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Target Organ Damage in African American Hypertension: Role of *APOL1*

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Abstract Apolipoprotein L1 (*APOL1*) gene association studies and results of the African American Study of Kidney Disease and Hypertension are disproving the longstanding concept that mild to moderate essential hypertension contributes substantially to end-stage renal disease susceptibility in African Americans. *APOL1* coding variants underlie a spectrum of kidney diseases, including that attributed to hypertension (labeled arteriolar or hypertensive nephrosclerosis), focal segmental glomerulosclerosis, and HIV-associated nephropathy. *APOL1* nephropathy risk variants persist because of protection afforded from the parasite that causes African sleeping sickness. This breakthrough will lead to novel treatments for hypertensive African Americans with low-level proteinuria, for whom effective therapies are lacking. Furthermore, *APOL1* nephropathy risk variants contribute to racially variable allograft survival rates after kidney transplantation and assist in detecting nondiabetic forms of nephropathy in African Americans with diabetes. Discovery of *APOL1*-associated nephropathy was a major success of the genetics revolution, demonstrating that secondary hypertension is typically present in nondiabetic African Americans with nephropathy.

Keywords African American · African sleeping sickness · Arteriolar nephrosclerosis · *APOL1* · Chronic kidney disease · Dialysis · End-stage renal disease · ESRD: Focal segmental glomerulosclerosis · Genetics · Glomerulosclerosis · Hypertension · Hypertensive nephrosclerosis · Kidney disease · Kidney donors · *MYH9* · Nondiabetic nephropathy · Racial differences · *Trypanosoma brucei rhodesiense* · Transplantation

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Introduction

End-stage renal disease (ESRD) occurs four times more often in African Americans than in European Americans [1], with life-time risk approximating 7.5% in African Americans and only 2% in European Americans [2]. Nondiabetic chronic kidney disease (CKD), particularly hypertension-attributed nephropathy, focal segmental glomerulosclerosis (FSGS), and HIV-associated collapsing glomerulopathy (also called HIV-associated nephropathy or HIVAN) demonstrates pronounced racial differences in incidence, with up to 50-fold higher rates of HIVAN in African Americans than in European Americans [1].

Until recently, the cause of the higher nephropathy risk in individuals of African ancestry remained elusive. Many investigators proposed environmental risk factors as major contributors, with particular emphasis on generally lower socioeconomic status, lack of access to adequate healthcare, and higher blood pressures in African Americans [3, 4]. Modern molecular genetic techniques have proven that variation in the apolipoprotein L1 gene (*APOL1*) explains the excess risk of nondiabetic ESRD in African Americans [5••, 6•, 7]. This breakthrough is leading to the reclassification of FSGS and other nondiabetic forms of nephropathy in African Americans, including forms long attributed to high blood pressure [8].

The Link between Hypertension and Nephropathy

American nephrologists classify nearly 35% of cases of ESRD in African Americans as being due to essential hypertension, so-called hypertensive nephrosclerosis or arteriolar nephrosclerosis [1]. Diagnoses in the US Renal Data System (USRDS) registry are provided by nearly 6,000 practicing clinical nephrologists without standardized diagnostic criteria and often without biopsy material. These diagnoses are frequently incorrect [9]. Accelerated and malignant forms of hypertension clearly initiate kidney disease, but direct evidence linking mild to moderate hypertension with the initiation of nephropathy in African Americans is weak [10]. Hypertension-attributed nephropathy is typically diagnosed in nondiabetic African Americans with unknown causes of kidney disease; renal histology is usually lacking, and diagnoses are often made without regard to the level of proteinuria [11].

The controversy has been fueled by the frequent absence of clinical data in African Americans with hypertension-attributed kidney disease [12]. A carefully performed study demonstrated marked physician bias, whereby renal diagnoses were often based on the patient's race rather than objective clinical and laboratory data [13]. Results of population-based epidemiologic studies involving predominantly hypertensive European Americans have frequently been extrapolated to the dialysis clinic, where they appear to be less applicable [14]. The possibility that high blood pressure in CKD patients was secondary to undiagnosed primary kidney diseases, as now appears to be a common scenario, typically was not considered [15].

Firmer evidence that essential hypertension did not commonly initiate nephropathy in African Americans came from renal histologic studies revealing the lack of correlation between arteriolar changes and systemic blood pressure in participants in the African American Study of Kidney Disease (AASK) Trial [16]. These individuals were clinically diagnosed with "hypertensive nephropathy." Kidney biopsies in a subset of 39 AASK participants revealed segmental or focal global glomerulosclerosis (FGGS), interstitial fibrosis, and arteriosclerosis/arteriolosclerosis [16]. Racially variable patterns of glomerulosclerosis have also been reported. Solidified glomerulosclerosis is present in African Americans more often than in European Americans [17]. Finally, the failure of blood pressure control to halt nephropathy progression in hypertensive African Americans, despite evidence of benefit in European Americans, strongly suggested that the underlying causes of nondiabetic nephropathy attributed to hypertension differed between the races [18, 19].

Excluding polycystic kidney disease, hereditary nephritis, and urologic disease, more than 30% of African Americans initiating renal replacement therapy who have common forms of nephropathy (e.g., clinically diagnosed hypertensive ESRD, diabetic ESRD, and chronic glomerular disease) have close relatives on dialysis, and many more have relatives with silent kidney disease manifesting as proteinuria and/or reduced glomerular filtration rate (GFR) [20, 21]. The pronounced familial aggregation of advanced kidney disease in African Americans, far stronger than that in European Americans [22], provided a major clue to the existence of an overarching nephropathy susceptibility gene [10, 23]. Most striking was the clustering of disparate forms of kidney disease within single African American families, including ESRD attributed to hypertension, primary chronic glomerular diseases (FSGS), HIVAN, systemic lupus erythematosus (SLE), and diabetes mellitus [24, 25]. The existence of a major "nephropathy susceptibility gene" underlying several common forms of kidney disease in African Americans was first proposed in the early 1990s [24, 26], but the concept was widely rebuked [27].

Hypertension: The Chicken or the Egg in Arteriolar Nephrosclerosis?

The debate over whether hypertension or nephropathy developed first in the vicious cycle of hypertension-attributed kidney disease contributed to the performance of the AASK Trial, sponsored by the National Institutes of Health [28]. AASK tested the benefits of drugs in three antihypertensive classes—angiotensin-converting enzyme (ACE) inhibitors (ramipril), calcium channel blockers (amlodipine), and beta-blockers (metoprolol)—as well as two levels of blood pressure control—low (mean arterial blood pressure goal <92 mm Hg) versus usual (102–107 mm Hg)—for nephropathy progression rates in 1,094 nondiabetic, hypertensive African Americans who met criteria for putative "hypertensive nephrosclerosis." Disease criteria included an initial estimated GFR of 20 to 65 mL/min/1.73 m^2 and proteinuria less than 2.5 g/day [28].

After 5 years, the AASK Trial demonstrated that baseline proteinuria was associated with more rapid progression of nephropathy, but the lower blood pressure target failed to slow nephropathy progression more than the usual target [29]. After completion of the AASK Trial, the remaining participants who had not reached a primary study end point were followed in the AASK Cohort phase; all used ACE inhibition with ramipril and the lower blood pressure goal. The AASK Cohort study subsequently confirmed the lack of benefit of the lower blood pressure goal and ACE inhibition in the overall study sample. Nearly 60% of participants reached a primary study end point (death, dialysis, or doubling of serum creatinine concentration) after 10 years [30••]. These interventions appeared to be somewhat beneficial in slowing nephropathy progression

rates among participants with baseline proteinuria, just as in patients with proteinuric glomerular diseases including FSGS [31]. However, it is now clear that lower blood pressures and ACE inhibition are ineffective in slowing nephropathy progression in hypertensive African Americans without proteinuria. We believe the results of this important study sever the link between high blood pressure and nephropathy in African Americans [32].

Chromosome 22q13.1 Genetic Associations in Nondiabetic Nephropathy

The AASK was initiated to identify treatment options for the chronic kidney disease that was attributed to hypertension. As such, AASK inclusion criteria are useful to capture a standard, accepted phenotype for hypertension-attributed nephropathy. Recently, *APOL1* and *MYH9* nephropathy risk variants were proven to be strongly associated with kidney disease in AASK participants, linking this disorder with FSGS, hypertension-attributed ESRD, and HIVAN [33]. Mapping by admixture linkage disequilibrium (MALD), also called admixture mapping, has proven to be useful for detecting genetic variants contributing to disease risk in admixed populations, in which ancestral populations have different disease frequencies [34, 35]. African Americans are an admixed population with approximately 82% African and 18% European ancestry, and kidney disease is far more common in individuals with African ancestry.

Kopp et al. [36] and Kao et al. [37] first applied MALD to kidney disease and detected an impressive genetic association between the non-muscle myosin heavy chain 9 gene (*MYH9*) E1 (Extended-1) haplotype and idiopathic FSGS, nondiabetic ESRD, and HIV-associated collapsing glomerulopathy in African Americans. The observation was soon extended to patients with C1q-associated collapsing glomerulosclerosis [38], clinically diagnosed hypertension-attributed ESRD [39], and type 2 diabetes–attributed ESRD [40]. In retrospect, the association with diabetic nephropathy likely resulted from inclusion of diabetic subjects with nondiabetic (proteinuric) nephropathy in the FSGS spectrum of disease [41, 42•]. *MYH9* risk alleles were not associated with essential hypertension per se in African Americans who lacked advanced nephropathy [43].

Within 2 years of the *MYH9* discovery, Genovese, Friedman, and colleagues demonstrated that two coding variants in *APOL1* (termed G1: non-synonymous coding variant 342 G:384 M and G2: a 6 bp deletion) had stronger genetic association with nondiabetic nephropathy than the *MYH9* E1 haplotype [5••]. At this time, coding variants in *MYH9* had not been detected despite extensive fine mapping efforts [44]. Newly available single nucleotide polymorphisms (SNPs) in Yoruba from the "1,000 Genomes" Project led to detection of *APOL1* association. Strong linkage disequilibrium between the SNPs in these adjacent genes on chromosome 22q13.1 contributed to the initial difficulty in detecting the causative gene; strong selective pressures were also felt to be operative in this region [5••, 45•]. The *APOL1* association has been independently replicated [6•]. The ApoL1 protein is associated with relative immunity to trypanosomal infection and protection from African sleeping sickness [46, 47]. Nephropathy risk variants were shown to encode proteins that effectively lysed *Trypanosoma brucei rhodesiense*, a property absent in those with wild-type (non-nephropathy) variants [5••]. Centuries ago, human biologic and genome evolution led to positive selection for *APOL1* nephropathy risk variants. The molecular basis of this adaptive evolution was from the protection conferred by these variants against the deadly parasitic disease transmitted by the tsetse fly in sub-Saharan Africa.

Idiopathic FSGS is strongly associated with *APOL1* G1 and G2 variants in an autosomal recessive fashion [5••, 7]. This finding is among the most impressive genetic associations in complex human disease. Individuals inheriting two *APOL1* nephropathy risk variants (G1 + G1, G2 + G2, or G1 + G2) have a 10.5-fold increased risk for FSGS. Clinically diagnosed hypertension-attributed ESRD is also strongly associated (odds ratio 7.3 recessive; $P=10^{-63}$). Together, hypertension-attributed ESRD and various forms of FSGS account for 40% of incident ESRD cases in African Americans [1]. As stated, *APOL1* risk alleles were also strongly associated with kidney disease in AASK participants, demonstrating that the kidney disease in AASK resides in the FSGS–FGGS spectrum of *APOL1*-associated nephropathy and is unlikely to relate to renal damage from high blood pressure.

Whether *MYH9* plays a residual role in renal disease susceptibility is under active investigation. Genovese et al. performed a conservative statistical analysis and concluded that essentially all of the chromosome 22q nephropathy risk resided in *APOL1* [5••]. Other investigators continue to detect an *MYH9* effect in their study samples after adjustment for *APOL1* G1 and G2 risk variants (personal communication 2011: JB Kopp – NIH FSGS; CD Langefeld – Wake Forest School of Medicine; WH Kao – Family Investigation of Nephropathy and Diabetes [FIND]). *APOL1* G1 and G2 nephropathy risk variants are exceedingly rare in European Americans, whereas *MYH9* variants appear to contribute to nephropathy risk in several European-derived populations [48, 49•, 50]. Because of strong selective forces and linkage disequilibrium in this region, it remains possible that *MYH9* association relates to SNPs in nearby genes (perhaps other *APOL1* coding variants or members of the *APOL2-6* gene family). Deep sequencing of the *APOL-MYH9* gene region will be necessary to clarify this question. Based on the weakly

dominant *APOL1* inheritance that was observed in hypertension-attributed ESRD, we feel it is likely that additional undetected nephropathy risk variants reside in the region [5••]. In this fashion, G1 or G2 would appear to have a dominant effect, but a second (undetected) risk variant would be present and maintain recessive inheritance. These remaining variants are likely to be less frequent than *APOL1* G1 and G2.

Clinical Applications of *APOL1* Genotyping in Renal Transplantation

Beyond the exciting possibility of identifying the cause, and ultimately a cure, for the kidney disease that has historically been attributed to hypertension in African Americans, *APOL1* genotyping is proving to have important clinical applications in the arena of transplant nephrology.

Race-driven outcomes exist in renal transplantation [51]. Kidneys donated by African Americans function for significantly shorter time periods than kidneys donated by European Americans [52–55]. African American live kidney donors are also more likely than other kidney donors to develop severe nephropathy after donation [56].

We reported that the risk of early graft failure in African American donated kidneys relates predominantly to *APOL1* genetic variation: deceased-donor kidneys harboring two *APOL1* risk variants function for significantly shorter periods than those with less than two risk variants [57••]. The effect of *APOL1* on renal allograft survival is far stronger than the effects observed for HLA matching, panel reactive antibodies (PRA), standard (vs expanded)-criteria donation, and cold ischemia time. Evaluation of ancestry informative markers across the genome localized the risk to *APOL1*, confirming that donor race per se is not the cause. In fact, African American donor kidneys with less than two *APOL1* risk variants functioned for a duration similar to that of kidneys from European American donors. Among failing kidneys from donors with two *APOL1* risk variants, 75% had histologic lesions compatible with *APOL1*-associated nephropathy, compared with 11.8% of failing allografts from non-risk donors.

We believe that *APOL1* risk variants likely contribute to the more frequent development of ESRD in living African American donors, relative to European Americans [57••]. Although not yet proven, 50% reductions in nephron mass in the presence of two *APOL1* risk variants is likely to accelerate the course of renal injury in at-risk individuals. Screening donor kidneys for *APOL1* risk variants has the potential to improve long-term renal allograft survival and simultaneously reduce the rates of subsequent ESRD in African American living kidney donors [58, 59].

Kidney Disease Screening

The usefulness of screening for *APOL1* risk variants in the general African American population remains unknown [60]. Of African American chromosomes (not individuals), 30% contain an *APOL1* nephropathy risk variant and 70% do not [5••, 7]. As such, 49% (70%×70%) of African Americans lack G1 and G2 variants; 51% inherit one or two risk variants, and approximately 12% of African Americans have two risk variants and are at high risk for kidney disease. As the majority of African Americans develop high blood pressure by late adulthood and *APOL1* (and *MYH9*) risk variants do not appear to be associated with hypertension, there is no a priori reason to screen only hypertensive individuals [43]. Until effective treatments for *APOL1*-associated nephropathy are available, general population screening would seem to have little benefit except in research settings, genetic studies in ESRD patients who lack definitive diagnoses based on renal biopsy material (see below), and potentially for screening African American kidney donors.

Not every individual who inherits two *APOL1* risk variants will develop ESRD, so a search for "second hits" (either gene-gene or gene-environment interactions) has begun [61]. HIV infection is an important environmental factor that can lead to the development of *APOL1*-associated nephropathy, and highly active anti-retroviral therapy (HAART) appears to provide protection. Preventing (or treating) environmental factors or exposures that may interact with risk genes has the potential to inhibit development (or slow the progression) of nondiabetic etiologies of nephropathy in individuals at risk based on *APOL1*.

APOL1 and *MYH9* genotyping provides the opportunity to detect African Americans with ESRD who have a high likelihood of renal lesions in the spectrum of FSGS and FGGS. This is particularly important in patients with systemic disorders such as type 2 diabetes mellitus and SLE, both common in African Americans, in whom proteinuric kidney disease can be related to the systemic process (diabetic nephropathy or lupus nephritis), idiopathic FSGS, or a combination of both lesions. We reported that a diabetic patient with two chromosome 22q risk variants had FSGS on kidney biopsy, despite a clinical diagnosis of diabetic nephropathy [41]. This finding has relevance for clinical trials treating nephropathy associated with diabetes or lupus: African Americans with two *APOL1* risk variants may need to be excluded or evaluated separately to ensure that idiopathic FSGS does not impact study results [62].

In a similar fashion, we demonstrated the utility of stratifying African Americans with type 2 diabetes mellitus and ESRD based on the presence of chromosome 22q risk variants in order to detect diabetic nephropathy susceptibility genes [42•]. A prior genome-wide association study

(GWAS) for type 2 diabetic nephropathy in African Americans failed to detect evidence of association of the 4.1 protein ezrin, radixin, moesin (FERM) domain containing 3 locus gene (*FRMD3*) [63], which was previously associated with type 1 diabetic nephropathy in European Americans [64]. Interactions appeared to exist between *MYH9* and *APOL1* risk variants and *FRMD3* in a genome-wide gene-gene interaction analysis [42•]. Opposing effects of *FRMD3* SNPs were observed in chromosome 22q risk homozygotes and non-risk homozygotes, suggesting the presence of different causes of kidney disease between these groups. In chromosome 22q non-risk homozygotes, likely enriched for true diabetic nephropathy, significant association was observed with multiple *FRMD3* SNPs. However, in *MYH9* and *APOL1* risk homozygotes, enriched for nondiabetic nephropathy (FSGS), evidence of *FRMD3* association was not detected. We propose that genotyping *APOL1* nephropathy risk variants can assist in the genetic dissection of FSGS-related disorders in African Americans with systemic diseases that may cause proteinuria and kidney failure.

Potential Mechanisms of *APOL1*-Associated Nephropathy

APOL1 nephropathy risk variants are trypanolytic via the effect of the ApoL1 protein, which functions as a chloride channel [47]. Once taken up by the trypanosome, ApoL1 undergoes a conformational change and inserts into the lysosomal membrane. Chloride permeability increases, with resultant swelling and lysosomal rupture and death of the parasite. However, the mechanism whereby *APOL1* gene expression in renal cells or ApoL1 proteins in the circulation (either free or bound to high-density lipoprotein [HDL] cholesterol) contributes to nephropathy risk remains unknown.

APOL1 encodes ApoL1, a secretory protein that associates with HDL cholesterol in the plasma [65]. Three mechanisms can be proposed by which ApoL1 variants contribute, either singly or in combination, to the development of nondiabetic nephropathy (Fig. 1). Altered plasma HDL particle concentrations appear to result from homozygosity for *APOL1* risk variants. These changes could lead to kidney disease via damage to the renal microcirculation. We recently measured HDL subclass concentrations in 73 African American first-degree relatives of patients with nondiabetic ESRD to detect differences that potentially may contribute to development of kidney disease [66]. HDL subclass concentrations were measured using nuclear magnetic resonance spectroscopy, and additive effects of the number of *APOL1* risk variants on natural logarithm transformed HDL subclass

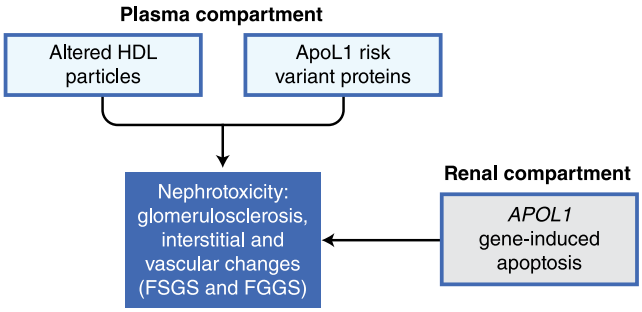

Fig. 1 Potential mechanistic pathways elicited by *APOL1* variants that may contribute to the development of nondiabetic nephropathy. *FGGS* focal global glomerulosclerosis; *FSGS* focal segmental glomerulosclerosis; *HDL* high-density lipoprotein

concentrations were computed. Mean ± SD medium-sized HDL concentrations were significantly lower for each additional *APOL1* risk variant: 9.0±5.6 μmol/L with two risk variants; 10.1±5.5 μmol/L with one risk variant; 13.1±8.2 μmol/L with no risk variants (P=0.0192 unadjusted, P=0.0190 triglyceride-adjusted). Hence, lower medium-sized HDL subclass concentrations were present with increasing numbers of *APOL1* nephropathy risk variants. Potential mechanistic roles for altered medium-sized HDL particle concentrations on *APOL1*-associated renal microvascular disease remain to be determined. Similar patterns of HDL particle concentration contribute to coronary artery disease susceptibility, suggesting potential effects on the vascular endothelium [67].

A second possibility is that nephropathy-associated ApoL1 variant proteins bind to HDL particles less avidly, circulate freely, cross the glomerular filtration barrier, and lead to glomerulosclerosis and/or interstitial fibrosis. This hypothesis is strengthened by the observation that circulating factors are often responsible for recurrent FSGS after renal transplantation [68]. Plasmapheresis removes these circulating factors and may lead to remission of proteinuria [69]. Moreover, ApoL1 has recently been implicated as a circulating factor that may underlie recurrent FSGS after kidney transplantation [70, 71]. This exciting finding could provide novel treatment options, if circulating variant forms of ApoL1 lead to altered glomerular permeability with progressive kidney failure. A third possibility is that nephropathy-associated *APOL1* variants may induce apoptosis or autophagy in podocytes, with resultant FSGS or FGGS. Podocytes express ApoL1 mRNA, and the apoptosis regulating B-cell lymphoma 2 gene (*Bcl2*) is closely related to *APOL1* [72]. Determining how the *APOL1* association with nondiabetic ESRD induces nephropathy is crucial to unraveling disease pathogenesis and offers hope for curing ESRD in affected African Americans in whom hypertension treatment alone has failed to significantly slow renal disease progression.

Non–Chromosome 22q Hypertensive Nephropathy Genes

The recent *APOL1* breakthrough demonstrates that true hypertension-attributed kidney disease occurs less often in African Americans than previously thought. In contrast, renal small blood vessel disease in European Americans appears to occur in relation to high blood pressure, hyperlipidemia, smoking, and a Western lifestyle. Hypertension treatment slows progression of this form of kidney disease in European Americans [18].

However, *APOL1* variants are not associated with all nondiabetic kidney disease in African Americans. Polymorphisms in the chromogranin A (*CHGA*) and methylenetetrahydrofolate reductase (*MTHFR*) genes have been shown to be associated with renal functional decline in African Americans with hypertension-attributed nephropathy [73, 74]. Similarly, podocin (*NPHS2*) mutations causing FSGS are occasionally identified in African Americans with hypertension-attributed ESRD [75]. Although *APOL1* variants associate with most cases of nondiabetic ESRD, other genes clearly make contributions.

Conclusions

The past few years have seen dramatic changes in our understanding of the disease process that had historically been labeled hypertensive nephrosclerosis. The majority of these cases in African Americans are associated with coding variants in the *APOL1* gene on chromosome 22q. The AASK Trial and Cohort studies revealed the lack of efficacy of aggressive blood pressure reduction using ACE inhibitor-based treatment regimens in nondiabetic, hypertensive African Americans with low-level proteinuria. *APOL1* has proven to be associated with kidney disease in AASK participants. Whether the inciting renal lesion in these forms of nephropathy resides in the glomerulus (FSGS or FGGS), the renal interstitium, or small blood vessels is yet to be determined, but it is clear that most cases of hypertension-attributed nephropathy are initiated by primary kidney diseases, and blood pressure is elevated secondarily. Molecular genetic techniques have once and for all resolved the issue of what came first: nephropathy clearly precedes hypertension in the majority of African American patients with nondiabetic nephropathy.

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Papers of particular interest, published recently, have been highlighted as:
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meta-analysis, only rs4821480 was associated with nondiabetic kidney disease. APOL1 *G1 and G2 risk variants did not account for the observed* MYH9 *signal, as they were exceedingly rare in these European-derived populations. This suggests that* MYH9 *SNP rs4821480 is associated with risk of nondiabetic nephropathy in individuals of European ancestry.*

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