



Epilepsia Partialis Continua a Clinical Feature of a Missense Variant in the ADCK3 Gene and Poor Response to Therapy

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Abstract

Introduction Coenzyme Q10 deficiency can be due to mutations in Coenzyme Q10-biosynthesis genes (primary) or genes unrelated to biosynthesis (secondary). Primary Coenzyme Q10 deficiency-4 (COQ10D4), also known as autosomal recessive spinocerebellar ataxia-9 (SCAR9), is an autosomal recessive disorder caused by mutations in the *ADCK3* gene. This disorder is characterized by several clinical manifestations such as severe infantile multisystemic illness, encephalomyopathy, isolated myopathy, cerebellar ataxia, or nephrotic syndrome.

Methods In this study, whole-exome sequencing was performed in order to identify disease-causing variants in an affected girl with developmental regression and Epilepsia Partialis Continua (EPC). Next, Sanger sequencing method was used to confirm the identified variant in the patient and segregation analysis in her parents.

Case Presentation The proband is an affected 11-year-old girl with persistent seizures, EPC, and developmental regression including motor, cognition, and speech. Seizures were not controlled with various anticonvulsant drugs despite adequate dosing. Progressive cerebellar atrophy, stroke-like cortical involvement, multifocal hyperintense bright objects, and restriction in diffusion-weighted imaging (DWI) were seen in the brain magnetic resonance imaging (MRI).

Conclusions A novel homozygous missense variant [NM_020247.5: c.814G>T; (p.Gly272Cys)] was identified within the *ADCK3* gene, which is the first mutation in this gene in the Iranian population. Bioinformatics analysis showed this variant is damaging. Based on our patient, clinicians should consider genetic testing earlier to instant diagnosis and satisfactory treatment based on exact etiology to prevent further neurologic sequelae.

Keywords Epilepsia Partialis Continua (EPC) · *ADCK3* · *COQ8A* · Coenzyme Q10 deficiency · Autosomal recessive spinocerebellar ataxia-9

Introduction

Epilepsia Partialis Continua (EPC) is a unique variant of prolonged focal motor status epilepticus with awareness, which is characterized by frequent myoclonic or clonic jerks usually

arrhythmic. At a short distance, EPC is followed by a gradually progressive neurological disorder (Mameniškienė and Wolf 2017). The etiological agents, which cause EPC, are divided into two categories: focal and systemic (Khan et al. 2020). The Focal etiologic causes of EPC include Rasmussen encephalitis, tick-borne encephalitis (TBE), AIDS, tuberculoma, Creutzfeldt–Jakob disease (CJD), Cat-scratch disease (CSD),

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Herpes simplex encephalitis (HSE), and Japanese encephalitis (JE) (Valentin et al. 2015). In addition, stroke, focal cortical dysplasia, and neoplastic disease can cause EPC (Ribeiro et al. 2015). On the other hand, systemic factors are mitochondrial diseases, metabolic disorders, idiopathic diseases, and autoimmunity (Atmaca et al. 2018).

Mitochondrial encephalomyopathies include a group of complaints which have failure oxidative metabolism in the central nervous system and skeletal muscles (Li et al. 2020). Berbel-Garcia et al. (2004) declared that treatment of mitochondrial diseases with Coenzyme Q10 (CoQ10) is effective (Berbel-Garcia et al. 2004). CoQ10 (also known as Ubiquinone) is a lipid-soluble component of the mitochondrial inner membrane, which plays an essential role in the mitochondrial respiratory chain (electron transport chain: ETC) function. By this role, CoQ10 acts as electrons carrier from complexes I (NDSH: Ubiquinone reductase) and II (succinate: ubiquinone reductase) to complex III (ubiquinol cytochrome c oxidase). Thus, it participates in ATP production (Mancuso et al. 2010). The reduced form of CoQ10 (Ubiquinol) also has antioxidant activity, protecting membrane lipids, proteins, and mitochondrial DNA (mtDNA) against oxidative stress (Dallner and Sindelar 2000).

CoQ10 deficiency includes several clinical manifestations such as severe infantile multisystemic illness, encephalomyopathy, isolated myopathy, cerebellar ataxia, or nephrotic syndrome (Lamperti et al. 2003). This deficiency can be caused by mutations in CoQ10-biosynthesis genes (primary) including *PDSS1*, *PDSS2*, *ADCK3*, *ADCK4*, *COQ2*, *COQ4*, *COQ6*, and *COQ9* genes, or genes unrelated to biosynthesis (secondary) (Potgieter et al. 2013). *ADCK3* (also known as *COQ8A*; OMIM: 606,980) is one of the numerous genes related to CoQ10 deficiency, which presents with epilepsy, progressive cerebellar ataxia, migraine, and psychiatric disorders (Hikmat et al. 2016). The secondary type occurs more frequently in patients with mtDNA depletion syndrome and/or mutations in *APTX*, *ETFDH*, *BRAF*, *NPC*, or *ACADVL* genes (Fragaki et al. 2016). In this study, we reported a case suffering from EPC with a mutation in the CoQ10-biosynthesis gene (*ADCK3*).

Materials and Methods

Ethical Standard Statement and Written Consent

Proband was selected during the ataxia project based on clinically interesting findings such as EPC. Written consent was obtained from parents as legal guardians of the proband. This study was approved by the local ethics committee of the National Institute for Medical Research Development (NIMAD) of Iran (Ethics ID: IR.NIMAD.REC.1397.508). Therefore, this research has been done in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Whole Exome Sequencing and Bioinformatics Analysis

At the first step, 10 ml of whole blood was collected from the patients and their parents, and extracting gDNA was performed based on the salting-out protocol (Gaaib et al. 2011). The concentration and quality of the extracted DNA were evaluated using agarose gel electrophoresis and spectrophotometry absorbance reading at 260 nm. Then, Whole Exome Sequencing was performed by the Agilent SureSelect Human All Exon V7 Kit from Illumina and using the NovaSeq 6000 platform with an average depth of about 100x. Based on similar studies (Mohammadi et al. 2021a, b, c; Tavasoli et al. 2022), an in-house bioinformatics pipeline was performed by the following bioinformatics tools:

- (A) FASTP tool was utilized to evaluate quality control (QC) of reading length and depth (GC content ~ 50%, Phred score > 20) (Chen et al. 2018).
- (B) BWA aligning tool was used to map the raw reads to the (GRCh38/hg38) human reference genome (Jo and Koh 2015).
- (C) SAM (Sequence Alignment/Map) file, obtained from the alignment step, was converted to BAM (Binary Alignment Map) file using Samtools software (Li et al. 2009).
- (D) SNVs and insertion/deletion (Indel) variant calling were performed by GATK Haplotypecaller, FREEBAYES, and DeepVariant callers. The VCF (variant call format) file was generated (Ren et al. 2018; Supernat et al. 2018).
- (E) The VCF file was annotated by the Ensemble VEP tool (Thormann et al. 2019). The annotated VCF contained 53,991 variants.

Segregation analysis and variant confirmation

Reverse and forward primers were designed by PrimerQuest tool and UCSC genome browser blat tools. Then, qualities and features of primers were checked by OligoAnalyzer Tool. At the next step, Sanger sequencing Applied Biosystems 3130 Genetic Analyzer was used to confirm the identified variant in the proband and to study segregation in the family. Finally, CodonCode aligner tool was utilized for the analysis of Sanger sequencing results.

Results

Case Presentation

An affected eleven-year-old girl, a known case of poorly controlled epilepsy and developmental regression, was admitted due to increasing seizure frequency and severity. As the

first child of the consanguineous parents (first cousin), she was born via normal vaginal delivery (NVD) at 38 weeks of gestational age without perinatal insult. Birth weight was 3.180 g and birth head circumference (HC) was 33 cm. Family history was unremarkable for epilepsy and developmental regression.

The patient's developmental milestones were normal until 24 months of age that her first seizure with fever occurred. The patient's seizures repeated as upward gaze and left focal clonic seizures. Phenobarbital was administered but seizures continued at least once per month. Gradually, developmental regression appeared first in motor aspects, including gait instability and ataxia, and later cognition and speech regression added. Also, her seizures were uncontrolled. Eventually, phenobarbital was not able to seizures controlling and she was admitted to another hospital for this problem at the age of 3 years old. Focal seizures and developmental regression were continued. At the age of 3 years, phenobarbital was stopped and sodium valproate and topiramate were started. According to uncontrolled seizures, topiramate was replaced with clobazam in the drug regimen. Focal seizures and developmental regression were continued.

We did not find any abnormality in the hematological and biochemical laboratory findings. Blood ammonia, blood lactate, ABG (PH) and bicarbonate (HCO_3) concentrations were 58 micromol/L (normal range: 16–60 micromol/L),

17 mg/dL (normal range: 2–20 mg/dL), 7.4 (normal range: 7/35–7/45), and 21 mmol/L (normal range: 22–26 mmol/L) respectively. The concentration of serum amino acids was in normal ranges. Tandem mass spectrometry (MS/MS) and urine organic acids were normal. Covid-19 PCR was negative. A central hypothyroidism ($\text{TSH}=0.06$ mIU/L [reference range 0.5–6.5mIU/L]) was reported in endocrinologist consult and Levothyroxine (50 mcg /day) was initiated. CSF analysis was normal, including glucose and protein were 65 mg/dL and 38 mg/dL, respectively. There were no white blood cell, red blood cell and bacteria in CSF. Echocardiography was performed at the age of 7 years and showed a mild to moderate mitral regurgitation and mitral valve prolapse. Ophthalmic examination and visual evoked potential were normal. Electroencephalography (EEG) revealed frequent lateralized epileptiform discharges and delta activities.

Brain MRI was performed at 2 and 3 years of age, revealing mild cerebellar atrophy and stroke-like signal changes. Also, multifocal cortical involvement and cerebellar atrophy (Fig. 1A, B) were observed at 5 and 7 years of age. At the age of 11 years, brain MRI (T1, T2, FLAIR, DWI, and ADC) was performed (Fig. 1C–H). The results showed progressive cerebellar atrophy, stroke-like cortical involvement, multifocal hyperintense bright objects, and restriction in DWI and ADC sequences.

At the beginning of hospitalization, the patient had persistent seizures which were not controlled with various

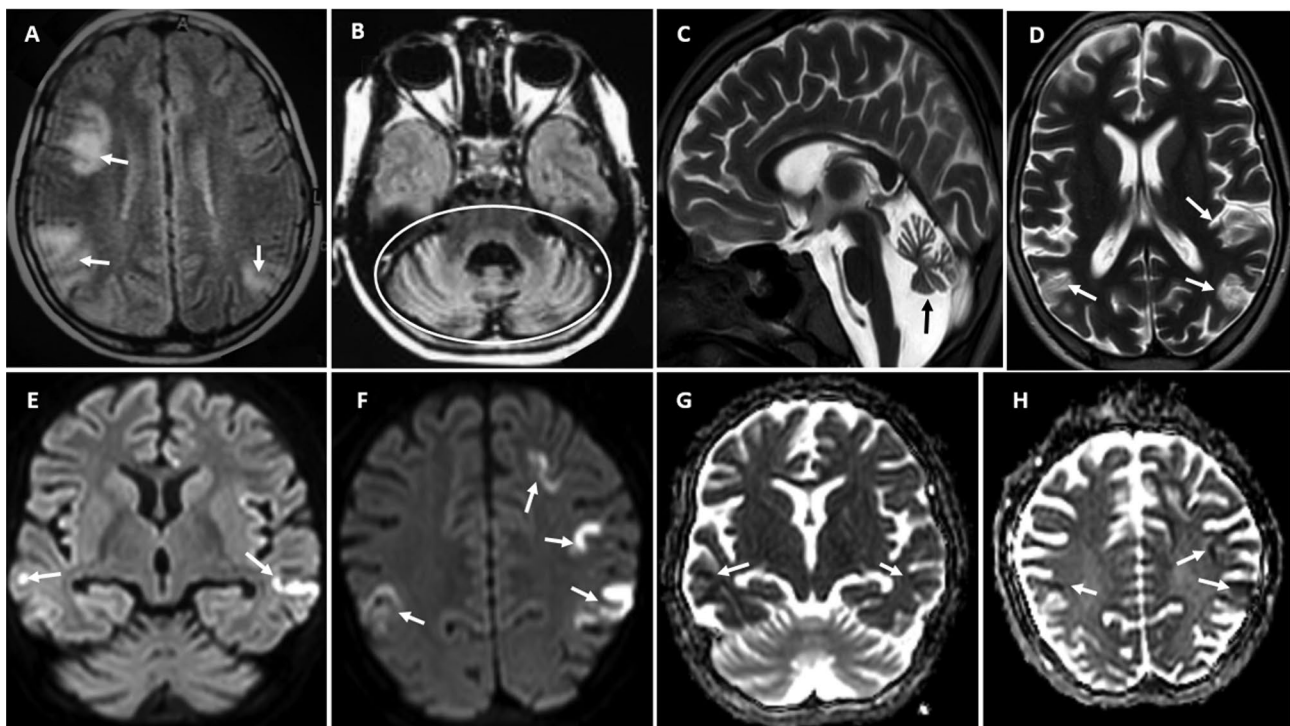


Fig. 1 Brain MRI. **A** and **B** Multifocal cortical involvement, a mild cerebellar atrophy at the age of 7 years and **C**, **D**, **E**, **F**, **G**, and **H** a progressive cerebellar atrophy, multifocal hyperintense bright objects,

stroke like cortical involvement (restriction in DWI/ADC), and intact basal ganglia at the age of 11 years

anticonvulsant drugs despite adequate dosing. Due to mitochondrialopathy, use of sodium valproate was stopped. The patient was intubated and treated with high doses of medications such as Midazolam and Fentanyl. However, EPC seizures were still seen both at the patient's bedside and in repeated EEGs. The patient was even treated with high-dose COQ10, after the preparation of WES result, but the seizures were not controlled.

Exome Results

Filtering the annotated VCF was performed by the R programming software to detect the most relevant variants in the proband by the following steps:

- (A) Removing variants with minor allele frequency (*MAF*) > 1%, based on GnomAD, ExAC, 1000Genome project, and Iranome. Remaining variants: 11,753.
- (B) Filtering synonymous, intronic, and noncoding variants based on consequence. Remaining variants: 1,109.
- (C) Removing variants which are not related to human phenotype ontology (HPO) terms. Remaining variants: 71.

According to the clinical and para-clinical findings, the genes related to the following HPO (The Human Phenotype Ontology) terms were considered in the analysis: Epilepsy HP:0,001,250, Developmental regression HP:0,002,376, Focal clonic seizure HP:0,002,266, Unsteady gait HP:0,002,317, Ataxia HP:0,001,251, Cognitive impairment HP:0,100,543, Cerebellar atrophy HP:0,001,272.

At the next step, 71 remaining variants were classified based on the American College of Medical Genetics and Genomics

(ACMG) guideline (Nykamp et al. 2017). Finally, we checked the depth of reads of final variants using IGV (Integrative Genomics Viewer) software (Thorvaldsdóttir et al. 2013).

A novel homozygous missense variant in the *ADCK3* gene [NM_020247.5: c.814G>T; (p.Gly272Cys)] was identified. ACMG classified this variant as likely pathogenic (class 2) (Table 1). Pathogenic variants in the *ADCK3* gene are associated with primary Coenzyme Q10 deficiency-4 (COQ10D4), also known as autosomal recessive spinocerebellar ataxia-9 (SCAR9) (Lagier-Tourenne et al. 2008). We confirmed the homozygous state for this variant in the proband, as well as the heterozygote state in the parents by Sanger sequencing (Fig. 2). As a result, the c.814G>T variant in the *ADCK3* gene segregated with the primary Coenzyme Q10 deficiency-4 in this family, and can be identified as the cause of disease in the proband. Therefore, based on the results of WES, the patient developed a Coenzyme Q deficiency, and she was treated with CoQ10; however, there were frequent increased seizures in the patient.

Discussion

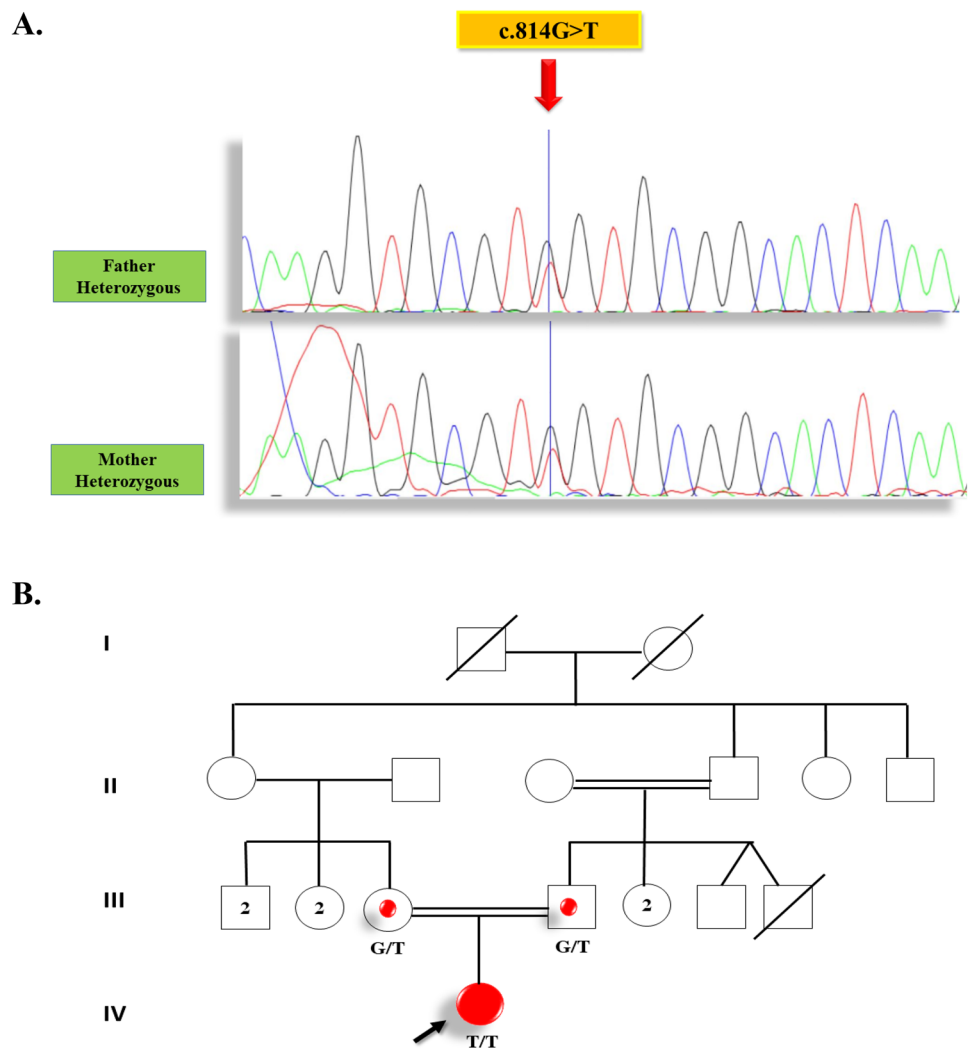
Homozygous or compound heterozygous mutations in the *ADCK3* gene cause COQ10D4, also known as SCAR9 (Lagier-Tourenne et al. 2008). In this study, WES identified a novel homozygous missense variant [NM_020247.5: c.814G>T; (p.Gly272Cys)] in an 11-year-old Iranian girl with EPC. The identified variant is in the Exon 6, which affects the atypical kinase chain, creates an amino acid change from Gly to Cys at position 272 (Fig. 3A). According to our knowledge, this is the first report from Iran.

Table 1 Features of the identified variant based on pathogenic prediction tools and online databases

Gene	Variant coordinates	In silico parameters	Allele frequencies*	Type and classification**	Zygosity	Novelty	ACMG rules	Cadd Phred
<i>ADCK3</i> (<i>COQ8A</i>)	Chr1(hg38):g 226,982,110 NM_020247.5 c.814G>T p.(Gly272Cys) Exon 6/15	MutationTaster: Disease causing FATHMM-MKL: Damaging EIGEN: Patho- genic SIFT: Damaging PolyPhen-2: Prob- ably Damaging PROVEAN: NA I-Mutant2.0: Decrease Stabil- ity ConSurf: Con- served	gnomAD: NA ExAC: NA Iranome: NA	Missense Likely pathogenic (Class 2)	Homozygous	Novel	PM1 PM2 PM5 PP2 PP3 PP4 PP5	31

*Genome Aggregation Database (gnomAD) Genome version:3.0, Exome Aggregation Consortium (ExAC) version:1.0 and Iranome; **Variant classification is based on ACMG recommendations: Class 1: Pathogenic, Class 2: Likely pathogenic, Class 3: Variant of uncertain significance (VUS), Class 4: Likely benign, Class 5: Benign

Fig. 2 **A** Sanger sequencing chromatographs shows heterozygous missense variant in the parents. **B** Family pedigree of the 11-year-old affected girl offspring of first cousin parents. The affected proband is shown by arrow. The genotype of the parents for the c.814G>T variant is depicted on the pedigree

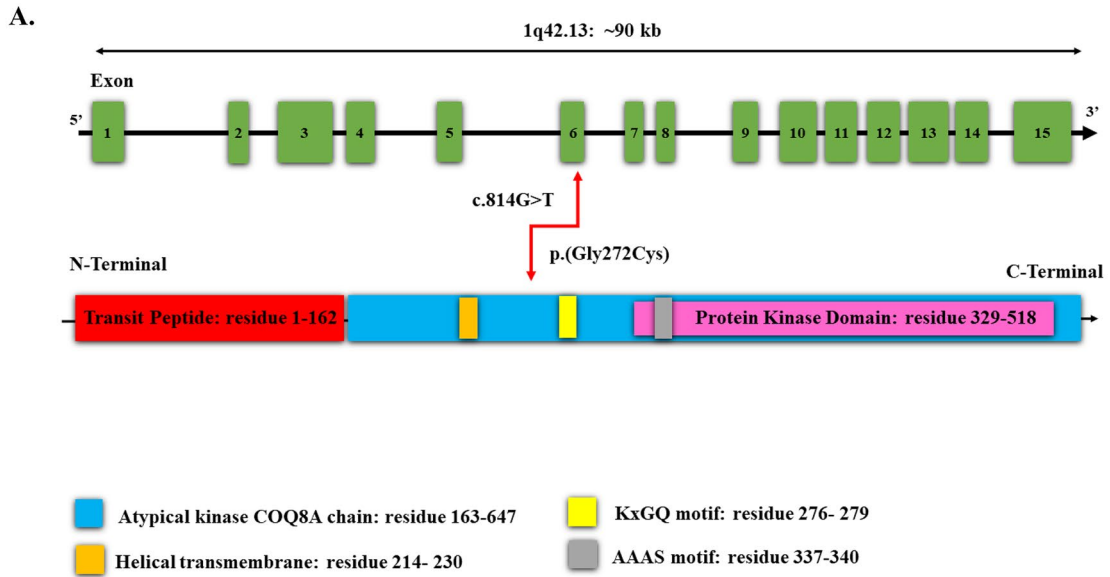


Alternative variants [NM_020247.5: c.815G>A; p.(Gly272Asp)] and [NM_020247.5: c.815G>T; p.(Gly272Val)] in the *ADCK3* gene were reported by Mollet et al. (2008), and Chang et al. (2018) (Mollet et al. 2008; Chang et al. 2018). Mollet et al. (2008) studied a progressive neurological disorder with cerebellar atrophy and seizures in four ubiquinone-deficient patients in three distinct families. In agreement with our study, all the cases showed ubiquinone deficiency in the enzymological studies (Mollet et al. 2008).

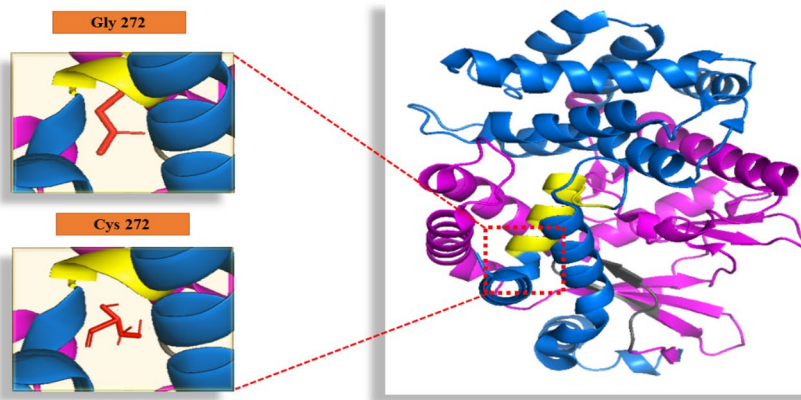
Chang et al. (2018) describe two new cases of neurological syndromes due to *ADCK3* mutations obtaining outstanding benefits from CoQ10. Despite the remarkable responses in some cases with ataxia and movement disorders (myoclonus, dystonia, tremor), these researchers were not, overall, able to identify variables to predict response to CoQ10 supplementation (Chang et al. 2018). These data are in contrast with our presented case.

In agreement with our data, Hikmat et al. (2016) showed that mutations in the *ADCK3* gene can cause a complex ataxia-myoclonus syndrome and acute epileptic

encephalopathy with stroke-like episodes. This finding suggested that *ADCK3* mutations can be responsible for differential diagnosis of mitochondrial encephalopathy with stroke-like cortical involvement. Typically, cases present with a complex neurological phenotype, with cerebellar ataxia as the main manifestation (Hikmat et al. 2016). Liu et al. (2014) declared that mutations in the *ADCK3* should be considered a potential cause of unexplained complex neurological syndromes even when cerebellar ataxia is not the major feature. Although the manifestations can start in early childhood or infancy, there are reports of juvenile-onset of CoQ10 deficiency, revealing that age of onset can vary (Liu et al. 2014). CoQ10 replacement therapy resulted in objective and subjective development in the case function and symptoms. Despite the fact that there were also improvements in ataxic symptoms as evaluated using the SARA scale, the most noticeable improvements were in a decrease of myoclonus and speech recovery. Our study declared that WES is a suitable method to detect mutations, mainly in unexplained complex syndromes with high genetic



B.



C.

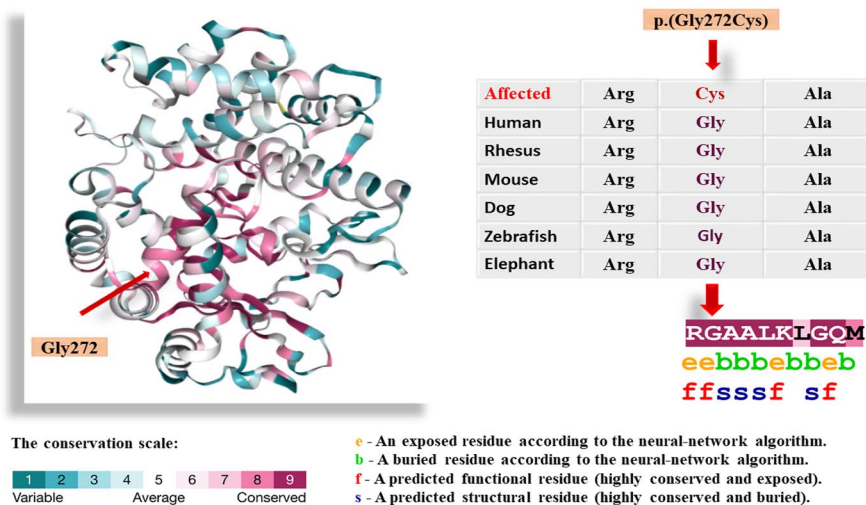


Fig. 3 **A** The *ADCK3* gene contains 15 exons and spans ~90 kb. Graphical view of the COQ8A atypical kinase protein updated from UniProt (UniProtKB-Q8NI60). The canonical isoform length of the protein (Identifier: Q8NI60-1) has 647 amino acids and N-terminal transit peptide (residue 1–162), helical transmembrane region (residue: 214–230), protein kinase domain (residue 329–518), KxGQ motif (residue 276–279), and AAAS motif (residue 337–340). The [c.814G>T, (p.Gly272Cys)] variant is in the Exon 6, which affects the atypical kinase chain, creates an amino acid change from Gly to Cys at position 272. **B** 3D structure of the protein, which is provided by the PyMOL software. The difference between the side chain of Gly272 and Cys272 has been locally enlarged (PDB: 4ped). **C** 3D structure which is designed by ConSurf server database. According to this structure and conservation analysis of amino acids by ConSurf, Gly272 is a highly conserved amino acid with score 9 of 9. Also, this amino acid is evolutionary conserved in different species including rhesus, mouse, dog, elephant, chicken, and zebrafish based on UCSC genome browser

heterogeneity. This finding is in concordance with the study of Liu et al. (2014).

In a similar study, Aure et al. (2004) studied a 7-year follow-up evaluation of a case with CoQ10 deficiency, revealing that CoQ10 defects may cause progressive neurologic disease despite Coenzyme supplementation. Early symptoms of exercise intolerance and hyperlactatemia improved noticeably with substitutive treatment. However, CoQ10 supplementation did not prevent the onset of cerebellar syndrome. A switch to idebenone treatment caused clinical and metabolic worsening, which disappeared with subsequent CoQ10 treatment (Aure et al. 2004). Central hypothyroidism arises from insufficient stimulation of the thyroid gland by TSH, for which secretion or activity can be impaired at the hypothalamic or pituitary levels. Central hypothyroidism should be evaluated in each patient with developmental delay (Konishi et al. 2021). Hypothyroidism is often seen in patients with mitochondrial disorders and ataxia-related phenotypes (Goldstein et al. 2013; Sun et al. 2019). To the best of our knowledge, hypothyroidism has not been reported in patients with disease-causing variants in the *ADCK3* gene.

Calculating the $\Delta\Delta G$ values of variants, the I-Mutant2.0 server revealed that p.(Gly272Cys) variant decreases the stability of COQ8A protein ($\Delta\Delta G = -0.89$, $\Delta\Delta G < 0$: decrease stability). 3D structure of the protein and difference between side chains shown in Fig. 3B. Evolutionary conservation analysis was performed using UCSC genome browser, showing that Gly at residue 272 of the COQ8A is conserved among different species including rhesus, mouse, zebrafish, elephant, and dog. Also, according to the ConSurf server, Gly272 is a highly conserved amino acid with a conservation scale of 9 out of 9 (Fig. 3C). Based on pathogenic mutation prediction (PMut) analysis, which predicts pathogenicity of all missense variants in the protein, all substitutions at the residue of 272 of COQ8A protein were

pathogenic, including Gly to Cys. This substitution was predicted as “disease” with a score of 0.88 (92%) out of 1.00. Pathogenicity prediction was predicted by computational prediction tools. FATHMM-MKL, PROVEAN, and SIFT specified the p.(Gly272Cys) variant as “damaging.” Based on EIGEN and REVEL tools, this variant was “pathogenic.”

Conclusion

The disease-causing variants in the *ADCK3* gene cause primary coenzyme Q10 deficiency-4, also known as autosomal recessive spinocerebellar ataxia-9. A small number of variants in the *ADCK3* gene may cause EPC. However, there are still several unknown variants, which cause EPC. These variants need to be determined in suspicious patients by genetic studies. There was a significant delay in diagnosis of this patient because of focusing on seizure control rather than prompt genetic testing for refractory seizures with underlying regression and ataxia. Therefore, clinicians should consider genetic testing earlier to instant diagnosis and satisfactory treatment based on exact etiology to prevent further neurologic sequelae.

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Author Contribution PM and MH conceived and designed the experiments. RSB, MRA, RH, AT, EP, and HGH conducted the experiments. PM, MH, ZR, RH, and NM analyzed and interpreted the data. RH and MRA contributed reagents/ materials/analysis tools. PM, RH, and MH wrote the paper. All authors reviewed the manuscript.

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Availability of Data and Materials Human variant and pertinent phenotypes have been reported to ClinVar (Submission ID: SUB8911007, Accession ID: SCV001477284).

Declarations

Ethics Approval and Consent to Participate Written consent was obtained from parents as legal guardians of the proband. This study was approved by the local ethics committee of the National Institute for Medical Research Development (NIMAD) of Iran (Ethics ID: IR.NIMAD.REC.1397.508). Therefore, this research has been done in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

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