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Genes involved in damage response caused by UV radiation in Ecuadorian population of different altitude regions

P.E. Leone[1,*], P. Guevara-Ramírez[1], A.K. Zambrano, A. Pérez-Villa, I. Armendáriz-Castillo, J.M. García-Cárdenas, S. Guerrero, A. López-Cortés, V. Yumiceba, C. Paz-y-Miño

Centro de Investigación Genética y Genómica, Facultad de Ciencias de la Salud, Universidad UTE, Quito, Ecuador

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ABSTRACT

Ecuador has various regions at different altitudes. It is known that at high altitudes, organisms experience multiple stressors, including exposure to ultraviolet (UV) radiation. The UV radiation exposure increases when getting closer to the Equator line. Consequently, cities in the Ecuadorian inter-Andean region and located at 2,800-3,000 m above sea level (masl) are exposed to UV levels approximately 40% higher than those of the lowlands. UV light is a carcinogen that causes mutations, DNA damage and cellular apoptosis. However, the *XPC*, *XPD* and *XPG* genes encode proteins that repair DNA caused by UV radiation. The aim of this study was to evaluate the distribution of three polymorphisms (rs2228001, rs13181 and rs17655) involved in the response to the damage caused by UV radiation in the Ecuadorian populations of high and low altitudes, and thus, correlate the ancestral proportions of these populations. Results showed that the behavior of both groups located at different altitudes is similar. The ancestry of these groups exhibited that the Native American component prevails, and the European and African component varies.

1. Introduction

Human exposure to UV radiation may have beneficial and harmful effects [1]. UV radiation causes a few beneficial healthy effects such as vitamin D3 formation, but it causes many detrimental effects such as sunburn, ocular damage, photoaging, immune suppression and skin cancer [2]. Several factors influence the amount of UV light that reaches the earth's surface, among them ozone depletion, latitude and altitude. UV doses increase with increasing altitude and decreasing latitude [3]. Ecuador has various regions at different altitudes: the coast at the sea level, and the Andean mountains at 3000 masl [4]. According to the World Health Organization, UV levels increase by 10–12% for every 1000 m in altitude due to the atmosphere filters less UV radiation at higher altitudes [5]. UV radiation produces DNA damage with formation of cyclobutane pyrimidine dimers creating mutations in tumor suppressor genes. However, cells have developed repair mechanisms such as nucleotide excision repair (NER) to counteract the DNA damage caused by UV. NER involves several genes such as *XPC*, *XPD* and *XPG* and each fulfills a specific function that repairs the DNA. Defects in NER increase susceptibility to carcinogenesis [6].

2. Materials and methods

2.1. Samples

A total of 140 healthy, non-related and randomly selected individuals were analyzed. The population belongs to different Ecuadorian regions; 80 individuals from the Highlands (1500–2850 masl) and 60 individuals from the Coastal Region and Amazon (6 to 900 masl).

2.2. DNA genotyping

DNA was extracted from peripheral blood using the PureLink Genomic DNA Kit (Invitrogen) and quantified using NanoDrop 2000 (ThermoScientific). Genotypes were amplified by PCR in a final volume of 20 µl containing 2 µL of DNA template (20 ng/µL), 11 µl of Mili-Q water, 0.5 µM of each deoxynucleotide triphosphate, 3 mM of $MgCl_2$, 5 U of Taq Polymerase, 3 µL of 5x buffer, 0.2 µM of forward and reverse primers. The cycle conditions consisted of an initial denaturalization at 95 °C during 5 min, followed by 35 cycles at 94 °C for 1 min, and different annealing temperatures for 45 s, being 64 °C for *XPC*, 67 °C for *XPD* and 61 °C for *XPG*, and a final extension step at 72 °C during 5 min.

* Corresponding author at: Mariscal Sucre Avenue and Mariana de Jesús Avenue, 170129 Quito, Ecuador.
E-mail address: paola.leone@ute.edu.ec (P.E. Leone).
[1] These authors contributed equally to the study.

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Table 1
Allele frequency and odds ratio of *XPC*, *XPD* and *XPG* genes.

Gene (SNP ID)	Allele distribution[1]			p value in Pearson Chi-square test	OR[2]	95% CI[3]	MAF[4]
	Allele	Highland	Lowland				
XPC (rs2228001)	A	51 (64%)	39 (68%)	0.020*	1.056	0.525 – 2.125	0.357
	C	29 (36%)	21 (33%)				
XPD (rs13181)	A	68 (85%)	48 (80%)	0.438	0.706	0.292 – 1.704	0.171
	C	12 (15%)	12 (20%)				
XPG (rs17655)	G	47 (59%)	40 (68%)	0.910	1.404	0.699 – 2.820	0.379
	C	33 (41&)	20 (33%)				

[1] Values represent the allele frequency and percentage in the population.
[2] OR, represents odds ratio.
[3] Cl, represents confidence interval.
[4] MAF, represents the minor allele frequency.
* represent significant level $p < 0.05$.

Amplicons were confirmed using electrophoresis in 2% agarose gel. Finally, it was sequenced using a BigDye Terminator Cycle Sequencing Kit v3.1, with the Genetic Analyzer ABI 3500 and analyzed by using Seq-Scape Software v2.6 (all from Applied Biosystems).

2.3. Ancestry informative markers

140 samples were genotyped by single multiplex PCR using 46 autosomal Ancestry Informative Markers (AIMs). Fluorescent DNA fragments were analyzed by capillary electrophoresis in the genetic analyzer, and were identified using the Genemapper v3.2 (Life Technologies) following allele nomenclature previously described [7].

2.4. Statistical analysis

differences of allele frequencies between highland and lowland groups were analyzed using Pearson' chi-square test, odds ratio (OR), 95% confidence intervals (95% CIs), and minor allele frequencies (MAF) were calculated. SPSS v24 was used for calculate all these parameters and $p < 0.05$ was considered statistical significant. Inference of ancestry proportions was obtained by Structure software v2.3.4 using Africans, Europeans and Native Americans as reference populations (based in tri-hybrid historic mixture).

3. Results

3.1. Population characteristics

62.1% were men and 37.9% woman. The mean age was 36 years (SD ± 5.15).

3.2. Allele frequency

Table 1 shows the observed allelic frequencies of each polymorphism for the population from highland and lowland. For *XPC* gene, rs2228001 was significantly different between highland and lowland ($p = 0.02$), implying that this variation was associated with high-altitude adaptation. So, the probability of the ability to altitude adapt was more 1.056 times for individuals with A allele that of C allele. The MAF of all variants were more than 0.05.

3.3. Ancestral membership proportions

The ancestry apportionment of population from highland and lowland were estimated. For highland group the ancestry proportion was: Native American 0.57, European 0.31 and Afro-Ecuadorian 0.12. The lowland group shown: Native American 0.58, European 0.37 and Afro-Ecuadorian 0.05.

4. Discussion

Ecuador has registered high levels of UV radiation in 2019. According to the Meteorology and Hydrology Institute, in the coast region the levels have been 9–11 points, while in the Highlands the levels have been extremely high (12–15 points) [8]. The native Andean populations have successfully high altitude adapted with low oxygen concentrations and high levels of UV radiation. The *HIF-1α* gene contributes to hypoxia adaptation [6]. This gene contributes to increased *XPC* transcription after UV exposure. Suggesting the relationship found between *XPC* and adaptation to high altitude.

5. Conclusions

The allele A of *XPC* gene could be considered as protective factor in stressful environments with high levels of UV radiation and high altitude, and high adaptation may be inferred by ancestral influence.

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Declaration of Competing Interest

None

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