INTRODUCTION

- Biallelic variants in TANGO2 (transport and Golgi organisation 2 homolog) have been described as a cause of a complex multisystemic neurometabolic syndrome (OMIM #616878). Approximately 50 cases have been reported since it was first described in 2016. It is characterised by recurrent episodes of severe rhabdomyolysis, encephalopathy, seizures, cardiac arrhythmia, endocrine dysfunction and metabolic crises with lactic acidosis and hypoglycaemia.
- The role of the TANGO2 protein was thought to be important in some aspects of Golgi function and organisation in drosophila. Some of the earlier studies on the role of TANGO2 protein suggest either a defect in membrane traffic or an unknown mitochondrial disorder. The discordant theory may be due to the clinical features resembling long-chain fatty acid disorders and mitochondrial disease in TANGO2 deficiency.
- We describe the phenotype of nine patients (two female and seven male) with TANGO2 deficiency in New South Wales.

PATIENT DEMOGRAPHIC

<table>
<thead>
<tr>
<th>Patient</th>
<th>Family</th>
<th>Ancestry</th>
<th>Consanguinity</th>
<th>Sex</th>
<th>Alive/Deceased</th>
<th>Age and cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F1</td>
<td>Italian</td>
<td>Y</td>
<td>M</td>
<td>A</td>
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</tr>
<tr>
<td>2</td>
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<td>Y</td>
<td>F</td>
<td>A</td>
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<tr>
<td>3</td>
<td>F2</td>
<td>Arab</td>
<td>Y</td>
<td>M</td>
<td>A</td>
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<tr>
<td>4</td>
<td>F2</td>
<td>Arab</td>
<td>Y</td>
<td>M</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>F3</td>
<td>Caucasian/European</td>
<td>N</td>
<td>M</td>
<td>D</td>
<td>Severe cardiomyopathy (5 years 3 months)</td>
</tr>
<tr>
<td>6</td>
<td>F3</td>
<td>Caucasian/European</td>
<td>N</td>
<td>F</td>
<td>A</td>
<td>VT/VF cardiac arrest (8 years 7 months)</td>
</tr>
<tr>
<td>7</td>
<td>F4</td>
<td>Arab</td>
<td>Y</td>
<td>M</td>
<td>D</td>
<td>Asystole cardiac arrest (4 years 9 months)</td>
</tr>
<tr>
<td>8</td>
<td>F5</td>
<td>Caucasian/European</td>
<td>N</td>
<td>M</td>
<td>D</td>
<td>Severe cardiomyopathy (2 years 5 months)</td>
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</table>

M: Male; F: Female; Y: Yes; N: No; A: Alive; D: Deceased; VF: Ventricular fibrillation; VT: Ventricular tachycardia
PHENOTYPIC EXPANSION IN TANGO2 DEFICIENCY

CLINICAL PHENOTYPE AND GENOTYPE

<table>
<thead>
<tr>
<th>Genotype</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>P5</th>
<th>P6</th>
<th>P7</th>
<th>P8</th>
<th>P9</th>
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<tbody>
<tr>
<td>Homozygous c.[98C&gt;T]; (120G&gt;A) p.[Pro33&gt;Leu]; (Trp40*)</td>
<td>Homozygous c.[98C&gt;T]; (120G&gt;A) p.[Pro33&gt;Leu]; (Trp40*)</td>
<td>Homozygous c.[547del] p. (Glu183Serfs*7)</td>
<td>Homozygous c.[547del] p. (Glu183Serfs*7)</td>
<td>Homozygous deletion exon 4-9 within TANGO2 gene</td>
<td>Homozygous deletion exon 3-9 within TANGO2 gene</td>
<td>Homozygous c.[220A&gt;C] p.(Thr74Pro)</td>
<td>Homozygous deletion exon 4-9 within TANGO2 gene</td>
<td>Focal homozygous TANGO2 deletion (includes exon 4-9** within a larger heterozygous 22q11.21 interstitial deletion</td>
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<td>Developmental delay/intellectual disability</td>
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<td>+</td>
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<tr>
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<tr>
<td>Other neurological signs</td>
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<td>Alternating hemiplegia</td>
<td>Alternating hemiplegia episodic ataxia, spastic diplegia</td>
<td>Spastic diplegia</td>
<td>Alternating hemiplegia episodic ataxia, dystonia, spastic diplegia</td>
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<td>Trigger for metabolic crises</td>
<td>Immunisation</td>
<td>Infection, chronic malnutrition</td>
<td>Anaesthesia</td>
<td>N/A</td>
<td>Infection</td>
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<td>Infection</td>
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<tr>
<td>Cardiac arrhythmia</td>
<td>LQTC, TdP, VT, VF</td>
<td>LQTC</td>
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<td>LQTC, tdp, VT, VF</td>
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<tr>
<td>Cardiomyopathy</td>
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<td>Occular abnormalities</td>
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</table>

LQTC: long QTc; tdp: Torsades de Pointe; VF: ventricular fibrillation; VT: ventricular tachycardia
** probe gap spans across exon 3

Figure 1: MRI brain of Patient 2 showing right posterior quadrant gliosis (A and B); MRI brain of Patient 1 demonstrating subtle white matter atrophy and ventricular dilatation
PHENOTYPIC EXPANSION IN TANGO2 DEFICIENCY

This cohort (n=9)

Lalani et. al. (n=12)

Kremer et. al. (n=3)

Dines et. al. (n=14)

Jennions et. al. (n=11)

Berat et. al. (n=20)

Mingirulli et. al. (n=9)

Seizures
6 (67%) 9 (75%) 3 (100%) 10 (71%) 6 (55%) 5 (25%) 7 (78%)

Cerebral Atrophy
2 (22%) 7 (58%) 3 (100%) 5 (36%) 2 (18%) NR 2 (22%)

Microcephaly
3 (33%) 1 (8%) NR 5 (36%) NR NR 1 (11%)

Intellectual disability/developmental delay
9 (100%) 12 (100%) 3 (100%) 12 (86%) 9 (81%) 17 (85%) 9 (100%)

Alternating hemiplegia/episodic ataxia
7 (78%) NR NR NR 6 (55%) 8 (40%) NR

Rhabdomyolysis
8 (89%) 10 (83%) 3 (100%) 9 (64%) 9 (81%) 15 (75%) 9 (100%)

Prolonged QT/cardiac arrhythmia
4 (44%) 7 (58%) 3 (100%) 6 (43%) 7 (64%) 12 (60%) 9 (100%)

Hypothyroidism
5 (56%) 4 (33%) 3 (100%) 7 (50%) 6 (55%) 12 (60%) 7 (77%)

BIOCHEMICAL FEATURES

• Severe rhabdomyolysis occurred in almost 90% of patients in our cohort. The creatine kinase levels rose rapidly to >100,000 IU/L in these patients during metabolic crises.

• Five patients developed primary hypothyroidism with negative thyroid autoantibodies and were treated with L-thyroxine. One patient had TSH elevation after an acute metabolic crisis but became euthyroid on subsequent follow-up.

• Urine organic acid analysis performed for eight patients identified lactic acid (P1, P2) and dicarboxylic aciduria (P1, P5, P7, P8, P9). Plasma acylcarnitine profiles showed mild elevations of C3 in P2, C3-C6 in P3, and, and C3 and C6 in P7. Fatty acid oxidation flux study performed on fibroblasts of two patients were normal (P8 and P9).

• Mitochondrial respiratory chain enzymology on muscle homogenate from three patients (P1, P5, P8) and liver homogenate from two patients (P8 and P9) showed borderline low Complex III activity, which could have been consistent with a respiratory chain disorder but was not diagnostic.
PHENOTYPIC EXPANSION IN TANGO2 DEFICIENCY

DISCUSSION

- Severe global developmental delay, cognitive impairment and neurological abnormalities are the main clinical features of TANGO2 deficiency
- Eight patients had at least one episode of acute metabolic crisis with encephalopathy, rhabdomyolysis and biochemical abnormalities. Four patients had QTc prolongation and two developed life-threatening cardiac arrhythmias during the acute episodes.
- Intercurrent infection is the main trigger for acute metabolic crises. Other triggers were routine vaccinations, general anaesthesia and chronic malnutrition.
- Cardiac complications were the leading cause of premature death in our cohort. Two patients died from severe cardiomyopathy, one had an asystole cardiac arrest and one had refractory broad-complex tachycardia.
- Ocular abnormalities were identified in six patients. These includes external ophthalmoplegia, episodic oculomotor apraxia, visual impairment and optic nerve abnormalities.
- No unique biochemical profile was identified in our TANGO2 cohort. Borderline-low Complex III activity was observed in muscle and/or liver homogenate in four patients but was not diagnostic for a primary mitochondrial disorder.
- We observed intrafamilial phenotypic variability in our cohort.

CONCLUSION

- TANGO2 deficiency is a multisystemic disorder with severe life-threatening complications
- The clinical and biological features seen in this cohort are similar to other previously reported cases
- Episodic ataxia and oculomotor apraxia have not been previously reported.
- Variants in TANGO2 are associated with variable expressivity.
- The disease burden of TANGO2 deficiency relates to cardiac and neurological complications.

REFERENCE