Expanding the Phenotypic Spectrum: LARS2 Gene Mutation (Case Review)

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Leucyl-tRNA Synthetase 2 (LARS2) encodes a mitochondrial aminoacyl-tRNA synthetase.
Pathogenic variants in this gene have been associated with Perrault syndrome characterised by hearing loss and premature ovarian insufficiency; and a severe multi-systemic disorder of hydrops fetalis, lactic acidosis, and sideroblastic anaemia (HLASA).
We describe the phenotype of LARS2 deficiency in two brothers from the same family.
LARS2 encodes the mitochondrial leucyl-tRNA synthetase, which attaches leucine to its cognate tRNA (Riley et al 2016)
Many of these disorders present in infancy with highly variable clinical presentations, usually with multisystem involvement

**Background**

- Leucyl-tRNA Synthetase 2 (LARS2) encodes a mitochondrial aminoacyl-tRNA synthetase.
- Pathogenic variants in this gene have been associated with Perrault syndrome characterised by hearing loss and premature ovarian insufficiency; and a severe multi-systemic disorder of hydrops fetalis, lactic acidosis, and sideroblastic anaemia (HLASA).
- We describe the phenotype of LARS2 deficiency in two brothers from the same family.
- LARS2 encodes the mitochondrial leucyl-tRNA synthetase, which attaches leucine to its cognate tRNA (Riley et al 2016)
- Many of these disorders present in infancy with highly variable clinical presentations, usually with multisystem involvement

(Lightowlers, Teylor & Turnbull 2015)
A 3 year old boy with a history of severe congenital anaemia and lactic acidosis at birth, was the first baby in NSW to be tested by whole exome sequencing through Australian Genomics Acute Care programme.

He was born via Caesarean section at 32 weeks gestation.

He later developed profound bilateral sensorineural hearing loss, penoscrotal hypospadias (with abnormal testes), hepatosplenomegaly, pulmonary hypertension, short stature, and severe global developmental delay.

MRI at corrected 3 months showed diffuse cerebral atrophy.

He was found to have pathogenic compound heterozygous variants c.388G>A and c.2099C>T in LARS2.

*In vitro* amino-acylation assay showed both variants have a damaging effect on LARS2 protein function (Riley et al 2021)

His older brother who was born at 33 weeks with severe anaemia and died on day 1 despite blood transfusion, also had the same two pathogenic variants.

The *p.(Ala130Thr) LARS2* variant found in the siblings had a 16-fold decrease in aminoacylation efficiency, mainly due to a decreased \( k_{\text{cat}} \) value. *p*.Ala130 lies in the catalytic domain and is highly conserved. The siblings led to a 3-fold loss in catalytic efficiency (Riley et al. 2020)

Development at age 3

- Non-verbal
- Learning sign language – frustration with communication, good receptive language, able to point for expressive language
- Wide-based gait – maximum 25 minutes walking
- Improving engagement with other children socially, does not share toys
- Cochlear implants in situ
- Enjoys music
- Food aversion
- Ongoing occupational therapy fortnightly, speech therapy weekly, feeding therapist
DNA sequencing and analysis

- Patient’s DNA and parental DNA underwent rapid trio exome sequencing using an Ampliseq RDY exome kit at the NSW Health Pathology Randwick Genomics Laboratory
- Reads were aligned to the Human Genome Reference Sequence Hb19/GRCh37, and single nucleotide and short insertion/deletion variants identified
- Data filtering was performed using a NATA-approved in-house pipeline (v2.0) based on Gemini v18 with annotation from the Variant Effect Predictor
- Targeted sequencing of LARS2 on stored DNA from the patient’s deceased sibling was performed by the NSW Health Pathology Randwick Genomics Laboratory (Riley et al 2021)

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>3 year old patient</th>
<th>Deceased brother</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LARS2 variants</strong></td>
<td>c.388G&gt;A; [2099C&gt;T]</td>
<td>c.388G&gt;A; [2099C&gt;T]</td>
</tr>
<tr>
<td><strong>NM_015340.3</strong></td>
<td>p.[(Ala130Thr)]; [(Thr700Ile)]</td>
<td>p.[(Ala130Thr)]; [(Thr700Ile)]</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>3 years old</td>
<td>Deceased at day 1</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td><strong>Birth</strong></td>
<td>32 weeks gestation with foetal distress</td>
<td>33 weeks gestation with foetal distress</td>
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<tr>
<td><strong>Hydrops</strong></td>
<td>Increased nuchal translucency, foetal anaemia, mild pleural effusions, polyhydramnios</td>
<td>Increased nuchal translucency</td>
</tr>
<tr>
<td><strong>Lactic Acidosis</strong></td>
<td>11 mmol/L</td>
<td>24 mmol/L</td>
</tr>
<tr>
<td><strong>Sideroblastic Anaemia</strong></td>
<td>Hb 71g/L</td>
<td>Hb 53g/L</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td>PDA resolved spontaneously</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td>Pulmonary hypertension, Hypoxic respiratory failure</td>
<td>Hypoxic respiratory failure</td>
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<tr>
<td><strong>Hepatic</strong></td>
<td>Hepatosplenomegaly, liver cyst</td>
<td>Hepatosplenomegaly</td>
</tr>
<tr>
<td><strong>Neuro</strong></td>
<td>Cerebral atrophy</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Developmental delay</strong></td>
<td>Developmental delay</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Hearing</strong></td>
<td>Sensorineural hearing loss</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td>Hypoglycaemia, hyperinsulinism</td>
<td>Hypoglycaemia, hyperinsulinism, low cortisol</td>
</tr>
<tr>
<td><strong>Gonadal dysgenesis</strong></td>
<td>Penoscrotal hypospadias, undescended testes</td>
<td>Micropenis</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td>Foetal long limb shortening</td>
<td>Foetal long limb shortening</td>
</tr>
</tbody>
</table>

(Riley et al 2021)
Graph showing trend of anaemia improving with age

Neuropathology of LARS2 leukodystrophy(A) Whole coronal brain slice shows mild dilatation of the lateral ventricles, indicating mild white matter atrophy, and discoloration of the hemispheric white matter with better preservation of the U-fibers (van der Knapp et al 2019).

Growth chart showing improvement of FTT

Length-for-age, 0-36 months, Boys

Weight-for-age, 0-36 months, Boys

Haemoglobin
Literature Review

- There have been few fatalities; in surviving individuals, ongoing developmental delay is a feature.
- In literature, three patients with a HLASA-like phenotype, an individual with Perrault syndrome whose affected siblings also had leukodystrophy, and an individual with a reversible mitochondrial myopathy, lactic acidosis, and developmental delay (Riley et al. 2021).
- One other HLASA case from another unrelated family identified.
- All were males with genital anomalies.
- Another survived multisystem disease in the neonatal period; both have developmental delay and hearing loss.
- A 55 year old male with deafness has not displayed neurological symptoms while his female siblings with Perrault syndrome developed leukodystrophy and died in their 30s (Riley et al. 2021).
- Pathology in one patient with LARS2 pathogenic variants displayed evidence of primary disease of oligodendrocytes and astrocytes with lack of myelin and deficient astrogliosis (van der Knapp et al. 2019).
- Analysis of muscle from a child with a reversible myopathy showed reduced LARS2 and mitochondrial complex I levels, and an unusual form of degeneration.
- A male with LARS2 Perrault syndrome had hypospadias while his sister had oligomenorrhea with a small uterus and ovaries (Demain et al., 2017).
- Analysis of recombinant LARS2 variant proteins showed they had reduced aminoacylation efficiency, with HLASA-associated variants having the most severe effect (Riley et al 2020).

Conclusion

- This report demonstrated a phenotypical expansion of LARS2 deficiency, with variable expressivity noted within the same family.
- Variants in LARS2 are associated with devastating outcomes including neurodevelopment complications and foetal death.
- If patients survive early decomposition, recovery with developmental progress is possible – long-term prognosis is uncertain.
- Future testing can help identify more individuals with this rare disorder.

References