

# A Novel Coq8a Mutation in a Case with Juvenile Onset Coq10d4: Case Report and Literature Review

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## Research Article

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# Abstract

Primary coenzyme Q10 deficiency-4 (COQ10D4) is an autosomal recessive disorder characterized by childhood-onset of cerebellar ataxia and exercise intolerance. Molecular pathology responsible for clinical findings is mitochondrial respiratory chain dysfunction. The main clinical manifestation involves early onset exercise intolerance, progressive cerebellar ataxia and movement disorders. Some affected individuals develop seizures and have mild mental impairment, indicating variable severity. *COQ8A* gene mutations are responsible for this disease. Here we present a patient with tremor and cerebellar atrophy in which we detected a new mutation in the *COQ8A* gene. The patient's clinical findings were compatible with juvenile onset COQ10D4. Therefore, we reviewed the clinical, laboratory and genetic findings of 11 juvenile-onset COQ10D4 patients reported to date, as well as the patient's presentation.

## Introduction

Primary coenzyme Q10 deficiency-4 (COQ10D4), also known as autosomal recessive spinocerebellar ataxia-9 (SCAR9), is an autosomal recessive disorder with mitochondrial respiratory chain dysfunction. The main clinical manifestations of COQ10D4 involves exercise intolerance, progressive cerebellar ataxia and movement disorders. Some affected individuals develop seizures and have mild mental impairment, indicating variable severity. It can also be presented with mitochondrial myopathy, hypogonadism and steroid-resistant nephrotic syndrome (Zhang and et al. 2020; Blumkin and et al.2014). The age of onset of the disease varies from infancy to late adulthood. COQ10D4 is caused by homozygous or compound heterozygous mutation in the *COQ8A* gene (*ADCK3* or *CABC1*). The *COQ8A* gene encodes a protein, the homologue of the yeast Coq8 gene, which is involved in the ubiquinone (Coenzyme Q10) biosynthesis pathway. Coenzyme Q10 is essential for proper functioning of the mitochondrial respiratory chain. CoQ10 acts as an electron carrier in the mitochondrial respiratory chain and plays a role as an antioxidant and membrane stabilizer. These two functions constitute the basis for supporting the clinical indication of CoQ10 (Awad and et al.2018; Yubero and et al.2018) .

In this study we report a 15year old- female patient with hand tremor, prominent handwriting impairment who was born to healthy consanguineous parents Brain MRI showed significant cerebellar atrophy. Whole exome sequencing revealed the presence of a novel mutation (p.I341T c.1022T> C) in the *COQ8A* gene, homozygous.

## Case

Our patient (pedigree showed in Figure 1) is a 15-year-old female who was born to healthy consanguineous parents and had one asymptomatic sibling. She was born after an uncomplicated pregnancy and delivery at term. She sat, rolled and crawled at appropriate ages. In her 10 years old she suffered from tremor in her hands. She started to experience awkwardness at 13 years of age and also complained of writing difficulty. Her past medical history is significant for successfully treated childhood febrile convulsion. Her uncle and cousin has similar complaints. She is not dysmorphic, but does have

epicanthus. Her eye movements are normal and she has no visual disturbance or nystagmus. Neurological examination revealed mild shakiness, bilateral dysmetria, intention tremor on nose-finger and heel-shin tests and inability to walk in tandem. Motor and sensory examination and deep tendon reflexes were normal. In serum, cholesterol, lactate and creatine kinase and thyroid antibodies were normal. The remaining blood tests, including liver function and plasma levels of vitamins (B12, A, D, E) were all normal. Electromyography revealed mild myopathy in the arms. No cardiac hypertrophy or fundus abnormalities were noted hearing were normal also. Magnetic Resonance Imaging (MRI) showed prominent cerebellar sulci with a loss of height of the cerebellar hemispheres and atrophy of the vermis (Fig. 2). The Wechsler intelligence test was normal. The consanguineous parents [first-degree cousins] showed no neurologic abnormalities.

SARA score was 9 (gait 2.0, stance 1.0, sitting 0, speech 0, finger chase 2.0, nose-finger test 2.0, fast alternating hand movements 2.0, and heel-shin slide 1.0). The result of 12-step stair test was normal with 10.6 s.

Whole exome sequencing (WES) examination was performed because of cerebellar atrophy, ataxia, positive family history and parental consanguinity. WES revealed the presence of a novel mutation (p.I341T c.1022T>C) in the *COQ8A* (*ADCK3*, NM\_020247.5) gene, homozygous. The clinical significance of this variant was not reported in the ClinVar and HGMD databases. The clinical significance of this variant was not reported in the ClinVar and HGMD databases. The VarSome modeling program predicted this variant as likely pathogenic. In the family study, it was shown that the mother, father and brother of the patient carried the same variant as heterozygous.

Homozygous or compound heterozygous mutations of the *COQ8A* gene cause primary coenzyme Q10 deficiency-4 (OMIM #612016). Primary coenzyme Q10 deficiency-4 (COQ10D4) is an autosomal recessive disorder characterized by childhood-onset cerebellar ataxia and exercise intolerance.

The patient was diagnosed with COQ10D4 because the family study results and the detected variant overlapped with clinical findings. CoQ10 supplementation was immediately started with ubiquinolone of 40 mg three times per day. After 2 weeks of therapy, her tremor notably improved. His SARA total score improved from 9 to 5.

## Discussion

Mutations in *COQ8A* gene can result in primary CoQ10 deficiency type 4 that patients typically present with clinical features including ataxia or a more subtle gait instability. Other neurological abnormalities have been reported include adolescence onset exercise intolerance due to fatigability, seizures, stroke-like episodes, intellectual disability, spasticity, ophthalmic involvement, decreased visual acuity, sensorineural hearing loss, depression (Traschütz and et al. 2020; Rahman and et al.2012).

Juvenile onset was characterized by a variable combination of writing difficulties clumsiness and tremor with ataxia, unsteady gait, myoclonus or dystonia. Clinical severity in reported juvenile onset (11–18

years) was classified mild: slow progression, less severe symptoms and absence of cognitive impairment] to severe (presence of severe epilepsy and/or regression, association with poor cognitive and/or motor outcome such that subjects are reliant upon caretakers for all activities of daily living). The clinical, laboratory and treatment response characteristics of juvenile onset COQ10D4 patients reported to date are summarized in Table 1.

Our patient showed a less severe course and as in literature cerebellar symptoms were mild, writing difficulties were obvious. Although the origin of hand clumsiness may in part be cerebellar, particularly when associated with gait ataxia, the dystonic nature of hand clumsiness and neck tremor has been demonstrated in COQ10D4 patients through electromyographic recordings CoQ10 levels are reduced in skeletal muscle and less frequently in fibroblasts, but their correlation with disease severity is still debated (Galosia and et al.2019).

It has been reported that there was no difference in patterns of clinical presentation between subjects with missense and nonsense mutations or for mutations distributed throughout specific regions of the protein (Blumkin and et al.2014).

Cognitive impairment is often observed in primary coenzyme Q10 deficiency cases with epileptic encephalopathy. Our patient exhibited relative normal cognitive state. The absence of seizures, exercise intolerance or ocular dismotility confirms the heterogeneity of this disorder and the lack of correlation between CoQ10 residual levels and disease severity This case emphasizes the importance of an early molecular diagnosis for suspected inherited ataxias, particularly given the availability of approved treatments for some subtypes similar to our patient.

The additional compelling evidence for the CoQ10 deficiency in our patient comes from clinical responses to CoQ10 supplementation, including the improvement in exercise intolerance and unsteady gait, a response similar to that found in the majority of cases of primary CoQ10 deficiency (Barca and et al.2019; Mignot and et al.2013) Dosage and course of CoQ10 supplement have not been standardized and results have been variable. The dose of oral CoQ10 (ubiquinone, ubiquinol, idebenone and ubidecarenone) ranged from 5 mg/kg/day to 3000 mg/day in treatment of CoQ10 deficiencies. Most COQ10D4 patients experienced symptomatic improvement (Jacobsen and et al.2018; Chang and et al.2018). Early and sustained CoQ10 supplementation appears to be important for a favorable outcome, suggesting that persistent ongoing damage to target tissues and irreversibility of established damages are determinants of therapeutic efficacy (Blumkin and et al.2014; Quinzii and et al.2010).

We administered oral ubidecarenone 100 mg, two times a day for 2 weeks to our patient, with an initial subjective improvement of fatigue followed by a remarkable improvement of tremor with a substantially lower (by five points) total SARA score. Regarding previous reported juvenile onset cases, ubiquinone therapy did not lead to significant improvement of the neurological status in most patients (Mignot and et al.2013; Gerards and et al.2010; Lagier-Tourenne and et al.2018). Severe forms seem to be less responsive to CoQ10 supplementation while patients with ataxia tend to have a better response.

CoQ10 is frequently reduced in muscle of patients with mitochondrial myopathy. It is unfortunate that the patient declined muscle biopsy since the HPLC assay for the CoQ10 level in skeletal muscle is the golden standard for CoQ10 deficiency.

Our aim is to highlight the clinical and genetic heterogeneity of CoQ10 deficiency and also to report a novel mutation of *COQ8A* gene that has not been previously reported in the literature. Gait ataxia, suggesting that cerebellar syndrome may be the common feature of juvenile onset patients. The atypical presentation with prominent writing deterioration, possibly representing the initial manifestation of cerebellar disease, is an example of the extreme phenotypic variability of CoQ10 deficiency.

## Declarations

Informed consent was obtained from the patient and parents.

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Conflicts of interest/Competing interests: Not applicable.

Availability of data and material : Not applicable.

Code availability: Not applicable.

Authors' contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Özge DEDEOĞLU, Ajlan TUKUN and Yahya LALELİ.

The first draft of the manuscript was written by Özge DEDEOĞLU and Ajlan TUKUN. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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## Tables

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

## Figures

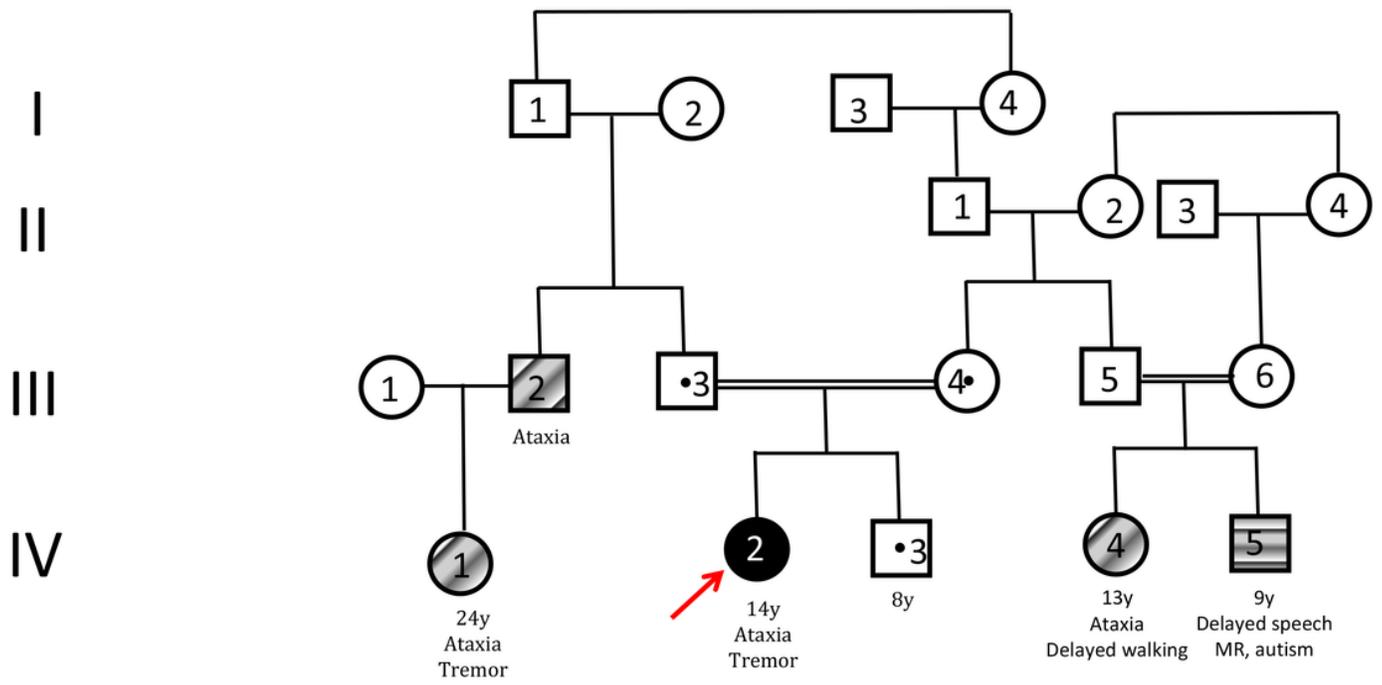


Figure 1. Pedigree of the patient

**Figure 1**

See image above for figure legend

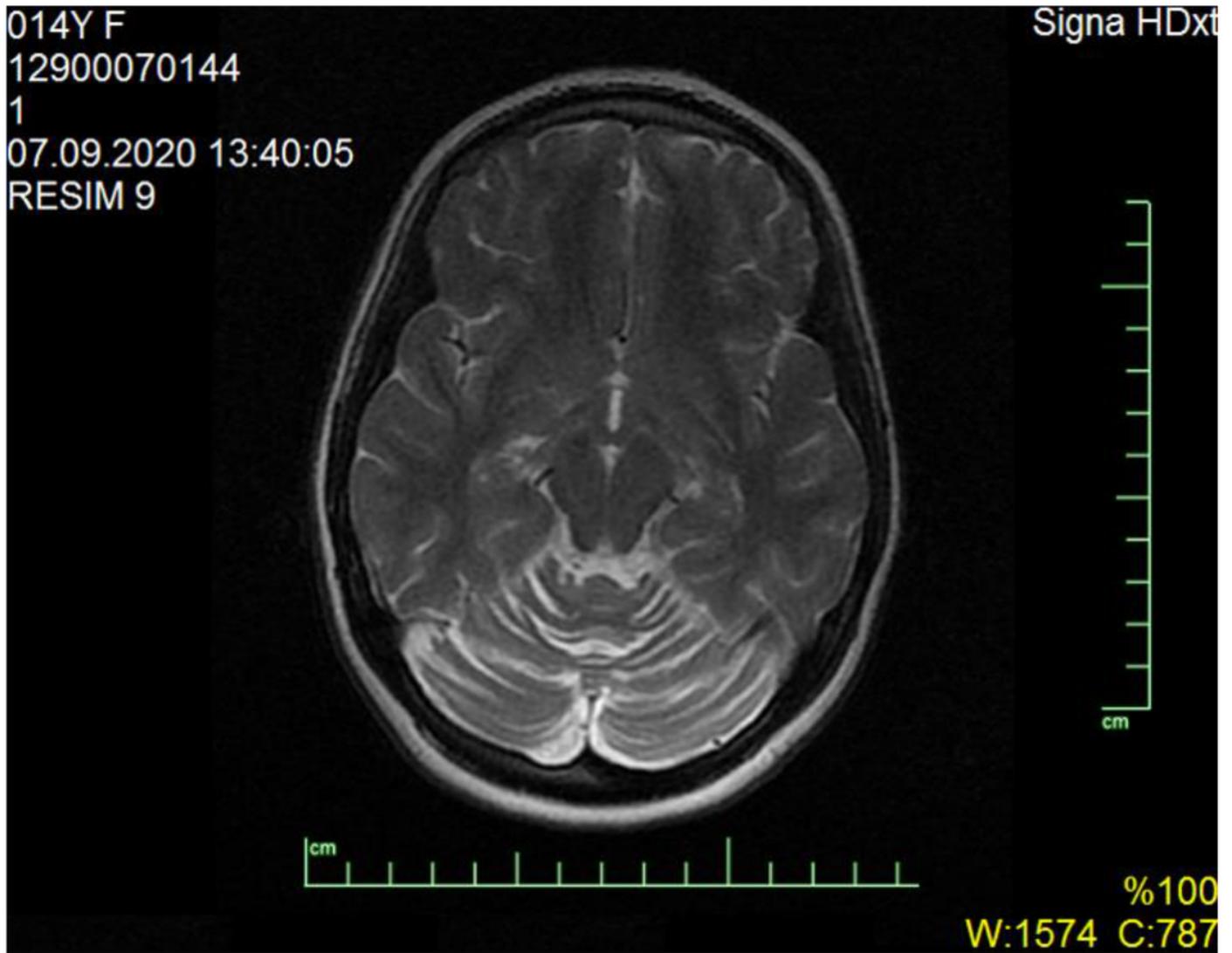


Figure 2. Magnetic Resonance Imaging (MRI) showed prominent cerebellar sulci with a loss of height of the cerebellar hemispheres and atrophy of the vermis

## Figure 2

See image above for figure legend

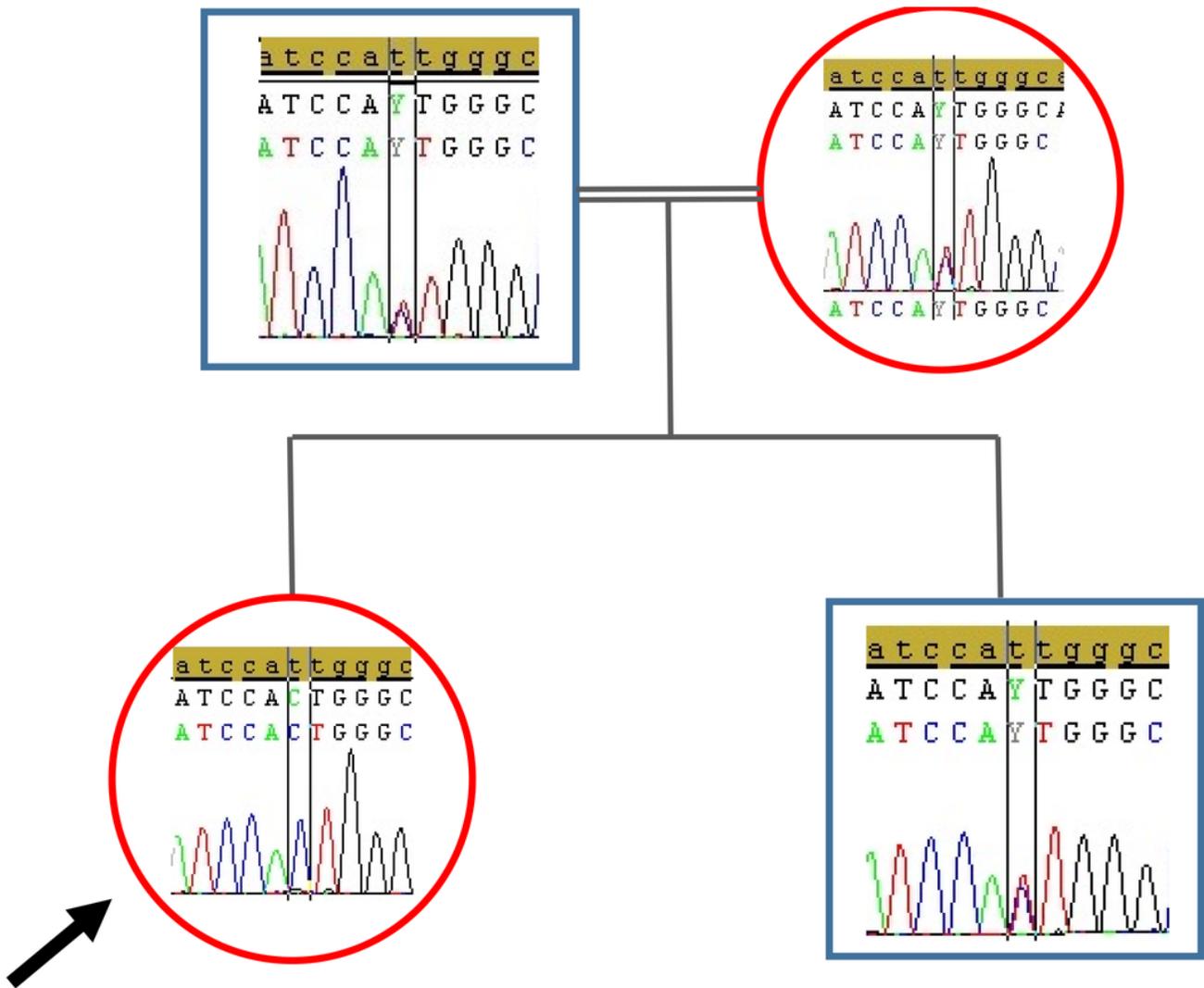


Figure 3. Sanger sequence images of father (A), mother (B), patient (C), and brother (D) for the c.1022T>C mutation in the COQ8A gene.

### Figure 3

See image above for figure legend

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table11.pdf](#)