Understanding Diseases of Mitochondrial DNA Maintenance

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Mitochondrial DNA Replication Group
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Outline of Talk

• Function of mitochondrial DNA (mtDNA)
• How mtDNA is copied (POLG, POLG2, TWNK, SSBP1)
• How mutations arise in mitochondrial DNA, the natural evolution of mtDNA
• Genetic diseases (POLG related diseases) that affect mtDNA replication
• MtDNA mutagenesis in POLG related diseases
• New therapies on the horizon
Mitochondria have their own DNA
The mitochondrial genome is a closed, circular DNA.

Maternally inherited
The mitochondrial genome is a closed, circular DNA.

Maternally inherited

Thousands of copies per cell

MtDNA copy number is very dynamic

Human mitochondrial DNA
Nuclear vs. Mitochondrial DNA

Mitochondrial DNA only accounts for ~0.3% of DNA in a cell.

nucDNA genome
~3,000,000 Kbp
>50,000 genes

mtDNA genome
≤17 Kbp
38 genes
Human mitochondrial DNA

GC rich (44%)
Densely coding
No introns

Gustafson et al., DNA Repair, 2020
How is DNA copied

DNA is copied or replicated by enzymes called “DNA Polymerases”
# 17 Human DNA Polymerases

<table>
<thead>
<tr>
<th>Polymerase</th>
<th>Family</th>
<th>Chromosome</th>
<th>Mol. Wt. (kDa)</th>
<th>Function/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>α (alpha)</td>
<td>B</td>
<td>Xq21.3-q22.1</td>
<td>165</td>
<td>Initiates replication</td>
</tr>
<tr>
<td>β (beta)</td>
<td>X</td>
<td>8p12-p11</td>
<td>39</td>
<td>BER, other functions</td>
</tr>
<tr>
<td>γ (gamma)</td>
<td>A</td>
<td>15q25</td>
<td>140</td>
<td>Mitochondrial replication &amp; repair</td>
</tr>
<tr>
<td>δ (delta)</td>
<td>B</td>
<td>19q13.3-.4</td>
<td>125</td>
<td>Replication, BER, NER, MMR</td>
</tr>
<tr>
<td>ε (epsilon)</td>
<td>B</td>
<td>12q24.3</td>
<td>255</td>
<td>Replication, checkpoint control</td>
</tr>
<tr>
<td>ζ (zeta)</td>
<td>B</td>
<td>6q22</td>
<td>344</td>
<td>yREV3 homolog, lesion bypass</td>
</tr>
<tr>
<td>η (eta)</td>
<td>Y</td>
<td>6p21.1</td>
<td>78</td>
<td>Lesion bypass, XPV, skin cancer susceptibility</td>
</tr>
<tr>
<td>θ (theta)</td>
<td>A</td>
<td>3q13.31</td>
<td>300</td>
<td>crosslink repair, <em>Dm308</em>, lesion bypass</td>
</tr>
<tr>
<td>τ (iota)</td>
<td>Y</td>
<td>18q21.1</td>
<td>80</td>
<td>Lesion bypass? BER?</td>
</tr>
<tr>
<td>κ (kappa)</td>
<td>Y</td>
<td>5q13.1</td>
<td>99</td>
<td>Lesion bypass, mutator when overexpressed</td>
</tr>
<tr>
<td>λ (lambda)</td>
<td>X</td>
<td>10q23</td>
<td>64</td>
<td>pol β homolog, meiosis? NHEJ</td>
</tr>
<tr>
<td>μ (mu)</td>
<td>X</td>
<td>7p13</td>
<td>55</td>
<td>TdT homolog, NHEJ</td>
</tr>
<tr>
<td>ν (nu)</td>
<td>A</td>
<td>4p16.3</td>
<td>100</td>
<td>lesion bypass, crosslink repair?</td>
</tr>
<tr>
<td>σ (sigma)</td>
<td>X</td>
<td>5p15</td>
<td>60</td>
<td>TRF4</td>
</tr>
<tr>
<td>Rev1</td>
<td>Y</td>
<td>2q11.1-.2</td>
<td>125</td>
<td>lesion bypass</td>
</tr>
<tr>
<td>TdT</td>
<td>X</td>
<td>10q23-24</td>
<td>57</td>
<td>Terminal transferase</td>
</tr>
<tr>
<td>PrimPol</td>
<td>AEP</td>
<td>4q35.1</td>
<td>65</td>
<td>Restart during replication stress, Mitochondrial TLS</td>
</tr>
</tbody>
</table>
Proteins involved in mitochondrial DNA replication

**POLG**: p140, catalytic subunit of Pol γ, polymerase and exonuclease

**POLG2**: p55, accessory subunit of Pol γ, functions as processivity factor

**TWNK**: replicative DNA helicase

**SSBP1**: single-stranded DNA binding protein

MtDNA
16,569 bp
Mitochondrial DNA mutations cause or are associated with various diseases

* Alpers Disease
* Barth syndrome
* Beta-oxidation Defects
* Carnitine-Acyl-Carnitine Deficiency
* Carnitine Deficiency
* Co-Enzyme Q10 Deficiency
* Complex I Deficiency
* Complex II Deficiency
* Complex III Deficiency
* Complex IV Deficiency
* Complex V Deficiency
* COX Deficiency
* CPEO
* CPT I Deficiency
* CPT II Deficiency
* Glutaric Aciduria Type II
* KSS
* Lactic Acidosis
* LCAD
* LCHAD
* Leigh Disease or Syndrome
* LHON
* LIC (Lethal Infantile Cardiomyopathy)
* MAD
* MCAD
* MELAS
* MERRF
* Mitochondrial Cytopathy
* Mitochondrial DNA Depletion
* Mitochondrial Encephalopathy
* Mitochondrial Myopathy
* MNGIE
* NARP
* Pearson Syndrome
* Pyruvate Carboxylase Deficiency
* Pyruvate Dehydrogenase Deficiency
* Respiratory Chain
* SCAD
* SCHAD
* VLCAD
MtDNA mutates or evolves faster than nuclear DNA, with estimates suggesting that MtDNA mutates/evolves ~20-100-fold faster than nuclear DNA.
Fidelity of nuclear DNA Replication: $10^{-10}$

1. Insertion fidelity (DNA polymerase): $10^{-5}$
2. Proofreading (Exonuclease): $10^{-2}$
3. DNA mismatch repair: $10^{-3}$

1. Typing
2. Delete (backspace)
3. Spell check
Fidelity of Human DNA Polymerase $\gamma$

- DNA polymerase $\gamma$ has high DNA synthetic fidelity at single base pairs. (<1 error per 1,000,000 nucleotides synthesized)

- Pol $\gamma$ proofreading contributes ~100-fold to base substitution and frameshift fidelity.

# Nuclear and Mitochondrial DNA Repair

<table>
<thead>
<tr>
<th>Repair system</th>
<th>Nuclear</th>
<th>Mitochondrial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleotide Excision Repair</td>
<td>XPA, XPC, RPA, TFIIH, XPF9, XPG Pol ε, PCNA, RFC, DNA ligase I/III</td>
<td>None</td>
</tr>
<tr>
<td>Mis Match Repair</td>
<td>hMSH2, hMSH3, hMSH5, hMSH6, hMLH1, PMS2</td>
<td>No clear MMR activity</td>
</tr>
<tr>
<td>Base Excision Repair</td>
<td>Base glycosylase, UDG, TDG APE, PARP Short patch repair – polβ Long patch repair – polδ/ε or polβ FEN1, DNA2, PCNA, RFC DNA ligase I/III</td>
<td>UDG, OGG, hMYH APE1 Short patch repair – pol γ Long patch repair – pol γ, FEN1, DNA2, DNA ligase III</td>
</tr>
<tr>
<td>Ribonucleotide Excision Repair</td>
<td>Rnase H2</td>
<td>None</td>
</tr>
</tbody>
</table>
MtDNA mutates or evolves faster than nuclear DNA, with estimates suggesting that MtDNA mutates/evolves ~20-100-fold faster than nuclear DNA.

The highly mutation rate is mostly due to the lack of mitochondrial mismatch repair.
The major driver of mtDNA mutations is spontaneous errors of mtDNA replication from POLG
Proteins involved in mitochondrial DNA replication

**MtDNA**: 16,569 bp

**Polymerase γ**

**POLG**: p140, catalytic subunit of Pol γ, polymerase and exonuclease

**POLG2**: p55, accessory subunit of Pol γ, functions as processivity factor

**TWNK**: replicative DNA helicase

**SSBP1**: single-stranded DNA binding protein

**Topoisomerase Twinkle**
**Minimal mtDNA Replisome Components**

- **DNA Polymerase γ**
  - Catalytic subunit: 137 kD monomer
  - >300 disease variants

- **POLG2**
  - Accessory subunit: 104 kD homodimer
  - 11 disease variants

- **mtSSB**
  - ssDNA binding protein
  - 61 kD homotetramer
  - 8 disease variants

- **Twinkle**
  - Helicase
  - 433 kD homohexamer
  - >50 disease variants

**Disease Outcomes Associated with Mutations**


- Chronic Progressive External Ophthalmoplegia, Ataxia Neuropathy Spectrum, Leigh Syndrome, Hepatocerebral Mitochondrial DNA Depletion Syndrome

- Optic Atrophy, Kearns-Sayre Syndrome, Pearson Syndrome, Leigh Syndrome

- Chronic Progressive External Ophthalmoplegia, Ataxia Neuropathy Spectrum, Hepatocerebral Mitochondrial DNA Depletion Syndrome, Infantile-Onset Spinocerebellar Ataxia, Perrault Syndrome
## Nuclear loci that affect the stability of mitochondrial DNA

<table>
<thead>
<tr>
<th>Gene</th>
<th>Disorder</th>
<th>Locus</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>mtDNA replication and repair</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POLG</td>
<td>PEO, Alpers, ataxia</td>
<td>15q25</td>
<td>Pol γ catalytic subunit</td>
</tr>
<tr>
<td>POLG2</td>
<td>PEO</td>
<td>17q23-24</td>
<td>Pol γ accessory subunit</td>
</tr>
<tr>
<td>TWNK</td>
<td>PEO, mtDNA depletion, IOSCA</td>
<td>10q24</td>
<td>Mitochondrial DNA helicase</td>
</tr>
<tr>
<td>MGME1</td>
<td>PEO, mtDNA depletion</td>
<td>20p11.23</td>
<td>Single-strand DNA nuclease</td>
</tr>
<tr>
<td>DNA2</td>
<td>mtDNA deletions, PEO</td>
<td>10q21.3-22.1</td>
<td>Mito/nuclear helicase-nuclease</td>
</tr>
<tr>
<td>RNASEH1</td>
<td>encephalomyopathy, mtDNA deletions</td>
<td>2p25</td>
<td>RNA/DNA hybrid endonuclease</td>
</tr>
<tr>
<td>TFAM</td>
<td>mtDNA depletion</td>
<td>10q21.1</td>
<td>Organizes mtDNA transactions</td>
</tr>
<tr>
<td>SSBP1</td>
<td>Optic atrophy, mtDNA dep/del</td>
<td>7q34</td>
<td>Single strand DNA binding protein</td>
</tr>
<tr>
<td><strong>nucleotide pool metabolism</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANT1</td>
<td>PEO</td>
<td>4q34-35</td>
<td>Adenine nucleotide translocator</td>
</tr>
<tr>
<td>TP</td>
<td>MNGIE, mtDNA deletions/depletion</td>
<td>22q13.32</td>
<td>Thymidine phosphorylase</td>
</tr>
<tr>
<td>DGUOK</td>
<td>mtDNA depletion</td>
<td>2p13</td>
<td>Deoxyguanosine kinase</td>
</tr>
<tr>
<td>TK2</td>
<td>PEO, mtDNA depletion</td>
<td>16q22-23.1</td>
<td>Mitochondrial thymidine kinase</td>
</tr>
<tr>
<td>MPV17</td>
<td>mtDNA deletions, depletion</td>
<td>2p23.3</td>
<td>Mito inner membrane protein</td>
</tr>
<tr>
<td>SUCLA2</td>
<td>mtDNA depletion</td>
<td>13q14.2</td>
<td>ATP-dep Succinate-CoA ligase</td>
</tr>
<tr>
<td>SUCLG1</td>
<td>mtDNA depletion</td>
<td>2p11.2</td>
<td>GTP-dep Succinate-CoA ligase</td>
</tr>
<tr>
<td>RRM2B</td>
<td>PEO, mtDNA depletion</td>
<td>8q23.1</td>
<td>p53-Ribonucleotide reductase, small subunit</td>
</tr>
<tr>
<td>ABAT</td>
<td>mtDNA deletions, depletion</td>
<td>16p13.2</td>
<td>4-Aminobutyrate aminotransferase</td>
</tr>
<tr>
<td><strong>mitochondrial homeostasis / dynamics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPA1</td>
<td>Dominant optic atrophy, mtDNA</td>
<td>3q28-29</td>
<td>Dynamin related GTPase</td>
</tr>
<tr>
<td>MFN2</td>
<td>DOA, mtDNA deletions</td>
<td>1p36.22</td>
<td>Mitofusin 2</td>
</tr>
<tr>
<td>FBXL4</td>
<td>mtDNA depletion, encephalopathy</td>
<td>6q16.1-16.3</td>
<td>Mitochondrial LLR F-Box protein</td>
</tr>
<tr>
<td>AFG3L2</td>
<td>Spinocerebellar ataxia, mtDNA deletions</td>
<td>18p11.21</td>
<td>Mitochondrial IM metalloprotease</td>
</tr>
<tr>
<td>SPG7</td>
<td>ataxia, spastic paraplegia</td>
<td>16:89.49-89.56</td>
<td>Mito IM metalloprotease component</td>
</tr>
<tr>
<td>GFEM5</td>
<td>mtDNA deletions, myopathy</td>
<td>16:1.98-1.99</td>
<td>Protein import to IMS</td>
</tr>
</tbody>
</table>
Mutations in DNA polymerase γ, POLG

Human POLG gene

- adPEO+ (Progressive External Ophthalmoplegia)
- arPEO+
- PEO, sporadic
- Single Nucleotide Polymorphism (*)
- Other
- Alpers and other Infantile Hepatocerebral Syndromes with mtDNA depletion
- Ataxia-Neuropathy Syndrome, MIRAS / SANDO / SCAE
- NRTI toxicity
- Male infertility / testicular cancer / Idiopathic Parkinson

http://tools.niehs.nih.gov/polg/
POLG Disease Burden

- POLG mutations are the most common cause of inherited mitochondrial disorders (Saneto and Naviaux, 2010).

- Approximately 2% of the population carries a pathogenic genetic variant of POLG (Saneto and Naviaux, 2010).

- The combined prevalence of recessive and dominant disease caused by POLG mutations is ~1:10,000.
### Major clinical syndromes associated with *POLG* mutations

<table>
<thead>
<tr>
<th>Age of Onset</th>
<th>Syndrome</th>
<th>mtDNA defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal/Infancy</td>
<td>Myocerebrohepatopathy spectrum (MCHS)</td>
<td>Depletion</td>
</tr>
<tr>
<td>Infancy/Childhood</td>
<td>Alpers-Huttenlocher syndrome (AHS)</td>
<td>Depletion</td>
</tr>
<tr>
<td>Adolescent/young</td>
<td>Ataxia neuropathy spectrum (ANS)</td>
<td>Deletions</td>
</tr>
<tr>
<td>adult</td>
<td>Myoclonus, epilepsy, myopathy, sensory ataxia (MEMSA)</td>
<td>Deletions</td>
</tr>
<tr>
<td></td>
<td>Progressive external ophthalmoplegia (PEO) with or without sensory ataxic</td>
<td>Deletions</td>
</tr>
<tr>
<td></td>
<td>neuropathy and dysarthria (SANDO)</td>
<td></td>
</tr>
<tr>
<td>Allele 1</td>
<td>Allele 2</td>
<td>Sex</td>
</tr>
<tr>
<td>-------------</td>
<td>--------------</td>
<td>-----</td>
</tr>
<tr>
<td>T251I+P587L</td>
<td>T251I+P587L</td>
<td>F</td>
</tr>
<tr>
<td>T251I+P587L</td>
<td>G848S</td>
<td>M</td>
</tr>
<tr>
<td>T251I+P587L</td>
<td>L304R</td>
<td>F</td>
</tr>
<tr>
<td>T251I+P587L</td>
<td>L304R</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td>Patient 1</td>
<td>Patient 2</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td><strong>Age at presentation</strong> (years)</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td><strong>Age at death</strong> (years)</td>
<td>5.5</td>
<td>Alive at 16</td>
</tr>
<tr>
<td><strong>Symptoms at presentation</strong></td>
<td>Seizures</td>
<td>Encephalitis-type presentation</td>
</tr>
<tr>
<td><strong>Clinical phenotype</strong></td>
<td>Alpers-Huttenlocher</td>
<td>MEMSA+</td>
</tr>
<tr>
<td><strong>Blood/CSF results</strong></td>
<td>GGT 170 IU/L (reference &lt;20 IU/L), AST 490 IU/L (reference range 5 to 45 IU/L)</td>
<td>↓lactate 2.6mmol/L (&lt;2) Liver function normal; ↑Plasma alanine 537 mc mol/L (150–450); ↑Plasma arginine 28 mc mol/L (40–120); CSF lactate 1.6mmol/L (&lt;2); ↑CSF protein 1.32 g/L (0.15–0.6); CSF 5MTHF 29 (46–120)</td>
</tr>
<tr>
<td><strong>Neurophysiology</strong></td>
<td>-</td>
<td>EEG: Intermittent runs of rhythmic delta activity; CS: sensory neuropathy affecting legs</td>
</tr>
<tr>
<td><strong>Radiology</strong></td>
<td>Chronic grey matter ischaemia</td>
<td>MRI: Bilateral occipital lesions around calcine sulci</td>
</tr>
<tr>
<td><strong>Neuropathology</strong></td>
<td>Cortical degeneration in the occipital and parietal lobes, typical of PNDC. Bilateral hippocampal sclerosis. Hepatic microstatis</td>
<td>Brain biopsy: Non-specific; Muscle histology: COX-negative fibres</td>
</tr>
<tr>
<td><strong>Muscle Respiratory Chain enzymes</strong></td>
<td>-</td>
<td>Complex I 0.126 (0.104–0.268); Complex II 0.159 (0.040–0.204); Complex IV 0.026 (0.014–0.034)</td>
</tr>
</tbody>
</table>

**Key:** 5MTHF, 5-methyltetrahydrofolate; AST, aspartate aminotransferase; COX, cytochrome oxidase; EEG, electroencephalogram; GGT, gamma-glutamyltranspeptidase; MELAS, mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes; MEMSA, myoclonic epilepsy, myopathy, sensory ataxia; NCS, nerve conduction studies; PNDC, progressive neuronal degeneration of childhood; SANDO, Sensory Ataxia Neuropathy Dysarthria Ophthalmoplegia.
GENETIC & ENVIRONMENTAL INTERACTIONS RESULTING IN MITOCHONDRIAL DYSFUNCTION

Environmental Factors

**Inhibitors**
- Smoking
- Cyanide
- Nitric Oxide
- Hydrogen Sulfide
- Fungal Toxins
- Pesticides
- Industrial Chemicals
- Streptozotocin
- Antibiotics
- Antivirals
- Anti-cancer drugs

**Activators**
- Benzofibrate
- Resveratrol
- Roziglitazone

mtDNA Variants

Ancient Adaptive Polymorphisms
Recent Deleterious Mutations

OXPHOS INHIBITION
and
MITOCHONDRIAL DYSFUNCTION

nDNA Variants

ANT1
POLG
POLG2
Twinkle
MGME1
SUV3
OPA1
MPV17
TK2
dGuoK
RRM2B
PPARγ
PGC-1α, β

nDNA Polymorphisms
Progressive External Ophthalmoplegia

- Weakening of the external eye muscles
- Ophthalmoparesis, inability to look right and left
- Bilateral ptosis, droopy eyelids
- Multiple deletions in the mtDNA
- Many other associated symptoms
Pipeline for MtDNA Deletion Detection and Mapping: **LostArc**

**LostArc TEAM**
Scott Lujan  
Matt Longley  
Maggie Humble  
Andy Lavender  
Adam Burkholder  
Robert Taylor, Newcastle, UK  
Robert McFarland, Newcastle, UK  
Grainne Gorman, Newcastle, UK  
Doug Turnbull, Newcastle, UK  
Tom Kunkel

Lujan et al., 2020 *Genome Biology* 21:248

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**Analyzed**
- 22 PEO patients with POLG mutations ranging in age from 17 – 80
- 19 Wildtype subjects, ages 19-93

**Identified:**
- 35 million mtDNA deletions
- 470,000 unique deletions
HEK293 cells (weighted mean, n = 3)

Detection limit of traditional NG sequence
HEK293 cells (weighted mean, n = 3)

M314 (WT POLG, 17 years old at biopsy)
HEK293 cells (weighted mean, n = 3)

M314 (WT POLG, 17 years old at biopsy)

M508 (A467T/A467T POLG, 45 years old at biopsy)

>70% of the mtDNA genomes carried a deletion
POLG A467T and T251I/P587L:

- Age of on-set at 45 yrs.
- Patient diagnosed with PEO, ptosis, and proximal weakness
- 25% COX negative muscle fibers and positive for ragged red fibers
- Long range PCR detected mtDNA deletions

Mito Deletion Mapping Results:

- Over 87 million reads aligned
- 79% of the mtDNA genomes contained a deletion
- 446,000 deletions detected
- 25,933 unique deletions
49 y.o. PEO patient: W748S / R1096C

**POLG W748S/R1096C:**
- This patient is a 49 y.o. male with age of on-set at 25 yrs
- Diagnosed with PEO, ptosis, peripheral neuropathy, and epilepsy
- Has 16% COX negative muscle fibers and 5% ragged red fibers

**Mito Deletion Mapping Results**
- Over 700 million reads
- 74% of the mtDNA genomes contained a deletion
- 2.9 million deletions detected
- 24,360 unique deletions
MtDNA deletion clusters

Samples cluster by deletion pattern, WT control samples independently from POLG patient samples.

Lujan et al., 2020 Genome Biology
What does the future hold for POLG-related disorder

More accurate and faster diagnosis

- Lots of published literature available for the clinicians, families and patients

- WGS and WES genome sequencing to quickly identify POLG and related disease mutation
  
  http://tools.niehs.nih.gov/polg/

- Sequencing mostly covered by health insurance
What does the future hold for POLG-related disorder

Better disease models to develop therapies

- Cell based models
- Mouse models of POLG, POLG2 and Twinkle
- Zebra Fish models of POLG and POLG2 disease
- Organoids
Mitochondrial DNA polymerase gamma is essential for mammalian embryogenesis

Nicole Hance, Mats I. Ekstrand and Aleksandra Trifunovic

Department of Medical Nutrition and Department of Biosciences at Novum, Karolinska Institute, Stockholm, Sweden

Received April 13, 2005; Revised and Accepted May 4, 2005

Polg2 is essential for mammalian embryogenesis and is required for mtDNA maintenance

Margaret M. Humble, Matthew J. Young, Julie F. Foley, Arun R. Pandiri, Greg S. Travlos and William C. Copeland

Human Molecular Genetics, 2013, Vol. 22, No. 5 1017–1025
doi:10.1093/hmg/ddt438
Advance Access published on November 29, 2012
What does the future hold for POLG-related disorder

Better disease models to develop therapies

• Cell based models

• Mouse models of POLG, POLG2 and Twinkle

• Zebra Fish models of POLG and POLG2 disease

• Organoids
Zebralfish polg2 knock-out recapitulates human POLG-disorders; implications for drug treatment


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Hallmark Molecular and Pathological Features of POLG Disease are Recapitulated in Cerebral Organoids

Anbin Chen, Tsering Yangzom, Yu Hong, Bjørn Christian Lundberg, Gareth John Sullivan, Charalampos Tzoulis, Laurence A. Bindoff, and Kristina Xiao Liang*
What does the future hold for POLG-related disorder

Therapies in the works

• Antioxidant therapy

• Anti-seizure, anti-epileptic drugs

• Nucleotide therapy

• Metformin

• Repurposing drugs and identifying new drugs

• Gene therapy
NOVEL VITAMIN K ANALOGS SUPPRESS SEIZURES IN ZEBRAFISH AND MOUSE MODELS OF EPILEPSY

J. J. RAHN, J. E. BESTMAN, B. J. JOSEY, E. S. INKS, K. D. STACKLEY, C. E. ROGERS, C. J. CHOU* AND S. S. L. CHAN*

Department of Drug Discovery and Biomedical Sciences, South Carolina College of Pharmacy, Medical University of South Carolina, Charleston, SC 29425, USA

National Institute of Neurological Disorders and Stroke (NINDS) Anticonvulsant Screening Program. Compound 2h reduced seizures particularly well in the minimal clonic seizure (6 Hz) and corneal-kindled mouse models of epilepsy, with no observable toxicity. As VK3 affects mitochondrial function, we tested the effects of our compounds on mitochondrial respiration and ATP production in a mouse hippocampal cell line. We demonstrate that these com-
What does the future hold for POLG-related disorder

Therapies in the works

• Antioxidant therapy

• Anti-seizure, anti-epileptic drugs

• Nucleotide therapy

• Metformin

• Repurposing drugs and identifying new drugs

• Gene therapy
Nucleoside supplements as treatments for mitochondrial DNA depletion syndrome

Eszter Dombi, Tony Marinaki, Paolo Spingardi, Val Millar, Nastasia Hadjichristou, Janet Carver, Iain G. Johnston, Carl Fratter and Joanna Poulton

Deoxyribonucleoside treatment rescues EtBr-induced mtDNA depletion in iPSC-derived neural stem cells with POLG mutations

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What does the future hold for POLG-related disorder

Therapies in the works

• Antioxidant therapy

• Anti-seizure, anti-epileptic drugs

• Nucleotide therapy

• Metformin

• Repurposing drugs and identifying new drugs

• Gene therapy
Nicotinamide Riboside and Metformin Ameliorate Mitophagy Defect in Induced Pluripotent Stem Cell-Derived Astrocytes With POLG Mutations

Anbin Chen1,2,4, Cecilie Katrin Kristiansen2,4, Yu Hong2,4, Atefeh Kiani2,6, Evandro Fei Fang5,6, Gareth John Sullivan7,8,9,10, Jian Wang1,2,11, Xingang Li1,2, Laurence A. Bindoff3,4, and Kristina Xiao Liang3,4,11
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Questions