Genetic Rarity: The First Case Report of *TMPRSS3* Mutation Coinciding with Multicystic Dysplastic Kidney

Dear Editor,

A 9-month-old male born to a non-consanguineous marriage was admitted with complaints of fever, lethargy, and reduced urine output. There was a history of two infant deaths in the family. He had hypoglycemia and severe hypernatremic dehydration. Physical examination revealed signs of dehydration. Blood gas analysis and renal function revealed severe metabolic acidosis and hypernatremia, and urea and creatinine levels were 144 and 3.5 mg/dL, respectively. His clinical and laboratory parameters improved with supportive management, and the hemogram and peripheral blood smear findings were normal. Urinalysis demonstrated nephrotic range proteinuria and microscopic hematuria. A sonogram of the abdomen and kidney–ureter–urinary bladder demonstrated a multicystic dysplastic kidney (MCDK) on the left side. He had persistent hypertension, which was managed with enalapril. Ocular and auditory evaluation did not reveal any abnormality. Genetic analysis was performed to look for inborn error of metabolism. It revealed a heterozygous variant (c.413C>A, p.Ala138Glu) in the *TMPRSS3* gene, pathogenic as per the American College of Medical Genetics and Genomics, and confirmed with Sanger sequencing [Figure 1, Supplementary Files]. Genetic counseling and surgical options were explained to the parents. Screening of the family members was normal.

Mutations in *TMPRSS3* are usually associated with autosomal recessive deafness in infants in heterozygous state.[1] *TMPRSS3* mutations have been reported to express themselves with nonsyndromic hearing loss previously in the heterozygous state.[2] Though the expression of *TMPRSS3* in the human kidneys has been less studied, this mutation has also been seen to play a role in pseudo-hypoaldosteronism type 1 and Liddle syndrome.[3] A splice variant of *TMPRSS3*, *TMPRSS3f*, has also been found in the kidneys of mice, which share 89% identity with the human *TMPRSS3f*.[4] So, it is likely that a mutation in *TMPRSS3* might produce structural renal anomalies along with deafness.

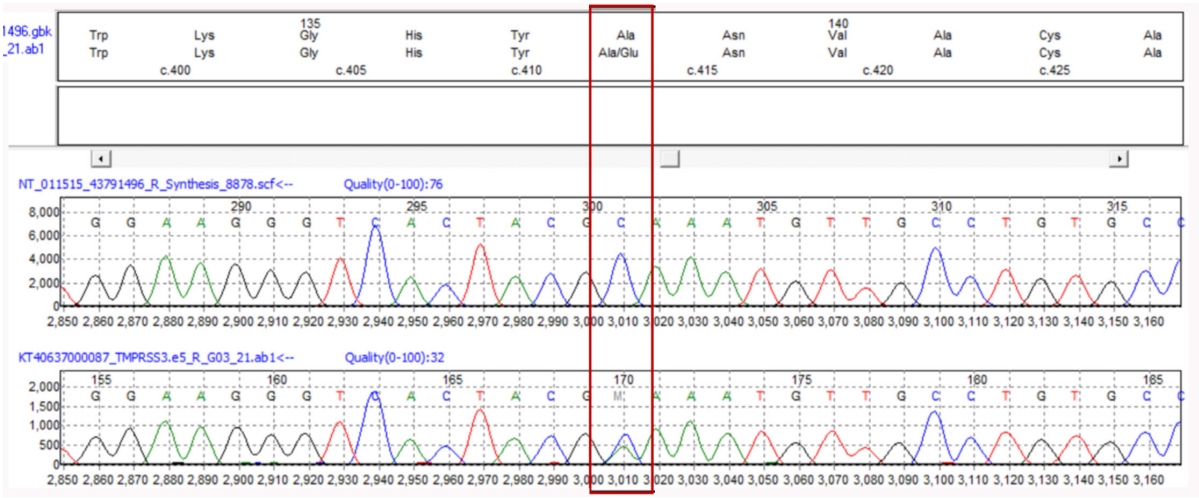

Figure 1: Sanger sequencing data (electropherogram) for the provided sample showing nucleotide change at chr21: c.413C>A,, (p.Ala138Glu) in *TMPRSS3* gene. Red, green, black, and blue colored peaks show thymine, adenine, guanine, and cytosine bases, respectively. The red rectangle in the image highlights a specific nucleotide change in DNA sequencing data (electropherogram).

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Conflicts of interest: There are no conflicts of interest.

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Severe Osteomalacia in an Adult HIV Patient on Tenofovir Disoproxil Fumarate

Dear Editor,

A 40-year-old with a HIV infection, on antiretroviral therapy which included tenofovir disoproxil fumarate for the last 14 years, presented with severe back pain. There was weakness of bilateral lower limbs, hypokalemia (2.4 meq/L), with normal anion gap metabolic acidosis, hypophosphatemia (1.5 mg/dl), hypocalcemia (3.8 mg/dl), elevated alkaline phosphatase, and serum creatinine (2 mg/dl) at presentation. Vitamin D and parathyroid hormone levels were within normal range. While urine analysis revealed glycosuria but nil albumin in the urine, the 24-hr collection had more than 1 g of protein. In the face of low serum phosphate, she had a 24-hr urine phosphate of 502.9 mg suggesting phosphaturia as the cause of low serum phosphate. Her autoimmune workup, serum, and urine electrophoresis also turned out negative.

Chest X-rays showed pseudo-rib fractures (Milkman's fracture) on the second and sixth ribs on both sides. A Tc99 bone scan demonstrated foci of abnormally increased tracer concentration in corresponding bones and other multiple sites, as seen in Figure 1.

A diagnosis of tenofovir disoproxil fumarate induced Fanconi syndrome with severe osteomalacia was made. Switching to another tenofovir prodrug, tenofovir alafenamide, and repletion of calcium, phosphates, potassium, and sodium bicarbonate by intravenous and oral routes resulted in significant improvement over a period of 2–3 weeks.

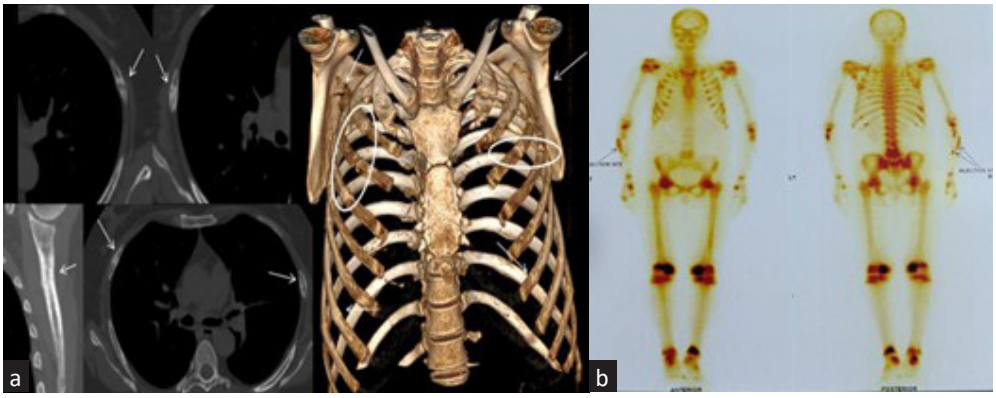

Figure 1: (a) Computed tomography thorax imaging and 3D reconstruction showing pseudofractures or Milkman's fractures of multiple ribs bilaterally and medial borders of both scapulae are shown by the white arrows and white circles respectively. (b) Tc 99 bone scan showing increased uptake in the same areas.

Vigilance during tenofovir treatment is recommended by the EASL and IDSA. Serum creatinine and electrolytes, including phosphate, should be obtained every 3 months in the first year and every 6 months thereafter.[1,2] TDF should be discontinued for serum phosphate below 2 mg/dL or creatinine clearance below 50 mL/min.[2] Stopping TDF typically leads to renal recovery over months, though there have been reports of persistent renal impairment.[3]

Conflicts of interest: There are no conflicts of interest.

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