Novel homozygous \textit{NPC1} mutation diagnosed in a 2 month old with cholestasis by rapid Whole-Genome sequencing

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BACKGROUND

- Niemann-Pick Type C disease (NPC) is an autosomal recessive inborn error of intracellular cholesterol trafficking
- Progressive neurologic disorder
- May present with cholestasis in infancy
- Targeted therapy approved in EU
- Promising experimental therapy available

CASE

- Term male
- Non-consanguineous parents
- Admitted at 7 weeks of age for failure to thrive, direct hyperbilirubinemia and elevated hepatic transaminases
- Exam: jaundice, hepatosplenomegaly, clinodactyly, hypotonia

WGS RESULTS

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genomic location</th>
<th>HGVS cDNA</th>
<th>HGVS Protein</th>
<th>Zygosity</th>
<th>Variant Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPC1</td>
<td>Chr18: 21119857 (on assembly GRCh38)</td>
<td>NM_000271.3 c.2713C&gt;T</td>
<td>p.Gln905Ter</td>
<td>Homozygous</td>
<td>Likely Pathogenic</td>
</tr>
</tbody>
</table>

DISCUSSION

- Youngest patient diagnosed with NPC
- Youngest patient to be started on Miglustat
- Rapid WGS allows for timely diagnosis and early targeted therapy
- Early diagnosis prompts debate regarding initiating therapy in such a young child

CLINICAL COURSE

- Time to diagnosis: 6 days
- Started on Miglustat therapy
- WGS results reported 16 days before clinical testing completed
- Cholestasis resolved

DIAGNOSTIC WORKUP

Electron microscopy: numerous concentric lamellar bodies

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