One in a Million: exploring the epidemiology of Riboflavin Transporter Deficiency (RTD)

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Introduction
Riboflavin transporter deficiency (RTD), formerly known as Brown-Vialetto-Van Laere syndrome (BVVL), is a rare, early onset, neurodegenerative disease with distinctive clinical phenotypes. RTD is caused by mutations in either the SLC52A2 or SLC52A3 genes that encode riboflavin transporters RFVT-2 and RFVT-3, respectively.

Historical Snapshot of BVVL/RTD
- 1894: first reported as an ‘infantile’ form of ALS with associated hearing loss.1
- <2010: less than 75 cases reported.
- 2010: SLC52A3 found to cause BVVL.2 High dose daily oral riboflavin treatment found to stabilize and even improve symptoms in patients.3
- 2012: SLC52A2 found to cause BVVL, patients also responded favorably to oral riboflavin therapy.5

Methods
Data obtained from the Cure RTD Foundation International Registry, and those obtained from published literature, were used to conduct a retrospective case review of individuals with genetically confirmed RTD.

Results

Overall:
1. N=132; Multi-ethnic case-series.
2. Slight female pre-domination (55% SLC52A2, 67% SLC52A3).
3. Similar prevalence of SLC52A2 and SLC52A3, with notable differences in clinical presentations.
4. 25 received cochlear implant, most with significant benefit.
5. Untreated, fatality at 9.2 years (SD 10.5 n=70).
6. Untreated, infection or fever often precipitate the initial manifestations or worsen existing findings.
7. Symptoms often improved or stabilized after riboflavin protocol, especially with early initiation:
   - 10 – 80 mg/kg/day children
   - 600 – 2800 mg/day adults

Recurrent Mutations:

- 30 novel mutations identified: 27 missense, 2 nonsense, and 4 deletion.

SLC52A2

- n=82 cases; 16 (20%) deceased (14 untreated).
- Mean age of onset: 3 years (SD=3.0, R: 0.3-19, n=70).
- Mean age of diagnosis: 14 years (SD=14.2, R: 0.8-66, n=63).
- 30 novel mutations identified: 27 missense, 2 nonsense, and 4 deletion.

SLC52A3

- n=50 cases; 11 (21%) deceased, all untreated.
- Mean age of onset: 7.8 years (SD=8.1, R: 0.2-33 n=61).
- Mean age of diagnosis: 19 years (SD=18.3, R: 0-62, n=28).
- 47 novel mutations identified (largely missense).

Table 1. Presenting features of SLC52A2 and SLC52A3

<table>
<thead>
<tr>
<th>Presenting Feature</th>
<th>SLC52A2</th>
<th>SLC52A3</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auditory Neurupathy</td>
<td>33% (1)</td>
<td>20% (1)</td>
<td>75% (1)</td>
</tr>
<tr>
<td>Pontobulbar Involvement</td>
<td>8% (8)</td>
<td>68% (6)</td>
<td>20% (2)</td>
</tr>
<tr>
<td>Sensory Gait Ataxia</td>
<td>64% (2)</td>
<td>5% (2)</td>
<td></td>
</tr>
<tr>
<td>Optic atrophy w/o nystagmus</td>
<td>29% (4)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Muscle Weakness</td>
<td>26% (UL)</td>
<td>10% (UL)</td>
<td></td>
</tr>
<tr>
<td>Respiratory Compromise</td>
<td>8% (5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Clinical features of SLC52A2 and SLC52A3 (untreated)

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>SLC52A2 n=33 (1)</th>
<th>SLC52A3 n=14 (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auditory Neurupathy</td>
<td>97%</td>
<td>93%</td>
</tr>
<tr>
<td>Pontobulbar Involvement</td>
<td>88%</td>
<td>93%</td>
</tr>
<tr>
<td>Sensory Gait Ataxia</td>
<td>100%</td>
<td>14%</td>
</tr>
<tr>
<td>Optic atrophy w/o nystagmus</td>
<td>100%</td>
<td>14%</td>
</tr>
<tr>
<td>Muscle Weakness (Axonopathy/Neurupathy)</td>
<td>94% (UL)</td>
<td>93% (UL)</td>
</tr>
<tr>
<td>Respiratory Compromise (Diaphragm/Muscle weakness/Apnea)</td>
<td>79% (1)</td>
<td>79% (1)</td>
</tr>
</tbody>
</table>

(1) >10 years from onset of first symptom untreated. Fatalities <10 years from onset were related to respiratory insufficiency.

Other features may include: upper motor neuron and cerebellar signs (Type 3); scoliosis, nausea/vomiting, autonomic dysfunction, seizures, and fatigue; cognition was normal in all cases.

SLC52A3 (RTD Type 3):

- n=52 cases; 11 (21%) deceased, all untreated.
- Mean age of onset: 7.8 years (SD=8.1, R: 0.2-33 n=61).
- Mean age of diagnosis: 19 years (SD=18.3, R: 0-62, n=28).
- 47 novel mutations identified (largely missense).

Table 3. Clinical features of RTD untreated

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Figure 1. SLC52A2 Gene Structure

Figure 2. Phenotypic characteristics of SLC52A2 (2.5 and 24 yrs). Severe weakness of neck extension and upper limbs with comparatively less weakness of lower limbs (A,B); Symmetrical atrophy of intrinsic hand muscles (B); Dysphagia requiring NG-tube (A), G-tube (B); Auditory and optic atrophy (A,B); Respiratory insufficiency requiring tracheostomy (B).

Laboratory findings:
Abnormalities were often minor or transient. In less than 50% of cases findings may include:

- Blood: Abnormal acylcarnitine profile with selective increase of short and medium-chains. Low flavin levels.
- Amino Acids: Mild signs of mitochondrial dysfunction.
- Urine organic acids: Elevated ethylmalonic acid.
- CSF: Mildly elevated proteins.
- Diagnosis confirmed by SLC52A2 & A3 gene sequencing.

Conclusion
This is the largest case series of RTD to date. Individuals affected by RTD present with a vast range of symptoms, and the diagnosis is often delayed. Early recognition and treatment are essential for survival and optimal outcomes in this population.

- Prevalence: The minimum prevalence of RTD is estimated to be 1 per million, with an estimated 50-100 new diagnoses worldwide per year.
- Variability: Significant phenotypic variability exists both within and between families and mutation type.
- Treatment: Early detection and early treatment with oral riboflavin is lifesaving.

Take Away Message
1. There is no known cure for RTD at present.
2. Clinical signs of RTD should be investigated promptly.
3. If suspected, treatment with riboflavin should commence immediately.
4. Notable differences in clinical presentation were observed in SLC52A2 compared to SLC52A3.
5. Symptoms, age of onset, and rate of progression are highly variable, even between siblings.
6. More research and complementary novel therapeutic strategies are needed.

References
2. Green et al (2010), PMID: 20206331
5. Foley et al (2014), PMID: 24253200