DISCLOSURE STATEMENT

• No financial relationships to disclose
CLINICAL HISTORY WITH NEUROIMAGING

Clinical History:
- Female neonate delivered at 39 weeks gestation via emergency Cesarean section due to non-reassuring fetal heart tones
- Routine prenatal care testing for 35-year-old G2P1 mother was unremarkable
- At birth, the infant’s respiratory effort was absent, and was subsequently intubated
- Infectious work-up and newborn screening tests were all negative
- Infant died on day 3 of life shortly after being transitioned to comfort care
- Permission for unrestricted autopsy was obtained from the parents

Brain MRI:
- Extensive areas of signal abnormality, T1 type hyperintensity, and cystic lesions
• Brain weight 299.67 g (expected 355+/-49 g for 39 weeks gestational age)
• Diffuse hemorrhagic lesions of chronological heterogeneity and cystic lesions
MICROSCOPIC FINDINGS

20X

40X
DIFFERENTIAL DIAGNOSIS & DISCUSSION?

(Audience Discussion)
DIFFERENTIAL DIAGNOSIS (CONTINUED)

• Congenital Vascular Malformations
• Congenital Coagulopathies
• Infection
• Connective Tissue Disorders
• Cancer
## ADDITIONAL FINDINGS

- Genetic testing and results

<table>
<thead>
<tr>
<th>Gene/Test</th>
<th>Technical Result</th>
<th>Variant Type</th>
<th>Clinical Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>COL4A1</td>
<td>c.2870G&gt;A; p.Gly957Glu</td>
<td>Heterozygous Missense</td>
<td>Pathogenic</td>
</tr>
</tbody>
</table>

### Athena Insight pathogenicity assessment

COL4A1 c.2870 G>A is a missense variant classified as pathogenic based on the following information:

<table>
<thead>
<tr>
<th>Benign</th>
<th>Likely Benign</th>
<th>Uncertain</th>
<th>Likely Pathogenic</th>
<th>Pathogenic</th>
</tr>
</thead>
</table>

**Variant:** COL4A1 c.2870 G>A (p.Gly957Glu)

- This variant has not been reported in large, multi-ethnic general populations.
- The current individual with this variant presents with clinical features associated with this gene.
- Majority of the pathogenic variants in this gene involve the substitution of a glycine residue in the triple-helix domain, resulting in disruption of protein function (PMID: 29632050, 21421911, 19344236).
- To the best of our knowledge, this variant has not been reported previously.
- Computational tools yielded predictions that this variant may interfere with normal RNA splicing.

**References:**

Genome Aggregation Database (gnomAD), Cambridge, MA (URL: http://gnomad.broadinstitute.org)
NEUROPATHOLOGICAL DIAGNOSIS:

Microangiopathic Leukoencephalopathy Associated With COL4A1 Mutation
COL4A1 MUTATION

- Type IV collagens comprise a major component to all basement membranes throughout the body
- COL4A1 gene is associated with autosomal dominant cerebral small vessel disease
- Almost all COL4A1 mutations reported have been missense mutations involving highly conserved glycine residues in a triple helical domain of the gene
- Clinical onset and symptoms widely vary among patients
  - 4 main phenotypes

(Mao, et al; 2015)
**COL4A1 MUTATION PHENOTYPES**

1. Perinatal hemorrhage with proencephalopathy in survivors

2. Hereditary infantile hemiparesis, retinal arteriolar tortuosity and leukoencephalopathy (HIHRATL)

3. Small vascular disease with Axenfeld-Rieger anomaly (anterior segment dysgenesis of the eye)

4. Hereditary angiopathy with nephropathy, aneurysms (typically of the internal carotid artery), and muscle cramps (HANAC)
REFERENCES


ACKNOWLEDGEMENTS

• Patient, family, and clinical teams
• Intermountain Primary Children’s Hospital (Salt Lake City, UT)
• Jessica Comstock, MD
• Christian Davidson, MD, Cheryl Palmer, MD, Qinwen Mao, MD, PhD, Joshua Klonoski, MD, PhD, Eric Goold, MD