Questioning the importance of genetic ancestry as a contributor to preterm delivery and related traits in African American women

TO THE EDITORS: We read with interest the article by Tsai et al[1] about a significant association between African genetic ancestry in African American women and preterm delivery (PTD). They conclude that "more intensive investigation of genetic admixture in African Americans" is needed to identify novel PTD-related susceptibility genes. Their conclusions, however, rely on inconsistent trends in ancestry levels and the use of potentially biased estimates of ancestry, and they neglect important alternative risk factors for PTD.

First, their conclusion that subjects with higher levels of African ancestry have a higher risk of PTD is not supported by the inconsistent trends they report across the 8 PTD traits. For some traits, the 2nd and 3rd quartiles of African ancestry are significantly associated; for others, the 4th quartile is significant. It is difficult to imagine what sort of biologic function that is related to PTD could be associated with intermediate levels, but not high levels, of African ancestry. Furthermore, the marginally significant associations, with probability values that range from .007 to .04, are likely to disappear after correction for multiple testing across the PTD-related traits.

Second, accurate estimation of ancestry is highly dependent on choosing a sufficient number of markers and accurate reference populations.[2] Tsai et al[1] relied on a small set of 57 markers and comparative populations of Yorubans from Nigeria and Mormons from Utah, which are unlikely to represent all West African and European diversity. They reported similar ancestry estimates when using fewer ancestry informative markers, but this approach did not test the need for more markers or alternative reference populations, which potentially could change their estimates and alter the association with PTD.

Third, Tsai et al[1] dismissed sociodemographic and environmental factors as unable to explain the racial disparity in PTD. Although they measured some environmental and behavioral variables (eg, education, drug use), they did not test for significant differences between cases and control subjects, despite finding higher rates of smoking and illicit drug use in PTD cases. Furthermore, previous research has shown strong associations between gestational outcomes and sociocultural factors (such as poverty, social support, residential segregation, and discrimination).[3] Including these sociocultural factors in the study by Tsai et al[1] may have caused the modest association between ancestry and PTD to disappear, as shown recently in a study of genetic ancestry and blood pressure in Puerto Rico.[4]

In the absence of specific evidence for race-specific susceptibility genes, it may be more productive to investigate potentially modifiable sociocultural and behavioral risk factors that clinicians and policymakers can address to reduce the risk for PTD. ■

Amy L. Non, MA, MPH
Clarence C. Gravlee, PhD
Connie J. Mulligan, PhD
Department of Anthropology
1376 Mowry Rd.
PO Box 103610
Gainesville, FL 32611
anon@ufl.edu

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REPLY

We thank Non et al for their comments. First, we observed an increasing trend in preterm delivery (PTD; odds ratio [OR], 1.5 vs 1.7), spontaneous PTD (OR, 1.3 vs 1.7), very PTD (OR, 1.4 vs 2.1), and PTD accompanied by histologic chorioamnionitis (OR, 1.1 vs 1.2), but not in other traits; specifically, medically indicated PTD (OR, 2.1 vs 1.9), near-term PTD (OR, 1.6 vs 1.5), and PTD with maternal hypertensive disorder (OR, 2.4 vs 2.2) were noted. This may be due to at least 2 reasons: (1) PTD has heterogeneous causes. The 7 traits may represent different subphenotypes of PTD, thus, may have different associations with ancestry informative markers; and (2) we may not have adequate statistical power because of a smaller sample size in each subgroup. Because we did not correct for multiple testing, we agree with Non et al that the detected signals may (or may not) be retained after correction for multiple testing.

Second, we agree it would not be ideal to use Yoruban and white subjects from the HapMap project as 2 parental populations. However, they may serve as surrogate ancestral

populations because those 2 populations have been used to estimate individual admixture in existing literatures.[1] In addition, as pointed out in the second paragraph in the "Comment" section, "the estimates in the study sample were comparable with those reported in previous studies." Therefore, we are confident regarding the estimates of individual admixture.

We agree that our study did not account for all the possible sociocultural factors (such as poverty, social support, residential segregation, and discrimination) when we examined the association between PTD and genetic ancestry. However, as indicated by decades of research and the recent Institute of Medicine report that sociodemographic risk factors cannot fully explain the striking and persistent racial disparity in PTD, PTD is likely a complex disease that is influenced by multiple genetic and environmental factors and their interactions.[2] Given the promise of admixture mapping in other diseases with prominent racial disparity,[3] our study represents a novel approach to search for other possible causes of PTD beyond sociocultural factors. ■

Hui-Ju Tsai, PhD
Xiaobin Wang MD, MPH, ScD
Mary Ann and J. Milburn Smith Child Health Research Program
Children's Memorial Hospital and Children's Memorial Research Center
Department of Pediatrics
Feinberg School of Medicine
Northwestern University
2300 Children's Plaza, Box 157
Chicago, IL 60614

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