# What is the impact of an Abnormal pathogenic variant in COQ8A/ CYP17A1 in pediatric patient - A case report

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## ABSTRACT

**Background:** Primary coenzyme Q10 deficiency-4 (CoQ10D4) and isolated 17,20-lyase deficiency (ILD) are both distinct and rare congenital mutations. Mutations in the CoQ8A gene are rare and cause CoQ10D4. Patients with pathogenic mutations in the CoQ8A gene exhibit symptoms such as ataxic gait, dystonia, seizures, exercise intolerance, and cognitive disabilities.

**Case presentation:** The presence of these two mutations in a patient is extremely rare. In this present case report, a 6-year-old identical twin female with CoQ10D4 and ILD began presenting with microcephaly with developmental delay at 4 years of age. She also had regression of milestones (loss of social interaction, grasp, visual interaction, and speech-babbling) without febrile seizures.

**Conclusion:** This case emphasizes the need for further research to elucidate the underlying mechanisms and potential targeted therapies for these rare genetic disorders, emphasizing the importance of a multidisciplinary approach in providing comprehensive care for affected individuals.

**Keywords:** MRI, CSF, CoQ8A, CYP17A1, isolated 17,20-lyase deficiency, abnormal pathogenic variant, pediatrics, ataxia, developmental delay.

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## Background

Primary coenzyme Q10 (CoQ10) deficiency is a group of autosomal recessive cerebellar ataxias with defective mitochondrial respiration caused by multiple genetic mutations [1]. The overall prevalence of ataxia is 26 cases per 100,000 children [2]. The manifestations of primary CoQ10 deficiency vary. Traditionally, clinical presentations have been classified into five distinct phenotypes: encephalomyopathy, cerebellar ataxia, severe infantile multisystem disease, steroid-resistant nephrotic syndrome, and isolated myopathy [3]. The age of onset ranges from infancy to late adulthood [1].

Deficiency in cytochrome p450c17 (MIM 202110) is an extremely rare form of congenital adrenal hyperplasia [4]. The human CYP17A1 gene is localized to chromosome 10q24.3. This gene is expressed in the adrenals and gonads, with minor amounts in the brain, placenta, and heart [5]. The mutations of CYP17A1 may lead to a complete combined 17alpha-hydroxylase/17,20-lyase deficiency or isolated 17,20-lyase deficiency (ILD) [4]. However, 17,20-lyase deficiency is less frequently described in the literature than 17α-hydroxylase deficiency [6]. It is characterized by variable degrees of hypertension, hypokalemia, female sexual infantilism, or male pseudohermaphroditism [4]. Since the first mutation was identified in a patient with 17OHD in 1988, more than 100 different mutations have been reported. Those mutations result in either combined or isolated 17α-hydroxylase/17,20-lyase enzyme deficiencies [7].

Hyperinsulinism is a condition of unregulated and inappropriate insulin secretion from pancreatic beta cells, which results in hypoglycemia and is the most common cause of persistent hypoglycemia in neonates. It manifests as persistent hypoglycemia in neonates and children and has a prevalence of roughly 1 in 40,000 live births [8]. Infants with hyperinsulinism are at increased risk of developing irreversible cerebral injury and long-term neurological deficits, including developmental delay and cerebral palsy [9]. Hyperinsulinism not only causes hypoglycemia but also suppresses lipolysis and reduces ketones, which act as alternative fuels to maintain brain neuronal function; therefore, hypoglycemia caused by congenital hyperinsulinism is detrimental to the brain, with adverse neurodevelopment in a third to half of children with congenital hyperinsulinism [10].

There are no published case reports about the presence of a mutation in [CoQ10] coinciding with a mutation in [CYP17A1] along with hyperinsulinism. Our patient expressed both mutations along with hyperinsulinism, making this a special and historical case.

## Case presentation

The patient (II:2, pedigree shown in Figure 1) is a 6-year-old identical twin female who was born to healthy consanguineous parents with no discovered family history of any nervous system disease. She was born after an uneventful pregnancy with an antenatal history of small for gestational age without asphyxia. Upon delivery, she had ambiguous genitalia and stayed in the neonatal intensive care unit for 2 months due to transient hyperinsulinism, which required high exogenous sugar and was discharged on Polycose.

## History and examination

At the age of 4 years, she had an abnormally small head circumference of 45 cm (microcephaly) for her age with developmental delay (inability to sit). She had regression of milestones (loss of social interaction, grasp, visual interaction, and speech-babbling) without a history of febrile seizures. In addition, she was unable to fix and follow the light, could not turn her head to a nearby voice, and had non-intelligible speech, gross hypotonia, mild scoliosis, pectus excavatum, and no visceromegaly without neurocutaneous stigmata.

## Imaging

The axial brain magnetic resonance imaging (MRI) showed prominent extra-axial cerebral spinal fluid (CSF) spaces and cerebellar folia (Figure 2). The sagittal brain MRI showed more interval prominence of the cerebellar folia associated with dilation of the fourth ventricle and the adjacent CSF spaces/bilateral cerebellopontine as well as cerebellomedullary cisterns denoting diffuse cerebellar volume loss/atrophy (Figure 3). Follow-up ultrasound pelvic sonography showed bilateral testicular-like structures seen within the inguinal canal of stationary appearance since a previous sonogram was done 6 months after birth. The pelvic examination failed to demonstrate female sex organs.

## Whole exome sequencing

Whole exome sequencing was performed on the patient and showed two abnormal genes. 1) Pathogenic variants in CoQ8A caused autosomal recessive primary coenzyme Q10 deficiency-4 (CoQ10D4), characterized by childhood-onset cerebellar ataxia and exercise intolerance. 2) Pathogenic variants in CYP17A1 caused autosomal recessive ILD, which is a rare disorder of sex development due to reduced 17,20-lyase activity that affects individuals with a 46XY karyotype and is characterized by ambiguous genitalia, including a micropenis, perineal hypospadias, bifid scrotum, cryptorchidism, and blind vaginal pouch.

## Discussion and conclusion

Mutations in the CoQ8A gene cause CoQ10D4, also known as spinocerebellar ataxia-9 or autosomal recessive cerebellar ataxia type 2. Patients with pathogenic mutations of the CoQ8A gene manifest symptoms such as ataxic gait, dystonia, seizure, exercise intolerance, and cognitive disabilities. The age of onset and severity of clinical symptoms vary. To date, more than 64 patients with 46 CoQ8A mutations have been reported. Most reported manifestations started from infancy and early childhood. In fewer cases, symptoms initiated in older ages. CoQ8A mutations, first described by Auré et al. [11] and Mollet et al. [12,13], present with a mild disease course [13,14]. Multiple genes contributing to the CoQ biosynthetic proteins, including PDSS1, PDSS2, COQ2, COQ4, COQ5, COQ6, COQ7, COQ8A, COQ8B, and COQ9, have pathogenic variants causing primary CoQ deficiency.

The typical presentations are progressive gait ataxia and movement disorders (dystonia, tremor, chorea, and jerk myoclonus) [13–15], similar to our patient. Other studies have described other neurological manifestations such as adolescence-onset exercise intolerance due to fatigability, seizures, stroke-like episodes, intellectual disability, spasticity, ophthalmic involvement, decreased visual acuity, sensorineural hearing loss, depression, and pes cavus. Our patient presented with microcephaly with developmental delay at 4 years of age. She also had regression of milestones (loss of social interaction, grasp, visual interaction, and speech-babbling) without febrile seizures. Other findings were an inability to fix and follow the light, not turning the head to the nearest voice, non-intelligible speech, gross hypotonia, mild scoliosis, pectus excavatum, no visceromegaly, and no neurocutaneous stigmata.

Based on our review of the literature, no CoQ8A mutation cases with renal impairment have been reported. Our patient had neither myopathic symptoms nor renal impairment and had normal RFT results. Mitochondrial disorders have been shown to be the cause of psychiatric symptoms in the literature. Depression is among the most frequently reported symptoms of *CoQ8A* mutation. A study done by Traschütz et al. reported psychiatric features such as anxiety, psychotic symptoms, depression, and aggression in about 25% of patients with CoQ8A mutation. Another study by Mancuso et al. showed conditions such as agoraphobia, panic disorder, major depressive disorder, and social anxiety disorder in about 20% to 25% of patients with mitochondrial disorders.

Cerebellar atrophy is the most common finding on radiological imaging in patients with the CoQ8A mutation. It can be localized, diffuse, or pan-cerebellar. Other findings consist of cerebral and brainstem atrophy, stroke-like signal changes, infra-tentorial T2 hyperintensities,

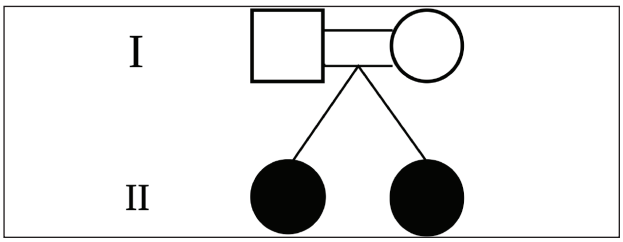


***Figure 1.*** *Pedigree chat in this family. The father and mother are consanguineous. The proband (identical twin) have the pathological variant COQ8A/CUP17A1 corresponding disease to a normal mother and father*

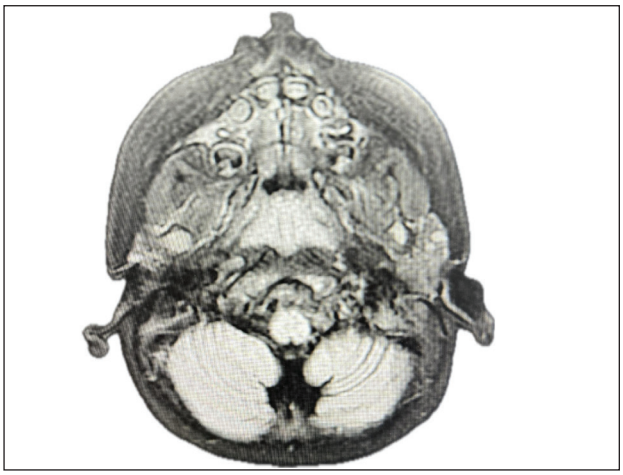

***Figure 2.*** *MRI brain T2 FLAIR, axial view showing prominent extra-axial CSF spaces and cerebellar folia.*

thin corpus callosum, enlarged ventricles, basal ganglia involvement, and thoraco-lumbar scoliosis. In this case, we found prominent extra-axial CSF spaces and cerebellar folia (Figure 2). A follow-up brain MRI showed more interval prominence of the cerebellar folia associated with dilation of the fourth ventricle and the adjacent CSF spaces/bilateral cerebellopontine as well as cerebellomedullary cisterns denoting diffuse cerebellar volume loss/atrophy (Figure 3).

Another rare autosomal recessive genetic disorder our patient presented with is ILD. ILD is an endocrine disorder that results in sex hormone deficiencies and clinically presents with female genitalia at birth irrespective of the genetic sex. It presents later, at puberty, with primary amenorrhea and lack of or disrupted development of secondary sexual characteristics in both 46,XY, and 46,XX genotypes. This could lead to patients looking somewhat like children at puberty if not treated. Since 17α-hydroxylase is not affected, neither cortisol deficiency nor mineralocorticoid excess have been reported in ILD patients. Therefore, unlike in combined CYP17A1 deficiency, hypertension, and congenital adrenal hyperplasia are not present. The clinical presentation of 46,XY individuals is male pseudohermaphroditism with feminized, ambiguous, or moderately underdeveloped external genitalia because of the disturbed synthesis of androgens in the testes.

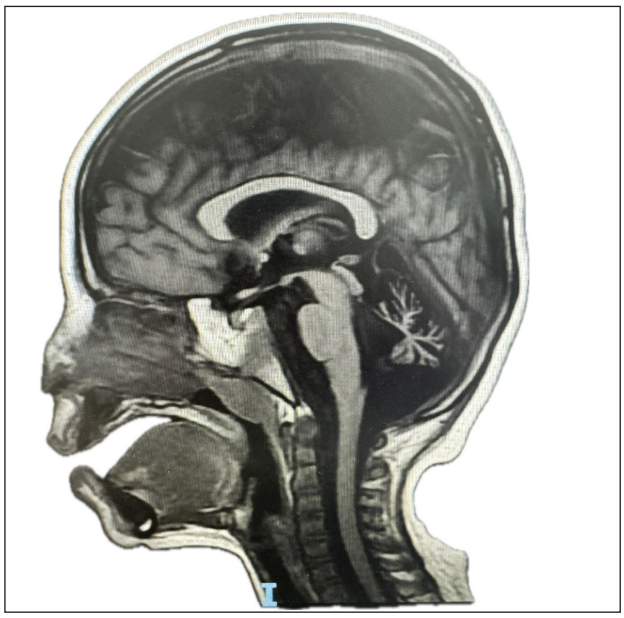

***Figure 3.*** *MRI brain T2 FLAIR, sagittal view showing diffuse cerebellar volume loss astophy*

Because of the low levels of androgen, the lack of suppression of estrogen synthesis can lead to low virilization and gynecomastia up to Tanner stage V. In 46,XX cases, amenorrhea or, in cases of only partial deficiency, oligomenorrhea, and enlarged cystic ovaries are seen. Other manifestations, such as hypergonadotropic hypogonadism; delayed, impaired, or fully absent adrenarche; puberty with an associated reduction in or complete lack of development of secondary sexual characteristics; impaired fertility or complete sterility; tall stature; eunuchoid skeletal proportions; delayed or absent bone maturation; and osteoporosis have been reported. Males and females are usually treated with hormone replacement therapy (i.e., with androgens and estrogens, respectively), which can lead to normal sex development and treat most symptoms. In a 46,XY case, patients who present phenotypically as female and/or identify with the female gender should be treated with estrogen instead. Other surgical corrections can be made depending on the case. Our patient presented with ambiguous genitalia at birth with no other abnormal features. Imaging showed testicular-like masses at 4 years of age, and a pelvic exam failed to identify female reproductive organs. Because of the unusual presentation and current age of this patient (6 years old), a management decision has not been reached.

## Identifying novelty

This case shows an extremely rare presentation of a patient presenting with primary CoQ10 deficiency causing childhood-onset cerebellar ataxia and ILD due to CYP17A mutation. This patient presented with ambiguous genitalia at birth and cerebellar ataxia at 4 years of age. According to the best of our knowledge, no such case has ever been reported in the literature.

## Limitations

While our study highlights a unique case of twins presenting with CoQ8A/CYP17A mutations, we only had data for one twin and not the other. Several laboratory test results are missing. No treatment such as CoQ10 supplementation has been used for this patient, although compelling evidence for clinical responses to CoQ10 supplementation, such as improvement in exercise intolerance and unsteady gait, has been reported. Very little attention was paid to ILD since we were focused on cerebellar ataxia.

## Implications

This report shows how unique it is for twins to carry rare autosomal recessive alleles. Having both twins present with ambiguous genitalia and later develop ataxia aids in the diagnosis of a genetic disorder. This report also highlights the potential hazards of consanguinity, which have been related to most cases reported in the literature. CoQ10D4 and ILD are both rare and extremely difficult disorders to treat, and avoiding consanguinity and receiving genetic counseling is advisable to prevent them.

## Directions for future research

While there are plenty of reported cases of hereditary ataxia, multiple mutations have been linked to it. These mutations result from deletion, insertion, point mutation, and so on. Different mutations have different clinical presentations, onsets, diagnostics, and treatments. Using supplements for deficiencies as a form of treatment has shown variable results in patients' quality of life. Further reports and studies are needed to identify all mutations, address their different clinical presentations, form clear pathophysiology, and come up with better treatment options.

### What is new?

Extremely rare presentation of a patient presenting with primary CoQ10 deficiency causing childhood-onset cerebellar ataxia due to CYP17A mutation.

## List of Abbreviations

| | |
|---|---|
| CoQ8A | coenzyme Q8A |
| CSF | cerebral spinal fluid |
| CYP17A1 | cytochrome P450 family 17 subfamily A member 1 |
| ILD | isolated 17,20-lyase deficiency |
| MRI | magnetic resonance imaging |

## Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

## Funding

None.

## Consent for publication

Due permission was obtained from the patient/parents/guardians of the patient to publish the case and the accompanying images.

## Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

## Author details

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## Summary of the case

| | | |
|---|---|---|
| 1 | **Patient (gender, age)** | 6 years, female, Twins |
| 2 | **Final diagnosis** | Pathogenic variant in COQ8A/CYP17A1 |
| 3 | **Symptoms** | Ataxia, developmental delay |
| 4 | **Medications** | Symptomatic treatment given |
| 5 | **Clinical procedure** | None |
| 6 | **Specialty** | Pediatric neurology |