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Short population report

4-Locus high-resolution HLA allele and haplotype frequencies in Costa Ricans from Guanacaste

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ABSTRACT

A total of 110 Costa Rican Mestizos from the province of Guanacaste were genotyped at high-resolution for the human leukocyte antigen loci HLA-A, -B, -C, and -DRB1 using sequence-based typing methods. The respective allele and extended haplotype frequencies, as well as Hardy-Weinberg proportions were calculated. The most frequent extended haplotype identified was A*24:02:01-B*35:12:01-C*04:01:01-DRB1*04:07:01G, with an estimated frequency of 2.73%. No deviation from Hardy-Weinberg Equilibrium was detected at any of the loci studied. The HLA genotypic data of the population sample reported here are available publicly in the Allele Frequencies Net Database under the population name “Costa Rica Guanacaste Mestizo” and the identifier AFN3609.

Costa Rica is a Central American country with an area of 51,000 km^2 and a mainly Spanish-speaking and admixed (Mestizo) population of approximately 5 million inhabitants. Regional genetic variation among Mestizos has been previously reported [1]. Its northwestern region, nowadays mostly corresponding to the province of Guanacaste, was the first to be colonized during the 16th and 17th centuries by Spanish conquerors travelling southwards from Nicaragua along the pacific coast of Central America. At their arrival, the Spanish established large haciendas in the region and brought with them African slaves as indentured workers. This led to the gradual establishment of an admixed population (CRGU) between these newcomers and the native Chorotega indigenous population. Importantly, the larger presence of African slaves in comparison to other regions, as well as more recent migrations from Cubans of African descent at the end of the 19th century, endowed the CRGU with a larger African component. This has been correlated with higher prevalence of traits associated with African ancestry, such as glucose-6-phosphate dehydrogenase deficiency [2,3] and hemoglobinopathies [4,5] in the admixed population from this region in comparison to those of other Costa Rican regions.

A total of 110 peripheral blood or saliva samples from unrelated healthy volunteer donors were included in this study. All donors traced their ancestry to the CRGU. Samples were collected in the cantons of Liberia, Santa Cruz, Nicoya, Bagaces, Cañas, Filadelfia, La Cruz, Hojancha, Las Juntas, and Puntarenas as part of the DNA biobank at the University of Costa Rica’s Centre for Research in Hematology and Related Disorders (Centro de Investigaciones en Hematología y Trastornos Afines, CIHATA), which continuously collects samples for the characterization of genetic variation across the country and its association with medically-relevant traits. DNA was extracted from blood or saliva by routine methods. All participants gave informed written consent as per CIHATA’s DNA biobank standard procedures. Sample collection under CIHATA’s biobank and this study were approved by the local ethics committee at the University of Costa Rica.

Abbreviations: AFND, Allele Frequencies Net database; CRGU, Costa Rican Mestizo from Guanacaste; EM, expectation-maximization; HWE, Hardy-Weinberg equilibrium

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High-resolution HLA typing was performed at Anthony Nolan by in house sequence-based typing methods, with generic amplification of exons 2, 3 and 4 for HLA-A, HLA-B, and HLA-C. For HLA class II, exon 2 of the HLA-DRB1 gene was amplified using in house allele group-specific primer pairs. Amplicons were purified and each exon was sequenced on an ABI 3730xL DNA Analyzer with specific forward and reverse primers using the Big Dye® Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems). Sequence analysis was done with Assign-SBT software (version 3.6+, Conexio Genomics, Freemantle, Australia) using IPD-IMGT/HLA database release 3.9.0 [6]. Ambiguities were further solved using allele-group- (HLA class I) or codon-86-specific (HLA class II) primer combinations and sequencing of the allelic products. For HLA class I, alleles with identical sequences at codons 2, 3, and 4 could not be distinguished, and were assigned the third-field name of the allele with the lowest numerically ordered name (which is usually the more common one). Hence, HLA class I allele frequencies given may in many cases represent the frequency of a group of alleles sharing sequences at these exons. Allele groups (G) were assigned to HLA class II alleles according to IPD-IMGT/HLA database specifications. All homozygous samples were confirmed by at least two determinations and using different techniques. Allele frequencies and compliance with Hardy-Weinberg equilibrium (HWE) were computed using the online tools available from the HLA-net platform (http://hla-net.eu/tools/) [7]. Haplotype frequencies were estimated by an in house implementation of the expectation–maximization (EM) algorithm [8].

All samples were successfully typed for HLA-A, HLA-B, HLA-C, and HLA-DRB1. A total of 33, 52, 25, and 36 alleles were identified for HLA-A, -B, -C, and -DRB1, respectively. Compliance with HWE was confirmed for all loci ($p > 0.5$). The five most common alleles per locus were A*02:01:01 (16.8%), A*24:02:01 (15.0%), A*30:02:01 (6.4%), A*01:01:01 (4.5%), A*29:02:01 (4.5%); B*40:02:01 (6.8%), B*07:02:01 (5.4%), B*15:03:01 (5.4%), B*35:01:01, B*35:43:01 and B*44:03:01 (all three 5.0%); C*04:01:01 (20.4%), C*07:01:01 (8.6%), C*05:01:01 (6.8%), C*07:02:01 (6.8%), C*01:02:01, C*02:10 and C*03:05 (all three 5.9%); DRB1*04:07:01G (15.0%), DRB1*07:01:01G (8.6%), DRB1*03:01:01G (7.3%), DRB1*13:01:01G (7.3%), and DRB1*11:01:02 (5.0%). The complete lists of alleles for each locus are given in Supplementary Table 1. The HLA gene profile of CRGU shows clear evidence of the presence of tri-ethnic admixture of its parental populations, with alleles from essentially putative European (e.g. A*25:01:01, B*37:01:01, B*35:08:01), Amerindian (e.g. A*02:22, B*35:43:01, C*03:05), and Sub-Saharan African (e.g. A*02:02, B*15:03:01, DRB1*11:01:02) origin found in the CRGU sample.

Based on the results for HLA typing, 4-locus haplotype frequency estimations based on the expectation–maximization algorithm were generated. The number of the extended haplotypes with an estimated frequency $> 1/2N$ was 178. Nine extended haplotypes have estimated frequencies of $> 1\%$, the most common being A*24:02:01-B*35:12:01-C*04:01:01-DRB1*04:07:01G (2.73%), A*24:02:01-B*35:43:01-C*01:02:01-DRB1*04:07:01G (2.27%), A*24:02:01-B*15:01:01-C*03:03:01-DRB1*01:01:01G (1.82%), A*34:02:01-B*44:03:01-C*04:01:01-DRB1*13:01:01G (1.82%), and A*30:02:01-B*18:01:01-C*05:01:01-DRB1*03:01:01G (1.82%). A complete list of estimated extended haplotypes is given in Supplementary Table 2. The HLA profile of the CRGU resembles previous partial reports [9], and shows a relatively high proportion of extended haplotypes of likely African origin (28%) [10], following admixture proportion estimations obtained with other genetic markers [11,12]. All genotype, as well as haplotype and allele frequency data are available in the Allele Frequencies Net database (AFND) [13] under the population name “Costa Rica Guanacaste Mestizo” and the identifier (AFN3609). Haplotype and allele data are available in “G” notation in the supplementary information accompanying this publication. However, the notation “G” is omitted in AFND due to format restrictions, and second-field level resolution is shown for the relevant alleles instead.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humimm.2019.05.005.

References

[1] B. Morera, R. Barrantes, R. Marin-Rojas, Gene admixture in the Costa Rican population, Ann. Hum. Genet. 67 (2003) 71.
[2] E. Beutler, W. Kuhl, G.F. Saenz, W. Rodriguez, Mutation analysis of glucose-6-phosphate dehydrogenase (G6PD) variants in Costa Rica, Hum. Genet. 87 (1991) 462.
[3] M. Chaves, G.F. Saenz, E. Quintana, A. Montero, J. Jimenez, Polymorphism of erythrocytic glucose-6-phosphate dehydrogenase in Costa Rica, Sangre (Barc) 33 (1988) 12.
[4] G. Sáenz, M. Chaves, E. Quintana, Las hemoglobinopatías en Costa Rica. Aspectos históricos, culturales y epidemiológicos, Rev Cost. Cienc. Méd 7 (1986) 95.
[5] G.F. Saenz, M. Altafulla, G. Sancho, M. Salgado, Abnormal hemoglobins and thalassemias in Costa Rica, other countries of Central America, and Panama, Bull. Pan Am. Health Organ. 22 (1988) 42.
[6] J. Robinson, J.A. Halliwell, J.D. Hayhurst, P. Flicek, P. Parham, S.G. Marsh, The IPD and IMGT/HLA database: allele variant databases, Nucleic Acids Res. 43 (2015) D423.
[7] J.M. Nunes, S. Buhler, D. Roessli, A. Sanchez-Mazas, collaboration HL-n: the HLA-net GENE[RATE] pipeline for effective HLA data analysis and its application to 145 population samples from Europe and neighbouring areas, Tissue Antigens 83 (2014) 307.
[8] H. Maldonado-Torres, J. Robinson, J.A. Madrigal, Marsh SGE: cactus, a population genetics analysis environment. ‘Genetics and The Immune Response’ Abstracts of the 35th Annual Scientific Meeting of the Australasian Society for Immunology and 14th International HLA & Immunogenetics Workshop, Tissue Antigens 66 (2005) 486.
[9] J.D. Carreon, M.P. Martin, A. Hildesheim, X. Gao, M. Schiffman, R. Herrero, et al., Human leukocyte antigen class I and II haplotypes and risk of cervical cancer, Tissue Antigens 66 (2005) 321.
[10] E. Arrieta-Bolanos, J.J. Madrigal-Sanchez, J.E. Stein, P. Orlich-Perez, M.J. Moreira-Espinoza, E. Paredes-Carias, et al., High-resolution HLA allele and haplotype frequencies in majority and minority populations of Costa Rica and Nicaragua: differential admixture proportions in neighboring countries, HLA 91 (2018) 514.
[11] J. Azofeifa, E.A. Ruiz-Narvaez, A. Leal, H. Gerlovin, L. Rosero-Bixby, Amerindian ancestry and extended longevity in Nicoya, Costa Rica, Am J Hum Biol (2017).
[12] Z. Wang, A. Hildesheim, S.S. Wang, R. Herrero, P. Gonzalez, L. Burdette, et al., Genetic admixture and population substructure in Guanacaste Costa Rica, PLoS ONE 5 (2010) e13336.
[13] E. Santos, A. McCabe, F.F. Gonzalez-Galarza, A.R. Jones, D. Middleton, Allele frequencies net database: improvements for storage of individual genotypes and analysis of existing data, Hum. Immunol. 77 (2016) 238.