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PERSPECTIVE

The mislaid clue to APOL1 kidney disease prevention in blacks

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APOL1-Mediated Kidney Disease or AMKD has in recent years been identified with a health crisis of almost staggering proportions among the 38 million African Americans of slave descent. The G1 and G2 variants of the apolipoprotein-L1 (APOL1) gene are found exclusively in West Africa and as a consequence carried by a third of Blacks in the United States. Those with both variants or two copies of one have a 13 percent risk of kidney failure from the AMKD form of Chronic Kidney Disease generated by a broad range of disorders, including focal segmental glomerulosclerosis, lupus nephritis, diabetic nephropathy, HIV-associated nephropathy, kidney allografts, coronary artery disease, cardiomyopathies and preeclampsia in childbirth [1]. However, the one disease symptom that has gained the least attention in the medical literature, but nevertheless signals the initiating stage of AMKD in Blacks is salt-sensitive hypertension [2, 3]. Americans of non-West African ancestry are also susceptible to chronic kidney disease. But lacking the G1 and G2 variants, their disease rather than being triggered by the singular APOL1 gene, has a wider range of causes. They include systemic rather than salt-sensitive hypertension, heart disease, polycystic kidney disease, autoimmune disorders, certain medications and other diseases.

It is the constancy of the sodium-triggered progression of Black susceptibility to chronic kidney disease that turned my thoughts back to the earliest years of my own academic career. As an aspiring historian, I had devoted nearly a decade to the rigorous study of classical Arabic, including the chronicles of 16–17th centuryTimbuktu. And that is how I first learned about the exceptional role that "*almilh alsakhriu*"[rock salt] played in the history of those communities that would eventually be transported to the Americas as slaves [4].

A map published in the Catalan (Spain) Atlas of 1375 depicted what little Europeans knew of the origination point of West Africa's famed gold-salt trade, which supplied gold coinage to much of medieval Europe. Seated on a gilded throne, and bedecked with a gold crown and orb, the Mansa Musa of Mali was presumed to be one of the wealthiest men in the world. Fig. 1 At that time, the merchant empires of the West African interior – ancient Ghana, Mali, Songhay and Timbuktu – procured their wealth on the rather lopsided pound for pound exchange of rock salt for pure gold. As for why the inhabitants of the gold fields, which dotted the landscape outside the boundaries of those states would strike such bargains was because they inhabited one of the most sodium-deficient regions on the African continent. The elites who controlled the region's gold fields displayed nuggets of rock salt in their dwellings as we might a collection of rare gems. The lowly peasant farmers, on the other hand, had never even tasted table salt, flavoring their food with the ashes of millet leaves (potassium chloride). Sea salt from the Atlantic ocean could not be traded so far inland because the sweltering heat of the tropics turned the impurities embedded in ocean salt rancid and thus unsellable. However, by the late 17th century much of the West African goldfields had been depleted and the Transatlantic slave trade had arisen to take its place. The most prized commodity in this new marketplace became "black gold". These were slaves from that same low-sodium region, who were captured and marched 1000 miles to the coast in chains. Those who survived were uploaded onto slave ships bound for the Americas. Only later in my career did genomic history evolve into a research obsession, as I recognized the crucial need to correct misinterpreted etiologies of certain diseases, caused by medical researchers' imprecise knowledge of African ecological environments. This was particularly the case when I learned from a MEDLINE search of every single article that had ever been published on AMKD in Blacks that researchers had locked themselves into the assumption that G1 and G2 APOL1 variants functioned in the Tsetse Belt of West Africa solely as a natural immunity to Trypanosomiasis (African sleeping sickness). While the concept known as "gene pleiotropy" demonstrates that genes can influence a multiplicity of phenotypes, no such leeway had been given for the APOL1 West African alleles.

Ironically, As early as January 2001, an article in *Hypertension* concluded: "Generalized upregulation of sodium channel activity may account for the high prevalence of salt-sensitive hypertension in the black population" [5]. As the field of genomic research gained steam, so did research identifying the West African G1 and G2 APOL1 variants' unique capacity to retain and re-absorb scant amounts of sodium (a requirement for survival in West Africa's low sodium interior). A 2013 study by Wanzhu Tu and J. Howard Pratt in *Current Hypertension Reports* observed:

"The characteristic low-renin, salt-sensitive hypertension of blacks is consistent with the kidney reabsorbing additional sodium (Na), which leads to an expanded plasma volume that drives the BP" [6].

By 2024, researchers had established that APOL1-mediated Na +/K+ (sodium/potassium) transport functions as "the proximal driver of APOL1-mediated kidney disease" [7]. But the APOL1 variants' sodium sensitivity was not linked to AMKD prevention. The racialized nature of medical research failed to differentiate between coastal West Africans and the ancestors of Black Americans descended from slaves, who emanated from the sodium- deficient interior. Coastal West Africans, given the availability of sea salt, share a similar dietary sodium intake as Europeans, ranging from 3000–5000 mg/day. However, interior West Africans, were adapted to a salt-less no-man's-land, that not

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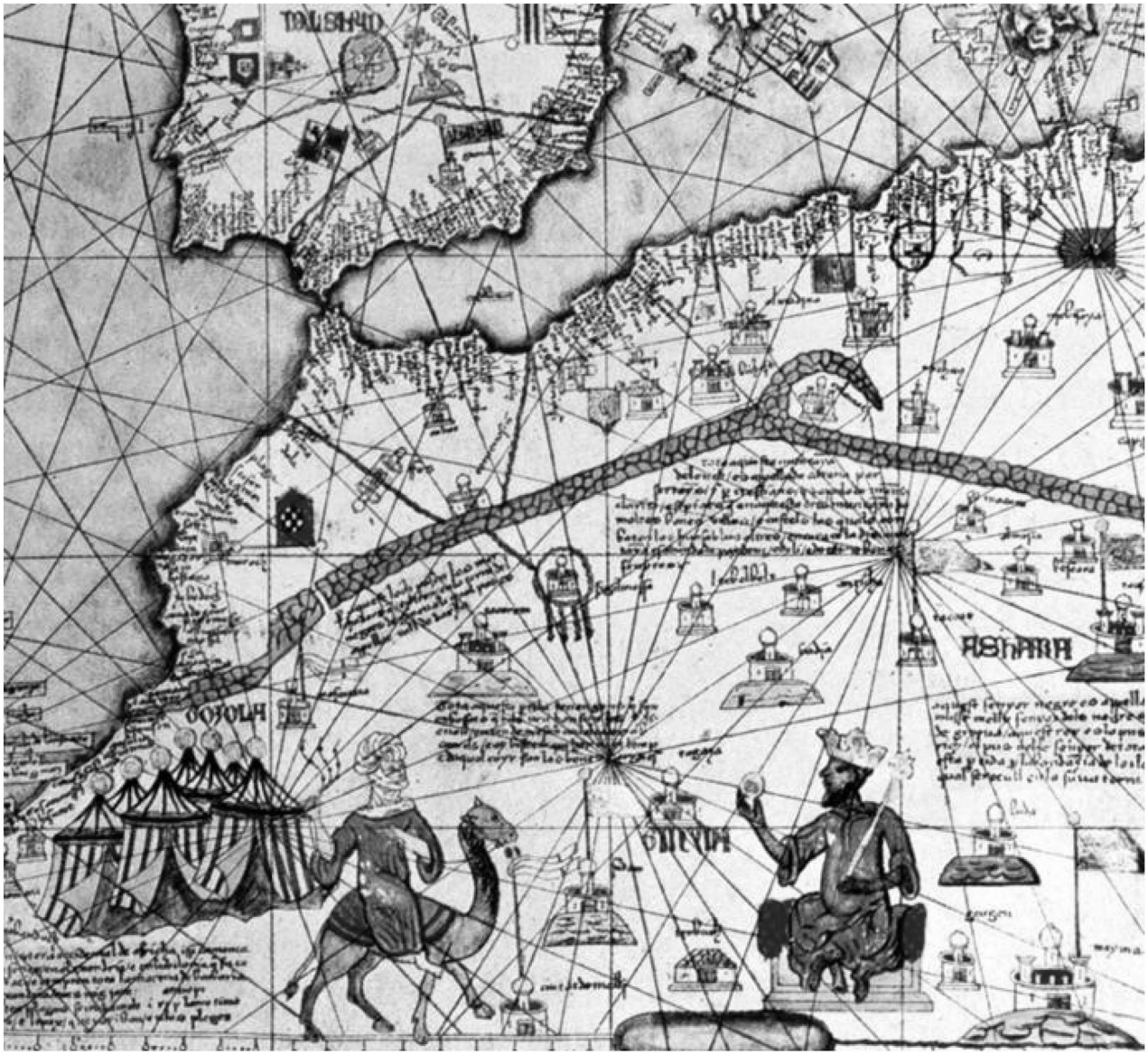

Fig. 1 The Catalan Atlas of 1375 depicts the "Golden Emperor" Mansa Musa of Mali. CPA Media Pte Ltd/Alamy Stock Photo.

even coastal Africans could countenance for long periods of time. Interestingly, a 2015 report of field work conducted in West Africa showed that virtually all of the highest frequency areas where the G1 and G2 variants were found are located in interior rather than coastal regions of West Africa. The single exception was the presence of the G1 variant in the area surrounding Lagos, Nigeria It may be worthwhile noting that large scale population movements to West African coastal cities in modern times have resulted in greater genetic admixture [8].

At the present time there is no cure for AMKD, and available kidneys for transplantation remain scarce. But it may be possible to prevent the disease from occurring in the first place. African Americans of slave descent inherited a precious gift from their ancestors. It is gene variants that increased kidney function efficiency to a level that allowed humans to survive in the salt-less West African interior. All Americans consume too much salt, on average 3400 mg/day. But those of us in the Black community can choose to honor our bodies and protect our unique genetic inheritance by limiting our intake to the 1500 mg/sodium/day that has already been established as the medical protocol for Americans susceptible to salt-sensitive hypertension.

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AUTHOR CONTRIBUTIONS

I confirm sole responsibility for the conception of the study, the execution of the research, the analysis of the data, the preparation of the manuscript, and the presentation of the results of: THE MISLAID CLUE TO APOL1 KIDNEY DISEASE PREVENTION IN BLACKS. I have reviewed all versions of the manuscript and approved the final version for submission.

COMPETING INTERESTS

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ADDITIONAL INFORMATION

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