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Case Report
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Identified UQCRH Homozygous Protein-Truncating Variant in A Patient with Recurrent Ketoacidosis and Hyperammonemia: A Case Report

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Abstract

Recurrent ketoacidosis and hyperammonemia are two of the symptoms of mitochondrial disorders. We report the case of a girl who presented with recurrent ketoacidosis, hyperlactatemia, and hyperammonemia. Between crises, the patient's cognitive function is completely normal. The parent-offspring trio underwent whole-exome sequencing (WES). Whole-exome sequencing (WES) was performed on the parent-offspring trio. The patient was homozygous for the UQCRH c.77T>A p. (Leu26) variant, which results in a premature stop codon within a biologically relevant subunit of mitochondrial complex III.*

Variants in this gene have only been described [1] in two affected cousins, presenting with recurrent episodes of severe lactic acidosis, hyperammonemia, and encephalopathy. A molecular genetic test was done in both cases and identified a homozygous deletion of exons 2 and 3 of UQCRH, which encodes a structural complex III (CIII) subunit. Complex III deficiencies are rare, and their phenotypes can vary significantly, even among patients with the same genotype. With this discovery, the differential diagnosis of hyperammonemia broadens and the challenge grows.

Keywords: *Tandem mass spectrometry; hyperammonemia; whole-exome sequencing; lactic acid; complex III deficiencies.*

Introduction

Mitochondria are the cell's "powerhouse," producing adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS) complexes found in the mitochondria's inner membrane. There are five known complexes: NADH stands for ubiquinone oxidoreductase (complex I), succinate dehydrogenase (complex II), ubiquinol–cytochrome c oxidoreductase (complex III, or cytochrome bc1 complex), cytochrome c oxidase (complex IV), and ATP synthase (complex IV) (Fig. 1).

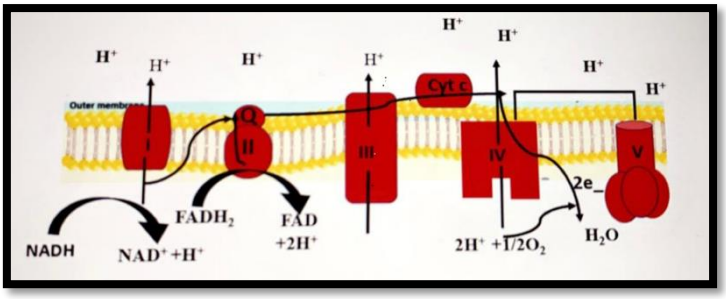

Figure 1: Mitochondrial respiratory chain.

The mitochondrial complex III deficiency has Variable clinical phenotype including, lactic acidosis, high ammonia, hypoglycemia, which may be exacerbated by febrile illness failure to thrive, it range from hypotonia, encephalopathy, and delayed psychomotor development.

Complex III (ubiquinol:cytochrome c oxidoreductase) is located at the center of the respiratory chain and is responsible for the transfer of electrons between ubiquinol and cytochrome c. CIII is made up of 11 subunits organized in a dimer and implanted in the inner mitochondrial membrane and is responsible for the transfer of electrons between ubiquinol and cytochrome c. CIII is made up of 11 subunits organized in a dimer and implanted in the inner mitochondrial membrane. Ten of them are nuclear-encoded, while one is mitochondrial-encoded. Aside from that, UQCRC1 and UQCRC2, as well as the core embedded subunit UQCRFS1, are the only subunits that have been identified. Domains transmembrane Each CIII subunit performs a unique function in the electron transfer process. The clinical presentation of mitochondrial diseases, complex III deficiency, had a variable presentation and multisystem involvement, including lactic acidosis, hypotonia, hypoglycemia, encephalopathy, and delayed psychomotor development, as well as some organ involvement like renal tubulopathy and liver dysfunction. Usually, symptoms start after birth. While many affected people pass away in their early years.

Mutations in various nuclear-encoded genes can cause mitochondrial complex III deficiency. Core proteins (encoded by UQCRC1 and UQCRC2), respiratory proteins (CYC1 and UQCRFS1), and low-molecular-weight proteins (encoded by UQCRFS1) are the three types (UQCRH, UQCRB, UQCRQ, UCRC, UQCR11, and UQCRFS1). However, it can also be caused by mutations in mitochondrial DNA in the MTCYB gene, which usually results in a milder phenotype.

UCQRH is a component of subunit 6 of the cytochrome bc1 complex found in the mitochondrial respiratory tract. This 11-kDa protein, also known as mitochondrial hinge protein, is required for the production of cytochrome c1 and cytochrome c complexes [3]. Two helices are joined by two disulfide bridges, and the complex has a highly acidic sequence [4]. UQCRH, a component of the respiratory complex, is expressed in the majority of tissues, especially in organs involved in high-energy metabolism [5].

Case Report

An 8-year-old girl, the second child of healthy Yamani consanguineous parents, presented to the emergency room with a one-day history of vomiting, lethargy, tachypnea, and tachycardia; no fever was documented. She has previously been well, with uneventful birth and neonatal periods, and she had normal growth and development prior to the recent crisis. with a history of recurring similar metabolic crises occurring more than four times, last one five months back. In this crisis, she came to the emergency room with lethargic, frequent vomiting, and poor feeding for the last two days. There was no fever and no history of abnormal movement.

She was admitted to the pediatric intensive care unit (PICU). A physical examination revealed the following: temperature, 37.1°C; pulse, 140 beats/min; respiratory rate, 69 beats/min; blood pressure, 103/63 mm Hg; oxygen saturation, 93%; and weight, 16.5 kg. Further observations were as follows: conscious-oriented. moderate dehydration, distress, slight cyanosis around the lips, skin elasticity present, deep breathing, coarse respiratory sounds in both lungs, no rales were heard, heart sounds were strong and rhythmic, no murmur was heard in the precordial area, the abdomen was soft, the liver and spleen were not enlarged, and intestinal sounds were normal. physiological reflexes were detected, the Kirschner sign and Bartholomew sign were negative, and the muscle tone of the extremities was normal. The Glasgow score was 16. Laboratory data on arterial blood gas showed the following: severe high-anion gap metabolic acidosis (pH 7.13, pCO2 10.6 mmHg, and HCO3 7.2 mmol/L). The ammonia level was 201 mcg/dl, and the plasma glucose level was 3.3 mmol/L. The lactic acid concentration is 6.1 mmol/L. oxygen saturation (SPO2): 95%, Na 134 mmol/L, K 3.8 mmol/L. The total leukocyte count was 16.45×10^9/L (4–10.5), and the absolute neutrophil count was 10.1×10^9/L. The percentage of neutrophils and lymphocytes was 61.4% and 32.9%, respectively. The red blood cell count was 5.01×10^{12}/L, hemoglobin was 104 g/L, the total platelet count was 397 × 109/L, and C-reactive protein was 89 mg/L. Blood biochemical tests showed that alanine aminotransferase was 59.5 U/L, aspartate aminotransferase was 101.3 U/L, albumin was 38.2 g/L, urea was 5.29 mmol/L, creatinine was 21.7 µmol/L, hyperlactacidemia was 11.34 mmol/L (0.5–1.7), creatine kinase isoenzyme (CK-MB) was 1.21 ng/mL (<0.05), and triglyceride was 3.33 mmol/L. Urine ketones were 3+. Based on critical acidosis, metabolic testing was performed (blood and urinary organic acid analysis) using gas chromatography/mass spectrometry (MS) and tandem MS (Newborn screening), quantitative amino acid levels were unremarkable, and the MRI brain was normal. Abdominal ultrasound and electrocardiography were normal. Patient managed by ventilator support, received intravenous D10 1⁄2 normal saline one and 1/2 maintenance sodium bicarbonate infusion, and hyperammonemia management with AMMONUL® (sodium benzoate and sodium phenylacetate) and arginine as follows: IV arginine doses are 250−400 mg/kg up to 600 mg/kg as a bolus in 90–120 minutes, then infusion was continuous over 24 and AMMONUL® was given as 250 mg/kg loading dose over 90 minutes followed by 250 mg/kg/day and continued infusion over 24 hours. The ammonia was dropped gradually over the course of treatment to 78 mcg/dl. The glucose level was maintained. The patient was improved dramatically, and oral feeding was introduced, which was well tolerated. This crisis was the sixth in her life, occurring about two times per year and lasting for a maximum of 48 to 72 hours without any sequelae. the significant history in this patient, she had an aversion to protein noticed early.

Method

Genetic analyses were performed after obtaining a signed informed consent from the patients' parent. Single nucleotide polymorphism (SNP) array did not detected any definite pathogenic copy number variant (CNV). WES was performed using the Double stranded DNA capture baits against approximately 36.5 Mb of the human coding exome (targeting >98% of the coding RefSeq from the human genome build GRCh37/hg19) are used to enrich target regions from fragmented genomic DNA with the Twist Human Core Exome Plus kit. The generated library is sequenced on an Illumina platform to obtain at least 20x coverage depth for >98% of the targeted bases. An inhouse bioinformatics pipeline, including read alignment to GRCh37/hg19 genome assembly, variant calling (single nucleotide and small deletion/insertion variants), annotation and comprehensive variant filtering is applied. All variants with minor allele frequency (MAF) of less than 1% in gnomAD database, and disease-causing variants reported in HGMD®, in ClinVar or in CentoMD® are considered.

The UQCRH variant c.77T>A p.(Leu26*) creates a premature stop codon within a biologically relevant subunit of mitochondrial complex III. variant causing premature truncation of protein product. Therefore, the detected variant is classified as class 2P (likely affecting protein function) according to CENTOGENE's internal guidelines.

Results

As no variant which could be clinically relevant to the described phenotype was identified in the exome dataset, the search filters were relaxed and the search was expanded to cover variants in genes with no or only partial experimental evidence for their involvement in human disease, with potential relevance to the described phenotype.

A novel homozygous nonsense variant NM_006004.3: c.77T>A p.(Leu26*) in *UQCRH* gene was detected (Table 1).

Table 1: Sequencing variant.

SEQUENCE VARIANTS							
GENE	VARIANT COORDINATES	AMINO ACID CHANGE	SNP IDENTIFIER	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES**	TYPE AND CLASSIFICATION***
UQCRH	NM_006004.3:c.77T>A	p.(Leu26*)	N/A	homozygous	PolyPhen: N/A Align-GVGD: N/A SIFT: N/A MutationTaster: Disease causing Conservation_nt: moderate Conservation_aa: N/A	gnomAD: - ESP: - 1000 G: - CentoMD: -	Nonsense Likely affecting protein function (class 2P)

This variant is predicted to create a premature stop codon within a biologically relevant subunit of mitochondrial complex III. A recent genetic study revealed a homozygous deletion mutation in *UQCRH* (hinge protein), which plays a role in the assembly of Complex III (Vidali et al). The nonsense variant c.77T>A p.(Leu26*) is very rare and was not reported before in Genome Aggregation Database (gnomAD), ClinVar, HGMD, Exome Sequencing Project (ESP), 1000Genome project (1000G) and CentoMD® (latest database available, June 2021). Therefore, and based on the ACMG recommendations, the detected variant was classified as likely affecting protein function (class 2P). Both parents were confirmed heterozygous carriers for this variant. (Fig. 2)

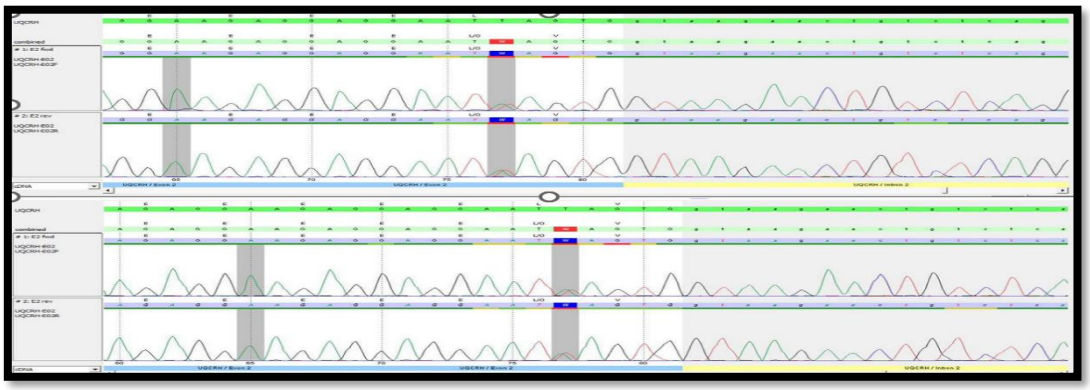

Figure 2: The variant's position on exon 2 of *UQCRH* gene (NM_006004.3) and its adjacent regions were PCR-amplified with flanking primers on both parents' DNA. PCR products were then sequenced on forward and reverse strand by Sanger sequencing, which confirmed the heterozygous carriership of the variant c.77T>A p.(Leu26*) in both parents.

In addition, no pathogenic or likely pathogenic variants that would be insufficient for a genetic diagnosis (e.g. heterozygous variants in genes related to autosomal recessive disorders) but would have led to recommend further testing (e.g. deletion/duplication analysis) were detected. A comprehensive mitochondrial gene panel analysis (CentoMito®) was performed and didn't detect any clinically relevant variants.

Discussion and Conclusion

A homozygous UQCRH deletion mutation was first described as a cause of mitochondrial disorder with recurrent episodes of severe lactic acidosis, hyperammonaemia, hypoglycemia, and encephalopathy. in two cousins, 8 and 11-year-old boys [1], born consanguineous with a normal clinical phenotype between crisis and good cognitive function. Our patient has similar clinical findings with the same UQCRH mutation, and this provided a more detailed description of the phenotypic spectrum of the cause of hyperammonemia (Algorithm attached) and Complex III deficiency.

Complex III deficiency is one of the most uncommon isolated respiratory chain defects, causing a wide range of symptoms in tissues with high energy demands. Of the ten nuclear-encoded structural subunits of CIII, only variants in *UQCRC2*, *UQCRB*, *UQCRQ*, and *CYC1* have been reported in mitochondrial disease cases associated with hypoglycemia, lactic acidosis, ketosis, and hyperammonaemia [6]. These phenotypes and the episodic nature of the metabolic decompensation are extremely similar to the patient presented here.

Despite the presence of intact brain structure, the encephalopathy seen in patients with mitochondrial disorders can impair cognitive function and motor skills, a phenotype seen in the UQCRH/mice [1]. Our patient, on the other hand, has shown no signs of developmental impairment or abnormal development, as in previous cases reported.In humans,[1]. Complex III deficiency is associated with a wide spectrum of phenotypes. Patients with UQCRC2 variations, for example, showed recurrent metabolic decompensation with lactic acidosis, hypoglycemia, and hyperammonemia without neurological impairment [7].

CIII deficiency is an autosomal recessive disorder that affects major metabolic organs such as the liver and kidney, as well as the heart, skeletal muscle, and the brain. Symptoms range from muscle weakness and fatigability to systemic multiorgan failure, depending on the severity of the OXPHOS impairment. They are characterized by hyperlactateemia and ketoacidosis, as well as abnormal glycemia. Hyperkalaemia, hyponatraemia, and

hypochloraemia were evident in the UQCRH model described [1].

In conclusion, our findings show that the homozygous UQCRH pathogenic mutation, as evidenced by the CIII defect in patients with recurrent metabolic crises and one of differential diagnosis of hyperammonemia.

Contribution list

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2. Dr Bader AL Haddad

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Our study did not require an ethical board approval because the analysis of datasets, open source and the informed consent was taken and no photo or personal information.

Ethics approval and consent to participate
Not applicable

Reference

1. Sanders C, Thompson K, Taylor R. Characterising a homozygous two-exon deletion in UQCRH: comparing human and mouse phenotypes. EMBO Mol Med. 2021 Dec 7;13(12): e14397.
2. Xia D, Esser L, Tang WK, Zhou F, Zhou Y, Yu L, Yu CA. Structural analysis of cytochrome bc1 complexes: Implications to the mechanism of function. Biochim Biophys Acta Bioenerg. 2013 Nov;1827(11-12):1278-94. Available from: https://doi.org/10.1016/j.bbabio.2012.11.008.
3. Kim CH, Balny C, King TE. Role of the hinge protein in the electron transfer between cardiac cytochrome c1 and c. Equilibrium constants and kinetic probes. J Biol Chem. 1987; 262:8103–8. Available from: https://doi.org/10.1016/S0021-9258(18)47534-5.
4. Ohta S, Goto K, Arai H, Kagawa Y. An extremely acidic amino-terminal presequence of the precursor for the human mitochondrial hinge protein. FEBS Lett. 1987; 226:171–5. Available from: https://doi.org/10.1016/0014-5793(87)80573-2.
5. Modena P, Testi MA, Facchinetti F, Mezzanzanica D, Radice MT, Pilotti S, et al. UQCRH gene encoding mitochondrial Hinge protein is interrupted by a translocation in a soft-tissue sarcoma and epigenetically inactivated in some cancer cell lines. Oncogene. 2003; 22:4586–93. Available from: https://doi.org/10.1038/sj.onc.1206472.
6. Haut S, Brivet M, Touati G, Rustin P, Lebon S, Garcia-Cazorla A, Saudubray JM, Boutron A, Legrand A, Slama A. A deletion in the human QP-C gene causes a complex III deficiency resulting in hypoglycaemia and lactic acidosis. Hum Genet. 2003; 113:118–22. Available from: https://doi.org/10.1007/s00439-003-0946-0.
7. Miyake N, Yano S, Sakai C, Hatakeyama H, Matsushima Y, Shiina M, Watanabe Y, Bartley J, Abdenur JE, Wang RY, et al. Mitochondrial complex III deficiency caused by a homozygous UQCRC2 mutation presenting with neonatal-onset recurrent metabolic decompensation. Hum Mutat. 2013; 34:446–52. Available from: https://doi.org/10.1002/humu.22257.