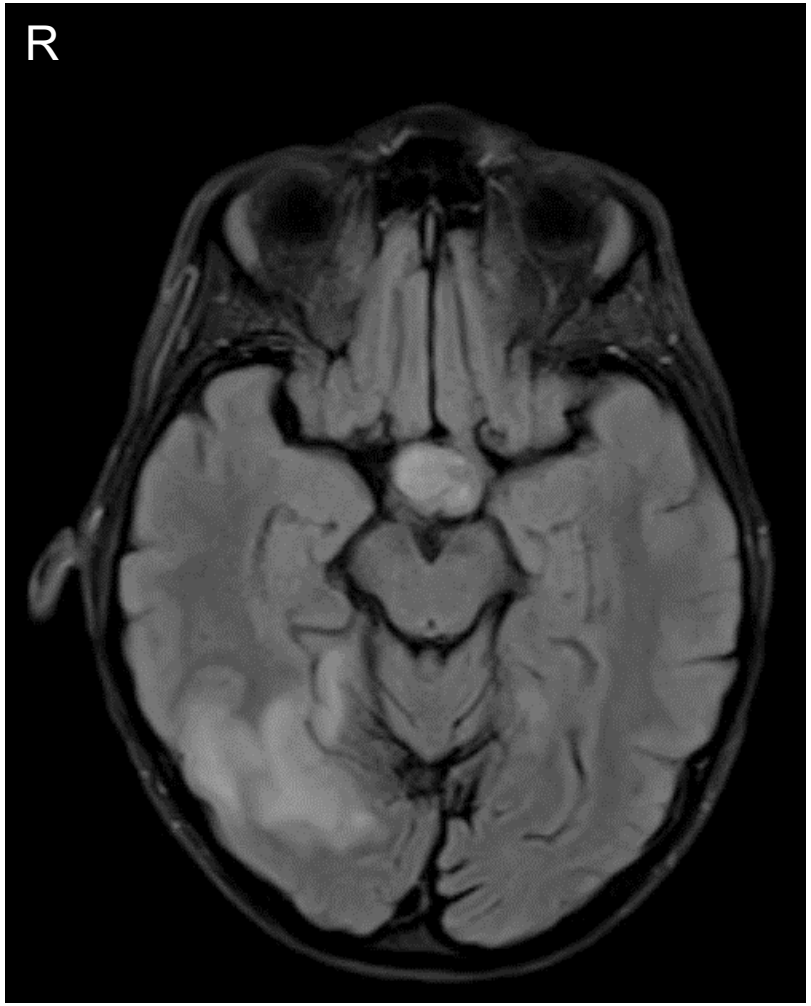
Diagnostic Slide Session
Case 2022 - 04

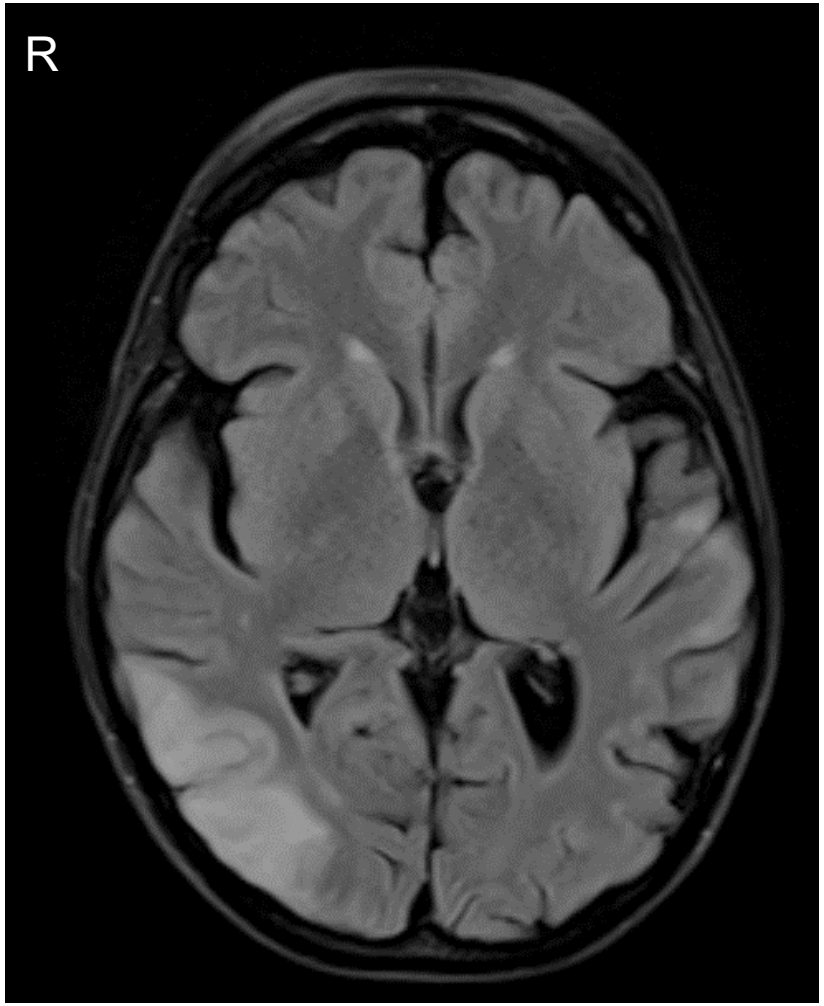
Submitted by Kathryn Eschbacher M.D.,
Margherita Milone M.D. Ph.D., and Rachael Vaubel M.D. Ph.D.
Mayo Clinic, Rochester, MN

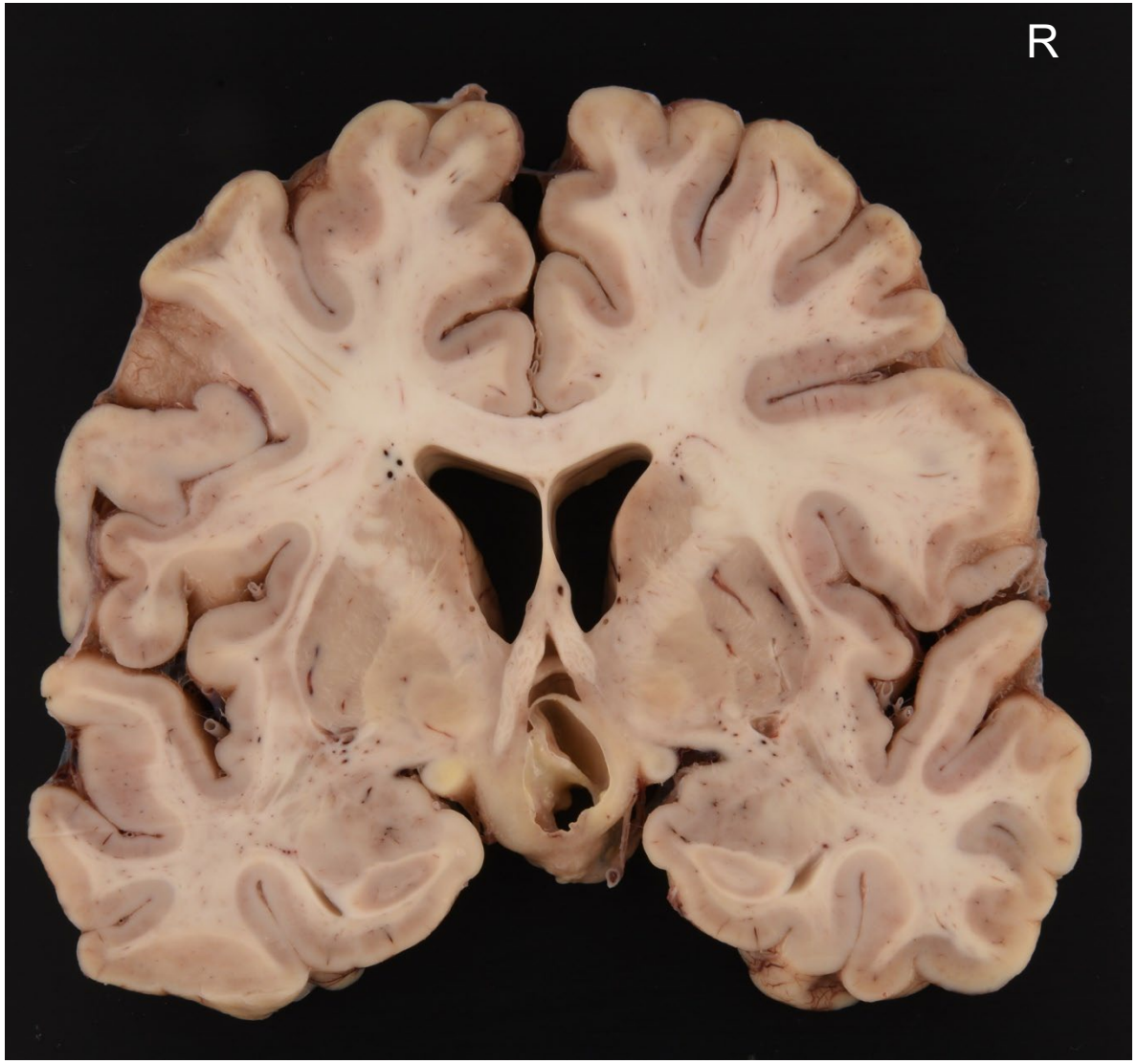
Clinical Summary

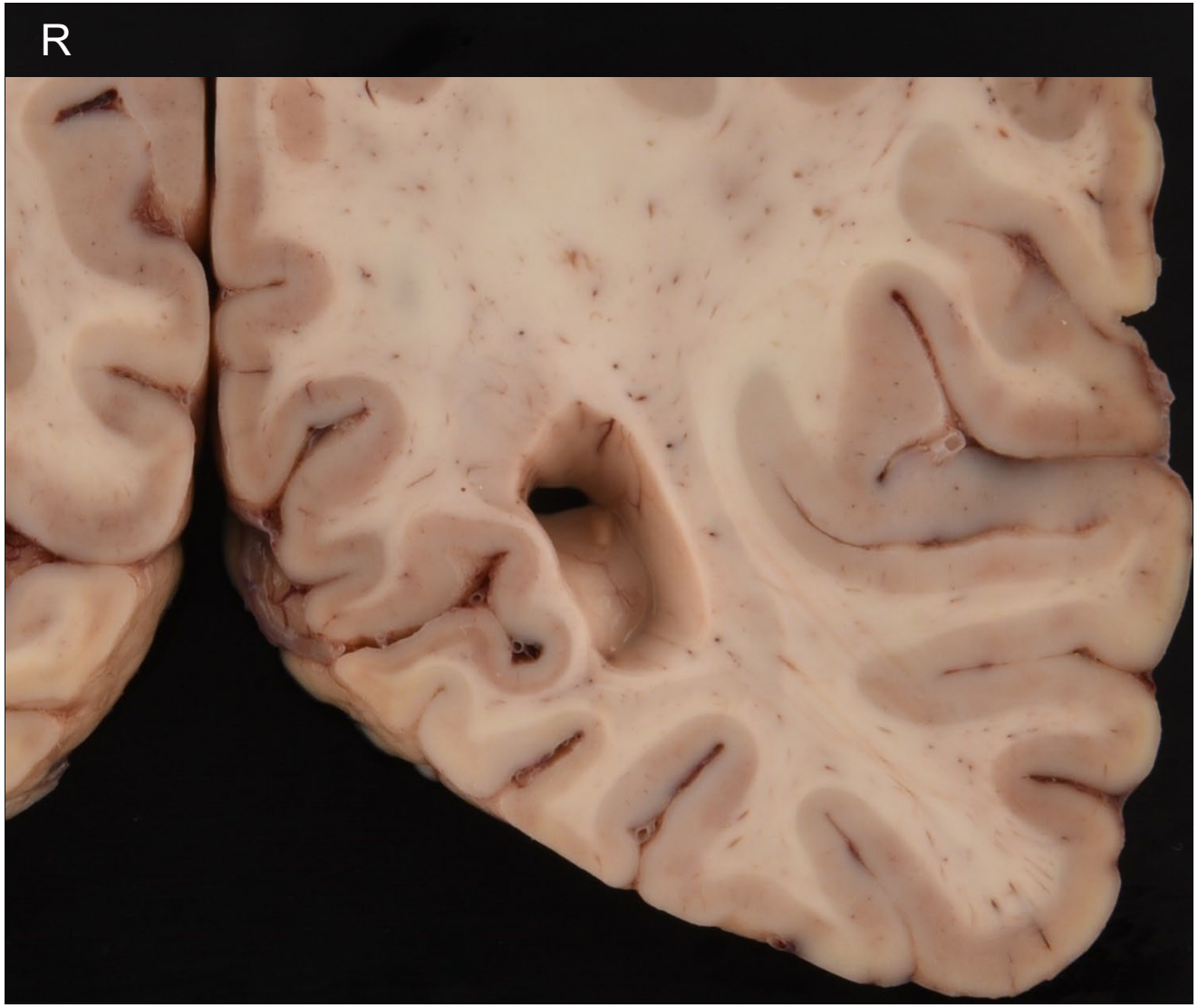
- 40-year-old woman with exercise intolerance since childhood
- Teens: left eyelid ptosis, progressive limb weakness
  - Heterozygous *POLG* c.2740A>C, p.Thr914Pro pathogenic variant
  - Mitochondrial DNA testing negative
- 30s: episodic hemisensory symptoms and hemiparesis with associated epileptic activity requiring anti-epileptics
- 40s: episode of visual changes – flashing lights, blind spot, difficulty understanding what she was reading
- Four months later: sudden onset dysarthria preceded by intermittent right lower limb numbness → status epilepticus, respiratory failure and death

Brain MRI at onset of visual symptoms
T2 FLAIR sequences

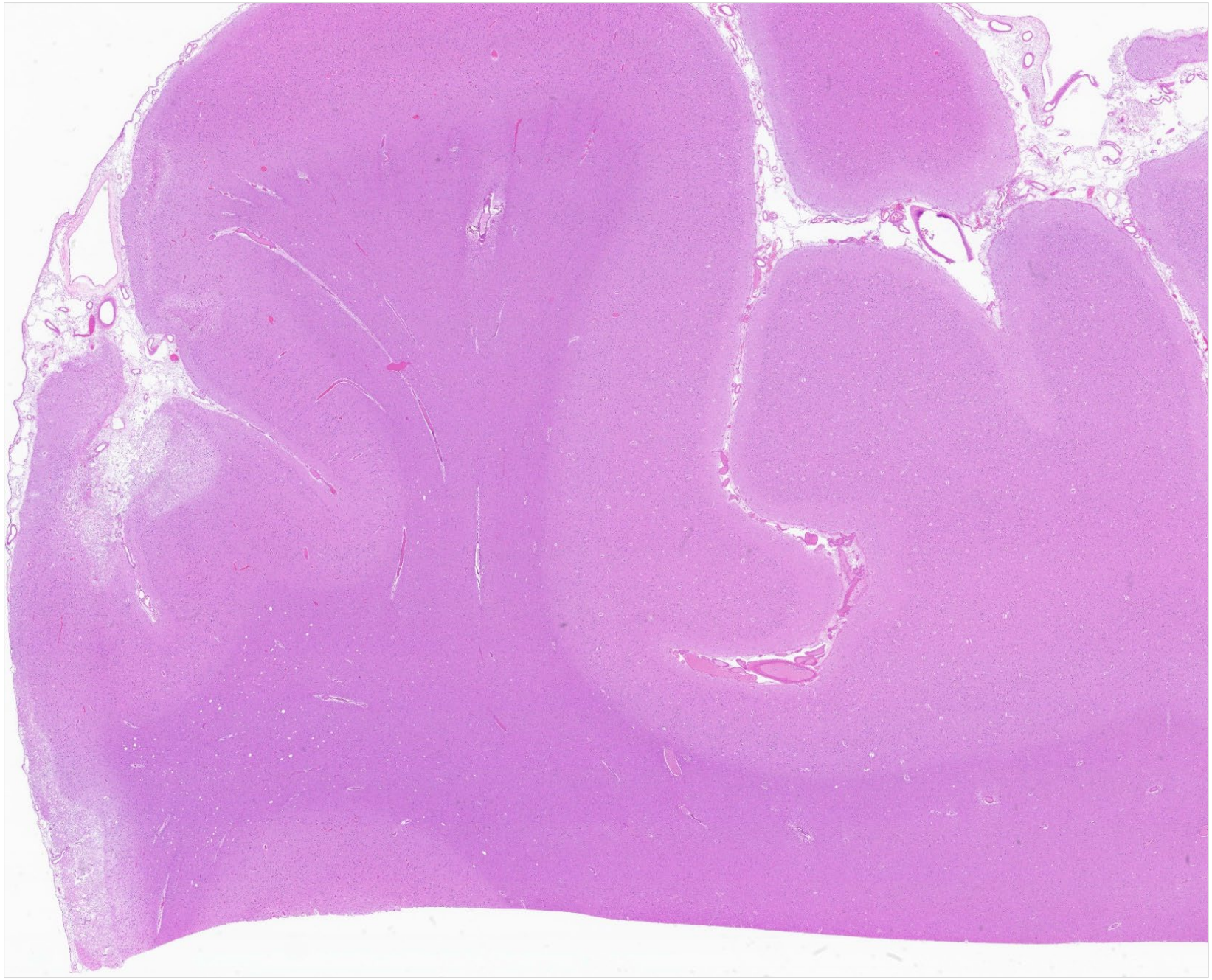


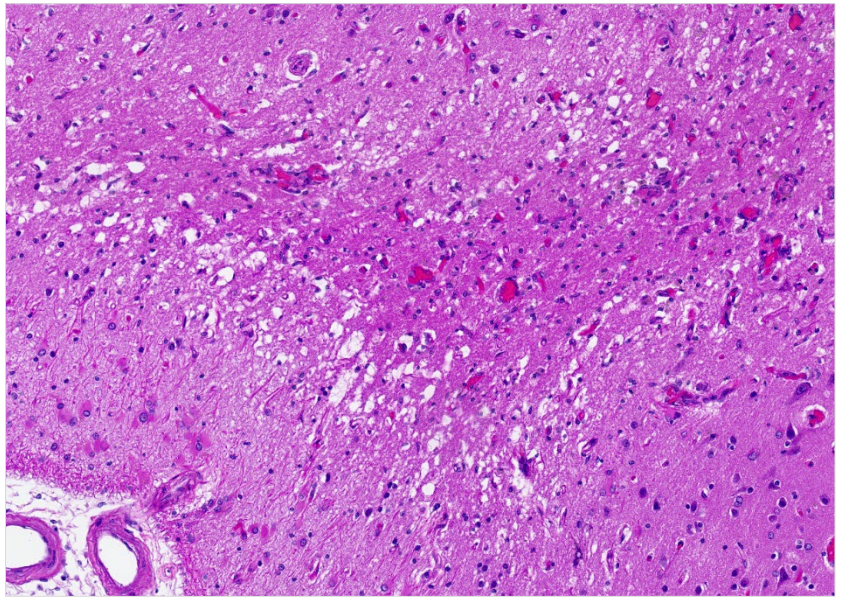


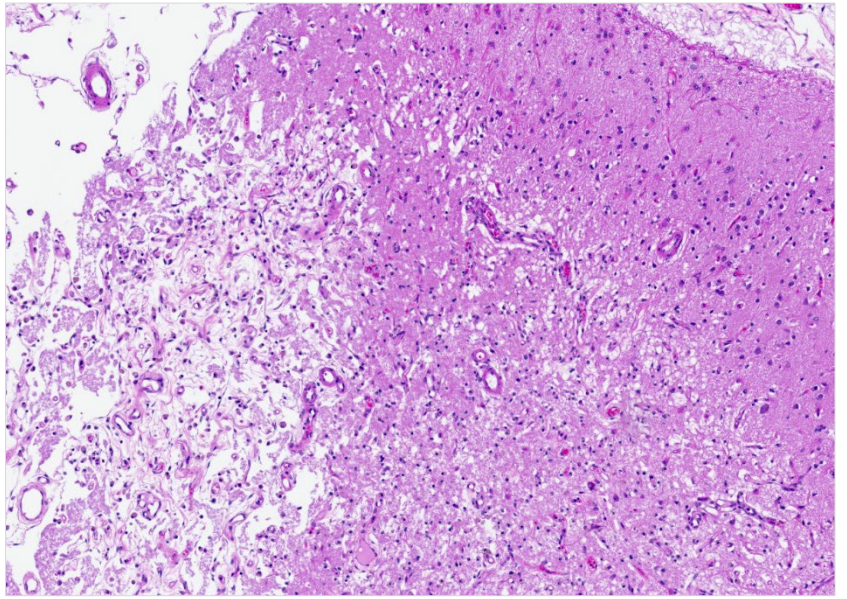

R


R

Right lateral occipital

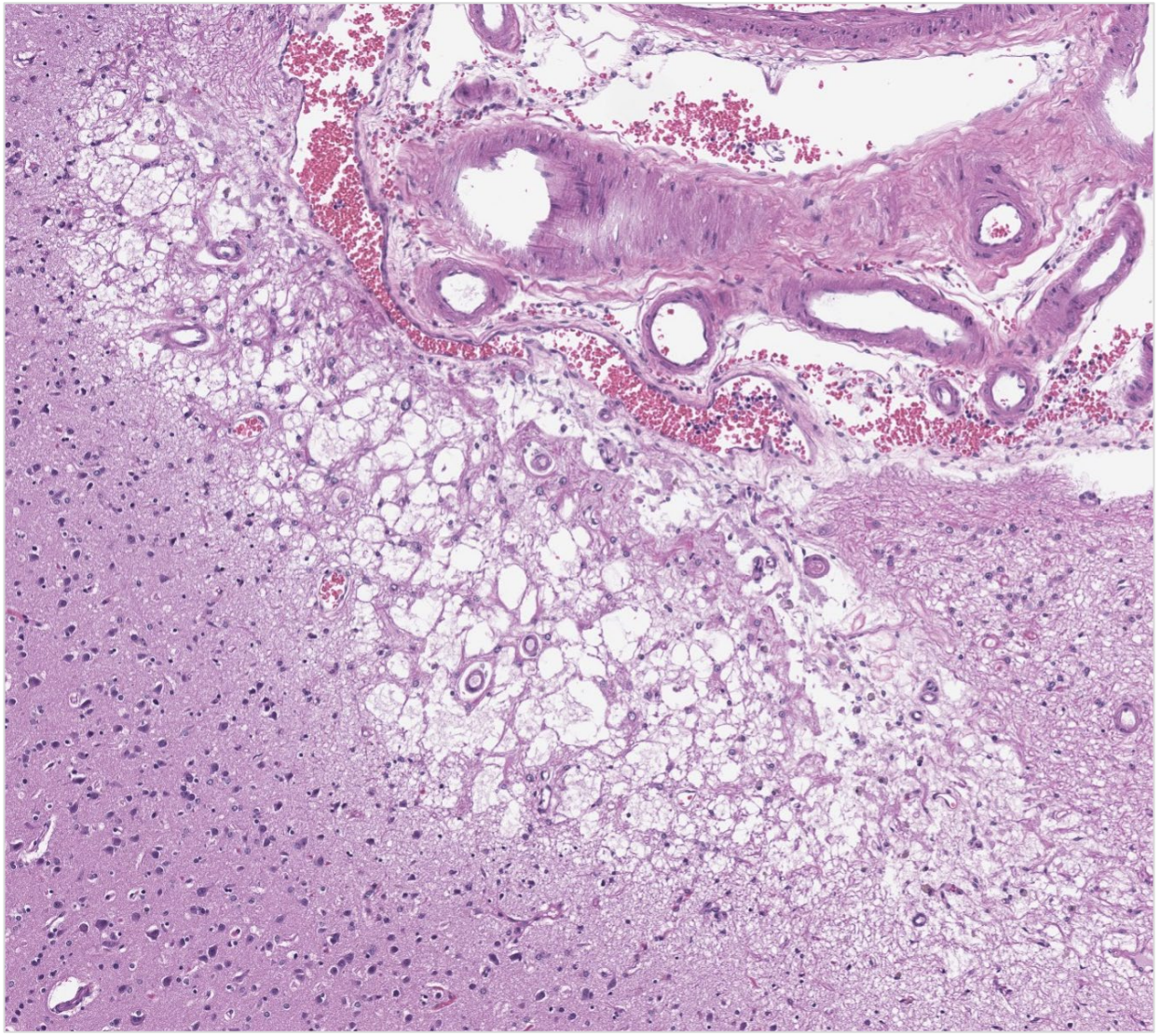




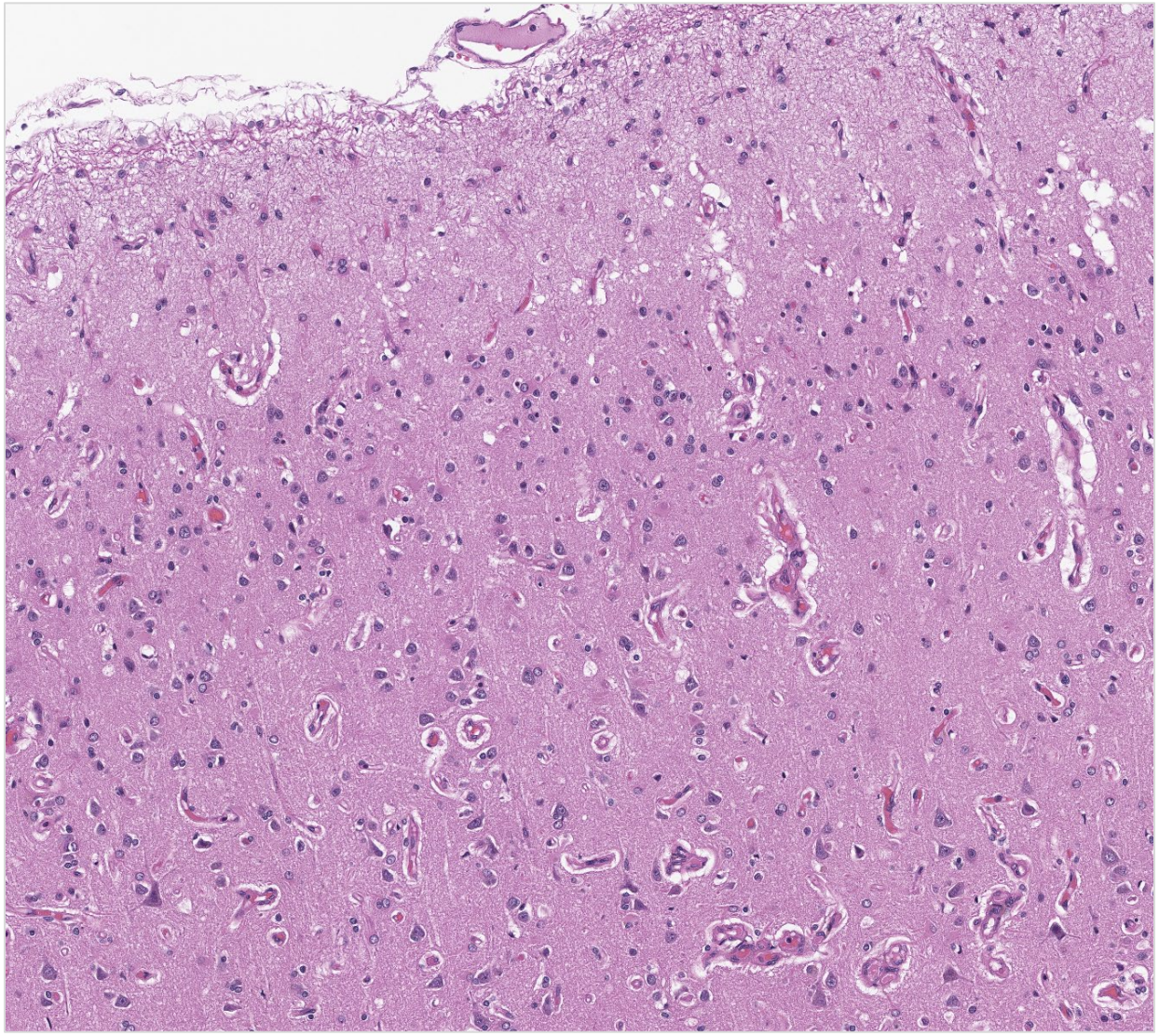


Diagnosis?

Right visual

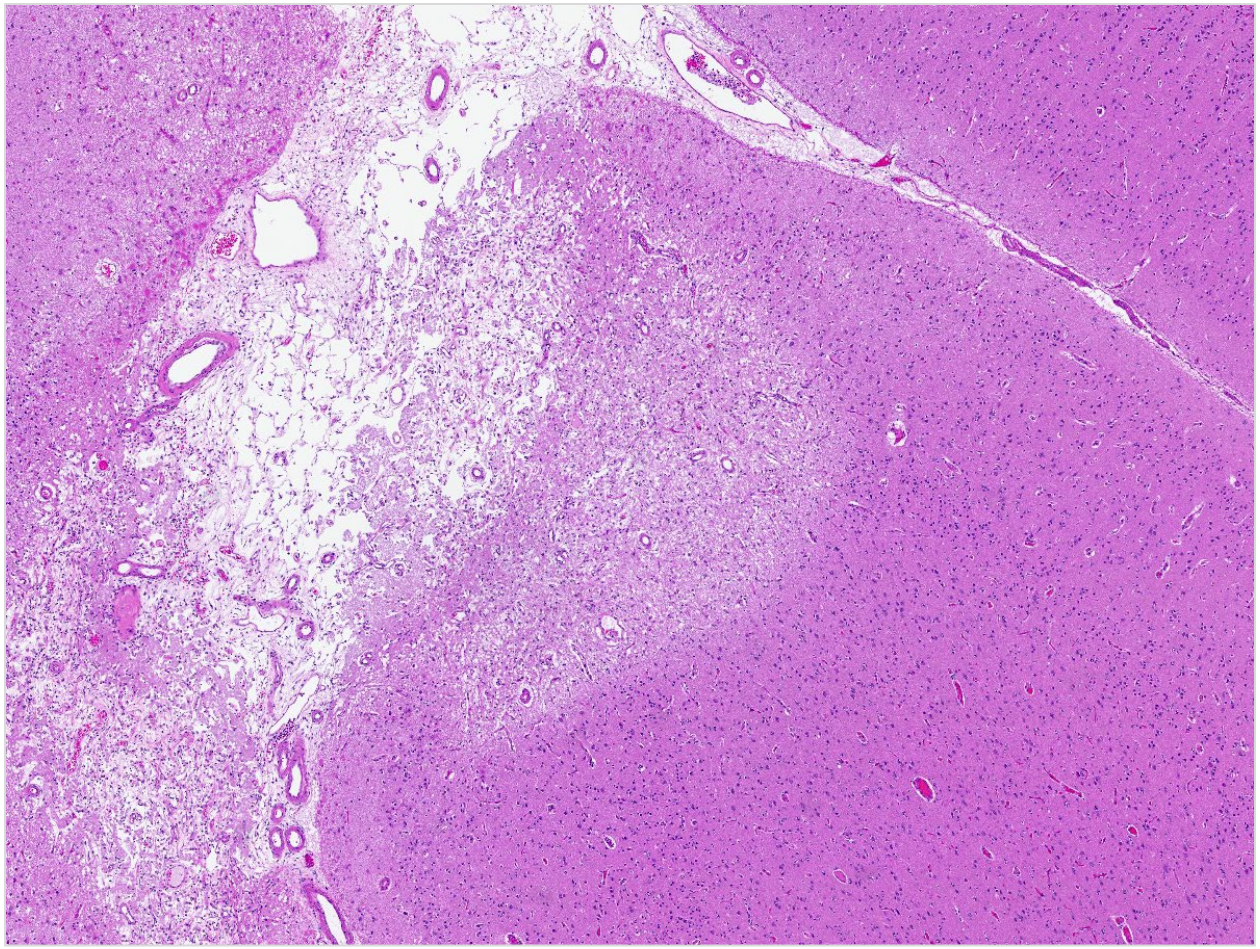


Right temporal

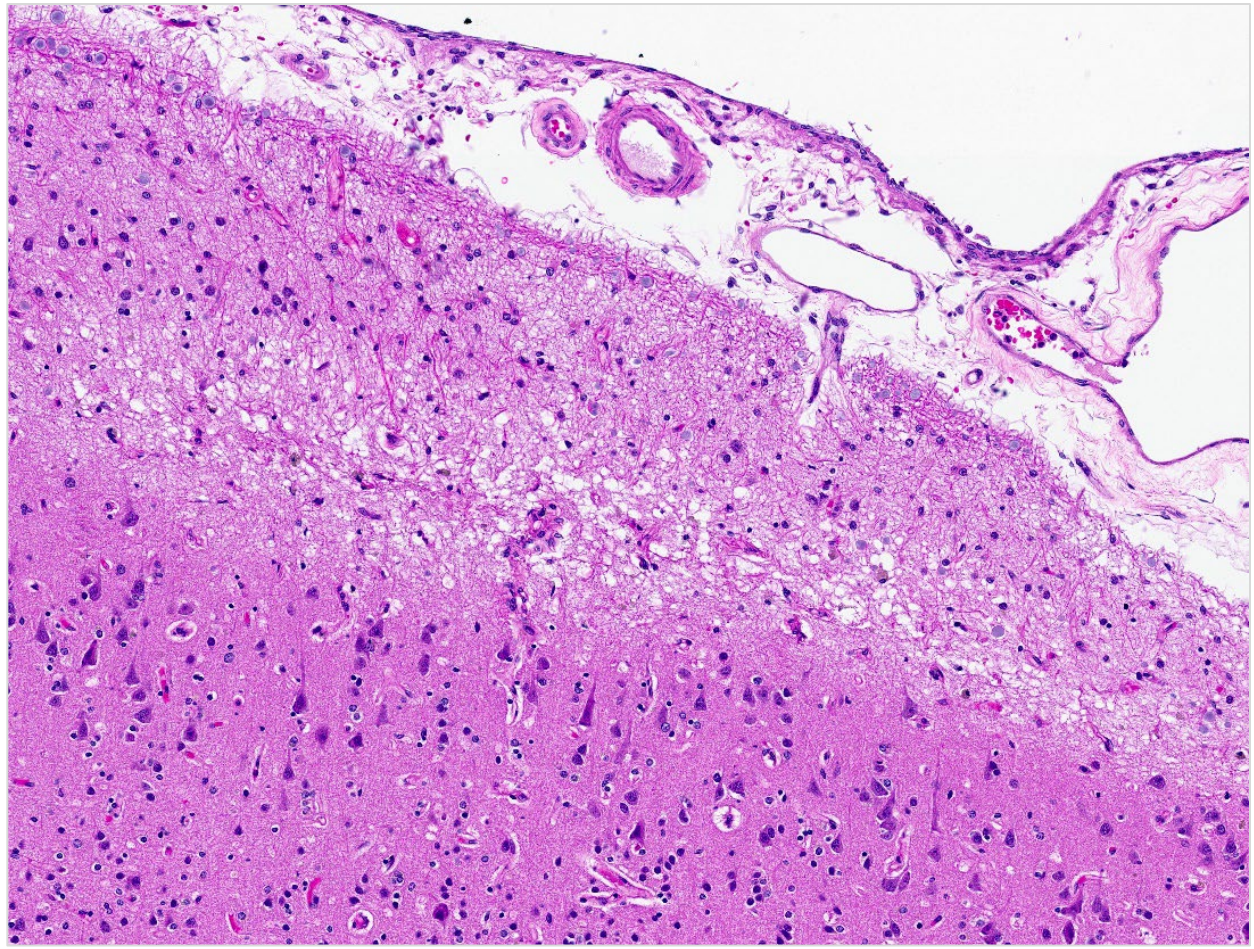


Cortical destructive lesions resembling infarcts of varying ages (predominantly remote) involving bilateral cerebral hemispheres, preferentially affecting crests of the gyri

Right lateral occipital



Left visual



Cortical destructive lesions resembling infarcts of varying ages (predominantly remote) involving bilateral cerebral hemispheres, preferentially affecting crests of the gyri

Differential Diagnosis

Mitochondrial encephalopathy

- Negative mitochondrial testing
- Clinical history
  Heterozygous *POLG* mutation

Hypoperfusion, multifocal

- Distribution of lesions
- Clinical history

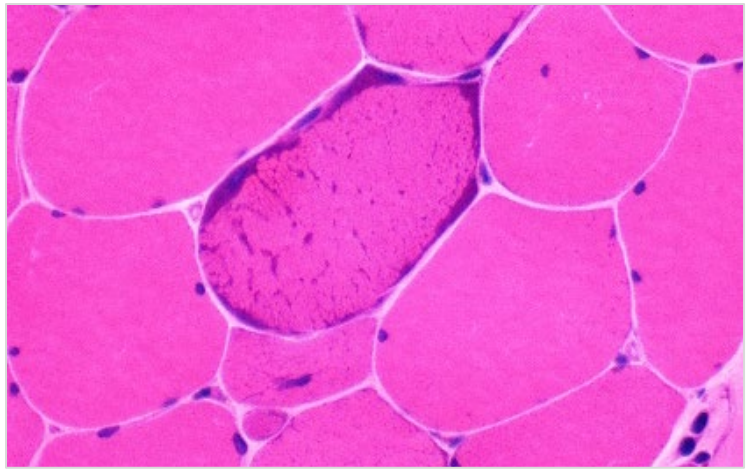
Infarct, thrombotic or embolic

- Distribution of lesions
- Clinical history

POLG mutations and related disorders

Autosomal Dominant Mutations

- PEO
  (Progressive external ophthalmoplegia)
  - Ophthalmoparesis ± limb myopathy, parkinsonism, ovarian failure, peripheral neuropathy



Muscle biopsy: Ragged-red, ragged-blue and COX negative fibers; biopsy can be normal

Autosomal Recessive Mutations

- Alpers syndrome
  (early onset psychomotor regression, intractable seizures, and liver failure)
- Ataxia neuropathy spectrum and Epilepsy
- PEO/ Isolated myopathy
- MELAS-like (rare) (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes)
- MNGIE-Like (rare) (mitochondrial neurogastrointestinal encephalopathy syndrome)

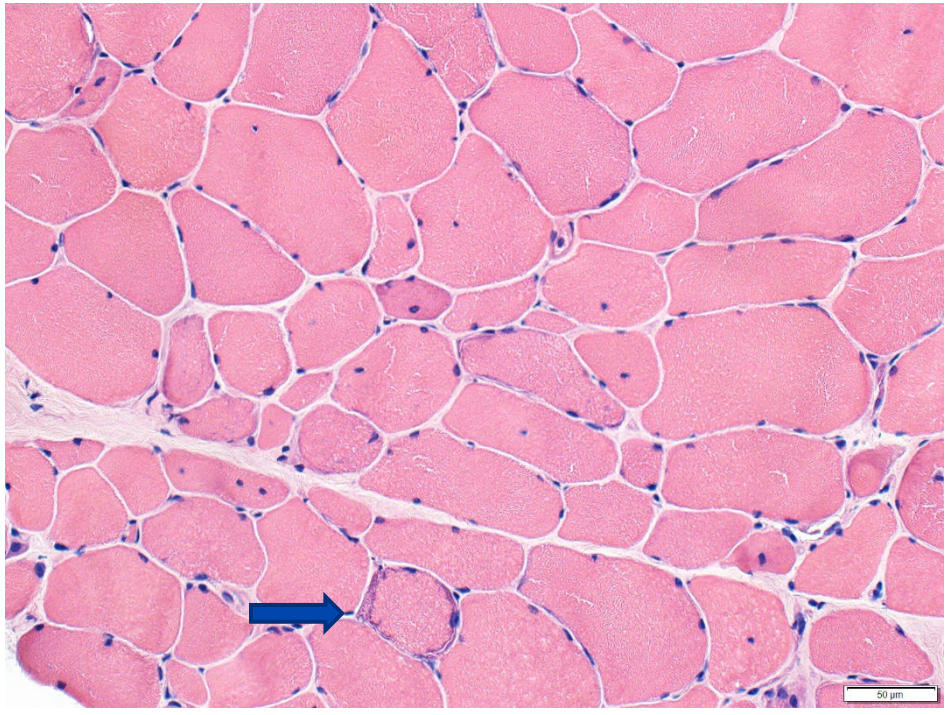
Additional history and evaluation

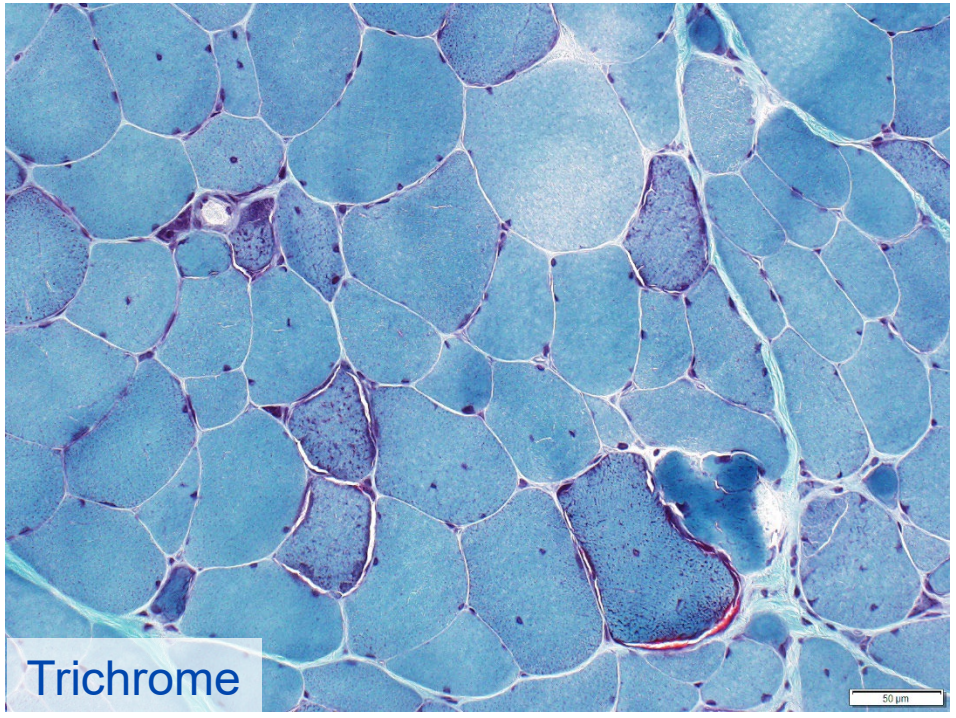
- **Heterozygous recessive *POLG* mutation does not explain the phenotype**

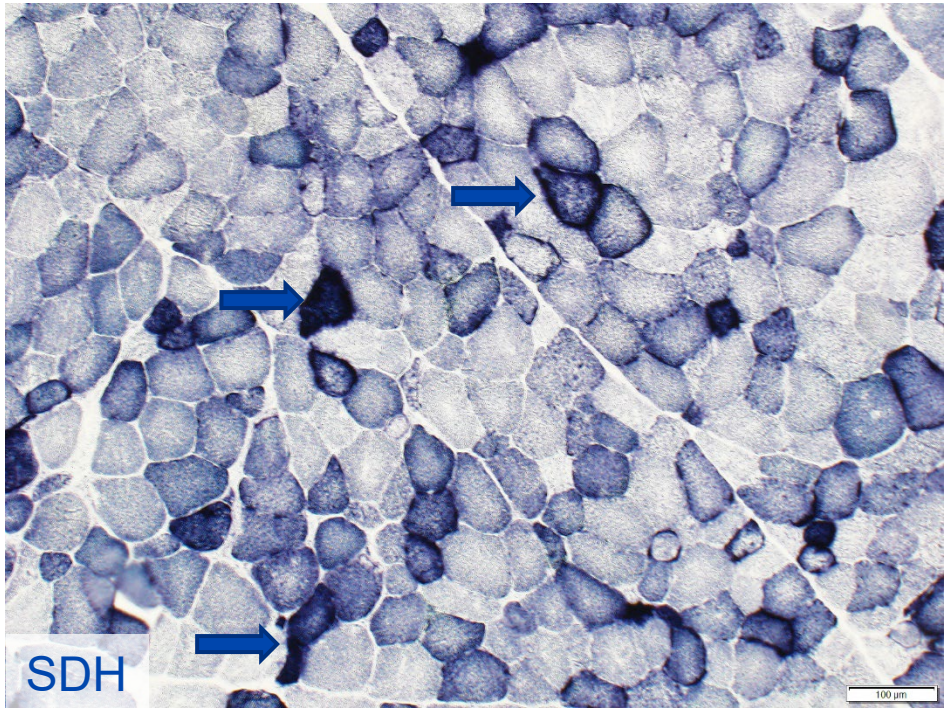
Additional History

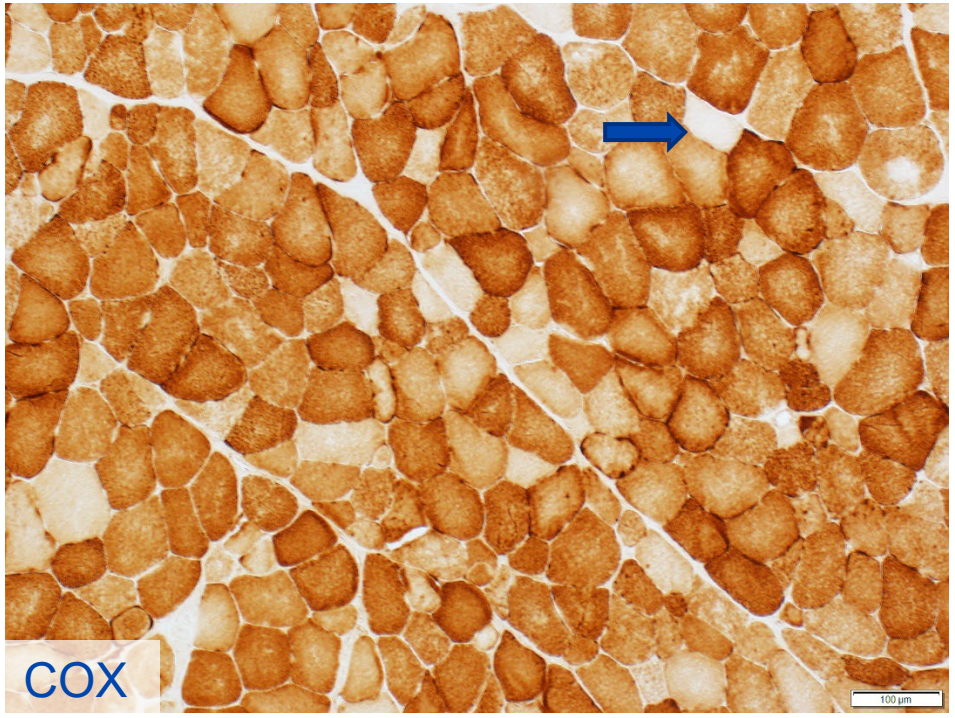
- Late teens progressive limb muscle weakness, bulbar weakness, cardiomyopathy
- Episode of rhabdomyolysis in her 20s
- Elevated lactate on multiple occasions
- Patient underwent muscle biopsy for mtDNA sequencing in muscle

Muscle biopsy (triceps)



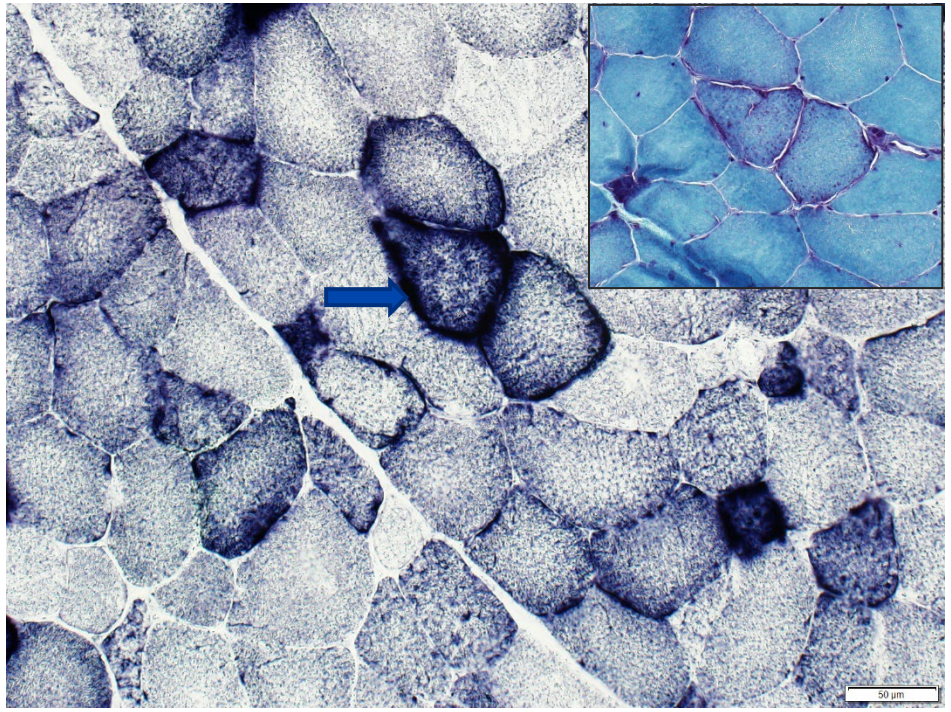




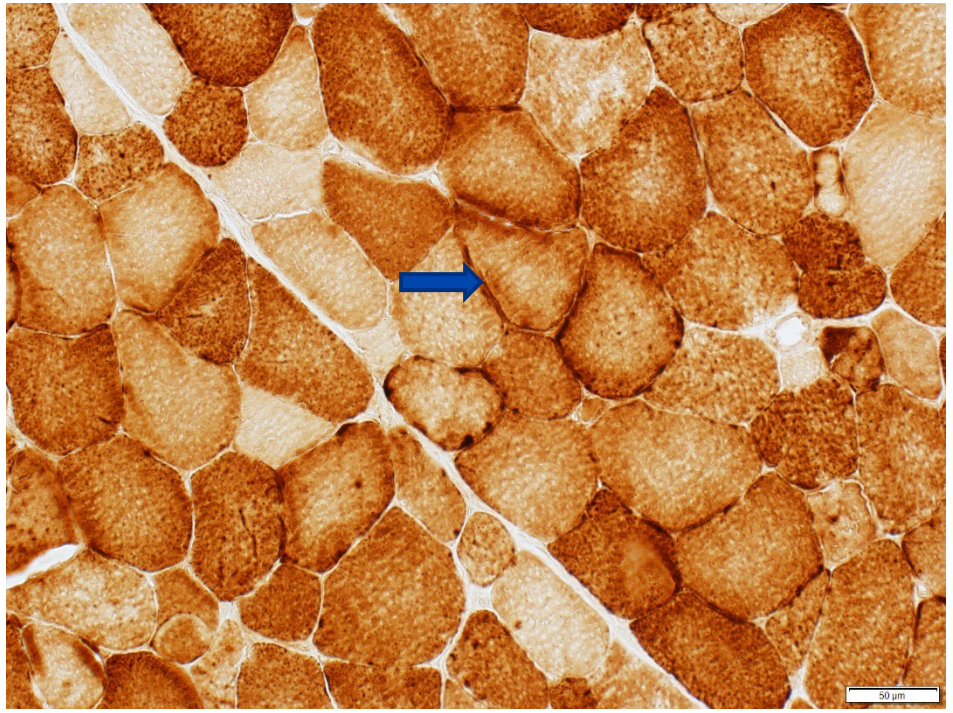


Muscle biopsy (triceps)

SDH & Trichrome (insert)



COX

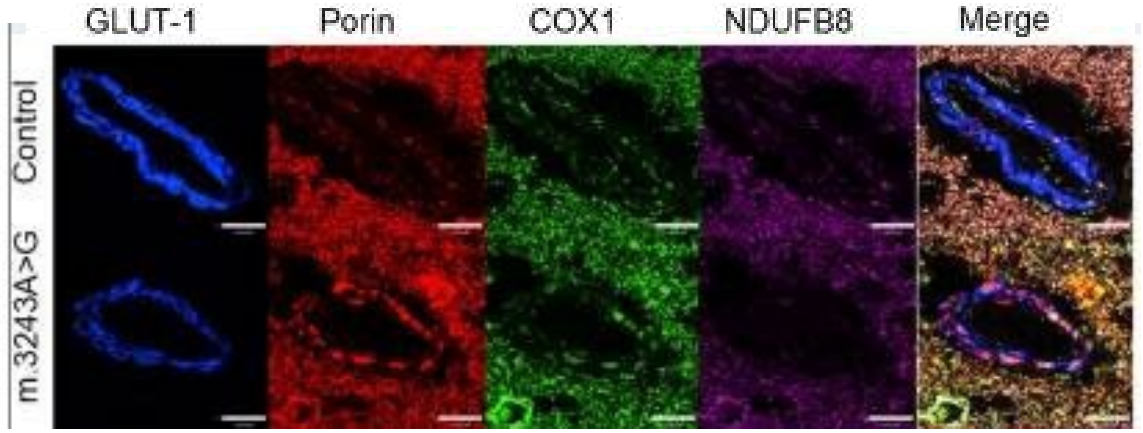


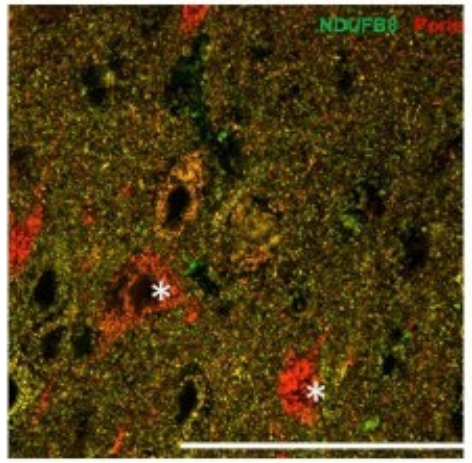
Arrow indicates a ragged-blue fiber with preserved cytochrome *c* oxidase reactivity

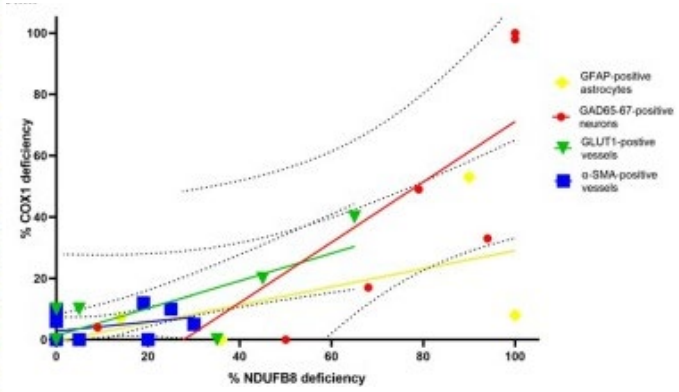
Muscle whole mitochondrial DNA sequencing: m.3251A>G (*MT-TL1*) 92% heteroplasmy

Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-like episodes (MELAS)

- Parieto-occipital stroke-like episodes ± encephalopathy, ↑ plasma/CSF lactate, seizures
- Most common mutation m.3243A>G in *MT-TL1* gene
- Respiratory chain dysfunction within cerebral tissue → focal deficit hours or days
- Brain: infarct-like lesions gyral crests, do not follow vascular territories
- Muscle: muscle fibers with mitochondrial proliferation (ragged blue) and preserved COX activity

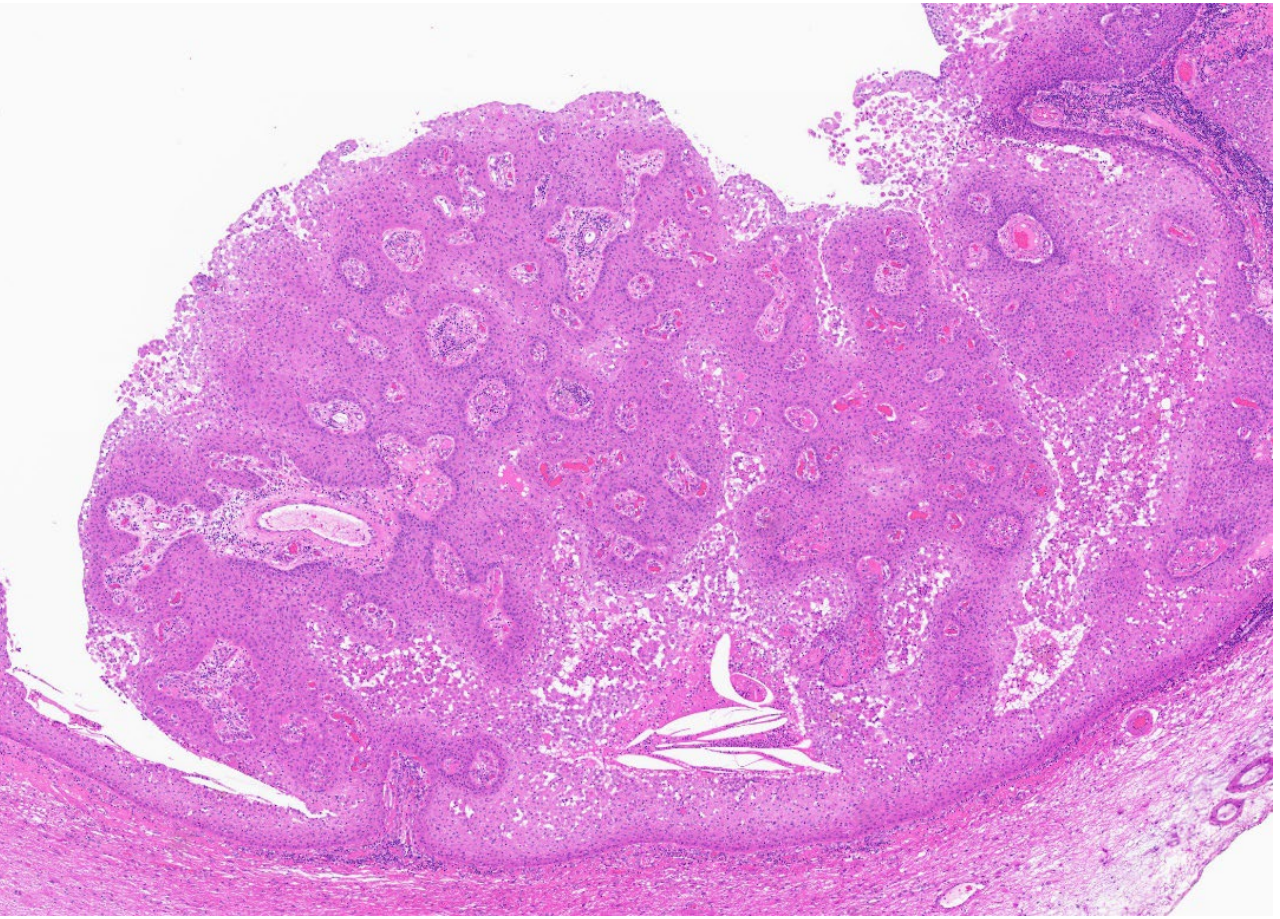


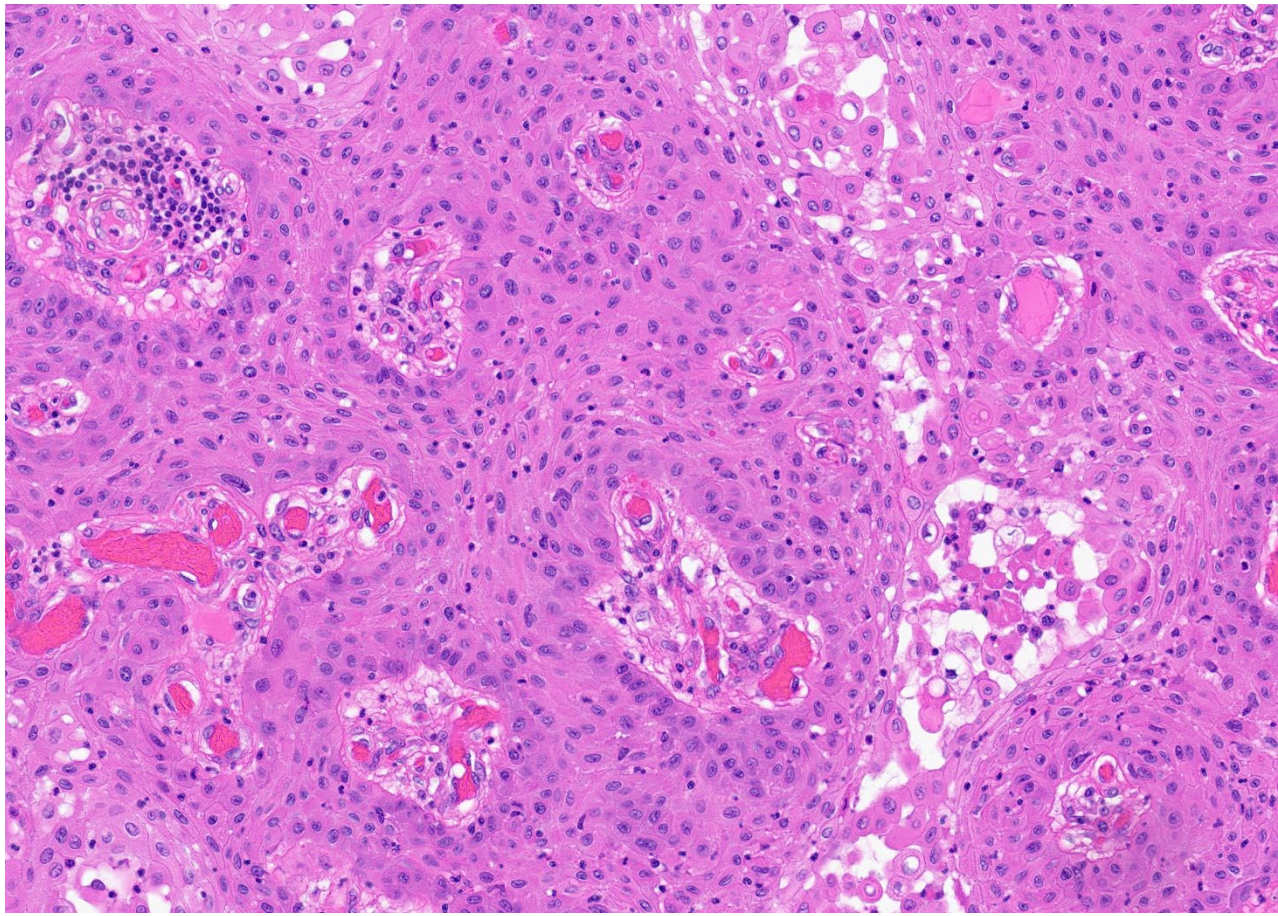




Ng YS, Lax NZ, Blain AP, et al. Forecasting stroke-like episodes and outcomes in mitochondrial disease. *Brain*. 2022;145(2):542-554.

Incidental papillary craniopharyngioma, 1.9 cm





References

1. Ellison D, ed. *Neuropathology: A Reference Text of CNS Pathology* 3. ed. Mosby, Elsevier; 2013.
2. Love S, Perry A, Ironside J, Budka H, eds. *Greenfield's Neuropathology*. 9th edition. CRC Press; 2015.
3. Milone M, Benarroch EE, Wong LJ. POLG-related disorders: defects of the nuclear and mitochondrial genome interaction. *Neurology*. 2011;77(20):1847-1852.
4. Milone M, Wong LJ. Diagnosis of mitochondrial myopathies. *Mol Genet Metab*. 2013;110(1-2):35-41.
5. Ng YS, Lax NZ, Blain AP, et al. Forecasting stroke-like episodes and outcomes in mitochondrial disease. *Brain*. 2022;145(2):542-554.

Thank you!

Questions?

