Further delineation of short chain enoyl CoA hydratase deficiency in the Pacific population

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Introduction

Short-chain enoyl-CoA hydratase (SCEH) deficiency due to biallelic variants in ECHS1 was first described in 2014 in siblings with fatal Leigh syndrome and increased excretion of S-(2-carboxypropyl)cysteine.1 It is potentially treatable with a valine-restricted, high-energy diet and emergency regimen.2,3 Recently, Simon et al4 described four Pacific-Samoan children harbouring a hypomorphic allele c.489G>A, p.(Pro163=). This synonymous variant was associated with reduced levels of normally spliced mRNA, was missed on standard genomic testing, and was highly prevalent in the Samoan population with an allele frequency of 0.17. They reported an asymptomatic parent who was homozygous for this variant, and homozygotes are also present in population reference databases.4

Figure 1: Valine catabolic pathway and metabolites associated with SCEH-deficiency

SCEH: short-chain enoyl-CoA hydratase, * Origin of 2,3DH2MB from acryloyl-CoA is indirectly inferred

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Method

Patients with bilateral globi pallidi T2-hyperintensity and one variant in ECHS1 were identified in New Zealand and Australian genomic and clinical databases. ECHS1 data were interrogated for the c.489G>A, p.(Pro163=) allele and clinical data were reviewed.

Results

Nine patients from 8 families were identified with compound heterozygous ECHS1 variants including the c.489G>A, p.(Pro163=) allele, which was inherited from a parent of Samoan (3/9), Māori (4/9), Tokelauan (1/9) or unknown (1/9) ethnicity. Age ranged from 2 to 47 years. Symptom onset was in early childhood, and was episodic or triggered by illness in 6/9. In a non-consanguineous family, a child and his aunt were both affected and had slowly progressive disease. All had dystonia, 4/9 had exercise-induced dyskinesia, 7/9 had optic atrophy and 3/9 nystagmus (Table 1). All had bilateral globi pallidi T2 hyper-intensity on brain MRI (Figure 2).

Table 1: Clinical data summary

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current age</td>
<td>2 years</td>
<td>5 years</td>
<td>6 years</td>
<td>7 years</td>
<td>9 years</td>
<td>13 years</td>
<td>26 years</td>
<td>30 years</td>
<td>47 years</td>
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<tr>
<td>Ethnicity of parent harbouring allele 2</td>
<td>Unknown</td>
<td>Tokelauan</td>
<td>Samoan</td>
<td>Māori</td>
<td>Samoan</td>
<td>Māori</td>
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<tr>
<td>Early childhood onset</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Globi pallidi T2 hyper-intensity</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Catabolic trigger</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Dystonia (Exercise-induced dyskinesia)</td>
<td>+</td>
<td>(+)</td>
<td>+</td>
<td>(+)</td>
<td>+</td>
<td>(+)</td>
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<tr>
<td>Optic atrophy (Nystagmus)</td>
<td>+</td>
<td>(+)</td>
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<td>Sensorineural hearing loss</td>
<td>+</td>
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<td>Intellectual impairment</td>
<td>+</td>
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<tr>
<td>Other features</td>
<td>Global developmental delay</td>
<td>Severe ketoacidosis at 13 months</td>
<td>Profound metabolic acidosis at 12 months</td>
<td>Leigh syndrome</td>
<td>Ketoacidosis at 9 months</td>
<td>Seizures</td>
<td>Spasticity</td>
<td>Dysarthria</td>
<td>Dysphagia</td>
</tr>
</tbody>
</table>
Results (continued)
Urine S-(2-carboxypropyl)cysteine-carnitine and other SCEH-related metabolites including erythro-2,3-dihydroxy-2-methylbutyric acid were normal to mildly elevated.

Figure 2: MRI brain in case five showing bilateral globi pallidi lesions (arrows) in A; T2, B; T1, C; DWI and D; ADC map images.

Conclusion
These data provide further support to the pathogenicity of a synonymous ECHS1 c.489G>A variant. This is the first report of this hypomorphic variant in wider-Pacific populations, including Māori. Biomarker levels can be subtly increased or normal in milder forms of SCEH deficiency, highlighting the need to search for a second variant in apparent heterozygotes with the appropriate phenotype, particularly in potentially treatable conditions such as SCEH deficiency. Establishing the carrier frequency Māori, and the impact of dietary treatment, are priorities for further work.

References
7. Olgiati S, et al. Paroxysmal exercise-induced dystonia within the phenotypic spectrum of ECHS1 deficiency. Movement Disorders (2016) 31(7); 1041–1048
10. Figure 1 created with BioRender.com