ePO15

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

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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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ePO16

Biochemical diagnosis of pterin defect after negative broad genetic evaluation

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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.

Conclusion: This case illustrates the need for further biochemical studies in patients with high clinical suspicion for disease and non-diagnostic comprehensive genetic testing. Establishment of diagnosis has been life altering for our patient and his family, as they have appreciated developmental gains within days of initiating appropriate neurotransmitter replacement and tyrosine supplementation. Without this biochemical evaluation, our patient would have suffered natural disease progression. Our experience shows one should consider further biochemical evaluation in a child with severe hypotonia with negative molecular sequencing.

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ePO17

GNE gene variants associated with thrombocytopenia with or without GNE myopathy

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Introduction: GNE Myopathy is a rare, degenerative skeletal muscle disease, first presenting with anterior tibialis weakness then progressing proximally, relatively sparing the quadriceps. Symptoms usually develop in early adulthood (between 20-40 years) and include bilateral foot drop and rimmed vacuoles on muscle biopsy. Most patients become wheelchair dependent within a decade after onset. Upper limbs are usually involved around a decade later than the lower limbs. GNE myopathy is caused by biallelic variants in *GNE*, which encodes the rate limiting bifunctional enzyme in sialic acid synthesis, UDP-N-acetyl-glucosamine-2-epimerase/N-acetylmannosamine kinase (GNE), leading to decreased sialic acid production. Sialic acid is a negatively charged sugar, that serves as the terminal sugar of many N- and O-linked glycoproteins; it serves many functions in cell interactions and signaling. Recently, *GNE* variants have been associated with thrombocytopenia, with or without manifestations of myopathy. To investigate this phenomenon, we performed a literature review and analyzed data of patients in our GNE myopathy prospective natural history (NH) study.
Methods: Data were collected through a prospective NH study of individuals with GNE myopathy (NCT1417533). Patients are admitted to the NIH Clinical Center for investigations, including physical function tests, questionnaires, blood analysis (including a complete blood count at each visit), and cardiac and pulmonary function tests. Patient platelet data were compared to normal values. For the literature review, two authors performed a search of all reports including *GNE* and thrombocytopenia. Clinical manifestations as well as variants identified were compared to those of our cohort.
Results: We analyzed a total of 126 platelet counts obtained from 51 GNE myopathy patients (61% female), between 21 and 65 years of age at their baseline to our NH study, with at least one platelet count obtained during subsequent visits. The average platelet count for females was 251 X 10^9 cells/L (range 144–390) and 205 X 10^9 cells/L for males (range 103-300), which are within the normal range for our laboratory (173–369 and 161-347, respectively). However, these values are lower than the expected means of 271 for females ($p < 0.001$) or 254 for males ($p < 0.0001$), based upon our lab's normal ranges. A total of 8 individuals were below the normal range at some point, but above the pathologic thrombocytopenia cutoff (100). None presented signs of thrombocytopenia. The literature review yielded 25 patients with thrombocytopenia (17 without myopathy and 8 with myopathy) and biallelic *GNE* variants. The *GNE* variants in the 25 patients included 7 novel variants not reported in individuals with GNE myopathy and 11 variants previously associated with GNE myopathy. The novel variants were not localized to specific functional GNE domains but were scattered across the entire *GNE* gene and found in Chinese, European, Pakistani, Thai, and Palestinian Arab populations. None of our 51 NH study patients had any of the 18 *GNE* variants associated with thrombocytopenia.
Conclusion: Although there was no evident thrombocytopenia in our NH study cohort, the average platelet count was slightly lower than expected, suggesting a potential role of GNE in platelet survival. Previous studies indicate that sialic acid has a significant role in platelet function. Mice deficient in a sialyltransferase had decreased sialic acid and platelet survival times, leading to thrombocytopenia. Patients with GNE myopathy and thrombocytopenia had increased reticulated platelets, suggesting that pathogenic *GNE* variants may contribute to platelet surface hyposialylation, resulting in increased platelet clearance by the Ashwell-Morell receptor.
Patients with GNE-related thrombocytopenia should be followed for developing signs of GNE myopathy, since most reported individuals were likely too young to develop signs of GNE myopathy. The addition of *GNE* on gene panels for platelet disorder gene panels should also be promoted. GNE myopathy patients should also have their platelets assessed and monitored. To better characterize this phenomenon, we have expanded our NH study to include other (non-muscle) *GNE*-related clinical conditions and younger individuals.

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ePO18

Late-onset congenital erythropoietic porphyria associated with myeloid malignancy

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Background: Congenital erythropoietic porphyria (CEP, OMIM #263700) is a rare disorder of heme biosynthesis characterized biochemically by elevated excretion of type I porphyrin isomers in urine and feces. The disorder is caused by decreased uroporphyrinogen III synthase (UROS) activity, leading to an overproduction of the dead-end metabolites uro- and coproporphyrinogen I, primarily in the bone marrow, and the subsequent deposition of type I porphyrin isomers in tissues.
In most cases, the CEP results from homozygous or compound heterozygous pathogenic variants in the *UROS* gene. More rarely, it presents in males with specific variations of the X-linked transcription factor GATA1, which leads to decreased UROS expression in erythroid precursor cells. The clinical severity of CEP is variable and ranges from hydrops fetalis due to hemolytic anemia *in utero* to a mild adult-onset form with cutaneous manifestations only. Typically, however, the disorder presents soon after birth with cutaneous photosensitivity and hemolytic anemia.
A small number of patients have been reported in the literature with clinical and biochemical features of CEP without pathogenic variants in the *UROS* or *GATA1* genes and with normal UROS activity in erythrocytes. These patients were all males with myeloid malignancy who first presented with symptoms of cutaneous porphyria after the age of 50. The underlying cause of the CEP-like phenotype in these patients is unknown. It has been hypothesized that in those