2019 Curt Stern Award Address[1]

Sarah A. Tishkoff[2,*]

Thank you, Neil, for the wonderful introduction. I also want to thank the members of the Awards Committee and the Society for this huge honor. I'm particularly excited to be sharing this award with Dr. Charles Rotimi. Charles and I organized one of the earliest working groups focused on the importance of including Africans in human genetics studies at the ASHG meeting in 2002, and it's exciting to see how much progress has been made since that time.

I want to start by acknowledging the people who have inspired me to study African genomics and have provided mentorship along the way. As an undergraduate student at UC Berkeley, I was inspired by Dr. Allan Wilson, who was one of the founders of molecular anthropology. While I didn't have an opportunity to work directly with Dr. Wilson, I did have an opportunity to work with two of his academic offspring, Dr. George Sensabaugh and Dr. Mary Claire King, who inspired me to pursue a career in human genetics and to use genetic information to make inferences about human evolutionary history and disease risk. It was Allan Wilson's group that first showed evidence for an African origin of all modern humans based on patterns of diversity in the mitochondrial genome. As a graduate student in Dr. Ken Kidd's lab at Yale, and co-mentored by Dr. Neil Risch, we were able to demonstrate support for an African origin of modern humans based on patterns of microsatellite haplotype variation in the nuclear genome.[1] We also observed that African populations not only had higher levels of genetic diversity, but that they had strikingly different patterns of diversity compared to each other, indicating high levels of genetic substructure compared to non-African populations. As a postdoctoral fellow with Dr. Andy Clark at Penn State University, I had an opportunity to expand my knowledge of population genetics and genetic signatures of natural selection. We identified a strong signature of recent positive selection for G6PD enzyme deficiency variants that may cause severe anemia but are protective against malaria infection.[2] In addition to being an excellent mentor, one of the other great things that Andy did—almost as soon as I arrived at his lab—was let me leave to spend time as a visiting research scientist working with Dr. Trevor Jenkins from the University of the Witwaterstrand in Johannesberg, South Africa. Trevor Jenkins is the person who deserves to be credited with initiating some of the earliest studies of African genetic diversity. My time in his lab had a major impact on the focus of my future research.

At the time, there were very limited numbers of DNA samples from Africa, particularly from minority populations practicing indigenous lifestyles. In order to alleviate this bias and to obtain knowledge about the extent of genetic variation in Africa, I initiated field work in Tanzania in partnership with Dr. Thomas Nyambo at Muhimbili University of Health and Allied Sciences and Dr. Audax Mabulla from the University of Dar es Salaam. When I started doing field work, I had no prior experience and had to learn as I went along. Clearly, I overpacked, but those of you who know me won't be surprised by that! Since that time, I've worked closely with collaborators in many countries throughout sub-Saharan Africa, and they all deserve to share in the recognition for this award because this research wouldn't have been possible without them. These include Dr. Muntaser Ibrahim from the University of Khartoum in the Sudan, Dr. Gurja Belay from Addis Ababa University in Ethiopia, Dr. Sabah Omar at Kenya Medical Research Institute in Kenya, Dr. Sununguko Wata Mpoloka and Dr. Gaonyadiwe George Mokone at the University of Botswana, and Dr. Alfred Njamshe and Dr. Charles Folkunang at the University of Yaounde in Cameroon. I also

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want to acknowledge the many students, postdocs, and research scientists who contributed to field work, often under very challenging conditions. We were very careful to conduct this research in an ethical manner, working closely with communities to ensure both community and individual consent. We felt that it was very important to keep communities informed about research studies and results. Training and capacity building are also very important, and it's been an honor to play a role in mentoring a number of African graduate students and postdocs who have made important contributions to research in my lab.

In 2009 we published a study of genomic variation in over 3,000 Africans from 121 ethnic groups in Africa and used computational approaches to infer genetic ancestry.[3] We identified extensive genetic substructure and high levels of admixture, reflecting the demographic history of African populations and demonstrating the importance of including ethnically diverse Africans in biomedical research. We've now extended these studies to include whole-genome sequencing and have identified millions of novel variants, many of which are predicted to be functional, and have used this data to reconstruct ancient demographic events in Africa.[4] We were also interested in studying how humans have adapted to different environments and diets in Africa. One of our earliest studies was of the genetic basis of lactose tolerance in African pastoralists. We identified several novel variants that regulate expression of the lactase gene and arose independently from the lactose-tolerance mutation in Europeans due to convergent evolution.[5,6] We identified one of the strongest signatures of natural selection in the human genome and estimated the age of the most common mutation to be 3,000–6,000 years old, corresponding to the time of introduction of cattle domestication into East Africa, an example of gene-culture evolution. More recently, we studied the genetic basis of skin pigmentation in Africa. We identified a number of novel variants and genes associated with skin pigmentation.[7] One of these genes, *MFSD12*, had never previously been characterized and was shown to have a dramatic impact on pigmentation in mice. More recently, this gene has been shown to play a role in risk for melanoma, demonstrating that the high levels of genetic and phenotypic variation in Africa can be informative for identifying biomedically relevant loci that impact global populations. I would like to thank the many grad students, postdocs, and research scientists who made important contributions to these studies. Without them, I wouldn't be receiving this recognition. I'd also like to thank my family, particularly my husband, Evan Leach, who has been an incredible source of support. And lastly, I'd like to thank the African participants for their generous contributions to this science.

References

1. Tishkoff, S.A., Dietzsch, E., Speed, W., Pakstis, A.J., Kidd, J.R., Cheung, K., Bonné-Tamir, B., Santachiara-Benerecetti, A.S., Moral, P., and Krings, M. (1996). Global patterns of linkage disequilibrium at the CD4 locus and modern human origins. Science *271*, 1380–1387.
2. Tishkoff, S.A., Varkonyi, R., Cahinhinan, N., Abbes, S., Argyropoulos, G., Destro-Bisol, G., Drousiotou, A., Dangerfield, B., Lefranc, G., Loiselet, J., et al. (2001). Haplotype diversity and linkage disequilibrium at human G6PD: recent origin of alleles that confer malarial resistance. Science *293*, 455–462.
3. Tishkoff, S.A., Reed, F.A., Friedlaender, F.R., Ehret, C., Ranciaro, A., Froment, A., Hirbo, J.B., Awomoyi, A.A., Bodo, J.M., Doumbo, O., et al. (2009). The genetic structure and history of Africans and African Americans. Science *324*, 1035–1044.
4. Fan, S., Kelly, D.E., Beltrame, M.H., Hansen, M.E.B., Mallick, S., Ranciaro, A., Hirbo, J., Thompson, S., Beggs, W., Nyambo, T., et al. (2019). African evolutionary history inferred from whole genome sequence data of 44 indigenous African populations. Genome Biol. *20*, 82.
5. Tishkoff, S.A., Reed, F.A., Ranciaro, A., Voight, B.F., Babbitt, C.C., Silverman, J.S., Powell, K., Mortensen, H.M., Hirbo, J.B., Osman, M., et al. (2007). Convergent adaptation of human lactase persistence in Africa and Europe. Nat. Genet. *39*, 31–40.
6. Ranciaro, A., Campbell, M.C., Hirbo, J.B., Ko, W.Y., Froment, A., Anagnostou, P., Kotze, M.J., Ibrahim, M., Nyambo, T., Omar, S.A., and Tishkoff, S.A. (2014). Genetic origins of lactase persistence and the spread of pastoralism in Africa. Am. J. Hum. Genet. *94*, 496–510.
7. Crawford, N.G., Kelly, D.E., Hansen, M.E.B., Beltrame, M.H., Fan, S., Bowman, S.L., Jewett, E., Ranciaro, A., Thompson, S., Lo, Y., et al. (2017). Loci associated with skin pigmentation identified in African populations. Science *358*, eaan8433.