DSS Case 2022-7

Tiffany Baker, MD, PhD
Neuropathology Fellow
Medical University of South Carolina
Charleston, SC, USA

NO PHOTOGRAPHY

OR SOCIAL MEDIA SHARING

The authors of this paper are not yet ready to share the results of this study beyond this meeting. No photography or social media sharing is allowed on this paper.
Thank you.

DSS Case 2022-7

- I have no financial disclosures.

Learning Objectives:

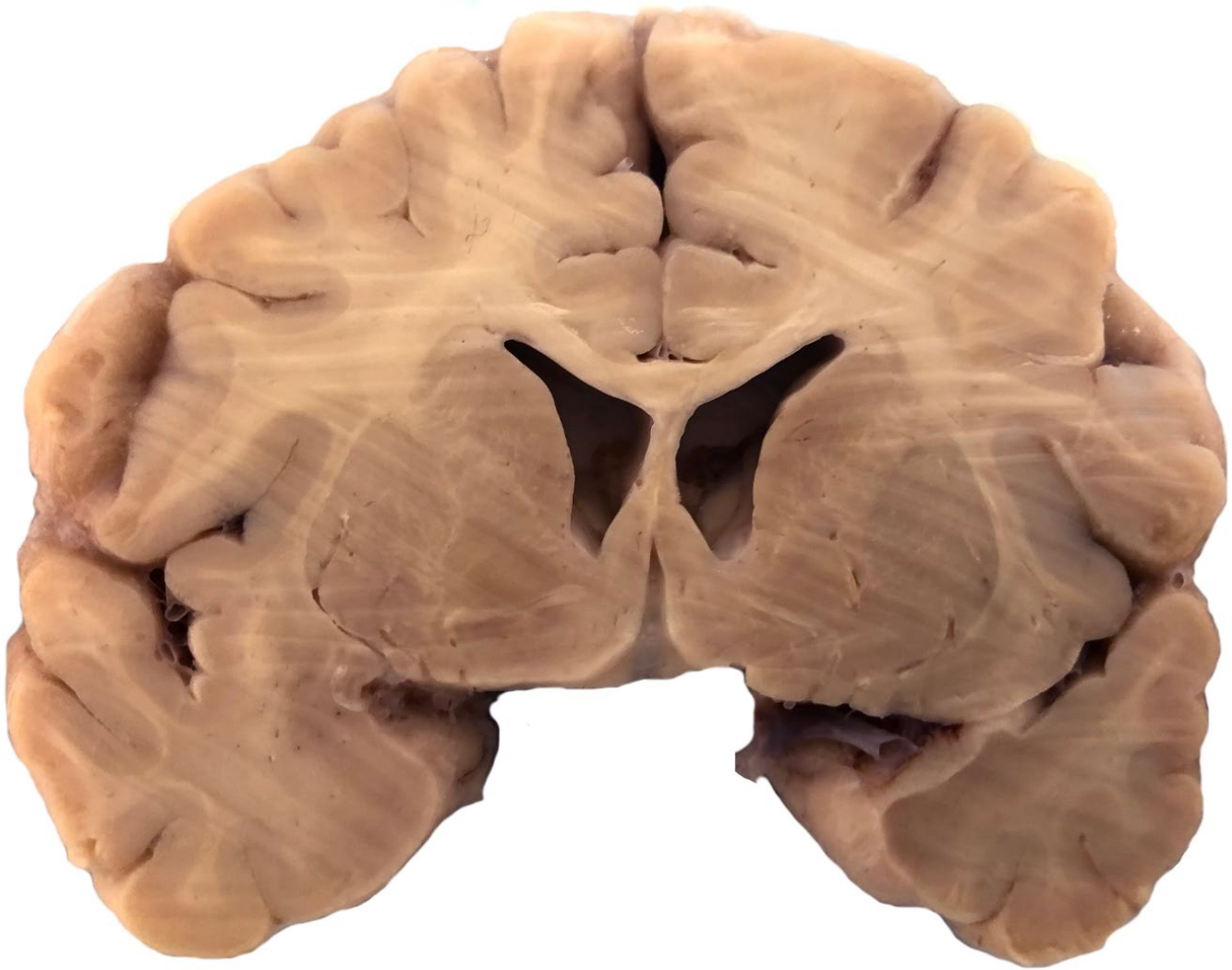
- Following the presentation, the learner will recall the first gene discovered in association with the diagnosis discussed.

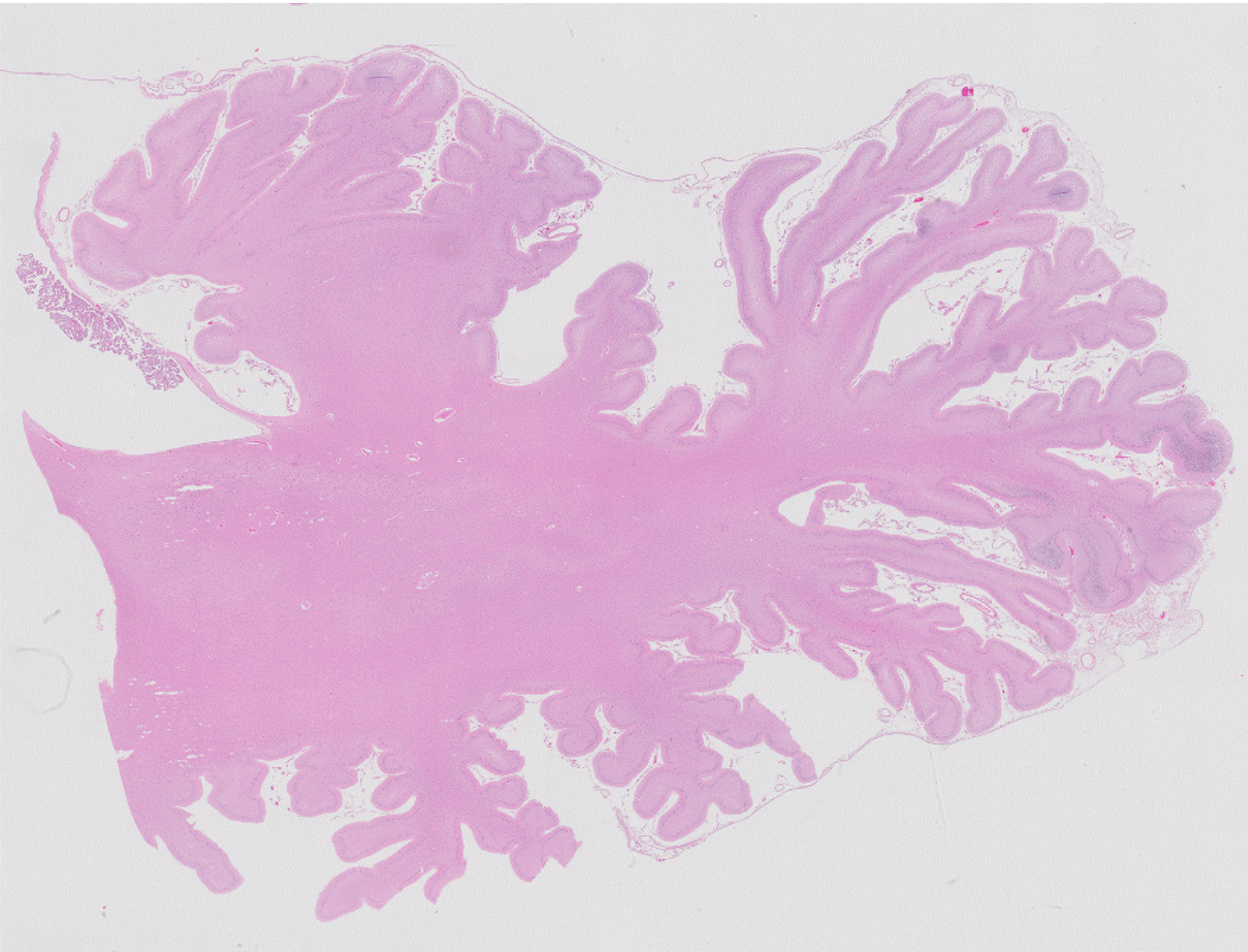
- Following the presentation, the learner will be able to identify the most common neuropathologic abnormalities associated with the diagnosis discussed.

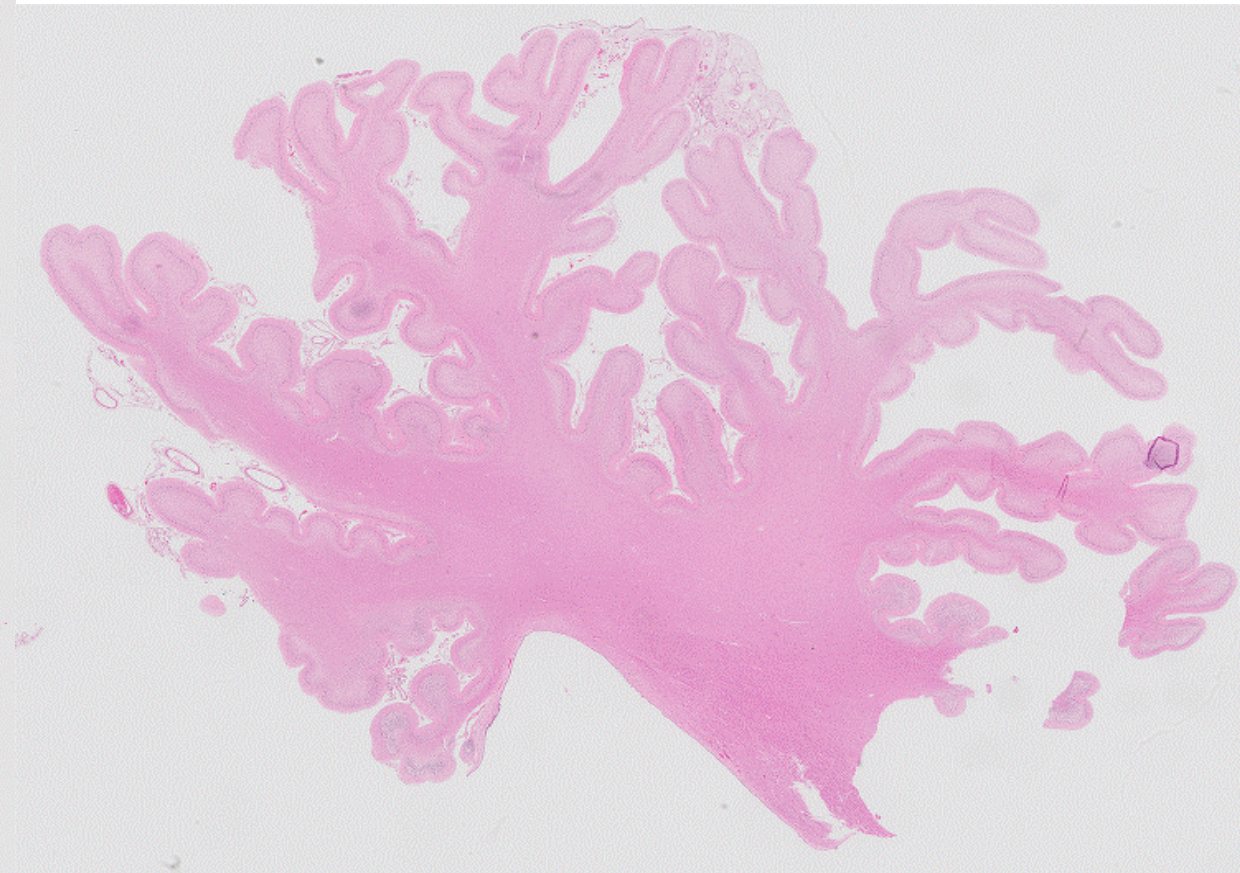
Clinical History (2022-7)

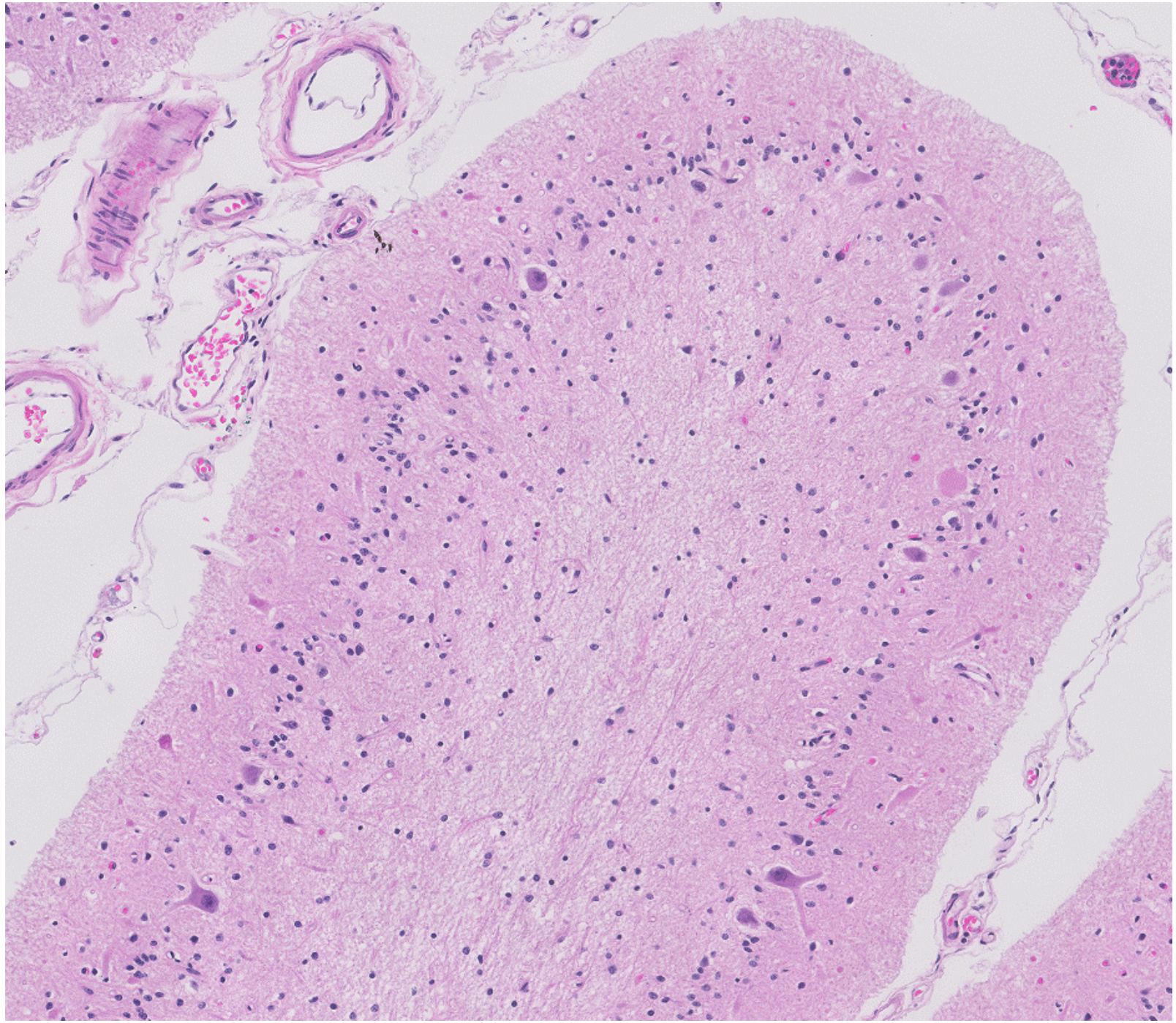
- History: 11 yo F with global developmental delay, seizures, cerebral palsy, and nephrotic syndrome. Family history of a similar condition. Succumbs to an infection / coagulopathy.
- Autopsy findings:
  - Microcephaly, dysmorphic facies
  - Malrotation of extremities and dorsiflexed feet
  - Surgical absence one kidney, thrombus vena cava
- Neuropathology findings:
  - 470 gram brain with mildly dilated ventricles and firm, small cerebellum

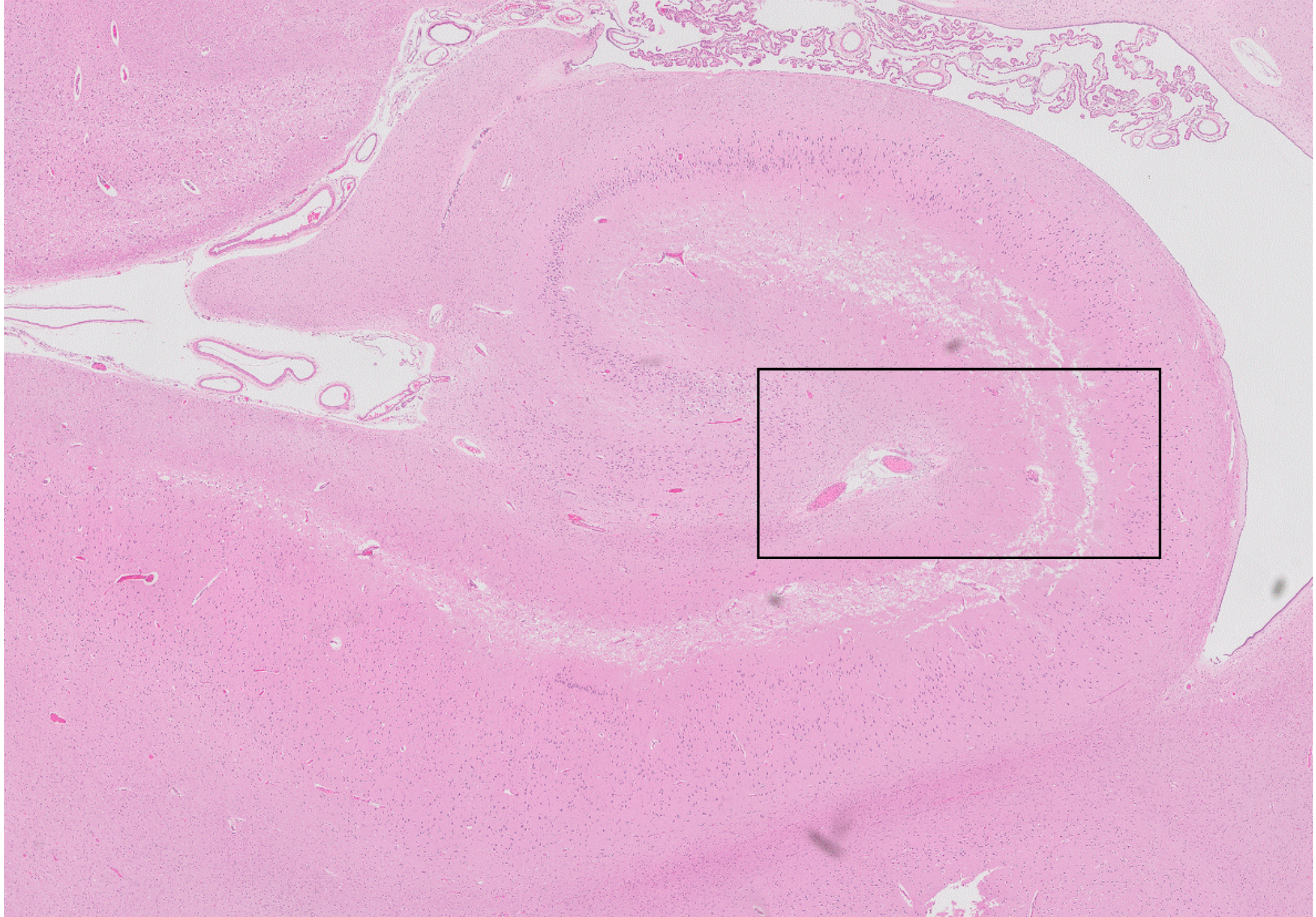
Gross photos (2022-7)

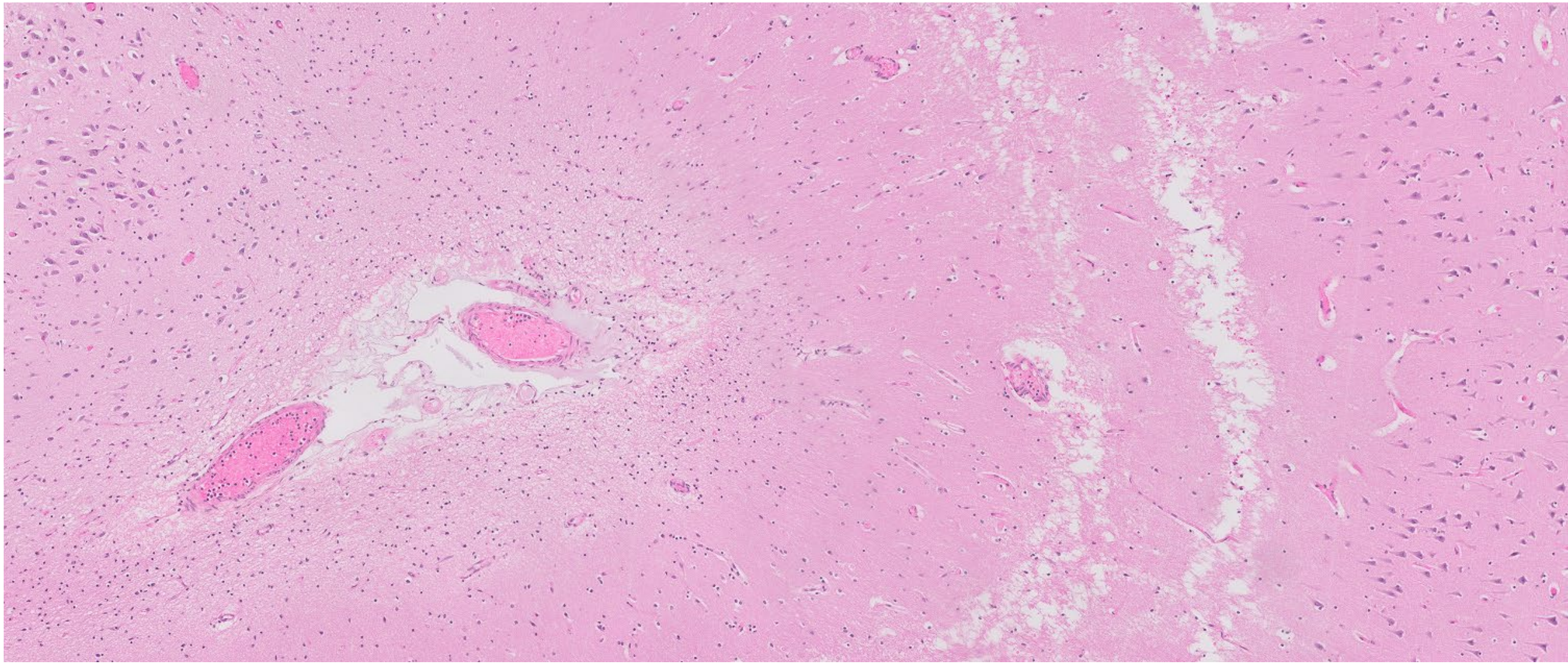












DIAGNOSIS?

Differential Diagnosis
Childhood Cerebellar Atrophy

Inherited

- Ataxia telangiectasia
- Spinocerebellar atrophy
- Infantile neuroaxonal dystrophy
- Lysosomal disorders
- Mitochondrial disorders
- Neuronal ceroid lipofuscinosis
- Many more…

Acquired

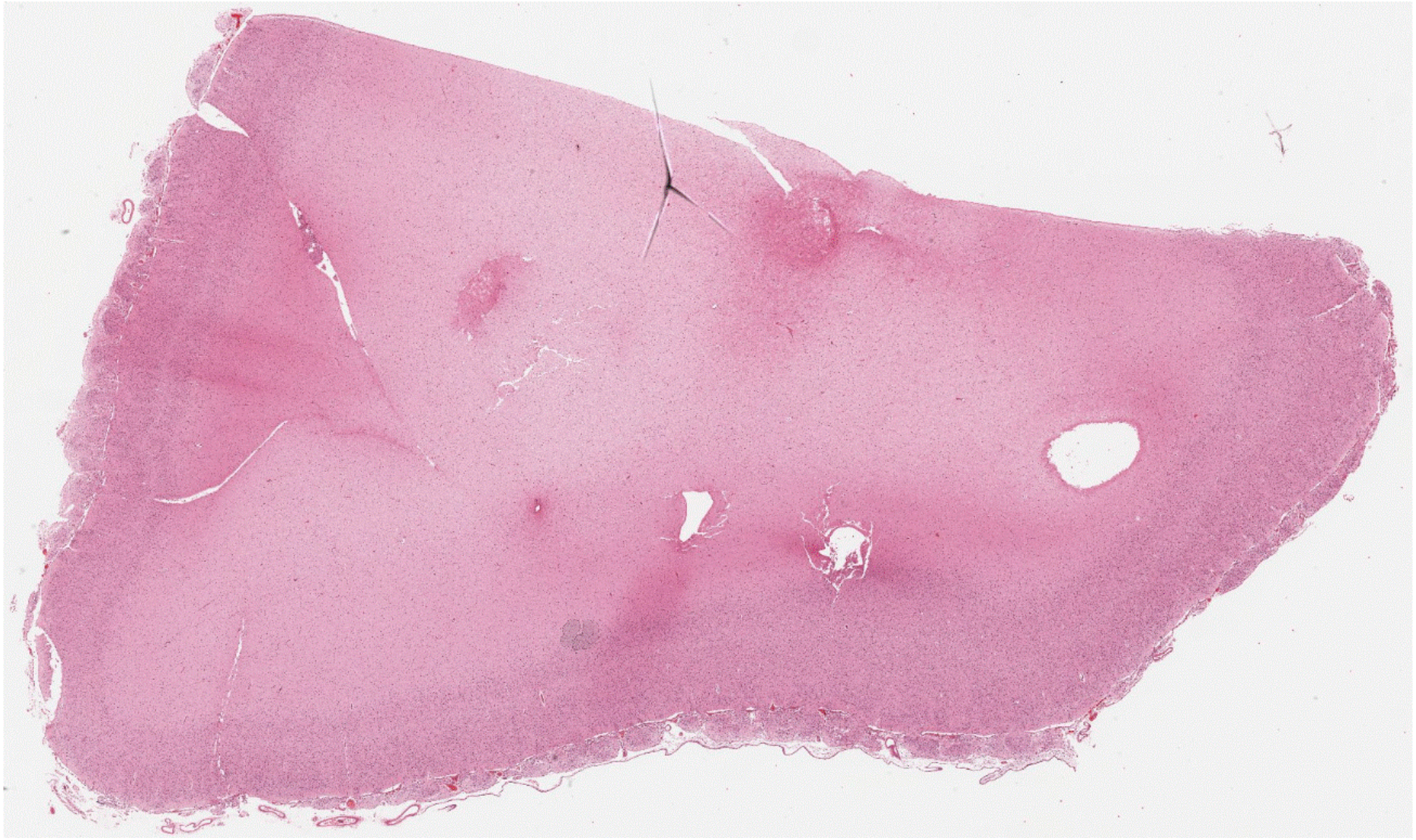
- Posterior fossa malformation
- Posterior fossa tumor, therapy
- Cerebellar hemorrhage / ischemia
- Immune-mediated
- Paraneoplastic syndrome
- Infection (viral)
- Medication/exogenous toxin

Clinically suspected diagnosis: Galloway-Mowat Syndrome (GAMOS)

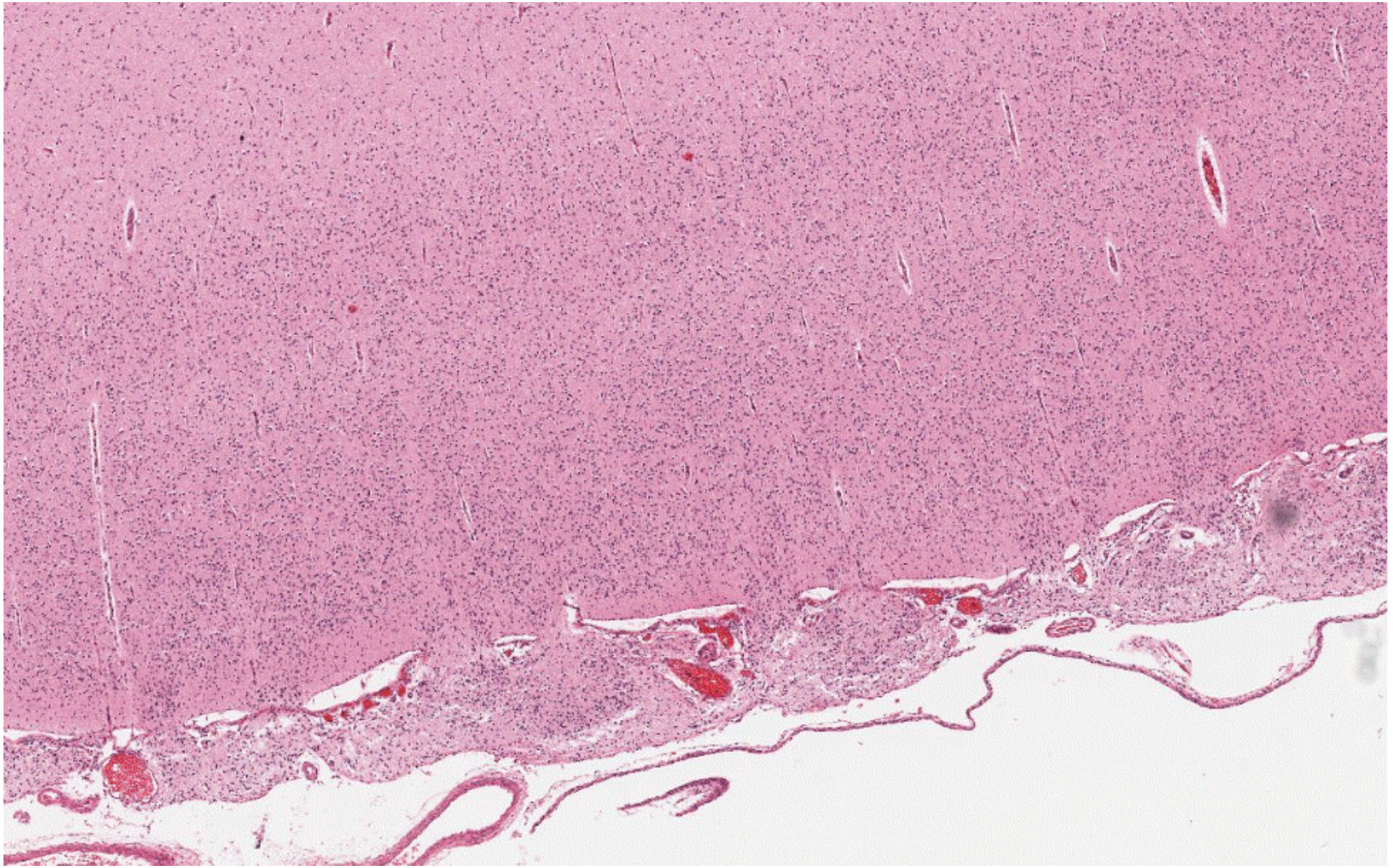
- Microcephaly and nephrotic syndrome, first described in 1968
- Multiple genes identified since 2014
  - GON7, LAGE3, NUP107, NUP133, **OSGEP**, PRDM15, TP53RK, TPRKB, WDR73, WDR4, and YRDC
- Variable constellations of neuropathologic findings
  - Most common: Small brain weight for age
  - Other findings: abnormal gyration (pachygyria), cortical lamination defects, cerebellar hypoplasia / atrophy, hippocampal changes, optic nerve gliosis and hypoplasia / atrophy of lateral geniculate nucleus, glioneuronal heterotopias leptomeninges, gray matter heterotopia, hypomyelination, changes of inferior olivary nuclei
  - Of note: cerebellar smallness documented prenatally (32 wks ga)

Green : affected genes with previously published neuropathologic findings
Red: current case

DSS 1994-09



DSS 1994-09



Genetic testing

- Targeted NGS of genes associated with Galloway-Mowat Syndrome
  - *GON7, LAGE3, NUP107, NUP133, OSGEP, PRDM15, TP53RK, TPRKB, WDR73, WDR4*, and *YRDC*

- Results:
  - Two heterozygous variants on *OSGEP,* in *trans*
    - *OSGEP* c.328T>C, p.Cys110Arg (previously published)
    - *OSGEP* c.365G>T, p.Gly122Val (novel)

- Diagnosis: Galloway-Mowat Syndrome 3

GAMOS 3, *OSGEP*

- *OSGEP* is the catalytic subunit of the KEOPS-complex
  - **K**inase, **E**ndopeptidase and **O**ther **P**roteins of **S**mall size
  - Functions of KEOPS-complex:
    - Regulation of tRNA modification (t^6A) required for accurate and efficient translation
    - Telomere length
      - Role in telomere-associated DNA-damage response (potentially linked to microcephaly)
    - Genome maintenance
  - OSGEP knockdown (zebrafish, mouse embryo) → primary microcephaly, early death
    - Impaired growth of yeast and cell proliferation in human podocyte cell lines

References

- Keith, J. et al. 2011. Neuropathological homology in true Galloway-Mowat syndrome. J. Child Neurol. 26:510.
- Jinks, R.N. et al. 2015. Recessive nephrocerebellar syndrome on the Galloway-Mowat syndrome spectrum is caused by homozygous protein-truncating mutations of *WDR73*. Brain 138: 2173.
- Boyer O, Mollet G, Dorval G. Neurological involvement in monogenic podocytopathies. *Pediatr Nephrol.* 2021;36:3571-3583.
- Braun, D.A. et al. 2017. Mutations in KEOPS-complex genes cause nephrotic syndrome with primary microcephaly. Nature Genetics 49:1529.
- Mann N, Mzoughi S, Schneider R, et al. Mutations in *PRDM15* Are a Novel Cause of Galloway-Mowat Syndrome. *J Am Soc Nephrol.* 2021;32:580-596.
- Al-Maawali, A. et al. 2012. Diagnostic approach to Childhood-Onset Cerebellar Atrophy: A 10-Year Retrospective Study of 300 Patients. J Child Neurol 27:1121-1132.
- Teng, H. et al. 2021. Novel variants in *OSGEP* leading to Galloway-Mowat syndrome by altering its subcellular localization. Clinica Chimica Acta 523:297-303.
- Lin, Pei-Yi et al. 2018. Galloway-Mowat syndrome in Taiwan: *OSGEP* mutation ant unique clinical phenotype. Orphanet Journal of Rare Diseases 13:226.
- Chen, Chih-Peng, et al. 2011. Galloway-Mowat syndrome: Prenatal ultrasound and perinatal magnetic resonance imaging findings. Taiwanese Journal of Obstetrics & Gynecology 50:212-216.
- Digital Neuropathology @ Pitt

Thank you!

- Medical University of South Carolina, Charleston, SC
  - Matthew Kilpatrick, MD
  - Nicholas Batalis, MD
  - Cynthia Welsh, MD
  - Daynna Wolff, PhD

- Greenwood Genetic Center, Greenwood, SC
  - Raymond Caylor, PhD
  - Jiyong Wang, PhD
  - Michael J. Friez, PhD

- Caterina Giannini, MD, PhD