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TRMT5 MUTATIONS ARE ASSOCIATED WITH FEATURES OF COMPLEX HEREDITARY SPASTIC PARAPARESIS

Mitochondrial DNA (mtDNA) encodes for 22 tRNAs (mt-tRNA) that undergo posttranscriptional modification.^{1,2} A specific nucleotide adjacent to the anticodon of mt-tRNA (position 37) is methylated (m¹G37) to enhance translational efficiency/fidelity.³ The gene tRNA methyltransferase 5 (*TRMT5*) encodes a protein involved in m¹G37 formation for some mitochondrial tRNAs^{3,4} and has been associated with combined oxidative phosphorylation deficiency 26 (COXPD26) (OMIM 616539).

Two patients have been described to date, both showing hypomethylation of guanosine at G37.⁵ One of the reported women died at 55 years of age with lifelong exercise intolerance, shortness of breath on exertion, spasticity, peripheral neuropathy, muscle weakness, liver cirrhosis, renal tubulopathy, and lactic acidosis. A boy, reported alive at age 7 years, demonstrated hypotonia, neuropathy, global developmental delay, lactic acidosis, growth retardation, intestinal pseudo-obstruction, and hypertrophic cardiomyopathy. Both patients showed complex I and IV deficiency in skeletal muscle.⁵

We report 2 additional patients.

Case reports. Patient 1 (46 years of age), the youngest in a sibship of 3 women, presented at age 27 years with a lifelong history of exercise intolerance, muscle weakness, and shortness of breath on exertion. Detailed phenotype data are listed in the table. Initial motor examination demonstrated normal bulk and tone with proximal muscle weakness (4/5 Medical Research Council) and normal muscle stretch reflexes. Toes were downgoing and vibration sensation was moderately impaired distally. EMG at 27 years of age was normal but later showed progressive axonal sensory neuropathy with absent sural sensory action potentials and reduced amplitude for the common peroneal nerve and tibial motor nerves at 43 years of age. Clinical examination at age 46 years showed progression of proximal weakness with a waddling and spastic gait with very brisk knee reflexes and upgoing toes. Mitochondrial respiratory chain analysis showed a decrease of complex I + III and IV activity typical of a tRNA defect. Cycle ergometry showed

a severe reduction in maximal oxygen capacity with a $\text{VO}_{2\text{max}}$ of 9.0 mL/kg/min (normal >25 mL/kg/min) and brain MRI showed nonspecific scattered deep white matter changes.

Patient 2 (51 years of age), the oldest sister of patient 1, presented at age 33 years for evaluation of worsening gait and an increased frequency of falls in the context of a diagnosis of cerebral palsy in childhood. She had been born at 32 weeks gestation at 4 pounds 9 ounces; showed gross motor, cognitive, and speech delays; was described as uncoordinated; and required educational assistance in school. Initial neurologic examination of upper extremities and cranial nerves was normal. In the lower extremities, she had mild proximal and severe distal weakness/atrophy, severe spasticity, and upgoing toes. At age 42 years, she had a stent placement for frequent urinary tract infections and right ureteropelvic junction stenosis. In the postoperative period she developed confusion, generalized tonic-clonic seizures with fluctuating level of consciousness, and psychosis, with the MRI showing a stroke crossing vascular territories, and was placed on antiepileptic medications. She became depressed and catatonic developed dementia. She now requires a wheelchair for mobility. An ECG at 50 years of age was normal.

Genetic testing. Genetic testing for the siblings included sequencing of muscle-derived mtDNA, *OPA1*, *ANT1*, *POLG1*, and 10 autosomal recessive hereditary spastic paraparesis genes. Whole exome sequencing completed through the Care4Rare Canada Consortium found both sisters were heterozygous for 2 variants in *TRMT5* (NM_020810): c.872G>A (p.Arg291His) in exon 4 and c.312_315del (p.Ile105-Serfs4X) in exon 2. Family studies confirmed that the variants are in *trans*. Both of these variants have been reported and shown to be deleterious to function.⁵

Discussion. This report highlights the phenotype of 2 additional patients with pathogenic mutations in *TRMT5*. The cases presented here match aspects of the previously described phenotypes: muscle weakness, exercise intolerance, neuropathy, and spastic diplegia⁵ (reported case ID 73901⁵, similar to both cases presented here), prematurity, and global developmental delay (reported case ID 65205⁵, similar to case 2 presented here).

Supplemental data
at Neurology.org

Table Clinical, microscopic, and biochemical features of the patients								
Patient	Age at onset	Phenotype	Respiratory chain complex enzyme activity, μmol/min/g		Muscle biopsy pathology	Lactate, mmol/L	Plasma alanine, μmol/L	Urine organic acids
1	Childhood	Lifelong exercise intolerance, shortness of breath on exertion, muscle weakness, spasticity, axonal sensory neuropathy	I + III	0.20 (0.5-1.9)	27 years: Marked COX deficiency (>50%), subsarcolemmal aggregates of mitochondria, mitochondria with PCIs	1.8-8.3 (<2.2)	390-749 (188-559)	Elevation of lactate, pyruvate, and ketones
			II + III	0.66 (0.57-2.3)				
			IV	0.20 (0.58-2.5)				
			Citrate synthase	11.54 (0.8-5.5)				
2	Childhood	Premature, global developmental delay, spasticity, progressive visual loss due to optic atrophy (20/200 OD; 20/100 OS)	ND		34 years: Internalized nuclei with abnormal shape and intranuclear inclusions; 44 years: mild variation in fiber size, no COX-negative fibers, significant PCIs	1.4-3.6 (<2.2)	457-820 (188-559)	ND

Abbreviations: COX = cytochrome c oxidase; ND = not done; PCIs = paracrystalline inclusions (respiratory chain complex enzyme activities were below age-matched controls with compensatory upregulation of citrate synthase, typical of tRNA defects [normal range]).

This case report confirms the role of *TRMT5* mutations in causing a neurologic phenotype that can present with exercise intolerance and muscle weakness or with developmental delay and spastic paraparesis. The collective data on the 4 reported cases suggest that *TRMT5* mutations should be considered in cases of hereditary spastic paraparesis, cerebral palsy, and myopathy/exercise intolerance. We also expand the clinical phenotype of this condition, as patient 2 experienced mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)-like features including acute encephalopathy, seizures, a stroke that crossed vascular territories, and visual loss with optic atrophy. The latter observation is not unexpected given that TRMT is best known to methylate tRNA-Leu, which is the region where most of the MELAS mutations exist.⁶

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