

Genome-wide Admixture Mapping of eGFR and CKD Identify European and African Ancestry-of-Origin Loci in US Hispanics/Latinos

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Chronic Kidney Disease and kidney failure are notable health disparities among US Black and Hispanic/Latino populations. Studies have shown associations between social determinants of health and higher rates of CKD, kidney failure, and kidney-related deaths among Black and Hispanic/Latino individuals compared with their White counterparts.^{1,2} Though structural inequities contribute to the high burden of CKD among underrepresented populations in the US, advancements in genomic technologies and analytic approaches have expanded our understanding of differential susceptibility of complex diseases. Critically, the majority of genetic discoveries have been in individuals of European ancestry, and non-European populations are largely under-represented in genome-wide association studies (GWAS) thereby perpetuating health disparities.³

Genomic research in diverse populations is essential given known differences in the genetic architecture of complex traits across ethnic/racial groups.³ Recent admixture among Black and Hispanic/Latino populations offers opportunity for novel gene discovery using admixture mapping. Admixture mapping exploits the differences in prevalence rates between disparate populations, which may be because of frequency differences in disease-causing genetic variants, to identify chromosomal segments harboring the causal alleles (Figure 1). In admixed populations, these genetic variants occur more often on chromosome (Chr) segments inherited from the ancestral population with the higher disease variant

frequency. Because fewer individuals are required for admixture mapping compared with traditional GWAS studies, this method is well-suited for gene discovery in admixed minority populations.⁴ Admixture mapping led to the discovery of several ancestry-specific loci associated with variable heritability for kidney disease, most notably with the Chr 22 region, a region subsequently found to harbor the *APOL1* G1 and G2 kidney risk alleles.^{5,6} Discovery of ancestry-specific loci not only provide insights into disease mechanisms and provide potential targets for drug therapies, but can inform personalized health care and public health interventions targeted to vulnerable populations.

In this issue of *JASN*, Horimoto *et al.*⁷ leverage admixture mapping to identify novel loci associated with CKD traits among 12,601 Hispanic/Latino biobank participants from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) recruited from four US centers. Hispanic/Latino genomes are a mosaic of European, African and Native American-derived ancestry. The authors identified three novel ancestry-of-origin loci: a Chr 2 locus (2p16.3) that consisted of two European-ancestry regions, encompassing the *FSHR* and *NRXN1* genes, and was associated with an increased risk for CKD; a European locus within the *DLK1-DIO3* imprinted domain on Chr 14 (14q32.2) that was associated with lower eGFR; and an African-specific locus associated with higher eGFR on Chr 15 (15q13.3–14) that included intronic variants of *RYR3*. To validate the admixture mapping findings, the authors performed admixture mapping on the chromosomes 2, 14, and 15 regions of interest in an independent sample of 3050 Hispanic/Latino and 8,191 Black women from the Women's Health Initiative (WHI). Only the two loci associated with eGFR were validated in the WHI cohort, and the Chr 15 locus showed opposing effects on eGFR from the association found in the HCHS/SOL cohort. The authors suggest the opposing result may be because of differences in proportion of protective and susceptible loci in the region resulting from differences in underlying genetic architecture between Hispanic/Latinos, a genetically heterogeneous group, and Black populations. The HCHS/SOL discovery and WHI replication cohorts differed by proportion of European, Native American, and African ancestries, prevalence of CKD, and participant characteristics, which may account for the lack of replication of the Chr 2 association with prevalent CKD. The initial admixture mapping included participants with Native American ancestry, which was not shared by Black women enrolled in the WHI. Finally, the authors performed a GWAS in the HCHS/SOL cohort and failed to identify the three loci discovered by admixture mapping, highlighting the value of multiple strategies to identify genes associated with CKD and eGFR. Marked differences in ancestry among cohorts, the opposite direction

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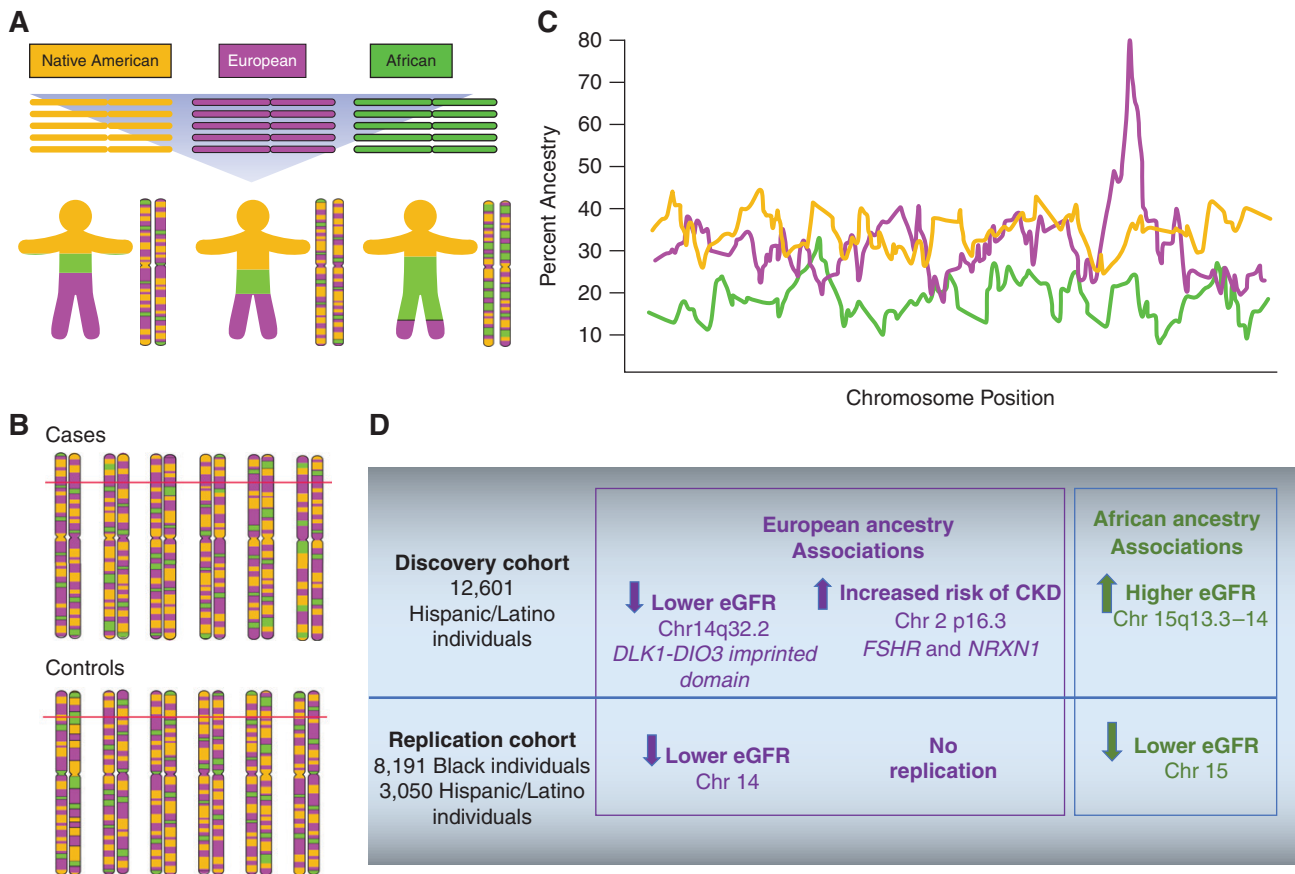


Figure 1. Chromosomal admixture. (A) Pattern of chromosomal ancestry resulting from recombination over approximately 8–20 generations for three-way admixture. Starting with the second generation, recombination produces chromosomal blocks of different continental ancestries. The present day Hispanic/Latinos have varying extent of overall global ancestry and blocks of local ancestry that vary in length because of the random nature of recombination and because the original chromosomes have been subject to recombination for differing numbers of generations. (B) Schematic of the pattern of chromosomal admixture around a disease/trait locus. The trait or disease gene locus which is more prevalent in (for this example) Europeans, shows an excess of European local ancestry in the chromosomal block harboring the causal allele (red bar). Among controls, the distribution of ancestry blocks is random across the chromosome. (C) A plot of ancestry across the chromosomes in the schematic in B, showing the peak of European ancestry that reveals the location of the disease locus. (D) Results of the admixture results showing European-ancestry associations with eGFR and African association with baseline CKD, defined by eGFR < 60 per ml/min per 1.73 m² in the discovery cohort comprised of Hispanic/Latinos. Associations were confirmed for Chr. 14 and Chr. 15 for eGFR, although the association for Chr. 15 went in the opposing direction, as shown. The association with Chr. 2 between African ancestry and prevalent CKD was not replicated.

of effect of the eGFR-associated locus on Chr 15 in the HCHS/SOL and the WHI cohorts, and the limited portability of traditional GWAS across populations, together underscore the need for further study into the differences in the genetic architecture of CKD among diverse populations.

Validation of the two eGFR-associated loci in Black women from the WHI offers new information about the genetic contributors to eGFR and is a notable strength in this study. In addition, this is the largest admixture study of CKD in Hispanic/Latinos to date and included analysis of an additional 375 adults compared with an earlier admixture mapping study by Kramer *et al.* performed on the same cohort.⁸ Interestingly, the earlier study found a significant association between albuminuria and African-ancestry specific *APOL1* G1 and G2

alleles and sickle cell trait (*HBB*). In contrast, the authors of this study found only a small proportion of global African ancestry in the overall cohort and consequently were under-powered to identify excess African ancestry on the Chr 22 region harboring *APOL1*, which is strongly associated with the development of albuminuria and progressive kidney disease.⁶ The difference between studies appears to relate to two factors. First, Horimoto *et al.* defined CKD only by low eGFR < 60 ml/min per 1.73 m² using The CKD Epidemiology Collaboration (CKD-EPI) creatinine equation. Based on this definition of CKD, less than 4% ($n=427$) of the cohort had kidney disease. Kramer *et al.* instead used the presence of albuminuria in their broader definition of CKD.⁸ Second, the two studies analyzed the HCHS/SOL cohort differently. Horimoto *et al.* analyzed the

cohort as a whole. Yet, most participants report Mexican (37%), Cuban (17.8%) and Puerto Rican (17.7%) backgrounds. The earlier study grouped participants into two representative categories: Mainland (55.4%) and Caribbean (44.6%) background groups. With these groupings, they found that the Caribbean background group, compared with the Mainland group, had a higher frequency of two *APOL1* alleles (1.0% versus 0.1%) and the *HBB* variant (2.0% versus 0.7%), and a significant association between the presence of *APOL1* alleles or sickle cell trait (*HBB*) with albuminuria and/or eGFR < 60. Limitations of the current study include the lack of longitudinal data regarding incident CKD and kidney disease progression, a narrow definition of CKD based only on low eGFR, no description on whether the authors used the race variable of the CKD-EPI equation, which is no longer recommended,⁹ and the small proportion of global African ancestry in the HCHS/SOL cohort. Together, this limited the authors' ability to show an association between *APOL1* and CKD risk and by extension, other putative CKD-associated genetic variants.

The recent 2020 census found that nearly 34 million people in the U.S. self-identify as multi-racial and a third identify as non-white or white in combination with another group.¹⁰ Thus, conducting genomic research in diverse populations is important for identifying new genes and novel mechanisms to account for differential disease risk, for discovering potential targets for drug interventions, and for ensuring equitable distribution of scientific advancements. Furthermore, Polygenic Risk scores (PRS) may become a useful tool in translational and precision medicine, but are limited by their lack of portability in non-European ancestry populations, which may exacerbate health disparities and medical discrimination.¹¹ The identification of genetic risk factors in diverse populations is critical for the development and application of pan-ethnic PRS to mitigate health disparities.¹¹

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All authors have nothing to disclose.

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REFERENCES

- Hall YN, Choi AI, Chertow GM, Bindman AB: Chronic kidney disease in the urban poor. *Clin J Am Soc Nephrol* 5: 828–835, 2010
- Peralta CA, Shlipak MG, Fan D, Ordoñez J, Lash JP, Chertow GM, et al.: Risks for end-stage renal disease, cardiovascular events, and death in Hispanic versus non-Hispanic white adults with chronic kidney disease. *J Am Soc Nephrol* 17: 2892–2899, 2006
- Popejoy AB, Fullerton SM: Genomics is failing on diversity. *Nature* 538: 161–164, 2016
- Lin M, Park DS, Zaitlen NA, Henn BM, Gignoux CR: Admixed Populations Improve Power for Variant Discovery and Portability in Genome-Wide Association Studies. *Front Genet* 12: 673167, 2021
- Kopp JB, Smith MW, Nelson GW, Johnson RC, Freedman BI, Bowden DW, et al.: MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis. *Nat Genet* 40: 1175–1184, 2008
- Genovesi G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, et al.: Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 329: 841–845, 2010
- Horimoto A, Xue D, Cai J, Lash J, Daviglus M, Franceschini N, Thornton T: Genome-wide admixture mapping of estimated glomerular filtration rate and chronic kidney disease identify European and African ancestry-of-origin loci in Hispanic and Latino individuals in the United States. *J Am Soc Nephrol* 33: 77–87, 2022
- Kramer HJ, Stilp AM, Laurie CC, Reiner AP, Lash J, Daviglus ML, et al.: African Ancestry-Specific Alleles and Kidney Disease Risk in Hispanics/Latinos. *J Am Soc Nephrol* 28: 915–922, 2017
- Delgado C, Baweja M, Crews DC, Eneanya ND, Gadegbeku CA, Inker LA, et al.: A unifying approach for GFR estimation: Recommendations of the NKF-ASN Task Force on reassessing the inclusion of race in diagnosing kidney disease. *Am J Kidney Dis* : S0272-6386(21)00828-3, 2021
- U.S. Census Bureau: Race and Ethnicity in the United States: 2010 Census and 2020 Census. 2021. Available at: <https://www.census.gov/library/visualizations/interactive/race-and-ethnicity-in-the-united-state-2010-and-2020-census.html>. Accessed October 4, 2021
- Martin AR, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ: Clinical use of current polygenic risk scores may exacerbate health disparities. *Nat Genet* 51: 584–591, 2019

See related article, "Genome-Wide Admixture Mapping of Estimated Glomerular Filtration Rate and Chronic Kidney Disease Identify European and African Ancestry-of-Origin Loci in Hispanic and Latino Individuals in the United States," on pages 77–87.