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EC NEUROLOGY
Case Report

A Rare Homozygous Deletion Mutation of *TMEM70* Gene Associated with 3-Methylglutaconic Aciduria and Cataract in A Saudi Patient

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Received: December 14, 2016; **Published:** December 23, 2016

Abstract

For the past, several years, the number of the patient's with nuclear genetic defects of the mitochondrial ATP synthase has been increased. The *TMEM70* gene mutation is one of the most common nuclear encoded genes that are affecting the ATP synthase. Here, we report a 9-months-old Saudi girl presenting with lactic acidosis, 3-methylglutaconic aciduria, hypertrophic cardiomyopathy and encephalopathy. The patient was genetically tested for Methylglutaconic Aciduria Nuclear Gene panel/sequencing and deletion/duplication analysis. She was positive for homozygous deletion of c.578_579delCA in exon 3 of the *TMEM70* gene. This is consistent with a diagnosis of ATP synthase deficiency. This case report will hopefully help in the diagnosis of future cases, as well as providing important information regarding prognosis and optimal managements.

Keywords: *TMEM70 Gene; 3-Methylglutaconic Aciduria*

Introduction

Transmembrane protein-70 gene (*TMEM70*, MIM # 612418) is recently identified as an autosomal recessive mitochondrial ATP synthase. It is located on chromosome 8q21.11 and consists of 3 exons. The gene *TMEM70* is an important factor for the biogenesis and stabilization of ATP synthase. The exact role has not been determined yet [1-4]. several studies have narrowed it down to the key enzyme of mitochondrial energy provision, catalyzes synthesis of ATP during oxidative phosphorylation (OXPHOS) system [5,6]. This system consists of five-multi-subunit complexes that act in a concert to generate cellular energy in the form of ATP. Genetic defects of OXPHOS result from mutations in either mitochondrial DNA (mtDNA) encoded proteins, nuclear genes encoding respiratory chain structural subunits or proteins crucial for the assembly of the OXPHOS complexes [7,8].

A nuclear defect in ATP synthase was first described in a neonate who presented with a fatal condition with severe lactic acidosis and heart failure that is caused by hypertrophic cardiomyopathy [9] to our knowledge, there are more than 48 *TMEM70* mutated patients have been described or reported. Most of these patients were European origin [2,3,10]. Most of the affected individuals showed neonatal lactic acidosis (Acidemia), hypertrophic cardiomyopathy with variation of the severity in the central nervous system, dysmorphic facial features, 3-methylglutaconic aciduria (3-MGA). This disorder has severed outcomes and usually the affected individuals at early ages and sometimes has a fatal course within the first 6 weeks of life [5,11]. Some clinical features expanded to include infantile onset cataract, early onset gastrointestinal dysfunction and congenital hypertonia with multiple contractures resembling arthrogryposis. The first characterization of fetal presentation of the syndrome is also provided; featuring significant intrauterine growth retardation, sever

oligohydramnios, fetal hypotonia and myocardial wall thickening [3]. Here, we report the clinical, biochemical and genetic disease in a Consanguineous Saudi family whom child with lactic acidosis, cardiomyopathy, 3-MGA, bilateral cataract and variable central nervous system involvement.

Case Representation

A 9-months-old female child was admitted to King Saud Medical City in Riyadh, Saudi Arabia with a history of fever, vomiting and poor feeding. She was born of consanguineous of Saudi parents. She has a healthy sibling and no history of abortion or death within the family. She was a full term and delivered via cesarean section with a birth weight of 2.1 Kg. Upon delivery, she transferred to the NICU for 13 days with recurrent episodes of low blood glucose level.

Clinical examination revealed that the infant was conscious, lethargic, mildly dehydrated and afebrile. Her face appeared dysmorphic with broad forehead, flat occiput, broad nasal bridge, long philtrum, wide thin mouth with flat upper lip and microretrognathia (Figure 1a and 1b). Growth parameters such as height, weight, head and chest circumference were within normal ranges. Breath sounds were normal. Abdominal examination revealed soft lax abdomen with no organomegaly (Figure 1c and 1d). Also, there was head lag and hypotonia. Echocardiography showed mild ventricular hypertrophy (Which side? Or is it bilateral?). Tandem mass spectrometry, abdominal ultra sound and MRI were normal. The laboratory investigations were as follows: WBC= $12X10^9$/L, Hb=10.3 g/L, Platelets= $548X10^9$/L; pH=7.1, PCo_2=18, HCO_3= 10.3, S Lactate=12 mmol/L, Ammonia=175 umol/L. Lipid and coagulations profile were normal. Urine GCMS showed for 3-methylglutaconic acid (3-MGA). A blood sample were obtained from the patient and sent to the genetics lab for testing using Methylglutaconic aciduria nuclear gene panel. The results showed: the patient is homozygous for 2-bases deletion mutation in the *TMEM70* gene, which is consistent with the diagnosis of ATP synthase deficiency. During her stay, on the first day, she kept NPO, dehydrated dextrose 10% maintained for one and half. Metabolic acidosis was corrected with bolus of sodium bicarbonate intravenously. She received IV carnitine and oral sodium benzoate. Ammonia was decreased to 47 umol/l. On the following day, the patient showed improvement and oral feeding was started gradually with low protein formula and oral carnitine.

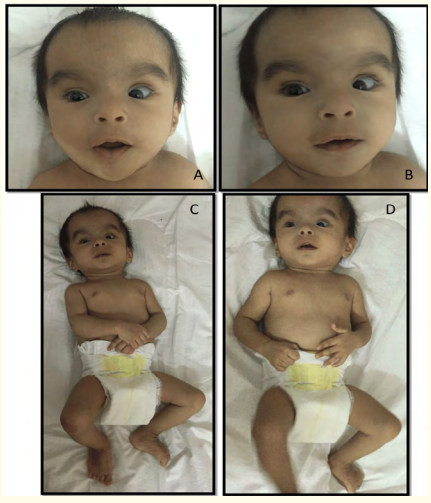

Figure 1: *The patient at age of 9 months.*

Material and Methods

This study was approved by (Ethic committee at the hospital). Blood sample in EDTA were obtained from the patient after informed written consent was given to the patients' parents. The sample was sent to Gene Dx, Inc. (Gaithersburg, MD, USA) for Methylglutaconic Aciduria Nuclear Gene panel test. The genomic DNA used from the submitted sample for the coding, regions and splicing junctions of the 10 genes in this panel (Table 1). These 10 genes were enriched by microdroplet PCR (RainDance Technologies) and sequenced simultaneously by massively parallel (NextGen) sequencing on an Illumina platform with single-end reads. Bi-directional sequence was assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC gh19 and analyzed for sequence variants. Capillary sequencing was used to confirm all potentially pathogenic variants and to obtain sequence for regions where fewer than 15 reads were achieved by NextGen sequencing. Concurrent deletion/duplication testing was performed foe the genes in the panel using exon-level oligo array CGH (Exon Array Dx) Data analysis was performed using gene specific filtering. Probe sequences and locations were based on human genome build GRCh37/UCSC gh19. Confirmation of copy number changes was performed by MLPA, qPCR, or repeat array CGH analysis. Sequence and array CGH alterations were reported according to the human genome variation Society (HGVS) or international system for Human Cytogenetics Nomenclature (ISCN) guidelines, respectively.

ATP5E	*AUH*	*OPA3*	*SERAC1*	*TAZ*
ATPAF2 (ATP12)	*DNAJC19*	*PLOG (PLOG1)*	*SUCLA2*	*TMEM70*

Table 1: *Methylglutaconic Aciduria Nuclear Gene Panel: Sequence Analysis and exon-level Deletion/ Duplication Testing of 10 Nuclear Genes.*

Results

The Methylglutaconic Aciduria Nuclear Gene panel test revealed that there is a homozygous for 2-bp deletion, c.578_579delCA:p. Thr193SerfsX6 (T193SfsX6) in the third exon of the *TMEM70* gene. The normal sequence with the bases that are deleted in braces is AGTA {CA} GTGT. This mutation has been reported previously in association with ATP synthase deficiency [3]. No other reportable variants were detected by sequencing and deletion/duplication testing of the 10 genes included on this panel (Table1). This deletion causes a frameshift starting with codon Threonine 193, changes this amino acid to a Serine residue and creates a premature Stop codon at position 6 of the new reading frame denoted p.Thr193SerfsX6. This mutation is predicted to cause loss of normal protein function through protein truncation. This finding is consistent with a diagnosis of ATP synthase deficiency in this patient. However, this result could also be seen if the patient had one allele with c.578_579delCA mutation and one allele that were refractory to amplification.

Discussion

Mutations in the *TMEM70* gene are the most recently reported as an autosomal recessive for ATP synthase deficiency. Typically, the clinical features are associated with lactic acidosis, cardiomyopathy, 3-MGA, hypotonia, faltering growth, short stature, microcephaly, developmental delay, and variable central nervous system involvement. Some of the less frequent, but reported, clinical features are inguinal and umbilical hernia, cataracts, strabismus, pigmentatal retinopathy and congenital heart defects, including pulmonary stenosis, aortic coarctation or bicuspidal aortic valve and Persistent pulmonary hypertension of the newborn (PPHN) [2,3].

Unfortunately, to all the different type of mutations in this gene, there is no genotype-phenotype correlation was possible due to the high number of private mutations in the *TMEM70* gene [2]. Proper management of metabolic crises is a more critical prognostic factor in affected children especially in neonates. These metabolic crises demonstrated as episodes of metabolic decompensation as it shows up in a worsening of biochemical parameters (lactic acidosis with corresponding hyperalaninaemia, and accompanied with hyperammoneamia) and marked increase of blood uric acid concentrations [12,13].

Until now, there is no curative therapies exist for patients with mutant *TMEM70* gene. Proper long medical management including frequent feeding supplemented with starch during acute febrile infections and infusion with glucose and lipid emulsions during vomiting or diarrhoeal illnesses. The frequency of feeding may be gradually decreased in older children, but with care since metabolic crises may develop even in the second decade. Also, Due to slow gastric evacuation in some patients resulting in food refusal or recurrent vomiting, the placement of nutritional gastrostomy should be considered early in the disease course. This may help to decrease the frequency of metabolic crises or even eliminate them. Indeed, the acute management of metabolic crises is extremely importance due to the fact of the affected mental capacity of the patients or its development after metabolic crises was often observed. It is important to emphasize regular monitoring of blood ammonia concentration in these patients, especially during infections or other stress conditions resulting in non-wellbeing of the child. It is worth noting that, due to the variable outcomes, adequate management of the patient, especially during the acute crises after birth or in early childhood are extremely important [2,14-16].

TMEM70 deficiencyshould be in the differential diagnosis of prenatally diagnosed hypertrophic cardiomyopathy (HCM). Children with *TMEM70* deficiency, have non-obstructive concentric HCM with preserved systolic function. Clinically, the most severe cardiomyopathies were detected in neonates. With the exception of neonates with heart failure, the prognosis of cardiomyopathy is common, because HCM is mostly non-progressive or even regressive during long-term follow-up [2,3,16,17].

In summary, *TMEM70* gene defects are important cause of nuclear originated ATP synthase deficiency. Disruptive mutation in this gene results in a specific phenotype, regardless of the type of the mutation involved. We hope, in the future, to prevent further diagnosis of TMEM70gene defects and other rare genetic disease by early detection and counseling. Also, we strongly recommend a mutation-specific carrier testing for family members and prenatal diagnosis for the parents of the child. Targeted carrier testing of both parents is necessary prior to or concurrently with any carrier testing or predictive testing in this family to determine whether this patient has inherited c.578_579delCA from each parent.

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Volume 4 Issue 2 December 2016