

POLG Liver Vulnerability Requires Genotype, mtDNA Maintenance and Regeneration-Stress Context

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Abstract

Background: POLG encodes the catalytic subunit of mitochondrial DNA polymerase gamma. POLG-related liver discussions often compress genotype, valproate exposure, acute liver failure severity, primary liver mitochondrial DNA content, and hepatocyte recovery into one explanation.

Objective: This working paper asks whether public primary sources distinguish a DNA polymerase gamma mtDNA-maintenance/regeneration-stress bottleneck from ordinary acute-liver-failure or valproate-toxicity explanations in POLG-related hepatic vulnerability.

Methods: Six complete public primary texts were source-coded: four central POLG/ALF records and two current-search boundary records. Endpoint classes were genotype association, human-cell proliferation, mouse CCl4 recovery, VPA boundary evidence, primary liver mtDNA content, patient-tissue specificity, and pediatric ALF incidence. The analysis was a non-pooling public source comparison with decision-changing, robustness, and exploratory sensitivity checks; it did not estimate clinical efficacy, patient-level risk, VPA safety, transplant outcomes, or a pooled biological effect.

Results: Stewart 2010 supplied the human VPA/POLG association and proliferation signal; Silva-Pinheiro 2021 supplied Polg A449T/A449T CCl4 recovery impairment and a VPA-negative mouse boundary; Helbling 2013 supplied the general ALF mtDNA-maintenance comparator; Schaller 2011 and Muller-Hocker 2011 supported primary-tissue liver depletion in POLG contexts; and McKiernan 2016 placed POLG inside a wider pediatric mitochondrial liver-disease differential. Removing Stewart or Silva-Pinheiro changed the research decision, while retaining Helbling prevented over-specific POLG assignment.

Conclusions: Current complete-text evidence supports a bounded research-design rule rather than a validated causal mechanism. POLG hepatic-vulnerability studies should measure genotype or POLgamma-function class, primary liver mtDNA content, stress exposure, and hepatocyte proliferation or regeneration endpoints together before interpreting liver failure as a POLG-specific regeneration-stress bottleneck rather than broader ALF mtDNA-maintenance vulnerability or ordinary drug/injury context.

Keywords: POLG; DNA polymerase gamma; liver failure; valproate; mitochondrial DNA depletion; regeneration stress

1 Introduction

POLG encodes mitochondrial DNA polymerase gamma's catalytic subunit, so POLG liver evidence has a specific connection to mtDNA maintenance rather than a generic mitochondrial-dysfunction label. The selected question is whether public primary sources support a liver-vulnerability state in which POLG or POLgamma defects weaken mtDNA maintenance and regeneration reserve under hepatic drug or injury stress.

The strongest competing interpretation is ordinary context. Under that account, acute liver failure and VPA hepatotoxicity can be explained by drug toxicity, seizure or status epilepticus context, infection, transplant selection, generalized mtDNA depletion, or broader mtDNA-maintenance variation, with POLG variants functioning as incidental risk markers rather than a liver-specific regeneration-stress bottleneck.

This paper therefore treats POLG hepatic vulnerability as a discriminability problem. A POLG-specific interpretation should require genotype or POLgamma-function evidence, primary liver mtDNA or POLgamma-function evidence, explicit hepatic stress context, and regeneration or proliferation endpoints. Liver failure, VPA exposure, or mtDNA depletion alone is insufficient because those observations are shared by the competing account.

The scope differs from prior Mito Map POLG working papers that addressed vascular conditioned-media transfer and finite POLGB capacity in catalytic-subunit turnover rather than hepatic stress, liver mtDNA depletion, and regeneration endpoints [7,8].

2 Methods

The reviewed selected dossier, archived public full-text sources, pre-draft pilot, portfolio context, and current primary-literature searches were checked on 2026-10-13. Complete central full texts were available for Stewart 2010, Silva-Pinheiro 2021, Helbling 2013, and Schaller 2011 [1-4]. Current search added complete public primary texts for Muller-Hocker 2011 and McKiernan 2016 as boundary sources [5,6]. A current indexed primary source reporting no association for common POLG p.Q1236H and p.E1143G variants in an epilepsy cohort was screened as contradictory literature, but complete text was not archived for this bundle; no detailed claim from that record is used as central evidence.

Eligibility required a public primary source directly relevant to POLG or mtDNA-maintenance liver vulnerability, VPA-associated liver toxicity, acute liver failure mtDNA content, primary liver tissue depletion, or hepatocyte stress recovery. Review-only sources, abstract-only leads, patient-specific medical advice, private inputs, and commercial opportunity signals were excluded from central evidence. Internal source identifiers were not treated as author metadata.

A machine-readable evidence and assumption ledger is provided in Supplementary File S1, with a readable companion in Supplementary File S2. The ledger records exact manuscript anchors, source identifiers, evidence excerpts, source-version hashes, actual quotation-check outcomes and unresolved assumptions; it is not a proof of biological truth, clinical validity or therapeutic efficacy.

Each source was coded for biological system, genotype or mtDNA-maintenance context, hepatic stress exposure, endpoint class, observed evidence, interpretation limit, and role in the competing-model analysis. The primary endpoint was source-level discrimination: whether the source adds POLG/POLgamma mtDNA-maintenance or regeneration-stress information beyond ordinary ALF or VPA toxicity context.

No pooled effect size was estimated because the sources differ by human DILIN enrollment, yeast and primary-cell functional assays,

mouse CCl4 injury, VPA challenge, transplant liver specimens, single-patient tissue studies, and pediatric ALF cohort design. Information gain was defined as the change in the next research design rather than as a biological effect estimate. Sensitivity checks were labeled as decision-changing, robustness, or exploratory in the machine-readable analysis results.

3 Results

The evidence step first separates source systems and endpoint classes, then asks whether any source changes the design rule under the same POLG hepatic-vulnerability question.

3.1 Evidence synthesis

The central human drug-stress source supports POLG relevance but not a complete regeneration mechanism. Stewart 2010 sequenced POLG in DILIN VPA liver-toxicity cases and evaluated functional consequences in primary human cells and yeast [1]. The source supports an association between heterozygous POLG variation and VPA-induced liver toxicity and reports that therapeutic VPA inhibited human cellular proliferation. That result makes proliferation and genotype part of the research design. It does not prove that every POLG variant produces a shared liver-regeneration defect or that VPA safety can be inferred for an individual patient.

The central mouse source adds stress-specific recovery evidence and a boundary. Silva-Pinheiro 2021 studied Polg A449T/A449T biology, corresponding to human A467T context, and reported impaired recovery after CCl4 liver injury [2]. The same model does not supply a simple VPA liver-failure replication. This makes the source useful because it separates regeneration-stress vulnerability from an automatic claim that every POLG mouse model recapitulates human VPA hepatotoxicity.

The general ALF comparator prevents over-specific interpretation. Helbling 2013 found reduced hepatic mtDNA content in many ALF transplant samples and reported a subset with variants in mtDNA-maintenance genes [3]. This is not a POLG-only result. It is therefore the strongest competing account: mtDNA-maintenance vulnerability may be a broader ALF feature rather than a VPA-specific POLG mechanism.

Primary tissue sources support tissue specificity. Schaller 2011 reported tissue-specific mtDNA depletion in a compound POLG Alpers case, and Muller-Hocker 2011 reported severe liver-predominant mtDNA depletion in fatal infantile hepatic failure with compound POLG mutations [4,5]. These records support measuring primary liver tissue when possible. They do not establish a general stress-regeneration mechanism because case-level tissue specificity is not the same as a matched stress experiment.

The pediatric ALF incidence source broadens the boundary. McKiernan 2016 found genetically proven mitochondrial liver disease in children younger than two years with ALF, including POLG cases [6]. This supports the need to treat POLG as a specific gene within a wider mitochondrial liver-disease differential rather than as a universal explanation for pediatric liver failure.

3.2 Evidence-coded sensitivity analysis

The decision-changing Stewart-removal check asks whether the source set still supports a POLG/VPA entry point without the DILIN association and proliferation evidence. It does not. The remaining sources can still motivate mtDNA-maintenance liver vulnerability, but the VPA/POLG human drug-stress axis becomes too weak for the selected question.

The decision-changing Silva-Pinheiro-removal check asks whether the source set still contains a direct regeneration-stress phenotype. It does not. Without the CCl4 recovery source, the analysis can recommend primary liver mtDNA measurement, but regeneration reserve becomes an inferred design need rather than an observed stress-recovery endpoint.

Table 1. Primary-source evidence matrix for POLG hepatic vulnerability. Abbreviations: ALF, acute liver failure; CCl4, carbon tetrachloride; mtDNA, mitochondrial DNA; POLgamma, DNA polymerase gamma; VPA, valproic acid.

ID	Model and perturbation	Key finding	Interpretive limitation
[1]	DILIN VPA liver-toxicity cases and controls; primary human cell lines and yeast functional assays.; POLG sequencing, VPA exposure, human-cell proliferation assays, and yeast p.Q1236H functional testing.	Heterozygous POLG variation was associated with VPA-induced liver toxicity, and therapeutic VPA inhibited human cellular proliferation.	Association and proliferation evidence do not prove a general POLG liver-regeneration mechanism or patient-level VPA safety decision.
[2]	Polg A449T/A449T mouse and mitochondrial replication models.; CCl4 liver injury challenge, VPA challenge, mutant POLgamma holoenzyme stability and mtDNA-replication assays.	Mutant mice showed delayed recovery after CCl4 liver injury while the same model did not establish VPA hepatic failure.	Mouse CCl4 regeneration stress cannot be transferred to human VPA hepatotoxicity without matched human hepatocyte or cohort evidence.
[3]	Acute liver failure transplant specimens and mtDNA-depletion controls.; Hepatic mtDNA-content measurement and nuclear mtDNA-maintenance variant screening.	Most ALF transplant samples had reduced hepatic mtDNA content and a subset had variants in mtDNA-maintenance genes.	This is the strongest comparator because mtDNA-maintenance vulnerability extends beyond VPA-specific POLG toxicity.
[4]	POLG Alpers case with fibroblast, muscle, and liver tissue testing.; Compound POLG p.A467T plus splice-site mutation; tissue mtDNA qPCR and OXPHOS assays.	mtDNA depletion was tissue specific and most pronounced in liver in a POLG Alpers context.	A single case supports primary-tissue measurement needs but cannot establish a general stress mechanism.
[5]	Fatal infantile hepatic failure with liver, skeletal muscle, and heart analyses.; Compound POLG A467T/K1191N mutations; morphology, enzyme histochemistry, immunocytochemistry, biochemistry, and molecular genetics.	The abstract reports severe mtDNA depletion most pronounced in liver and a POLG-linked tissue-selective impairment pattern.	This supports tissue specificity but not stress-specific regeneration or transfer across genotypes.
[6]	Children younger than two years presenting with acute liver failure.; Diagnostic workup for genetic mitochondrial liver disease and mtDNA-depletion syndrome.	Five infants in the cohort had genetically proven mitochondrial liver disease, including two POLG cases.	This broadens ALF context and reinforces that POLG is one member of a wider pediatric mitochondrial liver-disease set.

Public source-comparison workflow

Solid arrows indicate performed public analysis steps; dashed arrow marks exploratory current-literature screening.

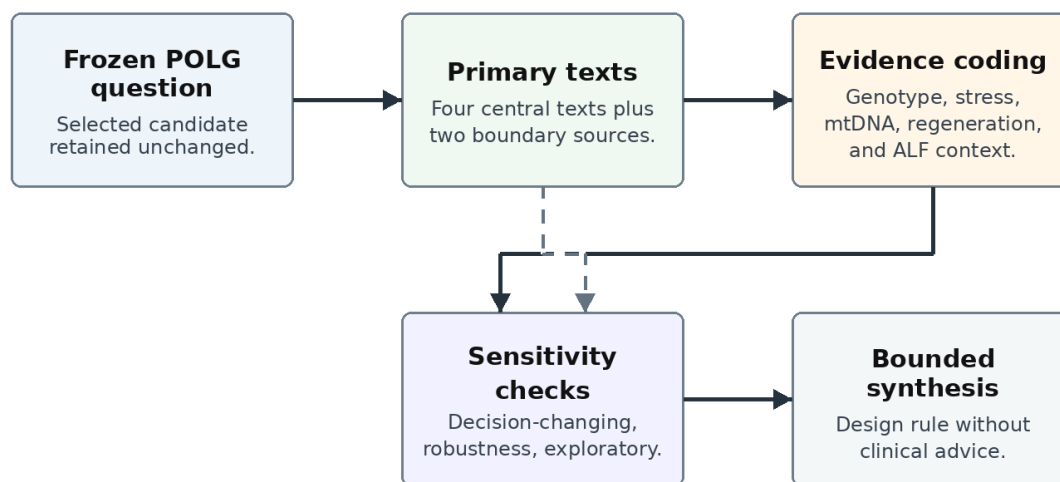


Figure 1. Source-comparison workflow. The workflow freezes the selected POLG question, archives complete public texts, codes genotype and endpoint classes, labels sensitivity analyses, and synthesizes a bounded design rule without clinical inference.

The robustness check retains Helbling as an active alternative. The POLG-bottleneck account and the ordinary-context account both predict liver failure, but they differ on whether genotype or POLgamma dysfunction, primary liver mtDNA content, and regeneration endpoints add discrimination under the same stress context. Helbling keeps the analysis honest by showing that mtDNA-maintenance findings in ALF are broader than VPA-specific POLG toxicity.

The exploratory boundary-source check adds Muller-Hocker and McKiernan. These sources strengthen the need for primary tissue and pediatric differential coding, but they do not validate mouse-to-human transfer, VPA causality, or a shared rescue mechanism across POLG variants.

4 Discussion

The contribution is a conservative research-design rule. POLG hepatic vulnerability should not be inferred from liver failure alone, from VPA exposure alone, or from mtDNA depletion alone. The public evidence supports asking for a matched quartet: genotype or POLgamma-function class, primary liver mtDNA or direct POLgamma evidence, explicit stress exposure, and regeneration or proliferation endpoints.

The same analysis could not simply be applied to any mitochondrial disorder. The discriminator depends on POLG/POLgamma catalytic-subunit biology, VPA-associated POLG evidence, Polg A449T/A449T CCl4 recovery, primary liver depletion in POLG

POLG hepatic stress interpretation boundary

Supported links are source-coded; the regeneration-reserve bridge remains a bounded hypothesis.

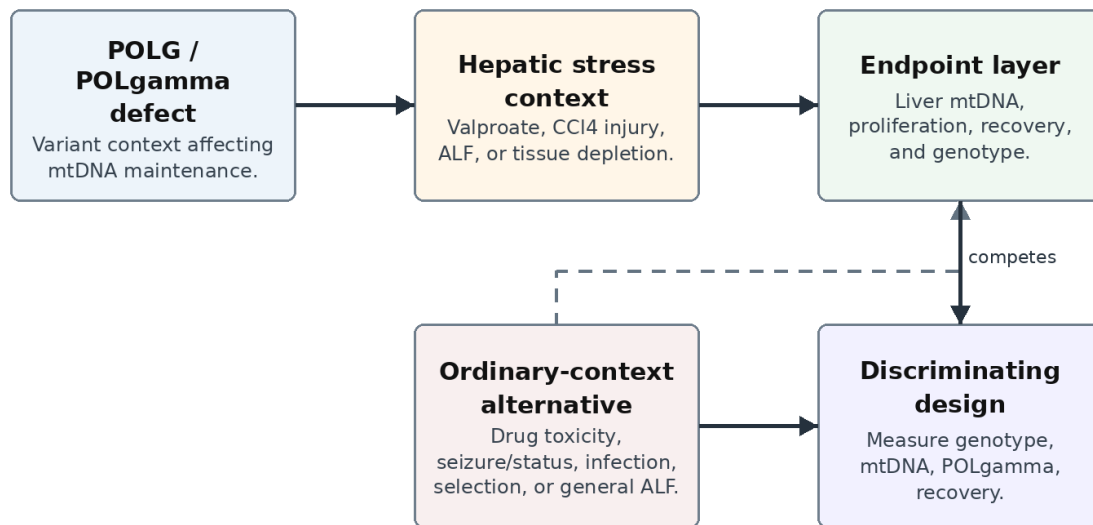


Figure 2. POLG hepatic stress interpretation boundary. The concept diagram separates POLG or POLgamma mtDNA-maintenance evidence, hepatic stress context, endpoint layer, ordinary-context alternatives, and discriminating future study design.

cases, and the difference between POLG-specific and broader mtDNA-maintenance ALF contexts. DGUOK, MPV17, TWNK, RRM2B, or non-genetic ALF may require parallel but distinct evidence matrices.

The negative result is scientifically useful. If a matched future dataset shows that VPA exposure, ALF severity, seizure/status context, infection, or transplant-selection context fully explains hepatic outcomes while POLG genotype, liver mtDNA content, POLgamma function, and regeneration endpoints add no discrimination, POLG liver manuscripts should avoid mechanism-specific regeneration-stress claims and prioritize broader ALF mtDNA-maintenance cohorts.

5 Limitations

This working paper is a public source-coded reanalysis and design-rule exercise. It does not reanalyze raw histology, patient-level records, mouse-level data, cell-culture wells, or transplant outcomes. It does not produce a pooled odds ratio, treatment recommendation, VPA safety recommendation, transplant recommendation, clinical-risk estimate, or proof of clinical efficacy.

The source systems are heterogeneous. Human VPA-associated DILIN cases, yeast, primary human cell lines, Polg A449T/A449T mice, transplant liver specimens, single-patient tissue studies, and pediatric ALF cohorts cannot be treated as biological replicates. Mouse CCl4 recovery cannot be assumed to transfer to human VPA injury. Missing genotype-specific transfer evidence remains unresolved.

The current search found contradictory and limiting literature, including a retrospective cohort abstract challenging association of common POLG variants with VPA hepatotoxicity or pancreatic toxicity. Because complete text for that record was not archived in this bundle, it is treated as a screened limitation rather than central evidence.

6 Conclusions

Current complete-text evidence supports a bounded POLG liver research-design rule: hepatic vulnerability claims should pair genotype or POLgamma-function class with primary liver mtDNA content and regeneration or proliferation endpoints under explicit stress context. The evidence is strong enough for a source-coded

working paper and future study design, but not for clinical guidance or a validated causal claim that POLG defects universally create VPA-specific liver failure.

Declarations

Data and code availability. The repository deposit includes the manuscript source, evidence table, source data, analysis code, figures, measured figure geometry, biological-audit supplements, layout reports, QA record, Gemini review and checksums needed to replay the table, counts, figures and artifacts. Private replay inputs are retained locally and excluded from public manifests.

Source verification. The biological audit is a manuscript-integrity ledger, not proof of biological truth or clinical efficacy. Corpus anchors and archived normalized source files were replayed against recorded hashes; UNKNOWN or NOT_RUN biological interpretation statuses remain visible.

Ethics statement. This literature synthesis used no identifiable patient data and required no new human-participant or animal research.

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Author contributions. Andrew Friedl conceived the project, directed the analysis, reviewed the evidence package, and approved the manuscript for repository review.

AI assistance. AI tools assisted literature synthesis, drafting, data visualization, formatting and QA preparation. Gemini independently reviewed the exact rendered PDF when artifact-bound review was available. Andrew Friedl remains solely responsible for the content and is the sole author.

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