly reliable based on measurement of day-to-day imprecision of frozen buffy coat aliquots from a single blood collection of a healthy individual (n=20; range 638–889 nmol/h/mg-prot; coefficient of variation=10%)[53]. All typical MNGIE patients showed less than 10% TP activity (10±15 nmol/h/mg-prot; mean±standard deviation) relative to the mean TP activity in controls (634±217)[53], thus, the assay is highly sensitive in identifying patients. In asymptomatic *TYMP* mutation carriers, TP activity was approximately 35% (222±89) of control mean, which is consistent with the homodimeric composition of TP. We also identified three patients with late-onset MNGIE (age-at-onset ~40 years) and milder TP deficiency (~15% residual activity) than typical patients[54]. Thus, there is a relationship between TP activity and clinical phenotypes: <10% of normal activity causes typical MNGIE, 10–20% residual activity produces less-severe late-onset MNGIE, and >30% activity does not cause overt disease.

TP deficiency causes accumulations of Thd and dUrd in plasma and tissues

To assess the consequences of loss of TP function, we measured thymidine and deoxyuridine in plasma and autopsy tissues using high-performance liquid chromatography (HPLC). Thymidine peaks were identified by retention time and confirmed by disappearance of the peak with TP treatment. Normal controls had no detectable thymidine in plasma (<0.05 µM, n=20) while all patients had markedly elevated thymidine (Thd) levels (8.6±3.4 µM, mean±standard deviation; normal controls <0.05), and deoxyuridine (dUrd) (14.2±4.4 µM, normal controls <0.05)[53, 55, 58]. The late-onset MNGIE patients had less dramatic increased in Thd (1.03±0.45) and dUrd (2.9±1.9). Interestingly, asymptomatic relatives with heterozygous *TYMP* mutations and reduced TP activity had no detectable thymidine in plasma (n=14). This finding has therapeutic implications because it indicates that 35% residual TP activity is sufficient to eliminate circulating thymidine.

Post-mortem analyses of tissues from five MNGIE patients (ages at death 29–39 years old), showed accumulation of dThd (range=1.9–80 pmol/mg-tissue) and dUrd (range 3–48 pmol/mg-tissue) whereas control tissues had no detectable nucleosides[81]. The highest concentrations of dThd and dUrd were detected in affected tissues peripheral nerve, small intestine, occipital white matter, and liver while kidney and heart, two unaffected organs and skeletal muscle, a less severely affected tissue, had lower levels of nucleosides.

Increased levels of Thd and dUrd cause deoxynucleotide pool imbalances and mtDNA instability

We hypothesized that elevated levels of Thd and dUrd nucleosides in MNGIE patients cause deoxynucleotide triphosphate (dNTP) pool imbalances, which, in turn, cause mtDNA instability (Figure 2). This notion is supported by *in vitro* studies. Dr. Christopher Mathew's lab demonstrated that Hela cells exposed to 50 μ M Thd for four hours had unbalanced mitochondrial dNTP pools with increased dTTP (260%) and dGTP (220%) and decreased dATP (78%) and dCTP (43%)[82]. After eight months in 50 μ M Thd, the Hela cells developed multiple deletions of mtDNA by PCR. Similarly, Dr. Vera Bianchi's group demonstrated that cultured quiescent fibroblasts, maintained in 10–40 μ M thymidine, had ~3.5-fold increases in cytosolic dTTP and ~3.7-fold increases in mitochondrial dTTP and ~50% depletion of mtDNA without deletions or point mutations[83, 84].

We have observed multiple deletions, depletion, and site-specific somatic mtDNA point mutations in cultured fibroblasts, blood, and tissues of MNGIE patients[47, 56, 57]. This selective effect on mtDNA may be explained by two factors. First, mitochondrial nucleotide pools are probably more vulnerable to the toxic effects of excessive dThd than are nuclear nucleotide pools because mtDNA is more dependent on dThd salvage than is nuclear DNA, which relies upon the *de novo* synthesis of dThd particularly in post-mitotic cells[83, 85, 86]. Second, human mitochondria apparently lack an effective DNA mismatch repair system[87, 88].

Our studies of TP/UP double knockout (TP^{-/-}UP^{-/-}) mice have also supported the hypothesized pathomechanism in MNGIE[60]. As a consequence of TP deficiency, the mutant mice showed 4–65-fold elevated tissue levels of Thd and dUrd relative to in wild-type littermates. Brain of TP^{-/-}UP^{-/-} mice showed increased dTTP (+60%) and decreased dCTP (-40%) in mitochondria, ~50% depletion of mtDNA with ~30% reductions of biochemical activities of mitochondrial respiratory chain complexes I and IV, and multiple vacuoles in white matter and showed increased MRI T2-signal in cerebral white matter.

Defects of mtDNA cause mitochondrial pathology in MNGIE

In our MNGIE patients, we found clear evidence of mitochondrial dysfunction. Specifically, resting serum lactic acid levels were elevated in 12/20 patients (60%), while skeletal muscle biopsies showed defects of mitochondrial respiratory chain enzymes in 7/14 individuals (50%), cytochrome *c* oxidase-deficient muscle fibers in 17/18 (94%), depletion of mtDNA in 12/15, and multiple mtDNA deletions in 9/18 samples tested by Southern blot analysis[49]. In contrast to muscle, other tissues do not have abnormal mtDNA bands by Southern blot analysis, but have detectable mtDNA deletions by polymerase chain reaction [57]. Furthermore, in autopsies of six MNGIE patients, we observed marked atrophy, mitochondrial proliferation, and mtDNA depletion in the external muscularis propria layer of the stomach and small intestine indicating a visceral myopathy[59, 89] due to lack of mtDNA.

Rationale for AHSCT for MNGIE

Our preliminary studies of MNGIE indicate that therapies to eliminate the toxic levels of thymidine and deoxyuridine from patients will be effective treatments for the disease[55, 58]. We have demonstrated that hemodialysis can transiently eliminate these nucleosides from blood, but was not effective as a long-term treatment in one patient[90]. To catabolize nucleosides, we have administered platelets (which contain abundant TP) to two patients[91]. In both individuals, plasma thymidine levels were reduced for 24–48 hours. The transient effects of platelet infusions suggest that permanent TP replacement therapy through AHSCT should be an effective treatment for MNGIE. While AHSCT will not restore total body TP levels to normal, our analyses of asymptomatic *TYMP* mutation carriers show that 30–50% of normal TP activity is sufficient to prevent MNGIE.

AHSCT has been successfully applied to other rare metabolic diseases caused by enzyme deficiencies[92, 93]. For example, over 200 bone marrow transplantations in patients with Hurler syndrome have resulted in resolution of the enlarged liver and spleen, improved cardiac function, reversibility of airway obstruction, and, in some cases, stabilization of neurological deterioration. In general, AHSCT in patients with lysosomal storage diseases leads to improvement of visceral organs with variable effects on neurological symptoms. Furthermore, AHSCT appears to be effective in purine nucleoside phosphorylase (PNP) deficiency, a disease that biochemically parallels MNGIE because loss-of-function mutations in the *PNP* gene lead to accumulations of purine nucleosides. The disease presents with immunological and neurological dysfunction and AHSCT can restore the immune system and may stabilize neurological functions[94, 95]. Based on positive results in other metabolic disorders, assessment of AHSCT therapy for MNGIE is merited.

AHSCT for MNGIE

As of 2010, of the 11 patients who underwent AHSCT, 5 were alive after successful transplant. All show normalization of blood TPase activity and reductions of plasma thymidine and deoxyuridine to barely-detectable levels; slight clinical improvements were noted after one year. A patient transplanted in 2005 exhibits markedly improved gastrointestinal function; she discontinued parenteral nutrition and gained 3 kilograms; her neuropathy has also improved as assessed clinically and by electrophysiological studies (Hirano, unpublished observation). A prospective clinical trial of AHSCT for MNGIE is being planned.

Conclusions

Because mitochondrial diseases are clinically and genetically heterogeneous disorders, no single therapeutic approach will address the diverse biochemical pathogenic mechanisms. CoQ₁₀ deficiency is an example of a mitochondrial syndrome caused by lack of a key metabolite, which can be successfully treated through supplementation. In contrast, MNGIE is a prototypical mitochondrial disease caused by toxic accumulations of metabolites, dThd and dUrd, which, if eliminated, can lead to clinical improvements. Although both disorders are treatable by normalizing paucity or excess of small molecules, not all CoQ₁₀ deficient patients have responded to ubiquinone supplementation and initial AHSCT for MNGIE have been successful in fewer than half of the patients. Thus, further studies will be required to optimize therapy for these readily treatable mitochondrial diseases.

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References

1. Turunen M, Olsson J, Dallner G. Metabolism and function of coenzyme Q. *Biochim Biophys Acta*. 2004; 1660:171–199. [PubMed: 14757233]
2. Kawamukai M. Biosynthesis and bioproduction of coenzyme Q10 by yeasts and other organisms. *Biotechnol Appl Biochem*. 2009; 53:217–226. [PubMed: 19531029]
3. Rahman S, Clarke CF, Hirano M. 176th ENMC International Workshop: Diagnosis and treatment of coenzyme Q(10) deficiency. *Neuromuscul Disord*. 2011 in press.
4. Emmanuele V, Lopez LC, Berardo A, Naini A, Tadesse S, Wen B, D'Agostino E, Salomon M, DiMauro S, Quinzii C, Hirano M. Heterogeneity of coenzyme Q10 deficiency: Study of 76 patients and literature review. *Arch Neurol*. 2012 in press.
5. Ogasahara S, Engel AG, Frens D, Mack D. Muscle coenzyme Q deficiency in familial mitochondrial encephalomyopathy. *Proc Natl Acad Sci U S A*. 1989; 86:2379–2382. [PubMed: 2928337]
6. Duncan AJ, Bitner-Glindzicz M, Meunier B, Costello H, Hargreaves IP, Lopez LC, Hirano M, Quinzii CM, Sadowski MI, Hardy J, Singleton A, Clayton PT, Rahman S. A nonsense mutation in COQ9 causes autosomal-recessive neonatal-onset primary coenzyme Q10 deficiency: a potentially treatable form of mitochondrial disease. *Am J Hum Genet*. 2009; 84:558–566. [PubMed: 19375058]
7. Lagier-Tourenne C, Tazir M, Lopez LC, Quinzii CM, Assoum M, Drouot N, Busso C, Makri S, Ali-Pacha L, Benhassine T, Anheim M, Lynch DR, Thibault C, Plewniak F, Bianchetti L, Tranchant C, Poch O, DiMauro S, Mandel JL, Barros MH, Hirano M, Koenig M. ADCK3, an ancestral kinase, is mutated in a form of recessive ataxia associated with coenzyme Q10 deficiency. *Am J Hum Genet*. 2008; 82:661–672. [PubMed: 18319074]
8. Lopez LC, Schuelke M, Quinzii CM, Kanki T, Rodenburg RJ, Naini A, DiMauro S, Hirano M. Leigh syndrome with nephropathy and CoQ10 deficiency due to decaprenyl diphosphate synthase subunit 2 (PDSS2) mutations. *Am J Hum Genet*. 2006; 79:1125–1129. [PubMed: 17186472]
9. Quinzii C, Naini A, Salviati L, Trevisson E, Navas P, DiMauro S, Hirano M. A Mutation in Para-Hydroxybenzoate-Polyprenyl Transferase (COQ2) Causes Primary Coenzyme Q10 Deficiency. *Am J Hum Genet*. 2006; 78:345–349. [PubMed: 16400613]
10. Aure K, Benoist JF, Ogier de Baulny H, Romero NB, Rigal O, Lombes A. Progression despite replacement of a myopathic form of coenzyme Q10 defect. *Neurology*. 2004; 63:727–729. [PubMed: 15326254]
11. Gironi M, Lamperti C, Nemni R, Moggio M, Comi G, Guerini FR, Ferrante P, Canal N, Naini A, Bresolin N, DiMauro S. Late-onset cerebellar ataxia with hypogonadism and muscle coenzyme Q10 deficiency. *Neurology*. 2004; 62:818–820. [PubMed: 15007142]
12. Sobreira C, Hirano M, Shanske S, Keller RK, Haller RG, Davidson E, Santorelli FM, Miranda AF, Bonilla E, Mojon DS, Barreira AA, King MP, DiMauro S. Mitochondrial encephalomyopathy with coenzyme Q10 deficiency. *Neurology*. 1997; 48:1238–1243. [PubMed: 9153450]
13. Mollet J, Delahodde A, Serre V, Chretien D, Schlemmer D, Lombes A, Boddaert N, Desguerre I, de Lonlay P, de Baulny HO, Munnich A, Rotig A. CABC1 gene mutations cause ubiquinone deficiency with cerebellar ataxia and seizures. *Am J Hum Genet*. 2008; 82:623–630. [PubMed: 18319072]
14. Rötig A, Appelkvist EL, Geromel V, Chretien D, Kadhon N, Edery P, Leblond M, Dallner G, Munnich A, Ernster L, Rustin P. Quinone-responsive multiple respiratory-chain dysfunction due to widespread coenzyme Q10 deficiency. *Lancet*. 2000; 356:391–395. [PubMed: 10972372]
15. Salviati L, Sacconi S, Murer L, Zaccello G, Franceschini L, Laverda AM, Basso G, Quinzii CM, Angelini C, Hirano M, Naini A, Navas P, DiMauro S, Montini G. Infantile encephalomyopathy and nephropathy with CoQ10 deficiency: a CoQ10-responsive condition. *Neurology*. 2005; 65:606–608. [PubMed: 16116126]
16. Diomedes-Camassei F, Di Giandomenico S, Santorelli FM, Caridi G, Piemonte F, Montini G, Ghiggeri GM, Murer L, Barisoni L, Pastore A, Muda AO, Valente ML, Bertini E, Emma F. COQ2

- nephropathy: a newly described inherited mitochondriopathy with primary renal involvement. *J Am Soc Nephrol.* 2007; 18:2773–2780. [PubMed: 17855635]
17. Montini G, Malaventura C, Salviati L. Early coenzyme Q10 supplementation in primary coenzyme Q10 deficiency. *N Engl J Med.* 2008; 358:2849–2850. [PubMed: 18579827]
 18. Mollet J, Giurgea I, Schlemmer D, Dallner G, Chretien D, Delahodde A, Bacq D, de Lonlay P, Munnich A, Rotig A. Prenyldiphosphate synthase, subunit 1 (PDSS1) and OH-benzoate polyprenyltransferase (COQ2) mutations in ubiquinone deficiency and oxidative phosphorylation disorders. *J Clin Invest.* 2007; 117:765–772. [PubMed: 17332895]
 19. Heeringa SF, Chernin G, Chaki M, Zhou W, Sloan AJ, Ji Z, Xie LX, Salviati L, Hurd TW, Vega-Warner V, Killen PD, Raphael Y, Ashraf S, Ovunc B, Schoeb DS, McLaughlin HM, Airik R, Vlangos CN, Gbadegesin R, Hinkes B, Saisawat P, Trevisson E, Doimo M, Casarin A, Pertegato V, Giorgi G, Prokisch H, Rotig A, Nurnberg G, Becker C, Wang S, Ozaltin F, Topaloglu R, Bakkaloglu A, Bakkaloglu SA, Muller D, Beissert A, Mir S, Berdeli A, Varpizen S, Zenker M, Matejas V, Santos-Ocana C, Navas P, Kusakabe T, Kispert A, Akman S, Soliman NA, Krick S, Mundel P, Reiser J, Nurnberg P, Clarke CF, Wiggins RC, Faul C, Hildebrandt F. COQ6 mutations in human patients produce nephrotic syndrome with sensorineural deafness. *J Clin Invest.* 2011; 121:2013–2024. [PubMed: 21540551]
 20. Musumeci O, Naini A, Slonim AE, Skavin N, Hadjigeorgiou GL, Krawiecki N, Weissman BM, Tsao CY, Mendell JR, Shanske S, De Vivo DC, Hirano M, DiMauro S. Familial cerebellar ataxia with muscle coenzyme Q10 deficiency. *Neurology.* 2001; 56:849–855. [PubMed: 11294920]
 21. Gerards M, van den Bosch B, Calis C, Schoonderwoerd K, van Engelen K, Tijssen M, de Coo R, van der Kooi A, Smeets H. Nonsense mutations in CABP1/ADCK3 cause progressive cerebellar ataxia and atrophy. *Mitochondrion.* 2010; 10:510–515. [PubMed: 20580948]
 22. Sykora P, Croteau DL, Bohr VA, Wilson DM 3rd. Aprataxin localizes to mitochondria and preserves mitochondrial function. *Proc Natl Acad Sci U S A.* 2011; 108:7437–7442. [PubMed: 21502511]
 23. Le Ber I, Dubourg O, Benoist JF, Jardel C, Mochel F, Koenig M, Brice A, Lomès A, Durr A. Muscle coenzyme Q10 deficiencies in ataxia with oculomotor apraxia 1. *Neurology.* 2007; 68:295–297. [PubMed: 17242337]
 24. Gempel K, Topaloglu H, Talim B, Schneiderat P, Schoser BG, Hans VH, Palmafy B, Kale G, Tokatli A, Quinzii C, Hirano M, Naini A, DiMauro S, Prokisch H, Lochmuller H, Horvath R. The myopathic form of coenzyme Q10 deficiency is caused by mutations in the electron-transferring-flavoprotein dehydrogenase (ETFDH) gene. *Brain.* 2007; 130:2037–2044. [PubMed: 17412732]
 25. Olsen RK, Olpin SE, Andresen BS, Miedzybrodzka ZH, Pourfarzam M, Merinero B, Frerman FE, Beresford MW, Dean JC, Cornelius N, Andersen O, Oldfors A, Holme E, Gregersen N, Turnbull DM, Morris AA. ETFDH mutations as a major cause of riboflavin-responsive multiple acyl-CoA dehydrogenation deficiency. *Brain.* 2007; 130:2045–2054. [PubMed: 17584774]
 26. Liang WC, Ohkuma A, Hayashi YK, Lopez LC, Hirano M, Nonaka I, Noguchi S, Chen LH, Jong YJ, Nishino I. ETFDH mutations, CoQ10 levels, and respiratory chain activities in patients with riboflavin-responsive multiple acyl-CoA dehydrogenase deficiency. *Neuromuscul Disord.* 2009; 19:212–216. [PubMed: 19249206]
 27. Ohkuma A, Noguchi S, Sugie H, Malicdan MC, Fukuda T, Shimazu K, Lopez LC, Hirano M, Hayashi YK, Nonaka I, Nishino I. Clinical and genetic analysis of lipid storage myopathies. *Muscle Nerve.* 2009; 39:333–342. [PubMed: 19208393]
 28. Matsuoka T, Maeda H, Goto Y, Nonaka I. Muscle coenzyme Q10 in mitochondrial encephalomyopathies. *Neuromuscul Disord.* 1991; 1:443–447. [PubMed: 1822356]
 29. Sacconi S, Trevisson E, Salviati L, Ayme S, Rigal O, Redondo AG, Mancuso M, Siciliano G, Tonin P, Angelini C, Aure K, Lomès A, Desnuelle C. Coenzyme Q10 is frequently reduced in muscle of patients with mitochondrial myopathy. *Neuromuscul Disord.* 2010; 20:44–48. [PubMed: 19945282]
 30. Cotan D, Cordero MD, Garrido-Maraver J, Oropesa-Avila M, Rodriguez-Hernandez A, Gomez Izquierdo L, De la Mata M, De Miguel M, Bautista Lorite J, Rivas Infante E, Jackson S, Navas P, Sanchez-Alcazar JA. Secondary coenzyme Q10 deficiency triggers mitochondria degradation by mitophagy in MELAS fibroblasts. *Faseb J.* 2011; 25:2669–2687. [PubMed: 21551238]

31. Geromel V, Kadhon N, Ceballos-Picot I, Chretien D, Munnich A, Rötig A, Rustin P. Human cultured skin fibroblasts survive profound inherited ubiquinone depletion. *Free Radic Res.* 2001; 35:11–21. [PubMed: 11697113]
32. Lopez-Martin JM, Salviati L, Trevisson E, Montini G, DiMauro S, Quinzii C, Hirano M, Rodriguez-Hernandez A, Cordero MD, Sanchez-Alcazar JA, Santos-Ocana C, Navas P. Missense mutation of the COQ2 gene causes defects of bioenergetics and de novo pyrimidine synthesis. *Hum Mol Genet.* 2007; 16:1091–1097. [PubMed: 17374725]
33. Rodríguez-Hernandez A, Cordero MD, Salviati L, Artuch R, Pineda M, Briones P, Gómez Izquierdo L, Cotán D, Navas P, Sánchez-Alcázar JA. Coenzyme Q deficiency triggers mitochondrial degradation by mitophagy. *Autophagy.* 2009; 5:19–32. [PubMed: 19115482]
34. Quinzii CM, Lopez LC, Von-Moltke J, Naini A, Krishna S, Schuelke M, Salviati L, Navas P, DiMauro S, Hirano M. Respiratory chain dysfunction and oxidative stress correlate with severity of primary CoQ10 deficiency. *FASEB J.* 2008; 22:1874–1885. [PubMed: 18230681]
35. Quinzii CM, Lopez LC, Gilkerson RW, Dorado B, Coku J, Naini AB, Lagier-Tourenne C, Schuelke M, Salviati L, Carrozzo R, Santorelli F, Rahman S, Tazir M, Koenig M, DiMauro S, Hirano M. Reactive oxygen species, oxidative stress, and cell death correlate with level of CoQ10 deficiency. *FASEB J.* 2010; 24:3733–3743. [PubMed: 20495179]
36. Lopez LC, Quinzii CM, Area E, Naini A, Rahman S, Schuelke M, Salviati L, Dimauro S, Hirano M. Treatment of CoQ(10) deficient fibroblasts with ubiquinone, CoQ analogs, and vitamin C: time- and compound-dependent effects. *PLoS One.* 2010; 5:e11897. [PubMed: 20689595]
37. Drose S, Krack S, Sokolova L, Zwicker K, Barth HD, Morgner N, Heide H, Steger M, Nubel E, Zickermann V, Kerscher S, Brutschy B, Radermacher M, Brandt U. Functional dissection of the proton pumping modules of mitochondrial complex I. *PLoS Biol.* 2011; 9:e1001128. [PubMed: 21886480]
38. Efremov RG, Sazanov LA. Structure of the membrane domain of respiratory complex I. *Nature.* 2011; 476:414–420. [PubMed: 21822288]
39. Lyon MF, Hulse EV. An inherited kidney disease of mice resembling human nephronophthisis. *J Med Genet.* 1971; 8:41–48. [PubMed: 5098070]
40. Sibalic V, Fan X, Loffing J, Wuthrich RP. Upregulated renal tubular CD44, hyaluronan, and osteopontin in kdkd mice with interstitial nephritis. *Nephrol Dial Transplant.* 1997; 12:1344–1353. [PubMed: 9249768]
41. Peng M, Falk MJ, Haase VH, King R, Polyak E, Selak M, Yudkoff M, Hancock WW, Meade R, Saiki R, Lunceford AL, Clarke CF, Gasser DL. Primary coenzyme Q deficiency in Pdss2 mutant mice causes isolated renal disease. *PLoS Genet.* 2008; 4:e1000061. [PubMed: 18437205]
42. Saiki R, Lunceford AL, Shi Y, Marbois B, King R, Pachuski J, Kawamukai M, Gasser DL, Clarke CF. Coenzyme Q10 supplementation rescues renal disease in Pdss2kd/kd mice with mutations in prenyl diphosphate synthase subunit 2. *Am J Physiol Renal Physiol.* 2008; 295:F1535–1544. [PubMed: 18784258]
43. Quinzii CM, Kattah AG, Naini A, Akman HO, Mootha VK, DiMauro S, Hirano M. Coenzyme Q deficiency and cerebellar ataxia associated with an *aprataxin* mutation. *Neurology.* 2005; 64:539–541. [PubMed: 15699391]
44. Bentinger M, Dallner G, Chojnacki T, Swiezewska E. Distribution and breakdown of labeled coenzyme Q10 in rat. *Free Radic Biol Med.* 2003; 34:563–575. [PubMed: 12614845]
45. Bhagavan HN, Chopra RK. Coenzyme Q10: Absorption, tissue uptake, metabolism and pharmacokinetics. *Free Radic Res.* 2006; 40:445–453. [PubMed: 16551570]
46. Ferrante KL, Shefner J, Zhang H, Betensky R, O'Brien M, Yu H, Fantasia M, Taft J, Beal MF, Traynor B, Newhall K, Donofrio P, Caress J, Ashburn C, Freiberg B, O'Neill C, Paladenech C, Walker T, Pestronk A, Abrams B, Florence J, Renna R, Schierbecker J, Malkus B, Cudkowicz M. Tolerance of high-dose (3,000 mg/day) coenzyme Q10 in ALS. *Neurology.* 2005; 65:1834–1836. [PubMed: 16344537]
47. Hirano M, Silvestri G, Blake DM, Lombes A, Minetti C, Bonilla E, Hays AP, Lovelace RE, Butler I, Bertorini TE, Threlkeld AB, Mitumoto H, Salberg L, Rowland LP, DiMauro S. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): clinical, biochemical, and genetic features of

- an autosomal recessive mitochondrial disorder. *Neurology*. 1994; 44:721–727. [PubMed: 8164833]
48. Garone C, Tadesse S, Hirano M. Clinical and genetic spectrum of mitochondrial neurogastrointestinal encephalomyopathy. *Brain*. 2011; 134:326–332.
 49. Hirano M, Nishigaki Y, Martí R. MNGIE: A disease of two genomes. *The Neurologist*. 2004; 10:8–17. [PubMed: 14720311]
 50. Nishino I, Spinazzola A, Papadimitriou A, Hammans S, Steiner I, Hahn CD, Connolly AM, Verloes A, Guimarães J, Maillard I, Hamano H, Donati MA, Semrad CE, Russell JA, Andreu AL, Hadjigeorgiou GM, Vu TH, Tadesse S, Nygaard TG, Nonaka I, Hirano I, Bonilla E, Rowland LP, DiMauro S, Hirano M. MNGIE: An Autosomal Recessive Disorder Due to Thymidine Phosphorylase Mutations. *Ann Neurol*. 2000; 47:792–800. [PubMed: 10852545]
 51. Hirano M, Yebenes J, Jones AC, Nishino I, DiMauro S, Carlo JR, Bender AN, Hahn AF, Salberg LM, Weeks DE, Nygaard TG. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) syndrome maps to chromosome 22q13.32-qter. *Am J Hum Genet*. 1998; 63:526–533. [PubMed: 9683610]
 52. Nishino I, Spinazzola A, Hirano M. Thymidine phosphorylase gene mutations in MNGIE, a human mitochondrial disorder. *Science*. 1999; 283:689–692. [PubMed: 9924029]
 53. Martí R, Spinazzola A, Tadesse S, Nishino I, Nishigaki Y, Hirano M. Definitive diagnosis of mitochondrial neurogastrointestinal encephalomyopathy by biochemical assays. *Clin Chem*. 2004; 50:120–124. [PubMed: 14633909]
 54. Martí R, Verschuuren JJ, Buchman A, Hirano I, Tadesse S, van Kuilenburg AB, van Gennip AH, Poorthuis BJ, Hirano M. Late-onset MNGIE due to partial loss of thymidine phosphorylase activity. *Ann Neurol*. 2005; 58:649–652. [PubMed: 16178026]
 55. Martí R, Nishigaki Y, Hirano M. Elevated plasma deoxyuridine in patients with thymidine phosphorylase deficiency. *Biochem Biophys Res Commun*. 2003; 303:14–18. [PubMed: 12646159]
 56. Nishigaki Y, Martí R, Copeland WC, Hirano M. Site-specific somatic mitochondrial DNA point mutations in patients with thymidine phosphorylase deficiency. *J Clin Invest*. 2003; 111:1913–1921. [PubMed: 12813027]
 57. Nishigaki Y, Martí R, Hirano M. ND5 is a hot-spot for multiple atypical mitochondrial DNA deletions in mitochondrial neurogastrointestinal encephalomyopathy. *Hum Mol Genet*. 2004; 13:91–101. [PubMed: 14613972]
 58. Spinazzola A, Martí R, Nishino I, Andreu A, Naini A, Tadesse S, Pela I, Zammarchi E, Donati MA, Oliver JA, Hirano M. Altered thymidine metabolism due to defects of thymidine phosphorylase. *J Biol Chem*. 2002; 277:4128–4133. [PubMed: 11733540]
 59. Giordano C, Sebastiani M, De Giorgio R, Travaglini C, Tancredi A, Valentino ML, Bellan M, Cossarizza A, Hirano M, d'Amati G, Carelli V. Gastrointestinal dysmotility in mitochondrial neurogastrointestinal encephalomyopathy is caused by mitochondrial DNA depletion. *Am J Pathol*. 2008; 173:1120–1128. [PubMed: 18787099]
 60. López LC, Akman HO, Garcia-Cazorla A, Dorado B, Martí R, Nishino I, Tadesse S, Pizzorno G, Shungu DC, Bonilla E, Tanji K, Hirano M. Unbalanced deoxynucleotide pools cause mitochondrial DNA instability in thymidine phosphorylase deficient mice. *Hum Mol Genet*. 2009; 18:714–722. [PubMed: 19028666]
 61. Kocaefe YC, Erdem S, Ozguc M, Tan E. Four novel thymidine phosphorylase gene mutations in mitochondrial neurogastrointestinal encephalomyopathy syndrome (MNGIE) patients. *Eur J Hum Genet*. 2003; 11:102–104. [PubMed: 12529715]
 62. Martin MA, Blazquez A, Martí R, Bautista J, Lara MC, Cabello A, Campos Y, Belda O, Andreu AL, Arenas J. Lack of gastrointestinal symptoms in a 60-year-old patient with MNGIE. *Neurology*. 2004; 63:1536–1537. [PubMed: 15505189]
 63. Said G, Lacroix C, Plante-Bordeneuve V, Messing B, Slama A, Crenn P, Nivelon-Chevallier A, Bedenne L, Soichot P, Manceau E, Rigaud D, Guiochon-Mantel A, Matuchansky C. Clinicopathological aspects of the neuropathy of neurogastrointestinal encephalomyopathy (MNGIE) in four patients including two with a Charcot-Marie-Tooth presentation. *J Neurol*. 2005

64. Slama A, Lacroix C, Plante-Bordeneuve V, Lombes A, Conti M, Reimund JM, Auxenfans E, Crenn P, Laforet P, Joannard A, Seguy D, Pillant H, Joly P, Haut S, Messing B, Said G, Legrand A, Guiochon-Mantel A. Thymidine phosphorylase gene mutations in patients with mitochondrial neurogastrointestinal encephalomyopathy syndrome. *Mol Genet Metab.* 2005; 84:326–331. [PubMed: 15781193]
65. Blazquez A, Martin MA, Lara MC, Marti R, Campos Y, Cabello A, Garesse R, Bautista J, Andreu AL, Arenas J. Increased muscle nucleoside levels associated with a novel frameshift mutation in the thymidine phosphorylase gene in a Spanish patient with MNGIE. *Neuromuscul Disord.* 2005; 15:775–778. [PubMed: 16198108]
66. Peker S, Necmettin Pamir M. Trigeminal neuralgia in a patient with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). *J Clin Neurosci.* 2005; 12:172–174. [PubMed: 15749422]
67. Celebi N, Sahin A, Canbay O, Uzumcugil F, Aypar U. Abdominal pain related to mitochondrial neurogastrointestinal encephalomyopathy syndrome may benefit from splanchnic nerve blockade. *Paediatr Anaesth.* 2006; 16:1073–1076. [PubMed: 16972839]
68. Schüpbach WM, Vadday KM, Schaller A, Brekenfeld C, Kappeler L, Benoist JF, Xuan-Huong CN, Burgunder JM, Seibold F, Gallati S, Mattle HP. Mitochondrial neurogastrointestinal encephalomyopathy in three siblings: clinical, genetic and neuroradiological features. *J Neurol.* 2007; 254:146–153. [PubMed: 17294068]
69. Yavuz H, Ozel A, Christensen M, Christensen E, Schwartz M, Elmaci M, Vissing J. Treatment of mitochondrial neurogastrointestinal encephalomyopathy with dialysis. *Arch Neurol.* 2007; 64:435–438. [PubMed: 17353390]
70. Monroy N, Macias Kauffer LR, Mutchinick OM. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) in two Mexican brothers harboring a novel mutation in the ECGF1 gene. *Eur J Med Genet.* 2008; 51:245–250. [PubMed: 18280229]
71. Taanman JW, Daras M, Albrecht J, Davie CA, Mallam EA, Muddle JR, Weatherall M, Warner TT, Schapira AH, Ginsberg L. Characterization of a novel TYMP splice site mutation associated with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). *Neuromuscul Disord.* 2009; 19:151–154. [PubMed: 19056268]
72. Laforce R Jr, Valdmanis PN, Dupre N, Rouleau GA, Turgeon AF, Savard M. A novel TYMP mutation in a French Canadian patient with mitochondrial neurogastrointestinal encephalomyopathy. *Clin Neurol Neurosurg.* 2009; 111:691–694. [PubMed: 19523753]
73. Cardaioli E, Da Pozzo P, Malfatti E, Battisti C, Gallus GN, Gaudiano C, Macucci M, Malandrini A, Margollicci M, Rubegni A, Dotti MT, Federico A. A second MNGIE patient without typical mitochondrial skeletal muscle involvement. *Neurol Sci.* 2010; 31:491–494. [PubMed: 20232099]
74. Massa R, Tessa A, Margollicci M, Micheli V, Romigi A, Tozzi G, Terracciano C, Piemonte F, Bernardi G, Santorelli FM. Late-onset MNGIE without peripheral neuropathy due to incomplete loss of thymidine phosphorylase activity. *Neuromuscul Disord.* 2009; 19:837–840. [PubMed: 19853446]
75. Petcharunpaisan S, Castillo M. Multiple cranial nerve enhancement in mitochondrial neurogastrointestinal encephalomyopathy. *J Comput Assist Tomogr.* 2010; 34:247–248. [PubMed: 20351514]
76. Baris Z, Eminoglu T, Dalgic B, Tumer L, Hasanoglu A. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): case report with a new mutation. *Eur J Pediatr.* 2010; 169:1375–1378. [PubMed: 20585803]
77. Oztas E, Ozin Y, Onder F, Onal IK, Oguz D, Kocaefer C. Chronic intestinal pseudo-obstruction and neurological manifestations in early adulthood: considering MNGIE syndrome in differential diagnosis. *J Gastrointest Liver Dis.* 2010; 19:195–197. [PubMed: 20593055]
78. Friedkin M, Roberts D. The enzymatic synthesis of nucleosides. I. Thymidine phosphorylase in mammalian tissue. *J Biol Chem.* 1954; 207:245–256. [PubMed: 13152099]
79. Gallo RC, Breitman TR. The enzymatic mechanisms for deoxythymidine synthesis in human leukocytes. II. Comparison of deoxyribosyl donors. *J Biol Chem.* 1967; 243:4936–4942. [PubMed: 5679973]

80. Marsh JC, Perry S. Thymidine catabolism by normal and leukemic human leukocytes. *J Clin Invest.* 1964; 43:267–278. [PubMed: 14162535]
81. Valentino ML, Marti R, Tadesse S, Lopez LC, Manes JL, Lyzak J, Hahn A, Carelli V, Hirano M. Thymidine and deoxyuridine accumulate in tissues of patients with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). *FEBS Lett.* 2007; 581:3410–3414. [PubMed: 17612528]
82. Song S, Wheeler LJ, Mathews CK. Deoxyribonucleotide pool imbalance stimulates deletions in HeLa cell mitochondrial DNA. *J Biol Chem.* 2003; 278:43893–43896. [PubMed: 13679382]
83. Ferraro P, Pontarin G, Crocco L, Fabris S, Reichard P, Bianchi V. Mitochondrial deoxynucleotide pools in quiescent fibroblasts: a possible model for mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). *J Biol Chem.* 2005; 280:24472–24480. [PubMed: 15878850]
84. Pontarin G, Ferraro P, Valentino ML, Hirano M, Reichard P, Bianchi V. Mitochondrial DNA depletion and thymidine phosphate pool dynamics in a cellular model of mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). *J Biol Chem.* 2006; 281:22720–22728. [PubMed: 16774911]
85. Bestwick RK, Mathews CK. Unusual compartment of precursors for nuclear and mitochondrial DNA in mouse L cells. *J Biol Chem.* 1982; 257:9305–9308. [PubMed: 7107570]
86. Bogenhagen D, Clayton DA. Thymidylate nucleotide supply for mitochondrial DNA synthesis in mouse L-cells. *J Biol Chem.* 1976; 251:2938–2944. [PubMed: 131801]
87. Croteau DL, Stierum RH, Bohr VA. Mitochondrial DNA repair pathways. *Mutat Res.* 1999; 434:137–148. [PubMed: 10486588]
88. Hirano M, Marti R, Vila MR, Nishigaki Y. MtDNA maintenance and stability genes: MNGIE and mtDNA depletion syndromes. *Mitochondrial Function and Biogenetics.* 2004; 8:177–200.
89. Giordano C, Sebastiani M, Plazzi G, Travaglini C, Sale P, Pinti M, Tancredi A, Liguori R, Montagna P, Bellan M, Valentino ML, Cossarizza A, Hirano M, d'Amati G, Carelli V. Mitochondrial neurogastrointestinal encephalomyopathy: evidence of mitochondrial DNA depletion in the small intestine. *Gastroenterology.* 2006; 130:893–901. [PubMed: 16530527]
90. la Marca G, Malvagia S, Casetta B, Pasquini E, Pela I, Hirano M, Donati MA, Zammarchi E. Pre- and post-dialysis quantitative dosage of thymidine in urine and plasma of a MNGIE patient by using HPLC-ESI-MS/MS. *J Mass Spectrom.* 2006; 41:586–592. [PubMed: 16498612]
91. Lara MC, Weiss B, Illa I, Madoz P, Massuet L, Andreu A, Valentino ML, Anikster Y, Hirano M, Marti R. Infusion of platelets transiently reduces nucleoside overload in MNGIE. *Neurology.* 2006; 67:1461–1463. [PubMed: 16971699]
92. Boelens JJ, Prasad VK, Tolar J, Wynn RF, Peters C. Current international perspectives on hematopoietic stem cell transplantation for inherited metabolic disorders. *Pediatr Clin North Am.* 2010; 57:123–145. [PubMed: 20307715]
93. Lachmann R. Treatments for lysosomal storage disorders. *Biochem Soc Trans.* 2010; 38:1465–1468. [PubMed: 21118108]
94. Myers LA, Hershfield MS, Neale WT, Escolar M, Kurtzberg J. Purine nucleoside phosphorylase deficiency (PNP-def) presenting with lymphopenia and developmental delay: successful correction with umbilical cord blood transplantation. *J Pediatr.* 2004; 145:710–712. [PubMed: 15520787]
95. Delicou S, Kitra-Roussou V, Peristeri J, Goussetis E, Vessalas G, Rigatou E, Psychou F, Salavoura K, Grafakos S. Successful HLA-identical hematopoietic stem cell transplantation in a patient with purine nucleoside phosphorylase deficiency. *Pediatr Transplant.* 2007; 11:799–803. [PubMed: 17910661]

Highlights

- CoQ₁₀ deficiencies can be primary (biosynthetic defects) or secondary (other causes)
- CoQ₁₀ deficiencies often improve with high-dose CoQ₁₀ supplements
- MNGIE is caused by thymidine phosphorylase deficiency
- MNGIE can improve after allogeneic hematopoietic stem cell transplantation

Figure 1. Coenzyme Q₁₀ biosynthetic pathway and electron transport role in the mitochondrial respiratory chain. Red arrows indicate coenzyme Q₁₀ biosynthetic pathway.

Figure 2.

Molecular pathomechanism of MNGIE. Loss of thymidine phosphorylase (TPase) activity causes toxic accumulations of thymidine and deoxyuridine nucleosides in plasma and tissues and dNTP pool imbalances, which, in turn impair mtDNA replication.