

Therapeutic advances in POLG-related mitochondrial disease

Abstract

POLG-related disorders are a spectrum of mitochondrial diseases resulting from mutations in the *POLG* gene, critical for mitochondrial DNA replication. These disorders are a rare group of neurodegenerative mitochondrial diseases affecting the genes encoding the alpha subunit of DNA polymerase gamma (Pol γ). Pol γ is the only DNA polymerase capable of replicating mitochondrial DNA (mtDNA), which is critical for mitochondrial function. Individuals with pathogenic *POLG* variants present with a spectrum of symptoms, including seizures, early-onset photophobia, myopathy, neuropathy, developmental impairment, and liver problems, which can lead to multiple organ failure. This is a progressive and degenerative disease with a prognosis ranging from 3 months to 12 years after diagnosis. In this mini-review, we explore the disorder, as well as emerging evidence surrounding the use of nucleoside supplementation as a novel therapeutic option. Preclinical and clinical trials suggest promising outcomes, including improved mitochondrial function and reduced disease severity, with nucleoside therapy, particularly in pediatric patients with mtDNA depletion syndromes. While findings are encouraging, further research using larger multicenter trials is necessary to validate these results across larger cohorts and broader phenotypes.

Keywords: POLG, mitochondrial DNA, mtDNA depletion syndrome, mitochondrial gene therapy, deoxythymidine, deoxycytidine, nucleoside therapy, mitochondrial disease

Volume 13 Issue 3 - 2025

Sakina Motiwala,¹ Munira Ziauddin,² Maria V Tejada-Simón^{1,3}

¹Department of Biology, College of Natural Sciences and Mathematics, University of Houston, Houston, Texas, USA

²Department of Psychology, College of Liberal Arts and Social Sciences, University of Houston, Houston, Texas, USA

³Department of Pharmacological and Pharmaceutical Sciences, College of Pharmacy, University of Houston, Houston, Texas, USA

Correspondence: Maria V Tejada-Simón, Department of Pharmacological & Pharmaceutical Sciences, College of Pharmacy, University of Houston, 4349 Martin Luther King Boulevard, Houston, TX 77204-5037, Tel (713) 743-7835

Received: June 03, 2025 | **Published:** June 25, 2025

Introduction

Mitochondrial diseases caused by nuclear gene mutations affecting mitochondrial DNA (mtDNA) maintenance represent a serious clinical challenge, with *POLG* mutations being among the most common causes. *POLG*-related disorders are a subset of mtDNA depletion syndromes characterized by mutations in the nuclear-encoded *POLG* gene, which directly impair the replication and repair of mtDNA. Unlike other mtDNA depletion syndromes caused by defects in nucleotide synthesis or transport (e.g., TK2, DGUOK, RRM2B),^{1,2} *POLG* disorders primarily involve dysfunction of the mitochondrial DNA polymerase itself, leading to a broader range of clinical phenotypes and often more complex management considerations.³ The *POLG* gene encodes the catalytic subunit of mitochondrial DNA polymerase gamma (Pol γ), essential for mtDNA replication and repair. Deficiencies can result in progressive external ophthalmoplegia, Alpers-Huttenlocher syndrome, ataxia-neuropathy syndromes, and other severe phenotypes. This mini-review fills a critical gap in the literature by synthesizing current evidence on emerging therapies, such as nucleoside supplementation, for *POLG*-related mitochondrial disorders, with particular focus on pediatric populations,⁴ evolving clinical trial findings, and the biochemical rationale underpinning these interventions.⁵ Given the complexity and heterogeneity of *POLG* mutations, this focused review highlights recent advances while identifying key areas where further clinical and translational research is needed to inform therapeutic decision-making.

POLG-related disorders

POLG-related disorders are a diverse group of mitochondrial diseases caused by mutations in the *POLG* gene, which encodes the mitochondrial DNA polymerase gamma (Pol γ), an enzyme essential for replication and repair of the mitochondrial genome

(Figure 1). These mutations impair mtDNA maintenance, resulting in mitochondrial DNA depletion or deletion syndromes (MDDS), manifesting in a wide array of clinical phenotypes.⁴

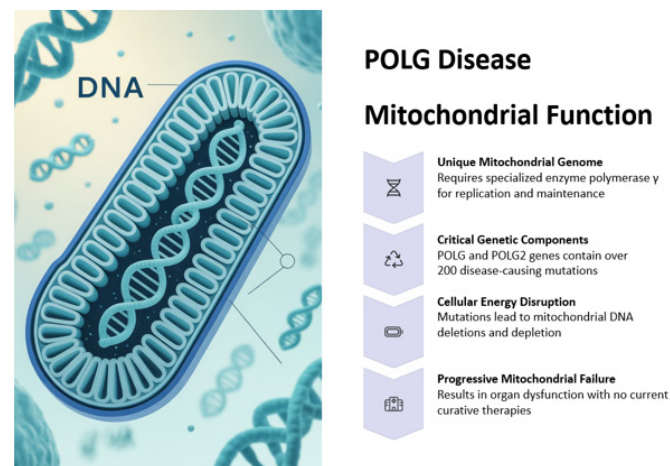


Figure 1 A summary description of *POLG*-related mitochondrial diseases.

More than 300 pathogenic variants of *POLG* have been identified.^{6,7} These disorders affect an estimated 1 in 10,000 live births, making them the most common inherited cause of mitochondrial dysfunction.⁸ Approximately 2% of the general population are carriers of *POLG* mutations,⁸ and mitochondrial diseases, as a whole, are estimated to affect 1 in 5,000 individuals worldwide⁸ (Table 1).

The clinical presentation of *POLG*-related disorders is highly variable and spans a spectrum that includes seizures, developmental regression, myopathy, hepatopathy (including liver failure), and peripheral neuropathy.^{6,8} Disease onset can occur at any age, from infancy to late adulthood, and is typically categorized into early-

onset, juvenile/adult-onset, and late-onset forms.⁶ Early-onset and juvenile/adult-onset variants are usually autosomal recessive, involving biallelic mutations, whereas late-onset presentations, such as progressive external ophthalmoplegia (PEO), are more commonly

linked to heterozygous pathogenic variants and follow an autosomal dominant pattern.⁶ One particularly severe phenotype, Alpers-Huttenlocher syndrome (AHS), occurs with an estimated incidence of 1 in 51,000 live births^{8,9} (Table 1).

Table 1 Summary of genotype-phenotype correlations on POLG-variants mitochondrial diseases (for a more comprehensive review¹)

Feature	Biallelic POLG variants	Monoallelic POLG variants
Inheritance pattern	Autosomal recessive	Autosomal dominant
Genetic profile	Mutations in both alleles (e.g., compound heterozygous or homozygous)	Mutation in one allele
Onset	Typically early childhood	Typically adulthood
Common phenotypes	Alpers-Huttenlocher syndrome (AHS) - Childhood epilepsy - SANDO - MIRAS	Progressive External Ophthalmoplegia (PEO) - Milder myopathy
mtDNA effect	Depletion	Multiple deletions
Severity	Often severe, systemic, progressive	Milder, often isolated features
Organs involved	Multisystem (brain, liver, muscle, GI)	Mostly muscle/nerve
Common variants	A467T, W748S, G848S (recessive combinations)	Y955C, G923D (dominant)
Prognosis	Often poor without intervention	Relatively stable; slower progression

Studies also suggest a modest influence of gender on disease expression. Although POLG-related disorders affect both sexes, disease onset and progression in females are often linked to hormonal changes, particularly during puberty.⁹ Furthermore, maternal folate deficiency has been proposed as a contributing risk factor, potentially exacerbating mitochondrial dysfunction by down regulating key components of the electron transport chain, such as cytochrome c oxidase.⁶

Treatment landscape and investigational therapies for POLG-related disorders

Supportive therapeutic strategies

The current management of POLG-related disorders is largely supportive, with a focus on alleviating symptoms and improving quality of life. Symptomatic treatment strategies include anticonvulsants for seizure control. However, caution is warranted with certain agents like valproic acid, due to its association with liver toxicity, particularly in individuals with mitochondrial dysfunction.⁸ Additional supportive measures include muscle relaxants and pain medications, as well as nutritional interventions such as ketogenic diets or feeding tubes, and respiratory support using bi-level positive airway pressure (BiPAP), continuous positive airway pressure (CPAP), or mechanical ventilation when necessary¹⁰ (Table 2).

Nutritional support

Nutritional interventions, such as the ketogenic diet, have gained attention as a therapeutic strategy in various mitochondrial disorders, including POLG-related diseases, though their effectiveness remains patient-specific and still investigational. The ketogenic diet is a high-fat, low-carbohydrate, adequate-protein nutritional plan that shifts the body's primary energy source from glucose to ketone bodies (e.g., β -hydroxybutyrate, acetoacetate).^{11,12} This shift reduces reliance on glycolysis and mitochondrial oxidative phosphorylation, which are often impaired in mitochondrial disease, and also provides ketone bodies as alternative fuel substrates that can bypass certain metabolic blocks and be more efficiently utilized by cells with compromised mitochondria.¹³ Researchers have shown that this diet enhances mitochondrial biogenesis, antioxidant defenses, and ATP production by activating PGC-1 α (peroxisome proliferator-activated receptor gamma coactivator-1-Alpha) signaling and SIRT1, a NAD⁺ dependent deacetylase involved in mitochondrial regulation.¹⁴ In POLG disorders, energy failure due to mtDNA depletion or faulty

replication results in progressive neurodegeneration, seizures, and myopathy.⁸ The ketogenic diet is especially considered for intractable epilepsy, a common and difficult to treat symptom in POLG patients. Several case reports and small studies suggest that the ketogenic diet can reduce seizure frequency and severity. Additionally, it might preserve neuronal function (given that ketones are neuroprotective), reduce glutamate toxicity, and improve mitochondrial function under stress. Finally, it also reduces lactate accumulation, which can occur due to impaired oxidative phosphorylation.⁸

Despite its potential, ketogenic diets must be used with caution in POLG-related disorders due to the risk of liver dysfunction.¹⁵ Many patients have hepatopathy, and the high-fat content of the diet can exacerbate this. Moreover, there is also a need for nutritional monitoring. Valproate is a medication primarily used to treat epilepsy, which is useful for preventing seizures. However, the use of Valproate in POLG-related conditions (which is contraindicated) further complicates the risk in patients because it is too associated with liver toxicity. Thus, patient selection for the use of supportive measures is critical because it may benefit patients with well-compensated liver function and prominent seizures but could be harmful for others (Table 2).

In addition, POLG-related conditions can present a risk of carnitine deficiency, growth retardation in children, and gastrointestinal issues.⁸ Motor, neurological, and visual impairments can be manifested.⁸ Those are typically addressed with physical and speech therapy, while vision and ptosis-related symptoms may benefit from corrective surgery or prescription lenses. Ptosis-related symptoms refer to clinical signs and complications associated with ptosis, which is the drooping of the upper eyelid.⁸ In the context of neurological or mitochondrial disorders (like POLG-related diseases), ptosis is often bilateral and progressive, resulting from weakness in the levator palpebrae superioris muscle or issues with the oculomotor nerve. Ptosis is a key diagnostic feature, often accompanied by external ophthalmoplegia, and reflects mitochondrial involvement in the extraocular muscles. Audiologic monitoring is also essential, with hearing aids or cochlear implants employed in moderate to profound hearing loss.¹⁰

Disease-modifying therapeutic strategies

Despite the multidisciplinary nature of this care, all these interventions do not halt disease progression, underscoring the need for disease-modifying therapies.

Table 2 Summary of the current and emerging therapeutic approaches for POLG-related mitochondrial diseases

Therapeutic approach	Description	Beneficial effects	Adverse effects	References
Supportive Therapies				
Anticonvulsants	Antiseizure and antiepileptic medication	For seizure control. Use with caution in liver failure. Valproate: Anticonvulsant medication primarily used to treat and prevent seizures, but its use is contraindicated in POLG-related conditions because of liver toxicity.	Liver toxicity	Rahman and Copeland ⁸
Muscle relaxant and pain medication		Help with muscle spasms and relief from discomfort	It affects the liver and kidneys. Dosage to be monitored closely.	UMDF ¹⁰
Small, frequent meals and a feeding tube		For nutritional support	none	UMDF ¹⁰
Respiratory Support	Breathing tubes, artificial ventilation/mechanical ventilation, CPAP (Continuous Positive Airway Pressure), and BPAP (Bilevel Positive Airway Pressure).	To treat breathing disorders and sleep apnea.		UMDF ¹⁰
Nutritional	High-fat, low-carb, adequate protein diet = ketogenic diet	Improves mitochondrial function under stress. Reduces frequency and severity of seizures. Preserves neuronal function (ketones are neuroprotective). Reduces glutamate toxicity. Reduces lactate accumulation.	Risk of liver dysfunction.	Abbasi J, ¹¹ Zhaoping L, ¹² Rahman and Copeland, ⁸ Pedersen ¹⁵
Physical speech therapy		To address motor and neurological impairments		UMDF ¹⁰
Disease-Modifying Therapies				
Antioxidants	Alpha Lipoic Acid (ALA) (600mg/day for 6-48 months)	Improves brain and skeletal muscle energy metabolism	No serious side effects	UMDF ¹⁰
	Arginine & Citrulline (precursor of nitric oxide, which stimulates vasodilation)	Reduces symptoms and frequency of stroke-like episodes. Improves cerebral blood flow and endothelial function.	Gastrointestinal disorders include diarrhea and nausea. Higher dose has more adverse effects.	
	Carnitine Carnitine deficiency may be seen in POLG-related disorders, which may cause growth impairment. In carnitine deficiency, the body cannot use fats for energy.	L-Carnitine supplementation can help improve lung function, cardiac function, and muscle strength.	Diarrhea, fatigue.	
	Coenzyme Q10 and Idebenone EPI-743 (Vatiquinone) derived from vitamin E	Few or no beneficial effects	Insomnia, rash.	
Nucleosides		Some promise in Leigh syndrome, but not tested in POLG-related conditions.	Gastrointestinal side-effects. No serious adverse effects were noted in clinical trials.	
	Nucleoside supplementation using deoxythymidine (dT) and deoxycytidine (dC), key substrates for mitochondrial DNA replication.	Delayed disease progression and improved survival	No serious safety concerns reported. Mild gastrointestinal-related symptoms.	Mitur A, ¹⁹ Lopez-Gomez, ²⁰ Marti et al., ⁵ Berrahmoune et al., ²¹ Pেকেles et al. ⁴

Antioxidants

Antioxidants, including Alpha Lipoic Acid (ALA), Arginine, Citrulline and Carnitine, have been used with variable results (Table 2). A limited number of experimental approaches have been explored in recent years. For instance, antioxidants such as coenzyme Q10 and idebenone have been trialed primarily aiming to mitigate oxidative

stress in mitochondrial diseases with inconsistent results. Other agents like EPI-743 (vatiquinone), a redox-active compound, have shown promise in Leigh syndrome, another mitochondrial disorder, but have not yet been extensively tested in POLG-related conditions.¹⁶ Similarly, targeting mitochondrial biogenesis through PGC-1 α pathways has been proposed but lacks clinical trial validation in this patient group.

Nucleoside supplementation therapy: A promising experimental approach

In POLG-related disorders, mutations in the *POLG* gene impair the function of DNA polymerase γ , the key enzyme responsible for mitochondrial DNA (mtDNA) replication and repair. This dysfunction leads to mtDNA depletion, particularly in post-mitotic tissues with high energy demand (e.g., brain, muscle, liver), where the de novo nucleotide synthesis pathway is limited.¹⁷

Supplementation with deoxycytidine (dC) and deoxythymidine (dT) helps overcome the resulting nucleoside imbalance by enhancing the mitochondrial salvage pathway, wherein these exogenous nucleosides are phosphorylated into deoxynucleotide triphosphates (dNTPs) within mitochondria. This process restores dCTP and dTTP pools essential for mtDNA synthesis (Figure 2), thereby bypassing the substrate limitations caused by POLG dysfunction.¹⁸ Experimental models have shown that dC/dT therapy reduces replication stalling and strand breaks, which are exacerbated by insufficient or imbalanced dNTP pools in POLG dysfunction.¹⁷ This supplementation also indirectly supports mitochondrial biogenesis by stabilizing mtDNA copy number, helping cells maintain adequate respiratory function. Mechanistic studies suggest that increasing mitochondrial dNTP availability can boost POL γ activity and promote mtDNA replication, even when upstream enzymatic pathways remain intact.⁵ Altogether, by restoring a balanced and sufficient mitochondrial dNTP pool, dC/dT supplementation offers a promising biochemical strategy to partially compensate for impaired POLG function, improving both replication fidelity and mtDNA maintenance.

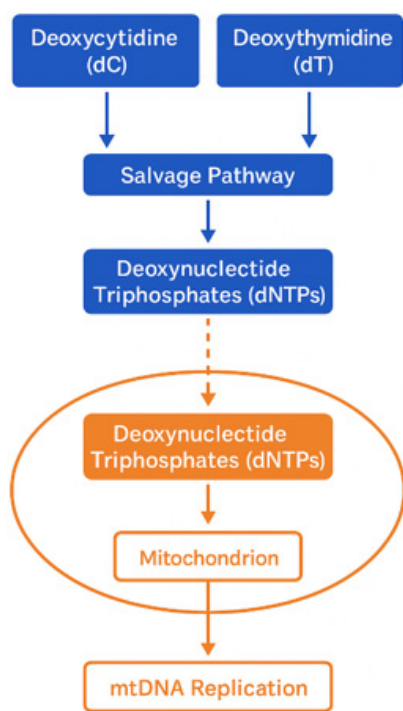


Figure 2 Pathway summarizing dC/dT metabolism and mtDNA replication.

Thus, nucleoside dC/dT supplementation is one disease-modifying strategy in POLG-related disorders (Table 3). These nucleosides are natural DNA building blocks and can be phosphorylated by mitochondrial enzymes such as thymidine kinase 2 (TK2), forming dCTP and dTTP, key substrates for mitochondrial DNA replication.¹⁹

Preclinical studies in TK2-deficient mouse models demonstrated that oral administration of dC and dT led to increased mtDNA levels, delayed disease progression, and improved survival.²⁰ Notably, these effects were seen after researchers determined that nucleotides like dCMP and dTMP are rapidly metabolized to their nucleoside forms, making dC and dT the more effective agents.

Table 3 Deoxycytidine/deoxythymidine (dC/dT) combination therapy in treating POLG-related disorders

Aspect	Details
Potential goal	Replenish mitochondrial dNTP pools to aid mtDNA replication
Drugs	Deoxycytidine + Deoxythymidine (oral or IV in studies)
Best evidence	TK2 deficiency models; limited data in POLG disorders
Clinical use in POLG	Experimental May be considered in early-onset mtDNA depletion syndromes
Challenges	Dosing, timing, genotype-specific response, and long-term safety

Building on this concept, Martí et al.,⁵ conducted an in vitro study using fibroblasts from patients with various *POLG* mutations. They found that supplementation with nucleosides promoted mtDNA repopulation across all mutation types studied, regardless of whether the mutations directly affected polymerase affinity for dNTPs. This suggested that the therapy could be broadly effective in POLG-related disorders, not just those with reduced nucleotide binding. In this context, recent experiments conducted a Phase II open-label trial to evaluate whether combined dC/dT therapy could safely improve outcomes in other patients with these disorders beyond POLG and TK2 subtypes. Results from eight patients with mtDNA depletion due to other gene mutations (FBXL4, SUCLG1, SUCL2, RRM2B) were encouraging, with Newcastle Mitochondrial Disease Scale (NMDS) scores improved in all participants except one who withdrew early, with statistically significant improvements at 1 and 6 months follow-ups.²¹ Additionally, of the five patients who had elevated levels of the mitochondrial dysfunction biomarker GDF15 at baseline, four showed reduced levels after treatment, including three cases of full normalization. No serious safety concerns were reported, concluding that dC/dT is a safe and therapeutically promising intervention for a broad range of mtDNA depletion disorders.

Another significant clinical validation comes from another Phase II open-label trial conducted at the Montreal Children’s Hospital, evaluating a 1:1 dC/dT mixture in 10 pediatric patients with confirmed *POLG* mutations.⁴ Over six months, patients showed a mean reduction in NMDS scores from 27.3 to 20.7, decreased serum levels of GDF-15 (a biomarker of mitochondrial stress), EEG improvements in 5 of 8 patients with abnormal baseline recordings, as well as no serious adverse events, with only mild, self-limited gastrointestinal complaints. While a few participants experienced these mild gastrointestinal symptoms, such as diarrhea and constipation, these effects were transient and did not lead to treatment discontinuation. Furthermore, biochemical markers, including hepatic and renal function parameters, remained stable, reinforcing the metabolic safety of this intervention.

Clinically, all these findings offer hope for the first effective treatment in this field, even though the research presents an open-label design, small sample size, and short follow-up, limiting firm

conclusions and underscoring the need for larger controlled studies to confirm efficacy.

Mechanistic insights of nucleoside therapy

Although the precise mechanism of action of dC/dT therapy in POLG-related disorders is not fully defined, it is hypothesized that supplementation enhances the intracellular pool of deoxynucleoside triphosphates (dNTPs), thereby supporting mtDNA replication even in the presence of dysfunctional POLG enzymes.^{4,5} This approach may help overcome reduced polymerase affinity caused by specific mutations.

Additionally, emerging in vitro research has suggested that dT supplementation may influence telomere biology, promoting elongation and stabilization, an effect of particular interest given reports of premature telomere shortening in POLG-deficient mouse models.²²

Compared to the standard of care, which is largely symptomatic and includes anticonvulsants, nutritional support, and physical or respiratory therapies, dC/dT therapy represents a potential disease-modifying treatment. Clinical improvements were observed in multiple domains, and these outcomes, coupled with the absence of serious treatment-related risks, underscore the promise of nucleoside supplementation as a therapeutic avenue distinct from current palliative strategies.

Potential for broader application

Nucleoside supplementation is already under evaluation for TK2 deficiency, a mtDNA maintenance disorder, and shares mechanistic parallels with POLG dysfunction.²⁰ The overlapping biochemical pathologies suggest that this strategy could be expanded to a wider range of mitochondrial DNA depletion syndromes (MDDS) if shown to be effective across different genotypic contexts. As current trials have used relatively conservative dosing regimens in POLG patients, further studies employing higher therapeutic doses, similar to those trialed in TK2 models, may yield even more robust clinical improvements. The pharmacokinetics of dC and dT also suggest they are safe in pediatric use, with minimal renal clearance and unclear hepatic processing in cases of renal impairment.¹⁹ Although not yet FDA-approved, the drug combination has an orphan designation for TK2 deficiency and is under continued investigation for POLG-related disorders.²³

Challenges and the need for continued evaluation

Despite the encouraging outcomes, dC/dT therapy remains investigational. The main data reported thus far come from a small, pediatric-only cohort within a single-center study, limiting generalizability. The treatment is not yet available to the broader patient population, and its long-term safety and efficacy remain to be fully established through extended follow-up and multicenter trials. Moreover, given the heterogeneity of POLG mutations (over 300 pathogenic variants identified to date), future studies must evaluate the mutation-specific responses to therapy, as well as their potential application in adult populations and other MDDS.

To advance the development of dC/dT therapy, there is a pressing need to 1) identify and enroll more patients with genetically confirmed POLG or MDDS diagnoses worldwide; 2) diversify patient cohorts to include broader age ranges and mutation types; 3) establish long-term monitoring protocols to assess sustained benefits and delayed adverse effects; and 4) compare different dosing strategies to determine

optimal therapeutic windows. Given the rarity of these disorders and their devastating clinical trajectories, even incremental improvements in treatment could translate into meaningful gains in patient outcomes and quality of life.

Gene-editing breakthrough: a novel therapeutic path for POLG and related disorders

A notable recent development in mitochondrial gene therapy has introduced new possibilities for targeted treatment strategies in POLG-related disorders.²⁴ This promising research optimizes *Platinum TALENs* (Transcription Activator-Like Effector Nucleases, or pTALENs) to bidirectionally alter heteroplasmy levels (presence of more than one type of mitochondrial DNA, mtDNA) in induced pluripotent stem cells (iPSCs) derived from patients with the common mtDNA mutation *m.3243A>G*. Their engineered mpTALENs (specially modified pTALENs) incorporate novel non-conventional repeat-variable di-residues or RVDs (e.g., LK, WK, NM, Table 4). These are key amino acid pairs in each module of a TALEN protein that determine which DNA base the TALEN will recognize and bind. In this study, the authors elegantly introduced obligate heterodimeric FokI domains, engineered versions of the DNA-cleaving component of the FokI restriction enzyme from *Flavobacterium okeanoikoites*, to enhance cleavage specificity and minimize off-target mitochondrial DNA damage. These tools successfully shifted heteroplasmy levels up or down in patient-derived cells while preserving pluripotency and differentiation potential.²⁴

Table 4 – Common and Non-Conventional RVDs - Lau, et al²⁵

RVD	Amino acids	Recognizes	Type	Notes
NI	Asn-Ile	Adenine (A)	Conventional	Naturally occurring
HD	His-Asp	Cytosine (C)	Conventional	High specificity
NN	Asn-Asn	G or A	Conventional	Less specifically, it can bind both G and A
NG	Asn-Gly	Thymine (T)	Conventional	Moderately specific
Non-Conventional RVDs Yahata et al. ²⁴				
RVD	Amino acids	Recognizes	Used for targeting	
LK	Leu-Lys	Guanine (G)	Improve specificity over NN, avoids cross-recognition with A	
WK	Trp-Lys	Thiamine (T)	Alternative to NG, good cleavage	
NM	Asn-Met	Adenine (A)	Alternative to NI, Used for wild-type mtDNA targeting	
HY	His-Tyr	Cytosine (C)	Alternative to HD, reduced off-target risk. Also tested for wild-type preference	

Although this study focused on the *m.3243A>G* mutation, linked to Mitochondrial Encephalomyopathy, Lactic Acidosis, and stroke-like episodes syndrome (MELAS syndrome), the approach, while still experimental, holds clear translational potential for POLG-related disorders by offering a model for precisely reducing mutant mtDNA burdens. The ability to selectively edit mtDNA in either direction represents a conceptual leap toward personalized, genotype-specific therapies in mitochondrial medicine, including conditions characterized by POLG dysfunction and mtDNA instability.

Conclusion

Nucleoside supplementation offers a potentially promising approach for POLG-related mitochondrial disorders. Encouraging results from early-phase trials and laboratory studies support further investigation. Future work should aim to clarify mechanisms, optimize dosing, and expand access to this treatment through larger, multicenter trials.

While not curative, dC/dT therapy may provide significant symptomatic relief and slow disease progression. While results are promising, challenges remain in generalizing findings due to small sample sizes and limited patient diversity. The mechanism of nucleoside therapy in the POLG context is not fully elucidated, and more extensive trials including adult populations and various genotypes are necessary.

There is also a need to explore dosing strategies, especially whether higher doses could yield stronger outcomes, investigate telomere stabilization, as emerging studies link nucleotide metabolism with telomere maintenance, which may be impacted in POLG-related aging phenotypes, perform multi-center studies to capture broader genotypic and phenotypic variance, as well as examine long-term outcomes, since existing studies report only short-term benefits.

In parallel, novel gene-editing strategies such as mitochondria-targeted TALENs (mpTALENs) offer an exciting frontier for directly manipulating mtDNA heteroplasmy. Although primarily studied in m.3243A>G disorders, their precise and bidirectional editing capacity may eventually be adapted to address mtDNA instability in POLG-related syndromes, expanding the therapeutic landscape beyond nucleoside supplementation.

Acknowledgments

None.

Conflict of interests

The authors declare there is no conflict of interest.

Funding

None.

References

1. El-Hattab AW, Scaglia F. Mitochondrial DNA depletion syndromes; Review and updates of genetic basis, manifestations, and therapeutic options. *Neurotherapeutics*. 2013;10(2):186–198.
2. Munro B, Hines D, Mueller JS, et al. Deoxynucleoside supplementation ameliorates the disease-associated phenotypes in a zebrafish model of RRM2B mtDNA depletion syndrome. *Hum Mol Genet*. 2025;34(11):967–977.
3. Franklin AD, Chaudhari BP, Koboldt D, et al. Polymerase gamma mitochondrial DNA depletion syndrome initially presenting as disproportionate respiratory distress in a moderately premature neonate: A case report. *Front Genet*. 2021;12:664278.
4. Pেকেles H, Berrahmoune S, Dassi C, et al. Safety and efficacy of deoxycytidine/deoxythymidine combination therapy in POLG-related disorders: 6-month interim results of an open-label, single arm, phase 2 trial. *EClinicalMedicine*. 2024;74:102740.
5. Martí R, Boyes B. Mitochondrial DNA maintenance disorders: Impact of impaired deoxynucleotide triphosphates metabolism. *EMJ Neurology*. 2023;11:82–90.
6. Cohen BH, Chinnery PF, Copeland WC. *POLG-related disorders*. In Adam, M.P.; Ardinger, H.H.; Pagon, R.A.; et al. (Eds.), *GeneReviews*®. University of Washington. 2020.
7. Russo NS, Shah EG, Copeland WC, et al. A new pathogenic POLG variant. *Mol Genet Metab Rep*. 2022;32:100890.
8. Rahman S, Copeland WC. POLG-related disorders and their neurological manifestations. *Nat Rev Neurol*. 2018;15(1):40–52.
9. Hikmat O, Naess K, Engvall M, et al. The impact of gender, puberty, and pregnancy in patients with POLG disease. *Ann Clin Transl Neurol*. 2020;7(10):2019–2025.
10. Leigh syndrome | UMDF. *United Mitochondrial Disease Foundation*. 2020.
11. Abbasi J. Interest in the ketogenic diet grows for weight loss and type 2 diabetes. *JAMA*. 2018;319(3):215–217.
12. Zhaoping L, Heber D. Ketogenic diets. *JAMA*. 2020;323(4):386.
13. Kim JA, Yoon JR, Lee EJ, et al. Efficacy of the classic ketogenic and the modified Atkins diets in refractory childhood epilepsy. *Epilepsia*. 2016;57(1):51–58.
14. Paoli A. Ketogenic diet for obesity: Friend or foe? *Int J Environ Res Public Health*. 2014;11(2):2092–2107.
15. Pedersen ZO, Holm-Yildiz S, Dysgaard T. Nutritional interventions for patients with mitochondrial POLG-related diseases: A systematic review on efficacy and safety. *Int J Mol Sci*. 2022;23(18):10658.
16. Enns GM, Kinsman SL, Perlman SL, et al. Initial experience in the treatment of inherited mitochondrial disease with EPI-743. *Mol Genet Metab*. 2012;105(1):91–102.
17. Blazquez-Bermejo C, Carreno-Gago L, Molina-Granada D, et al. Increased dNTP pools rescue mtDNA depletion in human POLG-deficient fibroblasts. *FASEB J*. 2019;33(6):7168–7179.
18. Dombi E, Marinaki T, Spingardi P, et al. Nucleoside supplements as treatments for mitochondrial DNA depletion syndrome. *Front Cell Dev Biol*. 2024;12:1260496.
19. Mittur A, VanMeter SA, Orujov E, et al. Pharmacokinetics and safety of a 1:1 mixture of deoxythymidine and deoxycytidine: Open-label phase 1 single ascending dose and food effect studies in healthy adults. *Clin Ther*. 2024;46(7):576–587.
20. Lopez-Gomez C, Levy RJ, Sanchez-Quintero MJ, et al. Deoxycytidine and deoxythymidine treatment for thymidine kinase 2 deficiency. *Ann Neurol*. 2017;81(5):641–652.
21. Berrahmoune S, Dassi C, Pেকেles H, et al. Investigating the safety and efficacy of deoxycytidine/deoxythymidine in mitochondrial DNA depletion disorders: Phase 2 open-label trial. *J Neurol*. 2025;272(4):307.
22. Mannherz W, Agarwal S. Thymidine nucleotide metabolism controls human telomere length. *Nat Genet*. 2023;55(4):568–580.
23. Search orphan drug designations and approvals. *U.S. Food and Drug Administration*. 2016.
24. Yahata N, Goto YI, Hata R. Optimization of mtDNA-targeted platinum TALENs for bi-directionally modifying heteroplasmy levels in patient-derived m.3243A>G-iPSCs. *Mol Ther Nucleic Acids*. 2025;36(2):102521.
25. Lau CH, Zhu H, Tay JCK, et al. Genetic rearrangements of variable di-residue (RVD)-containing repeat arrays in a baculoviral TALEN system. *Mol Ther Methods Clin Dev*. 2014;1:14050.