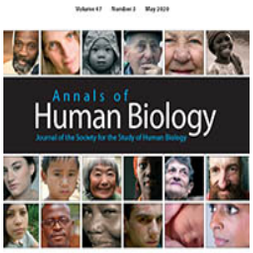

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SHORT REPORT

Angiotensin-Converting Enzyme (ACE) genetic variation and longevity in Peruvian older people: a cross-sectional study

Teodoro J. Oscanoa[a,b,c], Edwin C. Cieza[a,b,c], Frank A. Lizaraso-Soto[a], María L. Guevara[d], Ricardo M. Fujita[d] and Román Romero-Ortuño[e,f]

[a]Facultad de Medicina Humana, Instituto de Investigación, Universidad de San Martín de Porres, Lima, Perú; [b]Servicio de Geriatría, Hospital Nacional Guillermo Almenara Irigoyen, ESSALUD, Lima, Perú; [c]Facultad de Medicina, Universidad Nacional Mayor de San Marcos, Lima, Perú; [d]Centro de Investigación de Genética y Biología Molecular, Universidad de San Martín de Porres, FMH-USMP, Lima, Perú; [e]Discipline of Medical Gerontology, Mercer's Institute for Successful Ageing, St James's Hospital, Dublin, Ireland; [f]Faculty of Health Sciences, Global Brain Health Institute, Trinity College Dublin, Dublin, Ireland

ABSTRACT

Background: Some studies have suggested that the insertion(I)/deletion(D) polymorphism of the Angiotensin-Converting Enzyme (ACE) gene may be associated with human longevity, especially in centenarians. However, this association is still controversial. Besides, there have been no studies in Peruvians.

Aim: To describe the age distribution of the ACE polymorphism in a convenience sample of Peruvian older people.

Subjects and methods: This was a cross-sectional study in 104 Geriatric Day Hospital patients in Lima, Perú. The ACE polymorphism was determined in all patients. For the purpose of association with age, the sample was divided into four categories: young (< 65), youngest-old (65–74), middle-old (75–84) and oldest-old (85 or more).

Results: The distribution of genotype frequencies was consistent with a population in Hardy-Weinberg equilibrium ($p = 0.62$). The number (%) of D/D, I/D and I/I genotypes in the young was 2 (14.3%), 3 (21.4%) and 9 (64.3%), respectively; in youngest-old: 4 (11.4%), 15 (42.9%) and 16 (45.7%); in middle-old: 6 (12.2%), 20 (40.8%) and 23 (46.9%); and in oldest-old: 0 (0.0%), 4 (66.7%) and 2 (33.3%). A chi-square analysis showed no significant differences in genotype distribution between age groups ($p = 0.647$).

Conclusion: No significant age differences were found in the distribution of the ACE polymorphism in this sample. Further studies with greater statistical power are recommended.

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Longevity; ageing; ACE gene; Perú

Introduction

Human longevity is one of the most complex phenotypes to study because it is determined by multiple factors, including environment, lifestyle and genes. The heritability of human longevity has been estimated at 10–15% (Kaplanis et al. 2018; Ruby et al. 2018). Heritability is a statistical measure to estimate the degree of variation of a phenotypic trait in a population that could be attributed to genetic rather than environmental factors (Lynch and Bourrat 2017).

Researchers on longevity genetics are currently studying more than 300 candidate genes in the GenAge database (https://genomics.senescence.info/genes/) and more than 500 in the LongevityMap (https://genomics.senescence.info/longevity/); these are available in the Human Ageing Genomic Resources (HAGR: https://genomics.senescence.info) (Tacutu et al. 2018). In two recent reviews and meta-analyses, a genetic polymorphism in the ACE (Angiotensin Converting Enzyme) gene was among those significantly associated with exceptional human longevity (Garatachea et al. 2013; Revelas et al. 2018). The ACE gene is encoded in the long arm of chromosome 17 (17q23) and the presence or absence of a 288 bp element determines three genotypes: insertion (I/I), insertion/deletion (I/D) and deletion (D/D) (https://www.snpedia.com/index.php/ACE) (Sayed-Tabatabaei et al. 2006).

The role of ACE in the Renin-Angiotensin-Aldosterone system (RAAS) is to convert Angiotensin I to Angiotensin II. Angiotensin II is a potent vasoconstrictor (i.e. increases cardiac afterload) and it also stimulates smooth, cardiac and skeletal muscle growth. Therefore, ACE may play an important role in the pathogenesis of arterial hypertension, coronary artery disease, heart failure and longevity. A meta-analysis suggested that the ACE D-allele and the D/D genotype might confer a modest, albeit significant, advantage to reach exceptional longevity in humans (Garatachea et al. 2013).

The two above-mentioned meta-analyses (Garatachea et al. 2013; Revelas et al. 2018) did not include studies from South America. In addition, there have been no studies in Peruvians where the frequency of the ACE polymorphism has

CONTACT Teodoro J. Oscanoa tjoscanoae@gmail.com Facultad de Medicina Humana, Instituto de Investigación, Universidad de San Martín de Porres, Alameda del Corregidor 1531, La Molina 15024, Lima, Perú.

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been measured in different age groups of older people. In view of this, our aim was to describe the age distribution of the ACE polymorphism in a convenience sample of older Peruvians.

Subjects and methods

A cross-sectional study was carried out that included 104 participants older than 60 years of mixed Peruvian ancestry. The study was conducted at the Almenara Geriatric Day Hospital in Lima, Perú, between January 2016 and December 2018. The method of patient selection was not probabilistic, resulting in a convenience sample. The research project was approved by the Almenara Hospital Ethics Committee and all participants provided signed informed consent.

Genetic analysis

After signing the informed consent forms, blood samples for each participant were collected in EDTA tubes. DNA was extracted from the leukocytes using the standard phenol/chloroform method and amplified by a polymerase chain reaction process. The ACE I/D polymorphism (rs1799752) was detected using a method described elsewhere (Franken et al. 2004; Bouwman et al. 2014).

Sample characteristics

The following variables were used for clinical description of the sample: age, sex, level of education, Charlson Comorbidity Index (Charlson et al. 1994), Barthel Index (disability), timed get up and go (mobility) (Podsiadlo and Richardson 1991), Mini-Mental State Examination score (cognition) and body mass index (nutrition).

Statistical analyses

Descriptive statistics were presented as percentages (%), means with standard deviation (SD) and range or median with interquartile range, as appropriate. A chi-square analysis was used to assess deviation from Hardy-Weinberg equilibrium. To study the association between genotype and age, the sample was divided into four categories: young (< 65), youngest-old (65–74), middle-old (75–84) and oldest-old (85 or more) (Ihle et al. 2016). Additionally, we divided the total sample into two age groups (≤75 vs >75). A chi-square analysis was used to test the association between ACE genotypes and age groups. The level of statistical significance was set at $p < 0.05$. The SPSS statistical package was used for all the analyses.

Results

One hundred and four participants (46 men and 58 women) were recruited to the study. Their mean age was 73.7 years, with a range between 60 and 90 years. Table 1 summarises the demographic and clinical characteristics of this convenience sample and Table 2 shows the distribution of ACE genotypes. In all age groups except the oldest-old, the I/I genotype was the most prevalent, followed by I/D and D/D. The association between ACE genotypes and age groups was not statistically significant ($p = 0.65$). The frequency of the I allele was 68.3% ($n = 142$) and that of the D allele 31.4% ($n = 66$). The analysis of the distribution of genotype frequencies was consistent with a population in Hardy-Weinberg equilibrium ($p = 0.62$).

Table 1. Demographic and clinical characteristics of the sample studied ($n = 104$).

Variables	All sample
Mean age in years (SD)	73.7 (7.4)
Number of young (< 65 years) (%)	14 (13.5)
Number of young-old (65–74 years) (%)	35 (33.7)
Number of mid-old (75–84 years) (%)	49 (47.1)
Number of old-old (85+ years) (%)	6 (5.8)
Number of women (%)	58 (55.8)
Number of men (%)	46 (44.2)
Mean number of education years (SD)	11.7 (3.8)
Mean Charlson Comorbidity Index score (SD)	0.7 (1.0)
Mean Barthel Index (SD)	97.9 (4.7)
Mean Up & Go test (seconds) (SD)	12 (4.2)
Mean Mini-Mental State Examination (MMSE) score (SD)	29.0 (6.2)
Mean Body Mass Index (SD)	27.7 (4.0)

SD, Standard deviation.

Table 2. Distribution of the ACE polymorphism in the sample studied ($n = 104$).

ACE genotype	Total sample ($n = 104$)	Young ($n = 14$)	Young-old ($n = 35$)	Middle-old ($n = 49$)	Old-old ($n = 6$)
D/D	12 (11.5%)	2 (14.3%)	4 (11.4%)	6 (12.2%)	0 (0.0%)
I/D	42 (40.4%)	3 (21.4%)	15 (42.9%)	20 (40.8%)	4 (66.7%)
I/I	50 (48.1%)	9 (64.3%)	16 (45.7%)	23 (46.9%)	2 (33.3%)

ACE, angiotensin-converting enzyme; D, deletion; I, insertion.

The statistical association between two age groups (≤ 74 vs > 75) and the D and I alleles was not significant ($p = 0.745$). Neither did we find significant differences between those two age groups and genotypes D/D ($p = 0.837$), I/D ($p = 0.476$) or I/I ($p = 0.574$).

A multiple linear regression model in $n = 104$ was computed with age (longevity) as the dependent variable and the following independent predictors: female sex, years of education, Charlson Comorbidity Index, ACE I/I status, timed get up and go, Mini-Mental State Examination and body mass index. Results showed that ACE I/I status was not a significant predictor of longevity. In the model, only timed get up and go and body mass index were significant predictors, in the expected direction (i.e. lower timed get up and go and higher body mass index associated with higher longevity).

Discussion

In this convenience sample of older Peruvian attendees to a Geriatric Day Hospital, we found no statistically significant association between ACE genotype and age. Therefore, we could not replicate previous findings that the D-allele may be associated with increased longevity, as reported in two previous meta-analytical studies (Garatachea et al. 2013;

Revelas et al. 2018). However, those two meta-analyses included studies on Caucasian, Chinese and Korean populations and did not include any studies from South America.

Even though we found no association between ACE genotypes and age, we add value to the literature in that studies of the ACE polymorphism had not been conducted in a Peruvian sample before. In addition, only a few studies have described this polymorphism in younger-old groups (Forero et al. 2006; Kolovou et al. 2014). Although longevity studies tend to be focussed on nonagenarians and centenarians, the study of younger-old groups is important to help reveal possible age-related trends in the prevalence of ACE genotypes. The significant findings in our multiple linear regression model with regard to timed get up and go and body mass index are clinically expected and consistent with previously published literature (Bohannon 2006; Flegal et al. 2013).

To our knowledge, only two South American studies exist that provide context to our findings. In Colombia (Bogotá, mestizo population), Forero et al. (2006) found a significant lower prevalence of the D/D genotype in people over 65 years old compared to under 65 (16% vs 24%). This would be consistent with our results (Table 2). In Brazil (Rio Grande do Sul, Gaucho population, descendants of Italian and German Europeans), Da Cruz et al. (2003) found a higher prevalence of D/D and I/D genotypes in people aged over 60; in the latter study, there was a sub-group of Japanese descendants living in Brazil in whom no significant association was found between the D/D and I/D polymorphism and being over 60 years old. The latter is in keeping with some Asian population studies in the Han ethnic group in China and Korea (Choi et al. 2003; Yang et al. 2009), but differs with results from Xinjiang Uygur in China (Wufuer et al. 2004).

Our findings on the frequency of ACE genotypes in Perú are consistent with other South American studies reporting frequencies of I/I, I/D and D/D from 50–53%; 34–45%, and 5–13%, respectively (Rupert et al. 2003; Zorrilla et al. 2006; Bigham et al. 2008).

Our study has important limitations, including the small sample sizes (especially for those aged 85 or more years, with only six subjects) and being a secondary data analysis of a convenience sample. However, our findings can serve as a basis for studies with larger numbers of older people in Perú and other South American countries. Such studies could confirm our preliminary findings that the D allele does not seem to influence longevity and additionally study possible associations of allele I in conjunction with environmental and socioeconomic factors.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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ORCID

Teodoro J. Oscanoa http://orcid.org/0000-0001-9379-4767
Edwin C. Cieza http://orcid.org/0000-0002-8766-1412
Frank A. Lizaraso-Soto http://orcid.org/0000-0001-9993-9998
María L. Guevara http://orcid.org/0000-0001-5457-231X
Ricardo M. Fujita http://orcid.org/0000-0002-9617-5109
Román Romero-Ortuño http://orcid.org/0000-0002-3882-7447

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