# Diagnostic Exome Sequencing Identifies Alterations in the Newly Characterized Gene, *COQ4* Expanding the Phenotypic Spectrum

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Recently, biallelic mutations in *COQ4* have been reported in five individuals from four unrelated families with CoQ10 deficiency resulting in a wide phenotypic spectrum of mitochondrial disorders. Here we report an additional non-consanguineous family with two affected siblings with compound heterozygous mutations in *COQ4.* The proband is a 16 year old Caucasian girl with infantile onset seizures, severe intellectual disability, microcephaly, short stature, visual cortical dysfunction, neuromuscular scoliosis with restrictive lung disease, pancytopenia, recurrent infections, and epistaxis. She also has dysmorphic features including a prominent nose, extended nasal columella, small mouth, small hands and feet with significant contractures, and small limbs. Her 18 year old brother is similarly affected. A mitochondrial disorder due to autosomal recessive nuclear gene defect was suspected. Multiple genetic and metabolic tests were uninformative. Family centered diagnostic exome sequencing (DES) on the proband and her healthy parents revealed compound heterozygous c.469C>A (p.Q157K) and c.202G>C (p.D68H) missense alterations in *COQ4*. Both alterations are expected to be likely pathogenic, based on *in silico* and co-segregation data. Co-segregation analysis revealed that the affected brother was also compound heterozygous for both alterations and an unaffected brother was a heterozygous carrier of the p.D68H alteration. Consistent with a mitochondrial disorder, the patient's lactate and pyruvate normalized following CoQ10 supplementation. *COQ4* is a newly characterized gene that encodes a mitochondrial protein involved in the organization of a multienzyme complex for the biosynthesis of Coenzyme Q10 ($CoQ_{10}$). $CoQ_{10}$ is an essential mitochondrial inner membrane-associated lipid that acts as a carrier for electrons from respiratory complexes I and II to complex III. Previously reported patients with *COQ4* associated CoQ10 deficiency have varied clinical presentations ranging from early neonatal death due to acrocyanosis, bradycardia, hypotonia and respiratory insufficiency to hypertrophic cardiomyopathy, arthrogryposis, cerebellar hypoplasia, severe myoclonic epileptic encephalopathy, progressive ataxia, and scoliosis. Here we demonstrate the utility of family centered DES to diagnose a patient with a complex phenotype and expand the phenotypic spectrum of *COQ4* associated CoQ10 deficiency.