Beta-Ketothiolase deficiency in a patient with coexistence of homozygous *ACAT1* gene mutation and homologous constitutional translocation t(4;11)(q13;q23) and father with XYY syndrome

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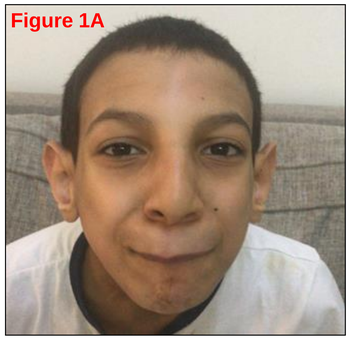
Background

Beta-ketothiolase deficiency [BKT, OMIM # 203750] is a rare metabolic disorder that is inherited in an autosomal recessive manner and is caused by pathogenic mutations in the *ACAT1* gene. BKT is also known as mitochondrial acetoacetyl-CoA thiolase that breaks down the ketone acetoacetyl CoA to acetyl-CoA, and also converts 2-methylacetoacetyl-CoA to propionic acid in the isoleucine catabolic pathway. Deficiency in BKT enzyme impairs the ability to process ketones during fatty acid metabolism and as well as impairing the normal breakdown of isoleucine. Homozygosity of balance translocation is an extremely rarely reported chromosomal aberration.

Here, we describe a 14 year-old Saudi boy for a first degree consanguineous parents with *ACAT1* homozygous variants mutation in *ACAT1* gene and homozygous balance translocation t(4;11)(q13;q23).

Case Presentation

A 14 year-old Saudi boy was referred to Genetic clinic due to developmental delayed. This patient is the first child born to a healthy first-cousin parents. The proband has one healthy sibling sister. Family history is unremarkable. Pregnancy care showed good fetal movement and no history of exposure to medication, teratogenic or infective agents. The patient was born at term by normal spontaneous vaginal delivery. At two weeks of age, he was admitted to Neonatal Intensive Care Unit (NICU) due to shortness of breath and likely metabolic acidosis



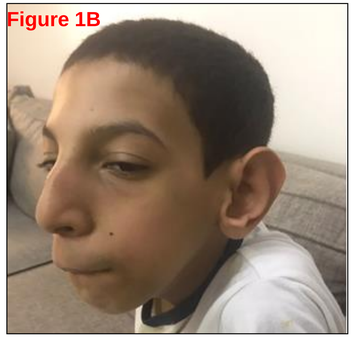


Fig. 1 Patient's dysmorphic features

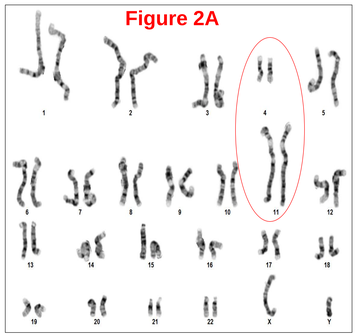


Fig.2A G-banding karyotype revealed a male with 46,XY, t(4;11)(q13;q23)x2.

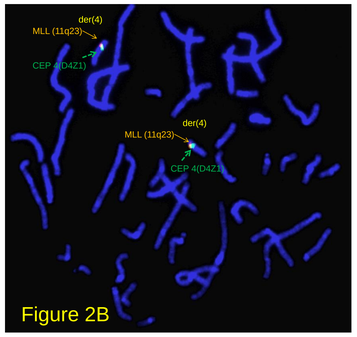


Fig.2B Patient Metaphase FISH probed with Ch.4 (CEP, Aqua) and Ch. 11 (MLL, Orang)

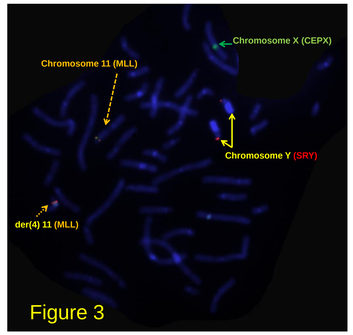


Fig.3 Father Metaphase FISH probed with Ch.4 (CEP, Aqua) , Ch. 11 (MLL, Orang) , Ch.X (Cep, Green) and Ch.Y (SRY, Red)

Methods

Patient's physical and radiological examinations, and further genetics investigations for whole exome sequencing (WES), chromosomal microarray (CMA) and conventional chromosomal analysis were performed.

At age of 12 year, the proband has dysmorphic features, global developmental delay, autism, attention deficit hyperactivity disorder, bronchial asthma, and excessive salivation.On physical examination, he has body weight of 23 kg (<3rd centile), a height of 136 cm (< the 3rd centile), and head circumference of 52 cm (5-10th centile). His dysmorphic features (Fig.1A&B) were included microcephaly, elongated face, prominent forehead, arched eyebrows, prominent nose, smooth philtrum, thin upper lips, large ears with unfolded helices and crowded teeth. The chest and lower extremity X-ray were normal. Pelvis X-ray is revealed that both hip joints were congruent within the acetabulum. Lumbar spine magnetic resonance imaging suggested that the vertebral bodies maintained their normal shape, height and marrow signal. A mild diffused disk bulge at L3-L4 and L4-L5 with narrowing neural foramen bilaterally were seen. The Electrocardiograms (ECG) and echocardiograms were normal. Abdominal examination revealed presence of small hiatal hernia and sever gastroesophageal reflux.

Result

The WES showed presence of homozygous c.410_418delinsT (p.Ser137Phrfs*37) pathological variant within exon 5 of the *ACAT1* gene. This mutation support the diagnosis of *Beta-ketothiolase deficiency* and was also confirmed by biochemical findings. Both parent were heterozygous for the c.410_418delinsT (p.Ser137Phrfs*37) variant within *ACAT1*. Conventional chromosomal analysis revealed presence of homozygous reciprocal balance 46,XY,t(4;11)(q13;q23) involving both homologues long arms of chromosomes 4 and 11 respectively (Fig. 2A). This abnormalities were confirmed by fluorescence in situ hybridization (FISH) analysis using designated probes (Fig.2 B). Both parents were carrier for the balance t(4;11)(q13;q23) and although, father has a 47 chromosomal account with XYY syndrome in additional to the t(4;11)(q13;q23) (Fig.3) Furthermore, CMA was unremarkable for both patient and his parent.

Conclusion

Having a genetic disorder that is inconsistent with its usual clinical presentation should alert clinicians to the possibility of having another disorder, particularly in a highly consanguineous population. Proper clinical evaluation, and laboratory investigations are important for a proper genetic counseling.

The authors declare that they have no competing interests