Received: 13 February 2017 | Revised: 11 August 2017 | Accepted: 19 August 2017

DOI: 10.1002/ajhb.23055

SHORT REPORT

WILEY American Journal of Human Biology

Amerindian ancestry and extended longevity in Nicoya, Costa Rica

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Funding information
Ministerio de Ciencia, Tecnología y Telecomunicaciones (MICITT) de Costa Rica, Grant/Award Number: FV-0439-2007; Universidad de Costa Rica, Grant/Award Number: 111-A6-320; Wellcome Trust, Grant/Award Number: 072406

Abstract

Objectives: The aim of this study was to address the hypothesis that Amerindian ancestry is associated with extended longevity in the admixed population of Nicoya, Costa Rica. The Nicoya Peninsula of Costa Rica has been considered a "longevity island," particularly for males.

Methods: We estimated Amerindian ancestry using 464 ancestral informative markers in 20 old Nicoyans aged ≥99 years, and 20 younger Nicoyans (60-65 years). We used logistic regression to estimate odds ratio (OR) and 95% confidence interval (CI) of the association of Amerindian ancestry and longevity.

Results: Older Nicoyans had higher Amerindian ancestry compared to younger Nicoyans (43.3% vs 36.0%, $P = .04$). Each 10% increase of Amerindian ancestry was associated with more than twice the odds of being long-lived (OR = 2.32, 95% CI = 1.03-5.25).

Conclusions and Implications: To our knowledge, this is the first time that ancestry is implicated as a likely determinant of extended longevity. Amerindian-specific alleles may protect against early mortality. The identification of these protective alleles should be the focus of future studies.

1 | INTRODUCTION

The increase in life expectancy, as a result of the reduction of preventable causes of mortality, represents—almost globally—one of the great legacies of the twentieth century for public health. Among its outcomes are a demographic transition to older populations and its concomitant epidemiological transition which demand transformations to both health and social institutions, that is, legal, economic, anthropological, spiritual, and so forth (Bengtson & Ssttersten, 2016; Kinsella, 2000).

Strong evidence shows that extended longevity has also a genetic component (Brooks-Wilson, 2013; Dato et al., 2017). Candidate gene studies and genome-wide association studies (GWAS) have identified genetic variants associated

Jorge Azofeifa, Edward A. Ruiz-Narváez, and Alejandro Leal contributed equally to this study.

The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the article.

with human longevity (Sebastiani et al., 2013, 2017; Yashin et al., 2010). Most of these studies have been conducted in populations of European or East-Asian ancestry, and little is known of the genetic contribution to longevity in Hispanic populations.

In Costa Rica, nonagenarian males have the highest life expectancy of the world (Rosero-Bixby, 2008), particularly in the Nicoya region, at the province of Guanacaste, where the probability of 60-year-old males becoming centenarian is seven times that of the Japanese males (Rosero-Bixby et al., 2013). This population is the product of an admixture process initiated during colonial times that produced a blend of Amerindian—mostly Mesoamerican (Hoopes and Fonseca-Zamora, 2003; Reich et al., 2012), European—mainly Spaniard, and sub-Saharan African genes (Lohse, 2005; Morera et al., 2003; Segura-Wang et al., 2010; Wang et al., 2010). Thus, the Nicoyan population offers a unique opportunity to evaluate the association of Amerindian ancestry with longevity.

2 | METHODS

2.1 | Study population

We followed a case–control design to study a sample of elderly people from the Nicoya Peninsula, Costa Rica. The group of centenarians (cases) included 11 males and 9 females. This group included 16 of the 25 centenarians alive in the Nicoya region in mid-2005, and 1 male and 3 females aged 99 years. Age range was 99–105 with a mean of 101 years. The control group consisted of 11 males and 9 females aged 60–65 from the same region. This was a subsample from a longitudinal nationally representative sample of 2,827 residents of Costa Rica aged 60 and older in 2005. The whole sample was based on the national census database from the year 2000 and was obtained by the Costa Rican Study on Longevity and Healthy Aging (CRELES, Spanish acronym for "Costa Rica Estudio de Longevidad y Envejecimiento Saludables"). More details can be found in Rosero-Bixby, Fernández, and Dow (2005). The Institutional Review Board of the University of Costa Rica approved the study. All participants provided their written informed consent.

2.2 | Age determination

Age of CRELES participants was computed from the date of birth recorded in the Costa Rican national birth registry, which also appears on the national identification card (*cédula*) that they had to present during the interviews. The system has been uninterrupted since 1883 and the ledgers are kept in safe vaults of the National Government in San Jose. Since the early 1970s, the registration system has also been kept in computer databases.

2.3 | Covariates

Sociodemographic and biological covariates were obtained through in-person interviews that included physical examinations and blood-draws by venipuncture. Body mass index (BMI, kg/m^2) was calculated from the measured weight and height. High glycosylated hemoglobin was defined as $\geq$6.5%. High triglycerides were defined as $\geq$200 mg/dl. Sitting systolic and diastolic blood pressures were measured twice during the interview and the average reading was used. High systolic blood pressure was defined as 140 mm Hg and above and high diastolic blood pressure as 90 mm Hg and above (Rosero-Bixby & Dow, 2012).

2.4 | Genotyping and quality control

Blood samples from 20 centenarians (ages 99–105) from the Nicoya region and 20 younger Nicoyan controls (ages 60–65) matched by sex were obtained between November 2004 and September 2006 and between October 2006 and July 2008. Each group comprised 11 males and 9 females. Samples were genotyped at the Broad Institute (Cambridge, MA) using the Illumina OmniExpress chip, which includes 467 Amerindian ancestral informative markers (AIMs) (Supporting Information, Table 1). Three AIMs (rs783146 in chromosome 6, rs17006702 in chromosome 12, and rs428453 chromosome 19) failed genotyping and were not included in any statistical analysis.

3 | STATISTICAL ANALYSIS

3.1 | Ancestry association analysis

We estimated Amerindian ancestry using the ADMIXMAP software (Hoggart et al., 2004) and genotype data of 464 successfully genotyped Amerindian AIMs. We used logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) of the association between individual percentage of Amerindian ancestry and longevity. Analyses were stratified by sex.

4 | RESULTS

Table 1 shows the general characteristics of the study participants. No statistical tests were made because of the small sample sizes; however, an exhaustive analysis of biomarkers in relation to mortality prediction in elderly Costa Ricans can be found in Rosero-Bixby & Dow (2012).

4.1 | Ancestry association analyses

Table 2 shows the results of the association analysis between Amerindian ancestry and longevity. Centenarians had a

TABLE 1 General characteristics of the study participants in Nicoya, Costa Rica

Characteristic	Centenarians	Younger controls
Sample size, *n*	20	20
Female, *n*	9	9
Mean age, years (range)	101 (99–105)	63 (60–65)
Mean body mass index, kg/m^2 (SE)	20.1 (1.0)	27.7 (1.2)
Mean systolic blood pressure, mm Hg (SE)	142.3 (7.2)	137.1 (5.7)
Mean diastolic blood pressure, mm Hg (SE)	74.9 (2.8)	80.8 (3.3)
Mean triglyceride levels, mg/dl (SE)	122.3 (12.2)	162.5 (19.2)
Mean HbA1c, % (SE)	6.0 (0.1)	6.3 (0.4)

SE = standard error of the mean.

higher percentage of Amerindian ancestry compared to younger controls (43.3% vs 36.0%, respectively, $P = 0.043$). Each 10% increase of Amerindian ancestry was associated with an OR = 2.32 (95% CI = 1.03–5.25) of being centenarian versus a younger control. Similar results were observed when stratifying by sex.

5 | DISCUSSION

In this case–control study of longevity in the Nicoya region, Costa Rica, we found that Amerindian ancestry is significantly higher among centenarians than in a sample of younger individuals. To our knowledge, ours is the first study reporting an association of genetic ancestry with extended longevity.

The particular demography of the older age groups of the Nicoya region, province of Guanacaste, Costa Rica (Rosero-Bixby et al., 2013) offers a good opportunity to search for clues about the genetic contribution to the extended longevity of its oldest old. Hence, we performed an ancestry association analysis using a case–control design, in a sample that includes 16 out of 25 of the living centenarians of the region at the sampling time (2005) plus 1 male and 3 females aged 99, a group that we call centenarians.

TABLE 2 Association analysis between Amerindian ancestry and longevity in Nicoya, Costa Rica

	% Amerindian ancestry			
Group	Centenarians ($n = 20$)	Younger controls ($n = 20$)	OR[a] (95% CI)	*P* value
Men	39.7	32.9	2.02 (0.77–5.33)	0.15
Women	47.6	39.8	3.09 (0.63–15.0)	0.16
Overall	43.3	36.0	2.32 (1.03–5.25)	0.043

[a]Odds ratio per 10% increase of Amerindian ancestry.

A limitation of this study is the small size. However, we must point out that centenarians included in the current work represent more than two thirds of the total of centenarians of the region. In addition, we did not lose too much power by using a 1:1 matching (ie, one young control per centenarian) relative to 2:1 or 3:1 matching designs. Our *a posteriori* power calculations show that we had 66% power to identify a significant difference of 7.3% Amerindian ancestry (ie, the observed difference in this study) between centenarians and young controls using 1:1 matching. If we had used 2:1 or 3:1 matching, the achieved power would be 75% and 80%, respectively. Another limitation is the cross-sectional design. Cases and controls come from different cohorts and, thus, differ in ancestry or in other characteristics not necessarily related to aging but perhaps due to cohort or period effects. Future longitudinal long-term follow-up studies should be able to control for any cohort effect. However, as discussed below, available evidence supports our hypothesis that Amerindian ancestry is a potential determinant of extended longevity.

The identified association of Amerindian ancestry with extended longevity suggests the presence of protective Amerindian-specific alleles. However, we cannot rule out the possibility that socioeconomic factors may explain at least part of the observed association of Amerindian ancestry with extended longevity. If protective Amerindian-specific alleles do exist, our present results may help to explain in part the observed overall lower mortality of Hispanics in the U.S. compared to non-Hispanic whites (Arias et al., 2010; Ruiz et al., 2013). Further evidence of the existence of beneficial Amerindian-specific alleles is provided by several studies reporting protective associations of Amerindian ancestry against hypertension in Hispanic-American women (Kosoy et al., 2012) and against Alzheimer's disease in the Brazilian population (Benedet et al., 2012). In addition, Amerindian ancestry has been found to be associated with higher survival rates in Brazilian patients with heart failure (Cardena et al., 2014). Finally, a recent study found that epigenetic aging is slower in U.S. Hispanics and Tsimane Amerindians from Bolivia compared to U.S. non-Hispanic whites (Horvath et al., 2016). These latter results together with ours suggest that the association between Amerindian ancestry and longevity could be mediated in part through epigenetic mechanisms.

In conclusion, the association of Amerindian ancestry with being a centenarian in Nicoya is suggestive of a

protective role of Amerindian-specific alleles. Future longitudinal studies with larger sample sizes should be able to map the Amerindian-specific protective alleles that could contribute to extended longevity.

ACKNOWLEDGMENT

The authors want to thank all the participants, and the field and lab workers for their dedication to a fine work.

CONFLICT OF INTEREST

The authors have no conflict of interests to declare.

AUTHOR CONTRIBUTIONS

All authors provided intellectual contributions and read and approved the manuscript.

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REFERENCES

Arias, E., Eschbach, K., Schauman, W. S., Backlund, E. L., & Sorlie, P. D. (2010). The Hispanic mortality advantage and ethnic misclassification on US death certificates. *American Journal of Public Health*, *100*(Suppl 1), S171–S177. https://doi.org/10.2105/AJPH.2008.135863

Benedet, A. L., Moraes, C. F., Camargos, E. F., Oliveira, L. F., Souza, V. C., Lins, T. C., … Nobrega, O. T. (2012). Amerindian genetic ancestry protects against Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *33*, 311–317. https://doi.org/10.1159/000339672

Bengtson, V. L., & Settersten Jr, R.A. (Eds.) (2016). *Handbook of theories of aging*. (3rd ed.). New York: Springer Publishing Company, LLC.

Brooks-Wilson, A. R. (2013). Genetics of healthy aging and longevity. *Human Genetics*, *132*(12), 1323–1338. http://doi.org/10.1007/s00439-013-1342-z

Cardena, M. M., Ribeiro-dos-Santos, A., Santos, S., Mansur, A. J., Pereira, A. C., & Fridman, C. (2014). Amerindian genetic ancestry is associated with higher survival rates compared to African and European ancestry in Brazilian patients with heart failure. *International Journal of Cardiology*, *176*, 527–528. https://doi.org/10.1016/j.ijcard.2014.07.039

Dato, S., Rose, G., Crocco, P., Monti, D., Garagnani, P., Franceschi, C., & Passarino, G. (2017). The genetics of human longevity: An intricacy of genes, environment, culture and microbiome. *Mechanisms of Ageing and Development.* https://doi.org/S0047-6374(16)30255-X

Hoggart, C. J., Shriver, M. D., Kittles, R. A., Clayton, D. G., & McKeigue, P. M. (2004). Design and analysis of admixture mapping studies. *American Journal of Human Genetics*, *74*(5), 965–978.

Hoopes, J. W., & Fonseca-Zamora, O. M. (2003). Goldwork and Chibchan identity: Endogenous change and diffuse unity in the Isthmo-Colombian Area. In J. W. Hoopes, & J. Quilter (Eds.), *Gold and power in ancient Costa Rica, Panama, and Colombia* (pp. 49–89). Washington, D.C.: Dumbarton Oaks Research Library and Collection Washington.

Horvath, S., Gurven, M., Levine, M. E., Trumble, B. C., Kaplan, H., Allayee, H., … Assimes, T. L. (2016). An epigenetic clock analysis of race/ethnicity, sex, and coronary heart disease. *Genome Biology*, *17*, 171. https://doi.org/10.1186/s13059-016-1030-0

Kinsella, K. (2000). Demographic dimensions of global aging. *Journal of Family Issues*, *21*(5), 541–558. Retrieved from 1432802

Kosoy, R., Qi, L., Nassir, R., Garcia, L., Allison, M., Shigeta, R., … Seldin, M. F. (2012). Relationship between hypertension and admixture in post-menopausal African American and Hispanic American women. *Journal of Human Hypertension*, *26*, 365–373. https://doi.org/10.1038/jhh.2011.52

Lohse, K. (2005). *Africans and their descendants in colonial Costa Rica* (Ph.D. Diss). Austin: University of Texas.

Morera, B., Barrantes, R., & Marin-Rojas, R. (2003). Gene admixture in the Costa Rican population. *Annals of Human Genetics*, *67*(1), 71–80.

Reich, D., Patterson, N., Campbell, D., Tandon, A., Mazieres, S., Ray, N., … Ruiz-Linares, A. (2012). Reconstructing Native American population history. *Nature*, *488*(7411), 370–374.

Rosero-Bixby, L. (2008). The exceptionally high life expectancy of Costa Rican nonagenarians. *Demography*, *45*(3), 673–691.

Rosero-Bixby, L., & Dow, W. H. (2012). Predicting mortality with biomarkers: A population-based prospective cohort study for elderly Costa Ricans. *Population Health Metrics*, *10*, 11.

Rosero-Bixby, L., Dow, W. H., & Rehkopf, D. H. (2013). The Nicoya region of costa Rica: A high longevity Island for elderly males. *Vienna Yearbook of Population Research*, *11*(1), 109–136.

Rosero-Bixby, L., Fernández, X., & Dow, W. H. (2005). CRELES: Costa Rican Longevity and Healthy Aging Study, 2005.

Ruiz, J. M., Steffen, P., & Smith, T. B. (2013). Hispanic mortality paradox: A systematic review and meta-analysis of the longitudinal literature. *American Journal of Public Health*, *103*, e52–e60. https://doi.org/10.2105/AJPH.2012.301103

Sebastiani, P., Bae, H., Sun, F. X., Andersen, S. L., Daw, E. W., Malovini, A., … Perls, T. T. (2013). Meta-analysis of genetic variants associated with human exceptional longevity. *Aging (Albany NY)*, *5*, 653–661. https://doi.org/10.18632/aging.100594

Sebastiani, P., Gurinovich, A., Bae, H., Andersen, S., Malovini, A., Atzmon, G., … Perls, T. T. (2017). Four genome-wide association studies identify new extreme longevity variants. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences.* https://doi.org/10.1093/gerona/glx027

Segura-Wang, M., Raventós, H., Escamilla, M., & Barrantes, R. (2010). Assessment of genetic ancestry and population substructure in Costa Rica by analysis of individuals with a familial history of mental disorder. *Annals of Human Genetics*, *74*(6), 516–524.

Wang, Z., Hildesheim, A., Wang, S. S., Herrero, R., Gonzalez, P., Burdette, L., . . . Yu, K. (2010). Genetic admixture and population substructure in Guanacaste Costa Rica. *PLoS ONE*, *5*(10), e13336. https://doi.org/10.1371/journal.pone.0013336.

Yashin, A. I., Wu, D., Arbeev, K. G., & Ukraintseva, S. V. (2010). Joint influence of small-effect genetic variants on human longevity. *Aging (Albany NY)*, *2*, 612–620. https://doi.org/10.18632/aging.100191

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Azofeifa J, Ruiz-Narváez EA, Leal A, Gerlovin H, Rosero-Bixby L. Amerindian ancestry and extended longevity in Nicoya, Costa Rica. *Am J Hum Biol*. 2017;e23055. https://doi.org/10.1002/ajhb.23055