Introduction

Fanconi Bickel syndrome (FBS) is a rare form of glycogen storage disease (GSD) inherited in an autosomal recessive manner. FBS is caused by mutations in the glucose and galactose transporter gene SLC2A2. The SLC2A2 gene encodes for GLUT2, a low affinity facilitative glucose transporter expressed in critical tissues involved in glucose homeostasis. This gene is expressed in hepatocytes, pancreatic β-cells, enterocytes, and renal tubular cells. Clinical and chemical features include fasting hypoglycemia, postprandial hyperglycemia, hepatomegaly, glucose and galactose intolerance, partial resistance to adrenaline and glucagon, rickets, and poor growth. Missense, nonsense, frameshift, and splice site pathogenic variants have been identified throughout the SLC2A2 gene in association with FBS, with homozygosity present in a large number of cases. Herein, we report a novel variant in the SLC2A2 gene in a female patient with classical features of FBS associated with diabetes mellitus at Qatar.

Methods

Whole Exome Sequencing (WES): Using genomic DNA from the patient, the exonic region and flanking splice junctions of the genome were captured and sequenced by NetGen sequencing on an Illumina system. Sequence and copy number alterations were reported according to the Human Genome Variation Society (HGVS) and International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively.

Sanger sequencing analysis was also performed for this patient. Target DNA was amplified by using Veriti 96-Well Fast Thermal Cycler, making fragments of different lengths and were cleaned using enzymatic cleanup, ExoSAP. Fluorescent "chain terminator" nucleotides mark the ends of the fragments and permit the sequence to be detected during running in Veriti 96-Well Fast Thermal Cycler. Precipitation method is used to remove unincorporated dye terminators from BigDye Terminator cycle sequencing reactions. Finally, the data were analyzed by two software: Applied Biosystems Sequencing Analysis Software v6.0 and Applied Biosystems SeqScape Software v3.

Case Report

We report a case of 19 years old FBS female patient associated with diabetes mellitus at Qatar, the second child of a first degree-cousin parents, who has presented with classical features of Fanconi-Bickel Syndrome (Figure 1). The patient presented with renal tubular acidosis, recurrent spontaneous pathological fractures and short stature. The patient suffers from thoracolumbar scoliosis and has multiple deformities in the upper and lower limbs (Figure 2), leading to non ambulation. Fasting hypoglycemia and postprandial hyperglycemia were detected. Urine analysis was significant for phosphaturia and evidence of proximal renal tubular acidosis (RTA) was noted (generalized aminoaciduria - Table 1). She was diagnosed with diabetes mellitus at the age of 17 years and is currently on insulin Aspart, Glargine, and Sitagliptin, maintaining a HbA1C of 6.6-7.5. Basal insulin level was within normal range, whereas C-Peptide of insulin was reduced (0.66 ng/ml, normal range 0.78-5.18).

Results

Whole Exome Sequencing showed c.613-T>G; IVS5-7-T>G in intron 5 in the SLC2A2 gene. The variant reported in the patient has not been reported previously as a pathogenic nor a benign variant. This variant reduces the quality of the splice acceptor site in intron 5 and creates a new cryptic splice acceptor site upstream of the natural splice site (Table 2). This is a newly reported homozygous mutation (c.613-T>T::G. IVS5-7-T>G in intron 5 of the SLC2A2 gene), confirmed by Sanger sequencing using the amplified DNA samples from the patient (Figure 3).

Conclusion

The c.613-T>T-G variant was not observed in approximately 6,500 individuals of European and African American ancestry in the NHGRI Exome Sequencing Project, indicating it is not a common benign variant in these populations. Therefore, we report c.613-T>T-G as a novel variant. The presence of this variant in the apparently homozygous state may be related to the reported features in this patient. The c.613-T>T-G variant is expected to cause abnormal gene splicing; however, in the absence of RNA functional studies, the actual effect of this sequence change in this patient is unknown. There is currently no targeted therapy for the underlying identified genetic defect; the mainstay of therapy for FBS patients is conservative management. The patient is on insulin, alfacalcidol, phosphate, sitagliptin, sodium bicarbonate and vitamin D. Future directions include validation of the patient RNA sequence and functional studies.

References

3. OMIM #318160

Disclosure - None of the authors have any potential conflict of interest.