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Population Ancestry and Genetic Risk for Diabetes and Kidney, Cardiovascular, and Bone Disease: Modifiable Environmental Factors May Produce the Cures

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Abstract

Variable rates of disease observed between members of different continental population groups may be mediated by inherited factors, environmental exposures, or their combination. This manuscript provides evidence in support of differential allele frequency distributions that underlie the higher rates of non-diabetic kidney disease in the focal segmental glomerulosclerosis spectrum of disease and lower rates of coronary artery calcified atherosclerotic plaque and osteoporosis in populations of African ancestry. With recognition that these and other common complex diseases are affected by biologic factors comes the realization that targeted manipulation of environmental exposures and pharmacologic treatments will have different effects based on genotype. The current era of precision medicine will couple one's genetic make-up with specific therapies to reduce rates of disease based on presence of disease-specific alleles.

Keywords

ancestry; *APOL1*; cardiovascular disease; diabetes mellitus; genetics; kidney disease

Advances in molecular genetics have made identification of gene variants associated with heritable disorders possible; although clarifying the cellular and mechanistic roles of risk variants remains incomplete. One of the most important challenges is the understanding of

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disorders that preferentially affect or have systematically poorer outcomes in groups with specific population ancestry. Many disease variants manifest similar effect sizes and allele frequencies across populations; others display markedly different frequencies between ethnic groups. These latter variants can profoundly influence population-specific rates of disease, as exemplified by the kidney disorders focal segmental glomerulosclerosis and immunoglobulin A nephropathy.

Molecular breakthroughs have not only clarified and linked previously misclassified kidney disorders as to underlying pathogenesis; they have also provided remarkable insights into our understanding of differences in population ancestry and risk for diabetes, atherosclerosis, and alterations in calcium and vitamin D metabolism underlying osteoporosis. With these developments comes realization that environmental factors are critical in many genetically mediated disorders, impacting disease expressivity, progression and/or severity. Modifying environmental risk factors may lead to novel treatments for kidney diseases with an inherited component, but they must be viewed in the appropriate context to maximize effectiveness and safety. We are nearing an era where genetic risk stratification coupled with targeted manipulation of environmental exposures will reduce the rates of complex kidney, cardiovascular and bone disease. In this era of personalized or precision medicine, practitioners should be aware that environmental manipulations may best be targeted based on underlying genetic risk; the same interventions will not be equally effective in all patients.

Genomics in complex disease: current status and limitations

Research tools available in the modern molecular era have led to the search for genes underlying susceptibility to virtually all human diseases, intermediate phenotypes, and laboratory test results. Much has been learned by performing genome-wide association studies (GWAS) in complex disease; particularly identification of previously unsuspected pathways involved in disease causation. Associated genes may one day serve as novel treatment targets. However, it has become apparent that the risk attributed to common genetic variants identified in GWAS, even those incorporating tens of thousands of participants is typically low.[1] Conversely, the number of variants needed to explain a significant fraction of the total variation observed in a trait is so large that their immediate clinical utility may be limited.[2] GWAS have not yet identified risk alleles specific for kidney disease progression versus initiation, or the behavior of these risk alleles in different subgroups.

While researchers struggle to identify the missing heritability in diseases such as type 2 diabetes mellitus (T2DM) and hypertension, limitations must be acknowledged. These disorders are heterogeneous.[3;4] Hypertension reflects the physical finding of elevated blood pressures, while diabetes simply reflects elevated blood sugars. The processes that lead to increased blood pressure and blood sugar often differ markedly between individuals and populations. In addition, the hallmark of inherited diseases is familial aggregation. Many GWAS have evaluated traits with limited evidence of familial clustering; these may not have a major genetic basis. Environmental contributors may be overlooked or difficult to account for in genetic studies and it is likely that unsuspected environmental factors contribute to risk. Even when data on known environment factors are available, genome-wide scans for gene-by-environment effects quickly become hard to power due to restricted significance thresholds imposed by the need to account for multiple testing and the paucity of existing replication data. Moreover, researchers may analyze convenient and available databases and need to appreciate their limitations. This is apparent when considering the United States Renal Data System (USRDS), a comprehensive and valuable registry.[5] Here, causes of kidney disease are provided by thousands of physicians, typically without kidney biopsy

material or standardized diagnostic criteria.[6] As such, many diagnoses in the USRDS are suspect. Bias has been observed in physician coding of the etiologies of kidney diseases among patients of different ethnicities.[7] These limitations are likely to be appreciated by nephrologists; however, they may be less apparent to epidemiologists, hypertension specialists, and basic–science researchers.

These many limitations complicate studies evaluating specific etiologies of end-stage renal disease (ESRD). However, disease classification may also benefit from detection of major kidney failure susceptibility loci associated with common disorders in general dialysis populations. This occurred with the apolipoprotein L1 gene (*APOL1*) association which re-classified several non-diabetic kidney diseases into a single spectrum.[8–10]

Differences in disease susceptibility and treatment response based on population ancestry

Physicians are trained to approach illness in patients of different population ancestries in uniform fashions. This is rational, as humans are all far more alike than different. At the DNA level, globally we share greater than 99% sequence homology taking into account all common forms of sequence diversity. [11;12] Differences in disease susceptibility between populations frequently relate to variable lifestyles, environmental exposures, and, unfortunately, differential access to healthcare. As such, environmental factors must be considered whenever variable disease risk is seen between groups with different population ancestry (Box 1).

Box 1

Effects of population ancestry on rates of disease

African ancestry – increased risk of focal segmental glomerulosclerosis and type 2 diabetes mellitus
Asian ancestry – increased risk of Immunoglobulin A nephropathy
European ancestry – increased risk of atherosclerosis and osteoporosis

Approximately 1% of the genome is known to vary between geographically isolated groups. This seemingly small difference in DNA sequence can have profound impacts on many aspects of public health, as discussed below for common disorders treated by nephrologists. It is unfortunate that the variable genetic foundations which may impact disease susceptibility are frequently ignored in attempts to avoid bias. Medical students and residents are often encouraged to present cases in ancestry-neutral fashions (*e.g.*, 62 year old woman); hence potentially useful (free) information that could be gleaned from self-reported ancestry may not be available. Bias or exclusion of individuals from receiving necessary medical care should never be the goal of reporting this information and we appreciate that population ancestry may sometimes be difficult to define, as for individuals who have relatives from multiple ancestral groups. However, equally obvious should be the potential value that this information can provide when it is appropriately applied and its limitations appreciated. The goal of genetics research is to identify specific risk variants causing disease; inherited genotypes are the primary sources of biologic variation. Nonetheless, differential distribution of risk alleles between groups with different population ancestry exists in many disease states and may provide valuable information. Using this sensitive information as a surrogate for environmental exposures can lead to stereotyping; this must be avoided.

Tables 1 and 2, respectively, list phenotypes based on population ancestry that are widely observed in patients with essential hypertension and T2DM. The different pathogeneses in these heterogeneous disorders may encourage different initial treatment choices based on ancestry. For example, calcium channel blockers and diuretics more effectively lower blood pressure in hypertensive patients with African ancestry; while renin-angiotensin system (RAS) blockers are more effective in patients with European ancestry.[13] This reveals that population ancestry–specific disorders producing the phenotype of high blood pressure exist. More broadly, this observation demonstrates that each genomic region has a population and ancestral history and emphasizes that individuals of a given continental population group may have disease-relevant variants typical for other population groups at a given locus. Hypertension is not a single disorder, but a physical finding contributing to risk of cardiovascular disease (CVD) and progression of kidney disease.

Response rates to pegylated interferon alfa-2a therapy for hepatitis C virus infection also vary markedly based on ancestry. Individuals of African ancestry have lower rates of sustained virologic remission relative to those of European ancestry. Approximately 50% of the difference in treatment response relates to allelic differences in the interleukin 28b gene (IL28b; human gene symbol *IFNL3*).[14] This demonstrates that pharmacologic responses can relate to population ancestry–related genotypes translating to treatment efficacy.

T2DM and metabolic syndrome

T2DM is a heterogeneous metabolic disease characterized by peripheral insulin resistance and pancreatic beta-cell dysfunction. Differential prevalence rates have been observed for European Americans, Hispanic Americans and African Americans (7.1, 11.8 and 12.6%, respectively). This leads to increased risk for development of T2DM in Hispanic Americans (66% higher) and African Americans (77% higher), relative to European Americans.[15] Although obesity is a known risk factor[16] with increased prevalence in ethnic minorities[17], epidemiologic data reveal a significantly higher risk of T2DM in African Americans and Hispanics Americans relative to European Americans after controlling for body mass index.[18] While these observations could relate to differences in fat storage[19;20] or increased insulin resistance in minorities[21;22], additional factors are likely involved in the differential disease prevalence (Table 2).

T2DM has a demonstrated genetic component that varies across population ancestries. In European-derived populations T2DM is estimated to have a heritability of 0.25, i.e. 25% of the variation observed in this trait within a population is due to genetic factors. In comparison, Hispanic Americans and African Americans have a higher estimated genetic component of 0.53–0.60.[23;24] Despite an increased genetic predisposition, genetic variants identified to date from GWAS of European-derived populations have limited effect in minority populations. Table 3 displays differential genetic associations in T2DM across population ancestry groups. These results suggest that a significant fraction of the causal variants may not be well covered on existing, largely Eurocentric genotyping chips and that larger, better powered studies are needed in minority populations to identify trait associations and aid in fine-mapping efforts.[25;26]

CVD

Based on the above discussions, it is critical to compare populations with equivalent healthcare access and account for the potential effects of population stratification and admixture before computing ancestry specific disease risks. There is no better example to demonstrate these effects than susceptibility to coronary artery disease (CAD) and myocardial infarction (MI). Here, inclusion of healthcare access, an environmental factor, reversed currently appreciated risk based on population ancestry.

African Americans and other minority groups in the general population have markedly higher rates of MI and CVD than European Americans.[27] Associated CAD risk factors (diabetes and hypertension) are also more frequent and severe in African Americans than European Americans. As such, many have assumed that inherently higher risk for CAD and MI exists in those of African ancestry, exacerbated by exposure to a western lifestyle.

However, a series of reports from medical systems providing uniform healthcare access regardless of population ancestry consistently demonstrates markedly *lower* risk for MI and CVD in minority populations, especially African Americans relative to European Americans.[28–30] These data included nearly one million patients cared for by the Veterans Administration (VA), Kaiser-Permanente Healthcare System, and the Center for Medicare and Medicaid Services–supported ESRD program. These studies evaluated equal healthcare access for periods of between 1.5 and 3 years during adulthood; they could not address prior decades of disparate access. Nonetheless, strikingly, 50% lower rates of MI were consistently observed in African Americans with diabetes, relative to European Americans. Dramatically lower rates of CVD and death are also observed in African Americans with ESRD on renal replacement therapy, compared to European Americans.[5]

How do we reconcile the markedly different associations between African ancestry and risk for MI and CAD in general populations versus in populations with equivalent healthcare access? Virtually all studies that evaluated the relationship between self-reported ethnicity and subclinical CVD or coronary artery calcified atherosclerotic plaque demonstrated markedly lower levels of coronary artery calcification in those of African ancestry (in the presence and absence of diabetes mellitus), despite greater exposure to conventional CVD risk factors.[31–36] Coronary artery calcification, which is assessed using computed tomography, is a well accepted measure of subclinical CVD, and strongly associates with risk of MI and CVD events in all population groups.[37] These observations suggest that biologic differences in CAD susceptibility are present between population ancestries, with higher risk for CAD and MI in individuals of European descent and lower risk in those with African ancestry.[38] GWAS for MI events (plaque instability and rupture) primarily in European ancestry populations demonstrate associations that are consistent with, and independent from calcified occlusive disease.[39–41]

Studies evaluating African Americans inMESA (Multi-Ethnic Study of Atherosclerosis), AA-DHS (African American-Diabetes Heart Study), and FHS-SCAN (Family Heart Study–Subclinical Atherosclerosis Network) proved this theory by demonstrating excess “European ancestry” in African American study participants with higher levels of coronary artery calcification.[42;43] In a report that applied regional admixture mapping, a genetic mapping approach useful in admixed populations whose ancestral populations have differential disease risk, eleven regions with genome-wide significant or suggestive evidence for harboring coronary artery calcification–associated genes were detected in African Americans. Strikingly, all eleven demonstrated excess European ancestry.

It is clear that susceptibility to coronary artery calcification and subclinical CAD in individuals with African ancestry can be mediated by European-derived risk alleles. African ancestry is relatively protective from coronary artery calcification and MI. This likely explains the markedly lower risk of MI seen in African Americans who have equivalent healthcare access as European Americans. Unfortunately, the adverse environmental factor of poor healthcare access appears to overwhelm the innate biologic protection in African Americans and lead to higher disease rates in general populations. This striking example demonstrates how ancestry-informative data and the environment interact to influence population-specific rates of disease. Equalizing healthcare access reverses the trends for risk

of MI in minority populations relative to those with European ancestry. Admixture mapping holds great promise for detecting CAD genes that affect all population groups.

Bone disease, calcium and vitamin D metabolism

The controversy over supplementing vitamin D to reduce the risks of osteoporosis, atherosclerosis and cancer led to the Institute of Medicine urging caution in widespread supplementation of calcium and vitamin D.[44;45] There is clearly benefit to supplementing vitamin D in those with low levels to treat osteopenia and osteoporosis, especially those of European descent. Potential benefits in CVD and cancer remain less clear.

Individuals with African ancestry have markedly lower circulating 25-hydroxyvitamin D concentrations than Europeans; an effect often attributed to darker skin pigmentation with reduced activation of vitamin D.[46] African Americans also have generally lower dietary calcium intake than European Americans.[47] These effects would be expected to cause higher rates of osteoporosis in individuals of African ancestry, the opposite of what is observed.[48;49] Regulation of calcium homeostasis between population groups reveals other marked differences; higher levels of 1,25-dihydroxyvitamin D and intact parathyroid hormone (with relative skeletal resistance to its effects) and enhanced renal tubular calcium reabsorption in African Americans as compared to European Americans, along with lower rates of calcified atherosclerotic plaque, osteoporosis, and calcium-containing kidney stones (Table 4).[46;50–52] These findings clearly demonstrate different inherited (biologic) factors impacting calcium homeostasis between population groups.[53] For example, greater degrees of African ancestry associated with greater bone strength in African American Women's Health Initiative participants.[54]

Additional clinically relevant observations are population ancestry differences in relationships between vitamin D with bone and vascular phenotypes. Inverse relationships exist between bone mineral density (BMD) and coronary artery calcification in populations of African and European ancestry.[55] We reported a surprising inverse relationship between 1,25 di-hydroxyvitamin D concentrations and BMD in African Americans.[56] This was subsequently supported by the Women's Health Initiative where higher vitamin D levels with supplementation protected women of European ancestry from fractures.[57] In contrast, paradoxically higher fracture rates were seen in African American women with higher vitamin D levels.

In addition, a positive association was detected between serum 25 hydroxyvitamin D and coronary artery calcification in African Americans in a cross-sectional analysis.[58] Physicians should focus on treating disease states such as osteoporosis, not simply serum vitamin D concentrations. Physicians accept that African Americans have higher muscle mass and resultant higher serum creatinine concentrations than European Americans.[59] Therefore, we adjust equations that compute estimated glomerular filtration rate (eGFR) based on ancestry. It is time to acknowledge that physiologic differences exist in 25 hydroxyvitamin D concentrations based on population ancestry; lower levels in individuals with African ancestry (relative to European ancestry) may not uniformly signify deficiency.[60]

Kidney Disease

Few disorders demonstrate the striking degrees of familial aggregation and population ancestry differences in risk than common forms of kidney disease. This holds true for bland forms of glomerulosclerosis (focal segmental glomerulosclerosis [FSGS] and focal global glomerulosclerosis formerly attributed to hypertension) in African Americans and immune complex mediated forms of glomerulonephritis such as Immunoglobulin A nephropathy

(IgAN) in Asian and European populations. Beyond diabetic nephropathy (DN), FSGS and IgAN, familial aggregation of common forms of severe kidney disease is considerably weaker in populations of European-ancestry, relative to African American populations.[61]

Many GWAS for the traits of eGFR and albuminuria were performed in predominantly European-derived general populations lacking kidney disease.[62–64] Although replicated genes regulating kidney function have been detected, their impact on variation in eGFR appears modest.[65] The uromodulin gene (*UMOD*), which encodes Tamm-Horsfall protein and which was initially identified in linkage analyses of families with medullary cystic kidney disease type 2 and familial juvenile hyperuricemic nephropathy, has since been associated with eGFR in population-based GWAS.[62;66] Beyond *UMOD*, many eGFR-associated genes appear to have limited effects on risk of chronic kidney disease (CKD), ESRD or DN.[67]

Based on the weaker familial aggregation of non-DN in European Americans, we focused our recruitment efforts from dialysis clinics on African Americans with DN and non-diabetic nephropathy (primarily FSGS and focal global glomerulosclerosis or hypertension-attributed nephropathy) and European Americans with DN. Unfortunately, these severe kidney diseases have smaller DNA sample numbers available for GWAS than population-based studies thereby limiting power. In the future, larger sample numbers will likely assist in identifying major susceptibility genes for kidney disease.

IgAN, one of the most common kidney diseases worldwide, is a frequent cause of ESRD.[5] It has long been appreciated that Asians are more often affected relative to other populations. European ancestry populations fall behind Asians, with the lowest rates of IgAN in those of African ancestry.[68] Familial aggregation of IgAN is widely observed and genetic risk variants have been detected.[69] It was initially unclear whether the low frequency of IgAN in African Americans reflected unequal healthcare access (fewer kidney biopsies); although it is now accepted that African Americans have lower rates of disease.

The biologic mechanism for these observations was uncovered in an elegant series of geospatial analyses in an ecological study.[70] The frequencies of risk alleles in seven IgAN-associated disease loci identified in prior studies containing approximately 1,000–2,000 subjects were compared across population groups. The highest frequency of risk variants was detected in Asian populations, followed by Europeans/European Americans, then African Americans. The heat map generated from continental maps of IgAN risk variants was consistent with population ancestry differences in disease risk. All individuals with risk variants will not develop hematuria or IgAN, it is anticipated that there are environmental exposures potentially triggering disease and partially explaining the variable expressivity. Nonetheless, the genetic make-up of Asians predisposes to IgAN more often than other population groups and this contributes to population ancestry–related differences in risk.

The fascinating breakthrough of *APOL1*-associated nephropathy has been extensively reviewed.[10;71;72] Herein we focus on advances that *APOL1* provides from the standpoints of clarifying disease classification, novel treatment options, improvements in performance of clinical trials and outcomes after kidney donation and transplantation. *APOL1* mediated risk explains many aspects of African American/European American disparities in development of kidney disease and outcomes after deceased donor kidney transplantation (Box 2).

Box 2

Effects of *APOL1* kidney disease alleles

- Odds ratio for association with HIVAN, FSGS, and hypertension-attributed kidney disease in African Americans are 29, 17, and 7.3, respectively
- Association reported in severe lupus nephritis and sickle cell nephropathy
- *APOL1* alleles explain higher rates of non-diabetic kidney disease in African Americans relative to European Americans
- *APOL1* alleles likely explain poorer allograft survival after transplantation of deceased donor kidneys from African ancestry donors, relative to donors of European ancestry
- Weaker association with mild kidney disease supports *APOL1* as a progression factor

Abbreviations: HIVAN, human immunodeficiency virus-associated nephropathy; FSGS, focal segmental glomerulosclerosis.

Two common *APOL1* nephropathy variants, G1 and G2, are present virtually only in those with west-African ancestry.[8;9] Here a risk variant is defined in terms of a genotype instead of a single allele, an individual carries 2 risk variants if homozygous for the G1 risk allele, homozygous for the G2 risk allele, or a compound heterozygote (one copy of the G1 and one copy of the G2 risk allele). These risk variants are present in high frequency (approximately 12% of African Americans have two and 39% one risk variant) and they are virtually absent in Asian, European and Hispanic populations (except select Hispanic populations in the northeastern U.S. where admixture with African Americans is common). The paucity of kidney disease risk variants outside of west Africa–derived populations reflects recent selection for the variants based on protection from African sleeping sickness mediated by Trypanosoma brucei rhodesiense and transmitted by the tsetse fly. Ethiopian populations in East Africa lack *APOL1* risk variants and infrequently develop HIV-associated nephropathy (HIVAN) despite exposure to HIV infection.[73] Prior to the identification of *APOL1*, kidney disease associations were attributed to variation in the adjacent non-muscle myosin heavy chain 9 gene (*MYH9*). This proved to relate to extensive linkage disequilibrium between markers in the region.[74–76]

APOL1 is strongly associated with the risk of five common and severe forms of non-DN; all occur more often in African Americans than European Americans. These include idiopathic FSGS; FSGS, collapsing variant (idiopathic and HIVAN-associated); hypertension-attributed kidney disease (not truly initiated by high blood pressure but reflecting cases with focal global glomerulosclerosis and/or FSGS with interstitial fibrosis and vascular changes as in African American Study of Kidney Disease and Hypertension (AASK) Trial participants); sickle cell disease-associated kidney disease; and progressive lupus nephritis (not mild lupus nephritis).[77–79] Due to stronger association with ESRD and severe kidney disease, it appears likely that *APOL1* underlies disease progression.[80;81] Mild kidney disease is less common in African Americans than European Americans; however, once present, kidney disease progresses to ESRD more rapidly in those with African ancestry. We postulate that *APOL1* contributes to the differential rates of kidney disease progression observed between groups with different population ancestry. The population attributable risk of *APOL1* in FSGS and HIVAN is 70%.[77] Thus, the prevalence of FSGS and HIVAN would be reduced by a staggering 70% if G1 and G2 risk variants were absent from the African American community.

Environmental factors also impact development of kidney disease in genetically susceptible individuals. This is demonstrated by the fact that at least 50% of those with two *APOL1* risk variants and untreated HIV infection develop HIVAN.[77] HIVAN manifests the greatest

African American/European American disparity of all kidney diseases and is also the most aggressive disease in the spectrum of *APOL1*-associated nephropathy. We postulated that additional non-HIV viral infections maintaining renal and/or urothelial reservoirs of infection (as for HIV) might interact with *APOL1* and affect risk of CKD. Preliminary work suggested that urinary tract JC polyoma virus infection may interact with *APOL1*-mediated risk and protect from kidney disease.[82] Potential mechanisms may include inhibition of urinary tract replication by more nephropathic viruses or effects on gene expression profiles. This is an exciting area of research. Inhibiting environmental factors that contribute to the development or progression of kidney disease in individuals at genetic risk holds tremendous promise for treating the refractory family of *APOL1*-associated disorders.[83] Here, standard therapies such as blood pressure reduction and aggressive use of angiotensin converting enzyme inhibitors failed to dramatically reduce rates of disease progression.[84]

APOL1 genotyping will improve the diagnostic precision in clinical trials targeting DN, when African ancestry populations are enrolled. Many patients with T2DM and CKD lack DN. CKD and diabetes are common and as many as 20% of individuals with a clinical diagnosis of type 2 DN have other causes of kidney disease on kidney biopsy. We demonstrated the powerful association of *APOL1* with non-diabetic CKD in individuals with African ancestry allowing for the genetic dissection of cases with kidney disease in the FSGS/focal global glomerulosclerosis spectrum from DN by removing individuals with two *APOL1* risk variants.[85;86] This process enriches for DN and would allow investigators to test potential therapies for effects on development and progression of DN, with less concern whether cases with non-diabetic kidney disease (which may be less likely to respond) were included.

A future clinical application of *APOL1* genotyping may be to optimize kidney donor selection. Variation in *APOL1* appears to underlie shorter allograft survivals in African ancestry deceased donor kidneys, relative to European.[87] Higher rates of ESRD are also seen after live kidney donation in African Americans than European Americans, although the overall risk appears to be low.[88;89] *APOL1* genotyping in living African ancestry kidney donors has been proposed for protecting donors at risk for subsequent kidney failure and optimizing transplant outcomes.[90] This may be critical in deceased donor kidney transplants where outcomes after transplantation of two *APOL1* risk variant kidneys are poor. Potential recipients of these kidneys should be made aware and allowed to elect whether or not to receive them, as for recipients of expanded criteria donation kidneys.

Modifiable environmental factors in genetic disease

With detection of risk alleles for disease (some population ancestry specific), comes the realization that variable expressivity reflects, in part, exposure to environmental triggers or requisite second hits. Environmental triggers may be modifiable. In addition manipulation of gene expression in relevant tissues via microRNA or small molecule technologies may also provide hope for prevention. The natural history of HIVAN changed with widespread use of highly active anti-retroviral therapy (HAART). Hence, those with two *APOL1* risk alleles and HIV infection are at far lower risk for HIVAN with HAART.[91] This led to a search for interactions between non-HIV viral infections with renal reservoirs and *APOL1*. By preventing infection with deleterious viruses (vaccination) or through intentional exposure to protective benign viruses that may reduce subsequent infections with more pathologic strains, we may be able to reduce development of kidney disease in those at high genotypic risk. Environmental factors may also explain the variable histologic patterns of *APOL1*-nephropathy; different modifying factors may produce focal global glomerulosclerosis, FSGS, or collapsing glomerulopathy.[82;83;92]

The same concept applies to pharmacogenomics: testing for responder genotypes may better direct medical therapy. This would provide a scientific approach to what is now done clinically. We typically assume that hypertensive African Americans are more likely than European Americans to be salt sensitive.[13] In truth, not all hypertensive individuals with African ancestry are salt sensitive and many European Americans are. Genetic results could guide effective therapies for hypertension, T2DM, CKD, atherosclerosis and osteoporosis; treatments may differ based on genotypes. In some cases, genotypes and treatments will diverge along the lines of ancestral origin.

Conclusions

Humans globally share 99% of their genomes taking into account all common forms of sequence diversity and there is more variation within population groups than between them. However, population ancestry–related differences in prevalence, severity, and trajectory are observed for a number of diseases. These differences reflect the complex interplay between genetic, environmental and socio-economic factors. Population ancestry related rates of diabetes, IgAN, FSGS, atherosclerosis, and osteoporosis between African and European populations likely relate, in part, to differential distributions of risk alleles.

Appreciating the diverse biology underlying population ancestry specific disease risk does not suggest superiority of one group over another. However, it can help us understand differences in the intermediate phenotypes that underlie complex traits and assist in identifying markers for those at risk. Novel treatments may ultimately ensue. Modifiable environmental factors interacting with genetic risk variants provide hope for developing interventions that may prevent or slow many diseases. Specific modifiable factors may differ between populations, since subtle differences in genetic profiles may alter risk. Physicians should remain open to exploring population ancestry related approaches to diagnosis and treatment when underlying biologic variation is responsible. However, equalizing access to healthcare and reducing modifiable risk factors should be provided to all regardless of ancestry.

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Table 1

Intermediate phenotypes in essential hypertension, based on population ancestry

Phenotype/Trait	Population Ancestry	
	African	European
Early onset hypertension	More common	Less common
Severe hypertension	More common	Less common
Salt sensitivity	More common	Common
Plasma renin activity	More commonly suppressed	May be suppressed
Excretion of a sodium load	Delayed	Rapid
Red blood cell intracellular sodium concentration	Elevated	Normal
Renal blood flow	Reduced	Normal
Catecholamine sensitivity	Increased	Normal

Table 2

Intermediate phenotypes in T2DM and metabolic syndrome, based on population ancestry

Phenotype/Trait	Population Ancestry		
	African	Hispanic	European
Age at onset of T2DM	Younger	Younger	Older
Presence of insulin resistance	Higher	Higher	Lower
Risk for kidney disease *	Higher	Higher	Lower
Risk for cardiovascular disease *	Lower	Lower	Higher
Plasma triglycerides	Lower	-	Higher
HDL-cholesterol concentration	Higher	-	Lower

* Assumes equivalent access to healthcare

Abbreviations: T2DM, type 2 diabetes mellitus; HDL, high-density lipoprotein.

Table 3

Differential genetic association with T2DM across population ancestries

SNP	NCBI37 Position (bp)	Nearest Gene	Population	Risk allele/nonrisk allele	Risk Allele Frequ ency	OR (95% CI)	P
SNPs showing consistent association with T2DM across population ancestries							
rs7903146	chr10:114758349	*TCF7L2*	European[93]	T/C	0.25*	1.37 (1.28–1.47)	**3.0E-23**
			African American[25]	T/C	0.31	1.30 (1.18–1.43)	**6.9E-08**
			Mexican American[94]	T/C	0.23	--[a]	**0.030**
			Asian[95]	T/C	0.03	1.43	**0.029**
rs864745	chr7:28180556	*JAZF1*	European[93]	T/C	0.50	1.10 (1.07–1.13)	**5.0E-14**
			African American[25]	T/C	0.74	1.10 (1.00–1.21)	**0.043**
rs972283	chr7:13046854	*KLF14*	European[96]	G/A	0.55*	1.07 (1.05–1.10)	**2.2E-10**
			African American[25]	G/A	0.85	1.24 (1.09–1.41)	**8.1E-04**
SNPs inconsistently associated with T2DM across population ancestries							
rs7578597	chr2:43732823	*THADA*	European[93]	T/C	0.90	1.15 (1.10–1.20)	**1.1E-09**
			African American[25]	T/C	0.73	1.04 (0.95–1.14)	0.42
			Han Chinese[97]	T/C	-	-	0.82
rs1801282	chr3:12393125	*PPARG*	European[93]	C/G	0.93*	1.18 (1.09–1.41)	**2.0E-04**
			African American[25]	C/G	0.98	0.82 (0.61–1.09)	0.18
rs4402960	chr3:185511687	*IGF2BP2*	European[93]	T/G	0.29*	1.17 (1.10–1.25)	**7.5E-08**
			African American[25]	T/G	0.52	1.02 (0.94–1.10)	0.71
			Han Chinese[97]	T/G	-	-	0.22
rs1544056	chr9:10279606	*PTPRD*	African American[25]	A/C	0.06	0.93 (0.70–1.23)	0.61
			Hispanic[98]	A/C		1.18† (1.11–1.26)	**1.2E-04**
			Han Chinese[97]	A/C	0.06	1.57 (1.36–1.82)	**3.1E-09**
Locus heterogeneity associated with T2DM across population ancestries							
rs231362‡	chr11:2691471	*KCNQ1*	European[96]	G/A	0.52*	1.08 (1.06–1.10)	**2.8E-13**
			African American[25]	G/A	0.79	1.07 (0.95–1.20)	0.25

SNP	NCBI37 Position (bp)	Nearest Gene	Population	Risk allele/nonrisk allele	Risk Allele Frequ ency	OR (95% CI)	P
rs2237892 ≠	chr11:2839 751	*KCNQ1*	African American[25]	C/T	0.89	1.25 (1.09–1.43)	**1.8E-03**
			Hispanic[98]	C/T	-	1.26† (1.14–1.40)	**2.3E-05**
			Japanese[99]	C/T	0.59	1.43 (1.34–1.52)	**3.0E-29**
			Asian[99]	C/T	0.61	1.41 (1.34–1.48)	**2.5E-40**

SNP – single nucleotide polymorphism; bp – base pairs; T2DM, type 2 diabetes mellitus; rs, reference SNP; OR, odds ratio; CI, confidence interval; chr, chromosome; NCBI37, National Center for Biotechnology Information human genome build 37.

[a]Relative risk for 1 copy, 1.09; relative risk for 2 copies, 1.24.

*Allele frequencies estimated from the HapMap European population;

†OR and 95% CI from meta-analysis of Hispanic and 2008 DIAGRAM (DIAbetes Genetics Replication and Meta-analysis) datasets;

≠linkage equilibrium in the HapMap European sample (r^2=0.10, D′=0.48).

Table 4

Relative impact of African and European ancestry on calcium and vitamin D metabolism

Phenotype/Trait	Population Ancestry	
	African	European
Serum 25 hydroxyvitamin D	lower	higher
Serum 1,25-dihydroxyvitamin D	higher	lower
Intact PTH	higher	lower
Skeletal effect of intact PTH	lower	higher
Bone mineral density	higher	lower
Calcified atherosclerotic plaque	lower	higher
Calcium-containing kidney stones	lower	higher
Renal tubule calcium reabsorption	higher	lower
Dietary calcium ingestion	lower	higher

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