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COQ5 compound heterozygous variants in a family with global developmental delay, seizures, spastic paraparesis, and stroke

Jorge Granadillo[1] and Samantha Toy[1]

[1]*Division of Genetics and Genomic Medicine, Department of Pediatrics, Washington University School of Medicine in St. Louis. St. Louis, MO*

Background: Primary Coenzyme Q10 (CoQ10) Deficiency is a heterogeneous group of mitochondrial respiratory chain disorders caused by pathogenic variants in any of the genes involved in the metabolism of CoQ10. To date, only one family with CoQ10 deficiency due to *COQ5* pathogenic variants has been reported. In 2018, 3 sisters were described with cerebellar ataxia, cerebellar atrophy, and other variable features, such as intellectual disability and seizures. They all had reduced CoQ10 levels in leukocytes, and reduced levels in the only muscle tissue available. The patients were found to be homozygous for a *COQ5* pathogenic variant. CoQ10 supplementation led to clinical improvement.

Case presentation: The patient is a 27-month-old former full-term female of European descent, product of an uncomplicated pregnancy and delivery. Developmental delays were first noticed at around 6 months of age. Currently, she laughs and babbles, but is nonverbal. She can finger feed, but does not have a pincer grasp. The patient has head control, and she rolled over at 6 months. She is unable to sit up on her own. She has not regressed. She receives most of her nutrition via gastrostomy feeds. She was found to have seizures at age 26 months, currently treated with levetiracetam.

The patient has undergone extensive testing. Metabolic testing at 19 months of age was notable for elevated lactate (4.4 mmol/L (normal value 0.5 – 2.2 mml/L)) and elevated alanine (678 nmol/mL (normal value 139 – 474 nmol/mL)). Repeat testing at 24 months showed elevated lactate (3.4 mmol/L), and normal alanine.

Brain MRI at age 21 months showed reduced diffusivity within the bilateral ventral thalami/cerebral peduncles with diffuse white matter volume loss, nonspecific. There was also T2 hyperintense signal measuring 4x4x12 mm without abnormal postcontrast enhancement. Repeat brain MRI at 25 months showed worsening of disease, with worsening of signal abnormality within the dorsal midbrain and medial thalami. There was also a new abnormality involving the left posterior cerebral artery territory suggestive of a subacute infarct. Magnetic Resonance Angiogram 3 days later did not show significant stenosis or occlusion. No vascular malformation. Most recent brain MRI at 26 months showed persistence of signal abnormalities, and mild decrease in the edema associated with the suspected subacute to chronic left posterior temporal/occipital lobe infarct. These findings were highly suggestive of a mitochondrial disorder.

Family history was notable for a 4-year-old brother with a history of neonatal stroke vs possible hypoxic ischemic injury; he has a diagnosis of cerebral palsy, epilepsy, and developmental delay. He is gastrostomy tube dependent, non-verbal, and does not walk.

Exam was notable for microcephaly, bilateral epicanthal folds, axial hypotonia, lower extremity spasticity, and patellar and Achilles hyperreflexia.

Exome sequencing was obtained, using samples from the patient, affected brother, and parents. It showed that both the patient and her affected brother were compound heterozygous for two variants in *COQ5* denoted NM_032314.4: c.177_178del, NP_115690.3: p.(S60Gfs*13) (inherited from the father), and NM_032314.4: c.353 G>A, NP_115690.3: p.(G118D) (inherited from the mother). These variants were classified as of uncertain significance by the clinical lab; however, there are several features that suggest pathogenicity: The paternal variant has not been previously reported in the general population, and it is predicted to result in nonsense-mediated decay; it was previously demonstrated that the variant found in their family resulted in decreased COQ5 expression, confirming that loss-of-function is the mechanism of disease. The maternal variant has a very low frequency in population databases (0.0021% in gnomAD) and in silico tools strongly suggest that it is deleterious (CADD-PHRED = 33). Moreover, both affected individuals in this family have the same genotype, and their phenotype is consistent with a primary CoQ10 deficiency.

Conclusion: To our knowledge, this is the second reported family with a likely primary CoQ10 deficiency due to *COQ5* variants, presenting with global developmental delay, seizures, spastic paraparesis, and brain MRI abnormalities. Functional studies and additional cases are required to fully understand the clinical spectrum of *COQ5*-related disorders.

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Biochemical diagnosis of pterin defect after negative broad genetic evaluation

Kirsten Havens[1], Joshua Baker[1], Erika Vucko[1], Sarah Jurgensmeyer[1]

[1]*Ann and Robert H. Lurie Children's Hospital of Chicago*

Background: Tetrahydrobiopterin (BH4) deficiencies comprise a group of several rare neurometabolic disorders characterized by insufficient synthesis of neurotransmitters due to a disturbance of BH4 biosynthesis. Patients may exhibit a wide spectrum of clinical severity. Common features of BH4 deficiencies are non-specific and may include hypotonia, impaired motor and cognitive development, and movement disorders. Pterin defects associated with hyperphenylalaninemia (HPA) may be identified on newborn screening, but do not identify every individual with a pterin defect.

Case presentation: We present a 14-month-old male with a complex medical history notable for developmental delay, epilepsy, infantile spasms, ocular anomalies, and concern for chorea-like movements; now diagnosed biochemically with a defect in the tetrahydrobiopterin pathway. He initially presented to genetics at 2 months of age with severe hypotonia. He developed significant developmental delay over the next several months, which prompted genetic testing including microarray and whole exome sequencing, both of which were non-diagnostic. Broad metabolic testing, including plasma aminos, was also sent and resulted within the normal reference range. At 11 months of age he underwent further evaluation with neurology. CSF studies at this time showed abnormal neurotransmitters: 5-hydroxyindoleacetic acid - 88nmol/L (129-520), homovanillic acid - 37nmol/L (294-1115), 3-O-methyldopa - 6nmol/L (<300). This prompted further evaluation for an underlying pterin defect. Urine pterins showed biopterin of 3.31mmol/mole Cr (0.78-2.68), neopterin total of 1.85 mmol/mole Cr (0.4-1.33) and biopterin as 64% of the sum of biopterin and neopterin. CSF dihydrobiopterin resulted at 1.8nmol/L (3-18), sepiapterin at <1nmol/L (<2), neopterin at 9nmol/L (7-65) and tetrahydrobiopterin at 5nmol/L (18-58). Dihydropteridine reductase activity in dried blood spots was found to be deficient. We believe this fits with a biochemical diagnosis of dihydropteridine reductase deficiency, however, repeat genetic testing has not identified underlying disease causing variants.