ANCESTRAL GENOMICS

The Etiology of APOL1 Kidney Disease Prevention in Blacks

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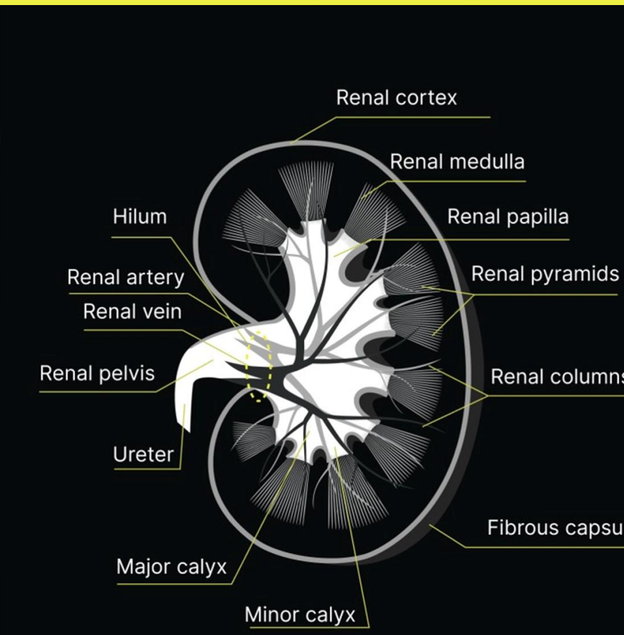
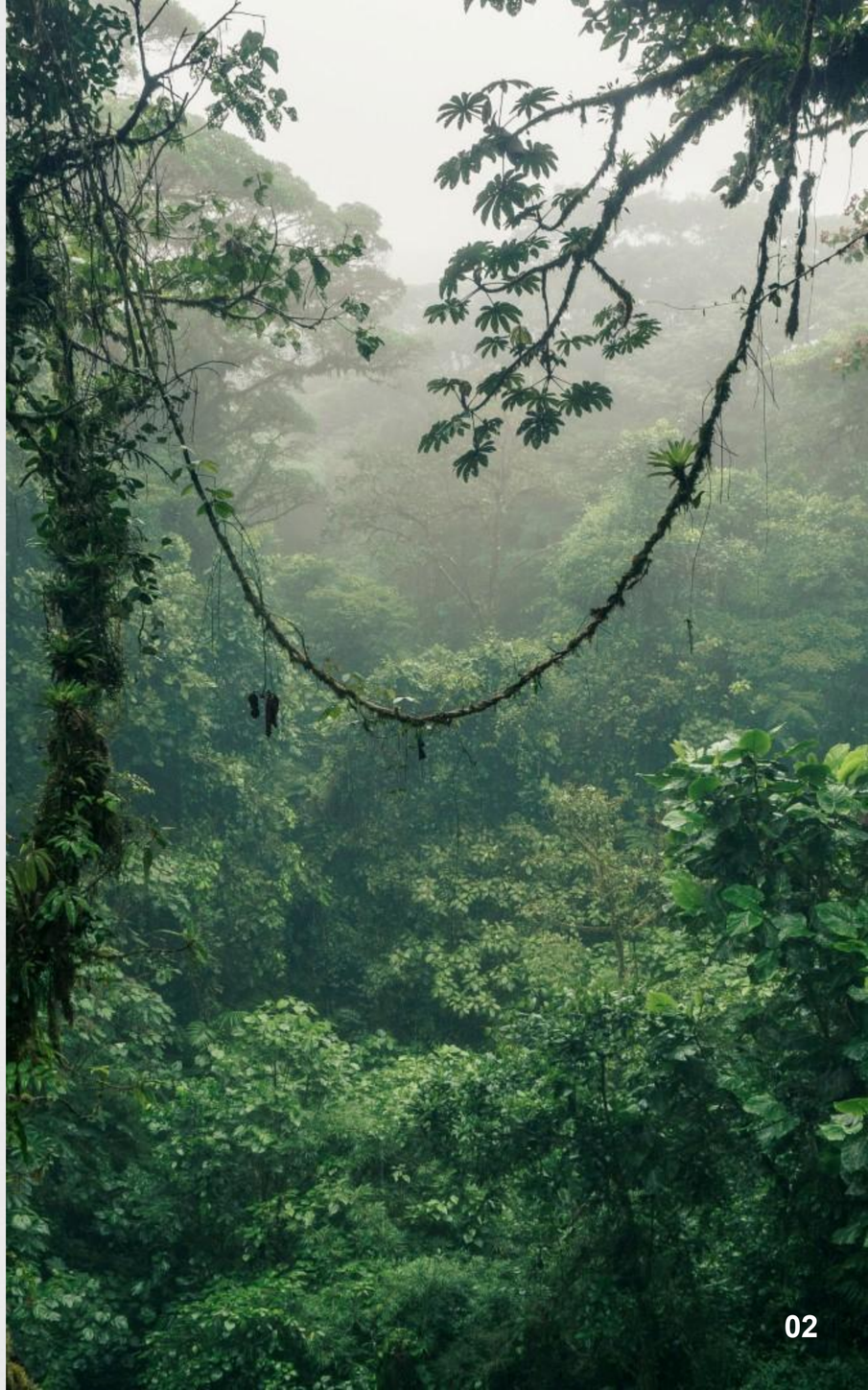


A genomic historian searches for health and medical clues in the ancestral history of genetic populations.



This talk will endeavor to show how & why a new methodological model can transform the way chronic kidney disease in Blacks is both understood and prevented. In order to clarify how it works, I will first offer background on:

1. **Why health & medical research need a new model to substitute for race in modern medicine;**

2. **And the contours of this non-racial ECOLOGICAL NICHE POPULATIONS MODEL.**

BEWARE the use of “RACE” in Public Health & Genomic Medicine

For Example Can You Tell Which is Which??

High Risk of Sickle Cell Anemia



Low Risk of Sickle Cell Anemia



Why We Must Use More Localized Ways

Lactose Tolerance is a straightforward example of a genetic trait that allows certain populations to digest the lactose in milk. But different gene variants create this function in different human communities. This is the pattern of many genetic functions as well a diseases, rather than the exception:

In Northern Europeans	⟶	the lactase-phlorizin hydrolase (LCT) gene 13910-T/T gene variants.
In **Eastern Europeans** and populations of **Northern India**	⟶	the LCT gene 22018A gene variants.
In Sudanese	⟶	LCT C/G-13907
In Kenyans	⟶	LCT T/G13915
In Tanzanians	⟶	LCT G/C-14010

ETC – ETC – ETC ...

*S.A. Tishkoff, F.A. Reed, A. Ranciaro, B.F. Voight, C.C. Babbitt, J.S. Silverman, et al. Nat Genet. 2007 Jan; 39(1):31-40

The 2003 Human Genome Project's Unanticipated Dilemma

THE GOAL:

Identifying disease at the genetic level in order to craft individualized cures.

THE HICCUP:

All humans share the same number of genes, approximately 22,000. In 2003, scientists believed that our species carried 2 million variants of those genes.

- ✓ But we now know that the actual number of gene variants is closer to **335 million** and they do not correspond to our racial classifications.
- ✓ In fact, the greatest amount of genetic diversity or variation remains on the African continent of our birth.

Medically, Who are African-Americans of Slave Descent?
What Health Disparities Does This Community Share in Common?

African-Americans suffer a 75% rate of hypertension

High stroke risk

High rate of kidney disease

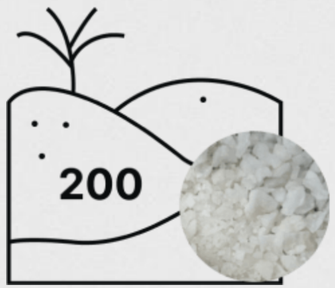
The ancestors of Black Americans came from the deep interior of West Africa.

This region is one of the most sodium deficient in the world.

These peasant farmers had never even tasted salt. They flavored their food with potassium chloride, derived from the ashes of burnt millet leaves.

On the other hand...

Coastal West Africans like Europeans were genetically accustomed to consuming between **3,000 and 5,000 mg/sodium/day.**



But the ancestors of African-Americans lived on **less than 500 mg/sodium/day.**

?

How was that possible, when American medical textbooks say that humans cannot survive on less than **500 mg/sodium/day?**

Mineral Deposits in Western Africa

The Components of an ECOLOGICAL NICHE POPULATION (ENP)

Defining an African-American/Sodium-Metabolic Disparities ENP

FACTOR "A"
Shared Geographic Factor:

(37 million descendants of Slaves brought to the U.S. before 1865, from low-sodium interior of West Africa)

FACTOR "B"
The Admixture Factor:

Median admixture ratio of:

West African	**74%**
Northern European	**24%**
Native American	**1%**

FACTOR "C"
Shared Disease Factor

- High Rates of Hypertension
- Strokes
- Kidney Disease

FACTOR "D"
Shared Disease-Triggering Genomic Profile :

- G1
- G2 variants APOL 1 gene

African-American/Sodium-Metabolic Disparities ENP

75% DNA

Niger-Kordofanian
\West African

200mg/day

+

25% DNA

Northern European

3000mg/day

=

100% DNA

African-American

1000mg/day

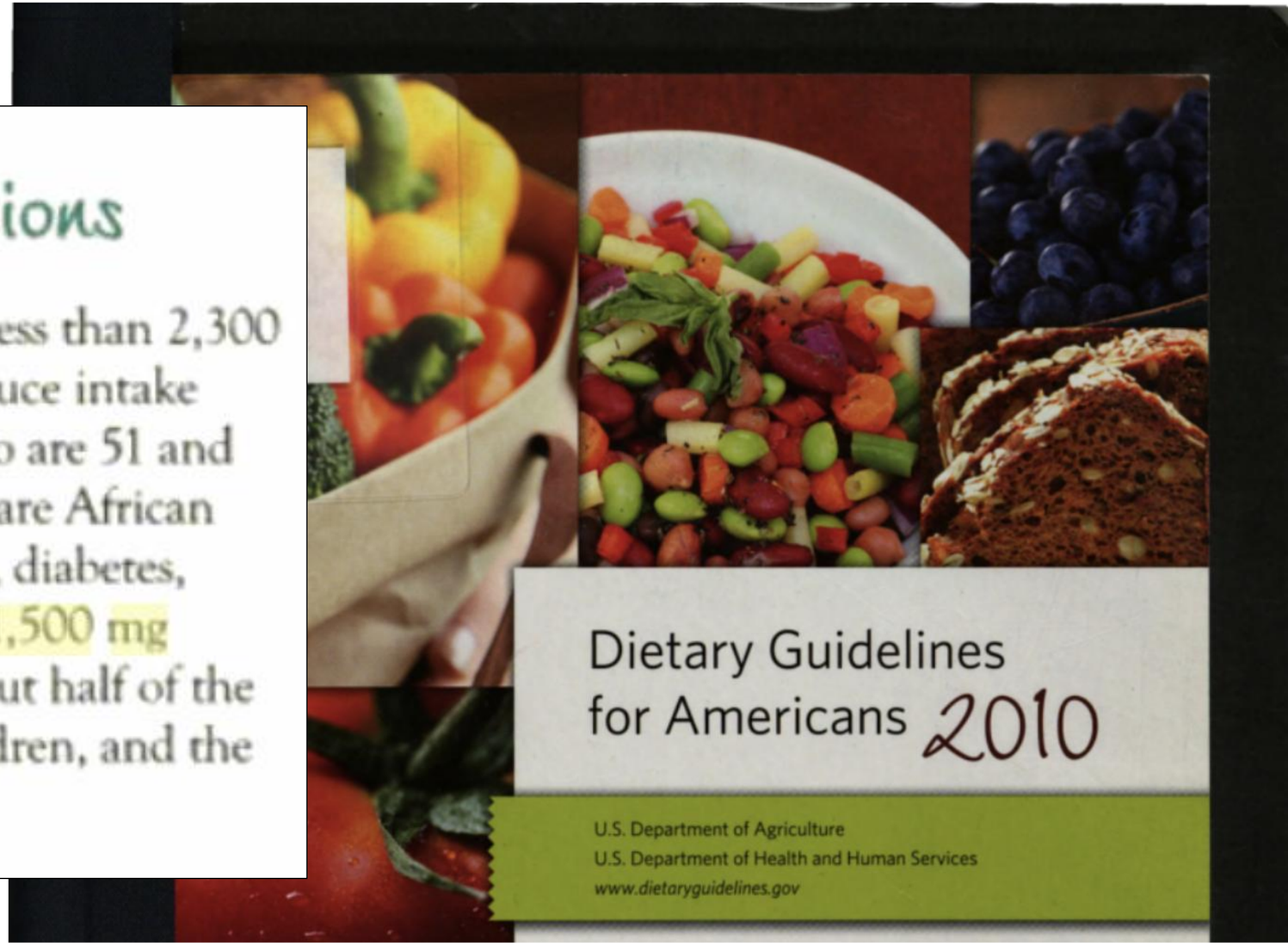
CALCULATION:

(200x.75) + (3000x.25) = **1000 mg/sodium/day**

As far back as 2010, the U.S. Department of Health & Human Services and the Department of Agriculture in its Dietary Guidelines report identified African-Americans as an at-risk group that should reduce sodium intake to 1,500 mg per day.

Key Recommendations

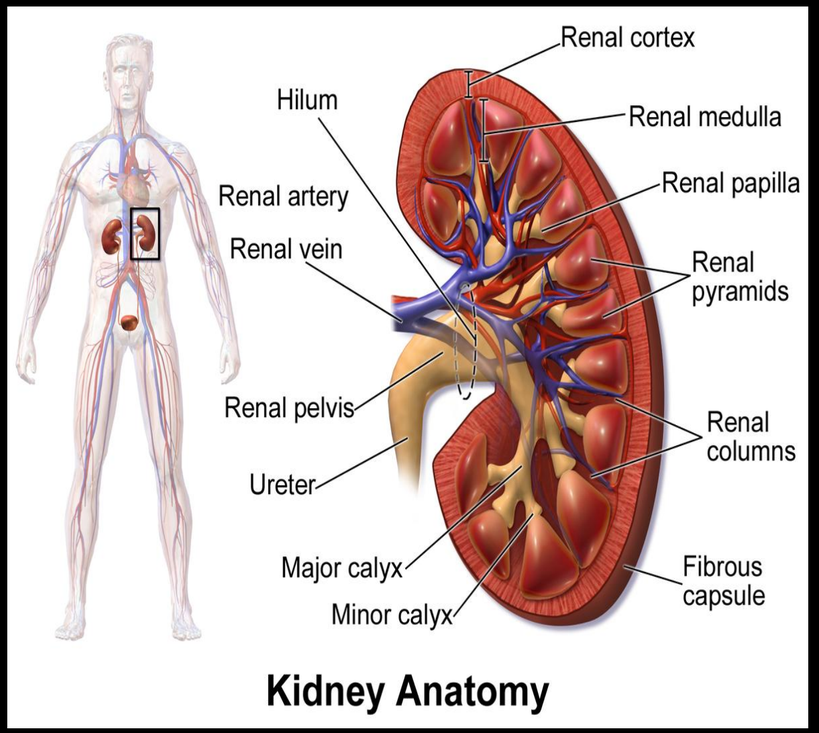
Reduce daily sodium intake to less than 2,300 milligrams (mg) and further reduce intake to 1,500 mg among persons who are 51 and older and those of any age who are African American or have hypertension, diabetes, or chronic kidney disease. The 1,500 mg recommendation applies to about half of the U.S. population, including children, and the majority of adults.



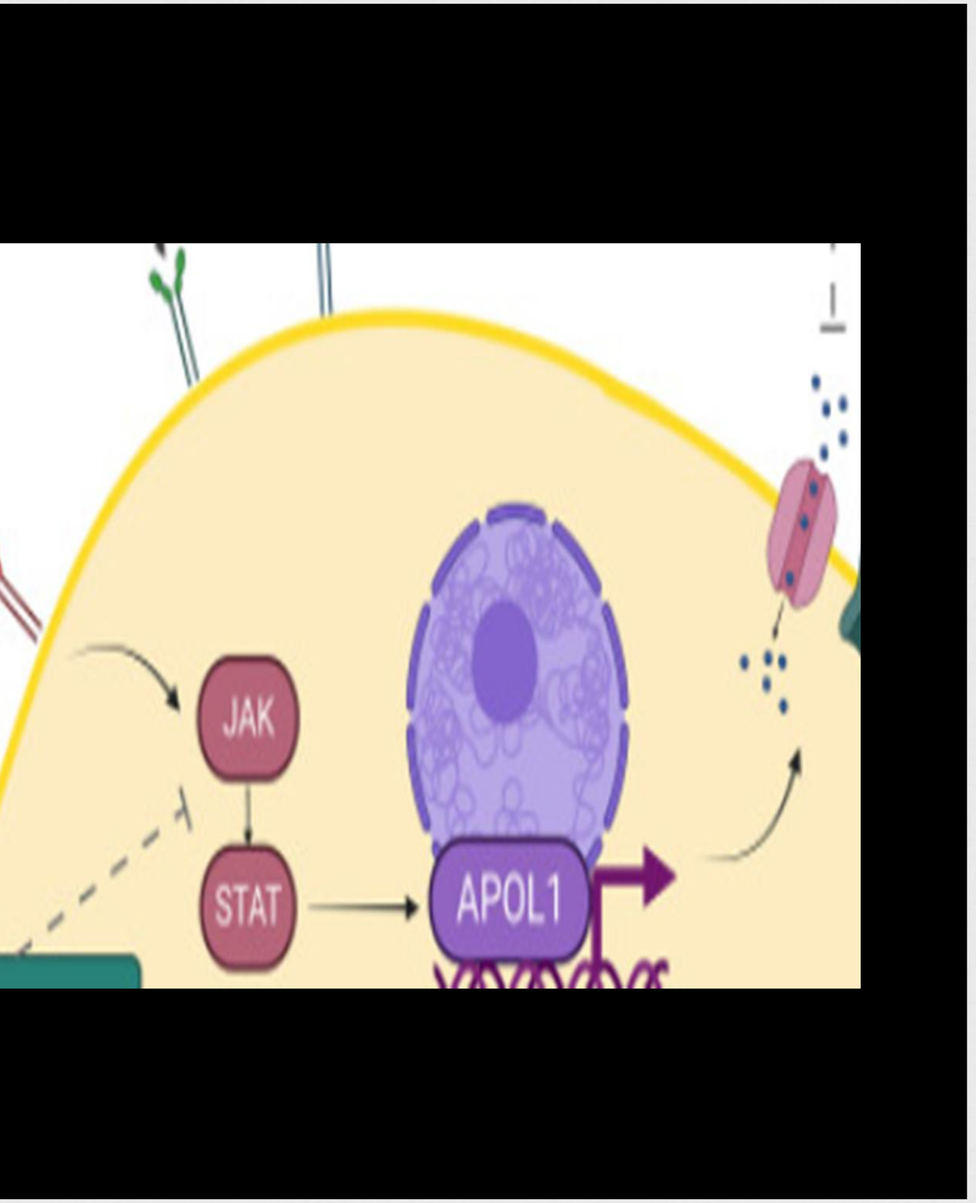
Using APOL1-Mediated Kidney Disease (AMKD) in Blacks as a FOUNDATIONAL Case Study

The G1 and G2 APOL1 gene variants were discovered in 2010. They are found almost exclusively in people of the West African interior.

Medical researchers have recently found that these variants are associated with a two-to-100-fold increased risk of kidney disease development. *



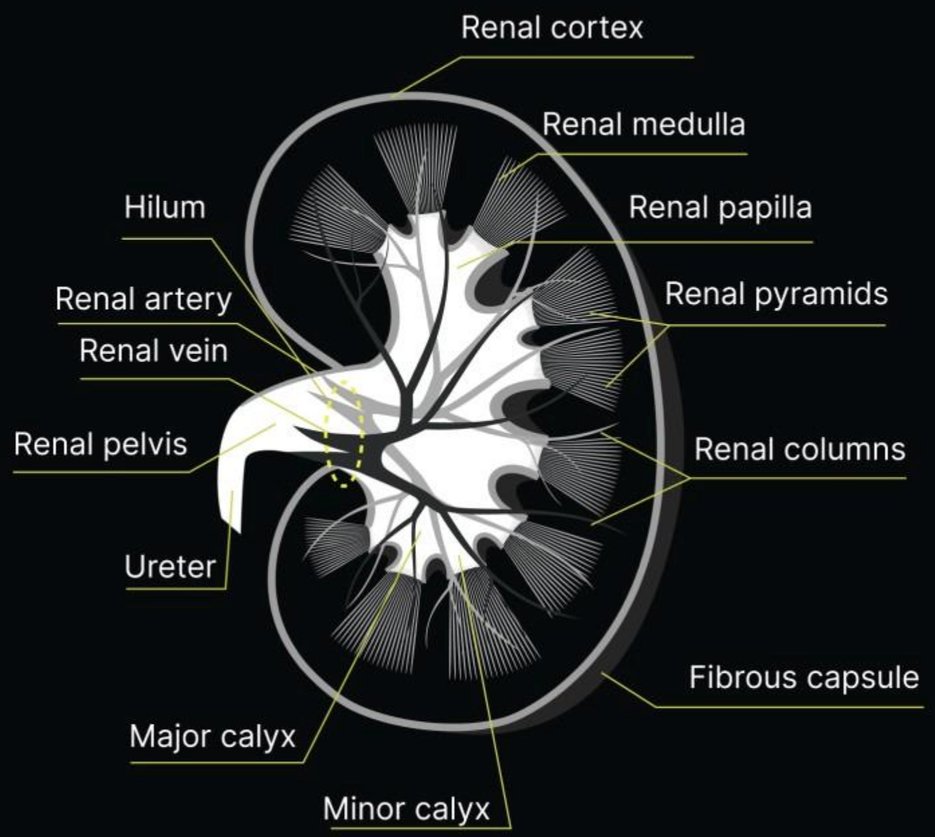
Kidney Anatomy



WHAT IS APOL1-MEDIATED KIDNEY DISEASE (AMKD)?

11,000 Black Americans die each year from AMKD. The G1 and G2 variants of the APOL1 gene are carried almost exclusively by populations of West African ancestry.

Kidney anatomy



The APOL1 gene variants

The G1 and G2 APOL1 gene variants are highly retentive of sodium. They are found almost exclusively in people of the West African interior.

Medical researchers have recently identified the function of these variants as being associated with high rates of hypertension and a two-to-100-fold increased risk of kidney disease development. *

*https://www.niddk.nih.gov/news/archive/2017/story-variants-unraveling-genetic-basis-elevated-risk-kidney-disease-african-americans

AMKD DISEASES

The initiating Disease in each case is:

SALT SENSITIVE HYPERTENSION:

Focal segmental glomerulosclerosis (FSGS)

Lupus nephritis

Membranous nephropathy

Nephrotic syndrome

HIV-associated nephropathy (HIVAN)

Preeclampsia leading to childbirth mortality

ALL OF WHICH LEAD TO KIDNEY FAILURE

A FLAWED MEDICAL CONSENSUS

APOL1 at 10 years: progress and next steps
BI Freedman, JB Kopp, MG Sampson, K Susztak - Kidney international, 2021 - Elsevier
… APOL1 G1 and G2 risk variants (RVs) modify susceptibility to African sleeping sickness. The … biological function of APOL1 is conferring protection against trypanosomiasis. To increase …

susceptibility associations with African trypanosomiasis
A Cooper, H Ilboudo, VP Alibu, S Ravel, J Enyaru… - elife, 2017 - elifesciences.org
… study to test the relationship between APOL1 G1 and G2 variants and susceptibility to the two different forms of human African trypanosomiasis, Tb rhodesiense in

HTML] The Apolipoprotein L1 Gene: Parasites vs Proteinuria–An Evolutionary Tug of War
L McLaughlin - clinicalcorrelations.org
… APOL1 is taken up by these trypanosomes and forms a chloride ion channel within the …
in West Africa evolved modified APOL1 proteins. The G1 and G2 alleles resulted from two …

- A MEDLINE search of every single article that had ever been published on AMKD in Blacks asserted that the 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 investigation has been conducted on the APOL1 West African alleles. Researchers did not see the need for it.

SODIUM– THE OVERLOOKED CLUE

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.” 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.”

By 2024, researchers had established that APOL1-mediated Na+/K+ (sodium/potassium) transport functions as “the proximal driver of APOL1-mediated kidney disease”. But the APOL1 variants’ sodium sensitivity was not linked to AMKD prevention.

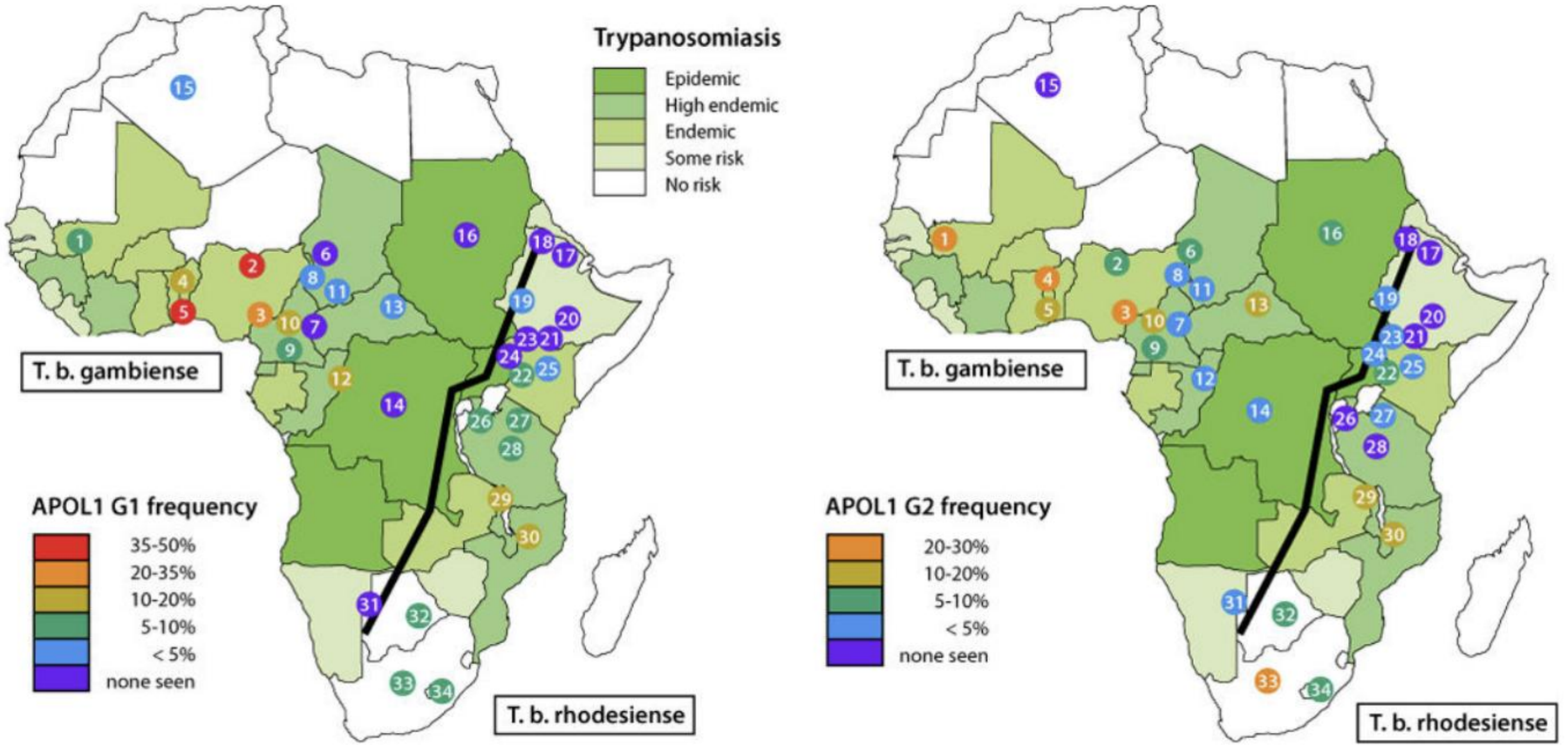


Figure 2.

Geographic distribution of *APOL1* risk alleles and of *Trypanosoma brucei* subspecies. Shown are the distributions of G1 and G2 alleles among population groups, mostly in sub-Saharan Africa, together with the population ranges for *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*.[18] The Great Rift Valley is shown as line running from southwest to northeast. The population numbers refer to Table 1.

But why should this “seemingly minor” genetic data be taken far more seriously?

The ancestors of African-Americans lived on a dietary sodium intake of less than 500 mg/day. They had become genetically adapted to inhabiting one of the most sodium-deficient regions of the world.

So let me ask in Conclusion:

What percentage of Black Americans have been made aware of the fact that their susceptibility to fatal, sodium-triggered diseases is dramatically higher than that of other groups?

0%

This is the challenge I bring to you as members of the public health community.

But let me also say that Blacks of slave descent carry one of the most precious gifts that nature could confer? It was the attunement of their bodies over time to the ecological niche their ancestors had inhabited.

But this ancestral gift can & must be protected from sodium toxicity. That is, Blacks of slave descent will need to reduce their sodium intake to 1500 mg/sodium a day.

I should like to thank the Michigan Osteopathic Association & Dr. Ramona Wallace as well as Melissa Budd for giving me the opportunity to share this research with you.

Thank you