March 9, 2021

Greetings Tough Beans Participants,

We learned two great cases this evening about APOL-1 nephropathy and resistant hypophosphatemia related to Fanconi Syndrome, presented by Dr. Mandayam and Dr. Polani, respectively. Please contact me if you need the full presentations or literature.

I summarized other take home messages from the discussion, especially from the APOL1 case.

1. *APOL1* G1 or G2 variant is gain of function mutation compared to wild type APOL1 G0. The risk allele overcomes the resistance of parasite (*Trypanosoma brucei rhodesiense)* and restores trypanolytic activity, which confers adaptive advantage. However, two copies of *APOL1* risk alleles (i.e. G1/G1, G1/G2 or G2/G2) greatly increase the risk of CKD. The odds ratio of the risk alleles is 1.5 in non DM CKD; and 89 in HIVAN in African population.

2. However, about 1/5 African Americans carry 2 high-risk *APOL1* alleles, and the majority of such individuals do not develop kidney disease.

3. Screening for APOL1 risk alleles can be considered in non DM CKD patients with unclear etiology. The role of screening APOL 1 risk alleles in kidney transplant donor and recipient is unknown and APOLLO (*APOL1* Long-Term Kidney Transplantation Outcomes Network) is a prospective study designed to answer this question.

4. The genotyping test can be done either by saliva or blood samples. The cost is about 400 dollars.

5. APOL1 protein is expressed in podocytes, glomerular endothelial cells, and proximal tubular cells. However, the function of APOL-1 in the kidneys remains unclear. Current clinical trial led by Dr. Mandayam is a phase 2a trial to investigate a medication that inactivates APOL1 gene product.

6. Urine phosphorus excretion less than 100mg in 24 hours is the cutoff to rule out renal phosphorus wasting in the setting of hypophosphatemia.

7. Severe hypophosphatemia can cause hemolysis.