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Allele Frequencies of Apolipoprotein E in a South Western Nigerian population on HAART

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Abstract
Objective: Increasing evidence has shown that ApoE polymorphism is associated with the early onset of cardiovascular and neurological diseases in patients on HAART. The frequency of occurrence of the alleles and the genotypes vary by race and population. The study describes the pattern seen among adults in Ibadan, Nigeria.
Methods: This cross-sectional study was conducted among 124 randomly selected HIV-infected persons on protease inhibitor therapy who receive care at the adult antiretroviral clinic of the University College Hospital (UCH), Ibadan. DNA was extracted from leucocytes using EDTA blood. ApoE genotypes were determined using the Seeplex ApoE ACE genotyping kit. The epidemiological distribution of apoE is figured with a pie graph.
Results: About four-fifth (79%) of the participants were females while about two-thirds (68%) were below 50 years of age. The most frequently occurring allele was the ε3 allele (82.2%) and the most common ApoE genotype observed was ε3/ε3. This genotype was present in 52 (41.9%) of the participants. At least one allele of Apo ε2, Apo ε3, and Apo ε4 was present in 28(22.5%), 102 (82.2%), and 50 (40.3) of the study participants respectively. Homozygosity for Apo ε2 and Apo ε4 was observed in 4.8% and 8.0% of participants respectively.
Conclusions: Allelic frequency seen is similar to that described in other studied populations and the frequency of genotypes observed was also similar to those described among world populations with a higher observation of ApoE4 allele as seen in people of African descent.

Keywords: Allele, Apolipoprotein E, HAART

Plain English Summary

All humans have a specific apoE genotype. These genotypes are inherited from both parents and so the type inherited from each parent constitutes an offspring's genetic makeup. The study aimed at identifying the number of times the six known variations in the apoE genotype were found in participants recruited from a hospital clinic in Ibadan.

The apoE gene was selected because it has been shown to predispose to developing blood cholesterol abnormalities which eventually can cause cardiovascular diseases and also a specific type of apoE genotype can predispose to the development of Alzheimer's disease. The HIV population was used because of the presence of HIV, the use of HAART can also predispose to diseases of the heart and brain and apoE genotype can increase the rate of developing these diseases in them.

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Blood samples were taken from 124 study participants who attended the HIV outpatient clinic and their blood was analyzed to see the type of apoE genotypes they have. The results of their sociodemographic and clinical characteristics are seen in the tables in the result section, more than 75% of them were females and more than 60% of them were older than 50 years. Their various apoE genotype is detailed in the pie chart included in the article.
All six genotypes of apoE were seen in the study participants. The most common genotype of apoE seen is the E3/E3 genotype. The E4-containing genotype had a higher frequency in our study than those seen in the Caucasian population. The E2-containing genotypes had the smallest frequencies.

Introduction

The human apolipoprotein E gene is located on the long arm of chromosome 19 clustering with genes coding for apolipoprotein CI and CII- other genes of importance in the metabolism of lipids. The genetic information on the apo E gene is located on four exons separated by 3 introns forming a total of 3597 nucleotide base pairs. Transcription of apo E in the hepatocyte is activated by the genetic regulators- liver X receptor and peroxisome proliferator-activated receptor γ. This activation induces the splicing of the introns and the transcription of the gene to produce its mRNA with 1163 nucleotides. Single nucleotide base substitutions of the gene produce the apo E isoforms- apo E2, apo E3, and apo E4. These isoforms differ in the amino acids present at positions 112 and 158 (1, 2). About 75% of the plasma apoE is synthesized primarily by liver parenchymal cells. The brain also synthesizes ApoE, however plasma apoE does not cross the blood-brain barrier therefore apoE in the brain is its de novo synthesis primarily by the astrocytes in the brain. The second organ synthesizing apoE is the brain, where it is produced primarily by astrocytes (1, 2).

Plasma apolipoprotein E is involved in lipid metabolism. ApoE is present on chylomicrons, VLDL- cholesterol, and HDL- cholesterol where it facilitates the uptake of chylomicron remnant and IDL by its interaction with the LDLRs, lipoprotein receptor-related protein 1 (LRP1), and HSPG. This results in the trapping, sequestration, and internalization of these lipoproteins, promoting their clearance from circulation (3). A reduced interaction of apoE with its receptor results in inefficient clearance of these remnants and may predispose to atherosclerosis (4).

The difference in apoE interaction with its receptors varies due to missense single nucleotide polymorphisms in the apoE gene and resulting structural changes in the protein product. The protein product is a single-chain polypeptide with 299 amino acid residues. The N-terminal domain on residues 1-191 is lipid-free and functions as the LDL receptor-binding domain while the C-terminal domain (on residues 222-299) is the lipophilic region that binds the lipids in the lipoprotein structure. The receptor-binding domain has been identified as the N-terminal end (amino acid positions 136 to 150), hence mutations resulting in amino acid substitutions in these regions result in impaired binding of ApoE to its receptor culminating in elevations in levels of triglyceride-rich VLDL-C, chylomicrons and their remnants (4). ApoE3 is the parent and most abundant isoform, with cysteine as residue 112 and arginine as residue 158. ApoE2 differs from apo E3 at residue 158, where arginine is substituted for cysteine and apoE4 contains arginine at residues 112 and 158. ApoE4 and apoE3 have a high affinity for the LDL receptor (LDLR) while apoE2 binds poorly (4, 5). ApoE polymorphisms have been associated with cardiovascular and neurological diseases (2). One such clinical disorder associated with ApoE is type III hyperlipoproteinemia (HLP), an apoE2 homozygous atherosclerotic cardiovascular disease risk condition, resulting in elevated levels of lipids (particularly, β-VLDL-C) in the plasma, especially with secondary stressors such as pregnancy, hypothyroidism, obesity, and HIV/HAART use (2). ApoE4 homozygousity has also been associated with Alzheimer's disease. Differences in the apoE allele have also been shown to play a significant role in individual response to lipid-lowering drugs and therapeutic lifestyle changes (4). The AACE/ACE guideline identified the E4 isoform as an intermediate risk for dyslipidemia (6). With the use of highly active antiretroviral agents, HIV has become coexisting morbidity now seen in the middle-aged and elderly population. In addition to age, HIV, and HAART as predisposing factors to neurocognitive disorders and cardiovascular diseases, studies have demonstrated that persons with HIV possessing the apoE4 allele develop neurocognitive disorders earlier compared with those who do not possess the apoE4 allele. The apoE genotype is also associated with elevations in LDL-Cholesterol popularly called the bad cholesterol, non E3/E3 carriers have been studied to be at risk of developing

hypertriglyceridemia seen with protease-inhibitor boosted HAART regimen (7, 8, 9).
This cross-sectional study identified genes to show the pattern of ApoE polymorphisms in a Nigerian population, an understudied gene in the Nigerian population, and an essential genetic variation to understanding- the phenotypic differences seen in lipid metabolism, an atherosclerotic cardiovascular disease risk factor and a predisposing factor to Alzheimer's disease. These allelic frequencies will serve as a pilot study for future research as evidence that genotyping for apoE may be required for a personalized treatment regimen in the management of HIV/AIDS with HAART.

Materials and methods

Study design and location

This was a cross-sectional study performed over six months. The study was conducted in the university college hospital, in Ibadan, Nigeria. The University College Hospital/the University of Ibadan (UCH/UI) ARV clinic was established by the Government of Nigeria in 2002. The hospital is a tertiary facility with an inpatient capacity of over 850 beds and a full complement of multispecialty services. The ARV clinic receives referrals from all departments within the hospital and other centers in the city. Activities in the clinic are coordinated by doctors, public health nurses, pharmacists, medical records officers, and other cadres of health workers.

Study population and sample size estimation

The study population was the HIV-positive individuals receiving treatment at the adult antiretroviral (ARV) clinic of the University College Hospital/the University of Ibadan, Ibadan (UCH/UI ARV clinic). All consented individuals that met the inclusion criteria; HIV patients on HAART, age 18 and above, and non-pregnant women were recruited into the study. One hundred and twenty-four non-pregnant adults aged 18 years and above who gave written consent were recruited for the study.

Sampling method, data collection tools, and techniques

Participants were randomly selected from the HIV-positive individuals receiving treatment at the adult antiretroviral (ARV) clinic of the University College Hospital/the University of Ibadan, Ibadan (UCH/UI ARV clinic). A semi-structured questionnaire was used as the survey instrument. The questionnaire included socio-demographic characteristics and clinical characteristics. The total number of participant that met the inclusion criteria were 124 and about 3-5ml of venous blood sample was withdrawn into an EDTA bottle for analysis.

Laboratory analytical methods

DNA extraction was done using whole blood and following the manufacturer's protocol for the QIAamp DNA blood mini kit (Qiagen biotechnology, Hilden, Germany) to ensure DNA yield in suitable quantity and quality for PCR amplification. Amplification and analysis of ApoE genotypes were determined using the Seeplex apoE ACE genotyping kit. This is a polymerase chain reaction DNA amplify, cation technique that uses a proprietary oligo technology called DPO (Dual Priming Oligonucleotide). It is designed to identify the six common apoE genotypes in one PCR step. Identification of the apoE genotype was done using electrophoresis. 5µL of PCR products and size markers were separated with electrophoresis using 2% agarose gel. Fragment sizes were estimated by comparison with known size markers.

Data management and analysis

Continuous variables are described as mean ± standard deviation or median with an interquartile range, whereas categorical variables are presented as numbers and percentages. The epidemiological distribution of apoE is figured with a pie graph. SPSS version 22.00 was used for all statistical analysis

Results

Table 1 describes the demographic characteristics of the study participants. A total of 98 (79%) participants in the study group were females while 26 (21%) of them were males. The mean (SD) age of the female participants was 47.39 (10.0) years, while the male participants had a mean age of 49.69 (8.00) years. The majority of the female participants 54(54.5) had their ages between 40 and 49 years, while the majority of the male participants 16 (61.6) were between ages 40 and 59. Most of the study participants had formal education with 52 (53.1) females and 14 (53.8) males having at least a secondary school education. The majority (98.4%) of the study participants were non-smokers. Although 16 (12.26%) of the participants had smoked in the past, only 2 (1.6%) were current smokers.

Table 1: Sociodemographic characteristics of study participants

Variables	Total	Female	Male	p-value
Number of participants	124	98 (79)	26 (21)	
Age (years) mean (SD)	48.12 (9.46)	47.39 (10.0)	49.69 (8.00)	0.22
Age Distribution (years)				
<40	22 (17.7%)	18 (18.4%)	4 (15.4%)	
40-49	62 (50.0%)	54 (54.5%)	8 (30.8%)	
50-59	18 (14.5%)	10 (10.2%)	8 (30.8%)	
≥60	22 (17.7%)	16 (16.3%)	6(33.1%)	0.029
Educational status				
None	6 (4.8%)	4(4.1%)	2 (7.7%)	
Primary	22 (17.7)	20 (20.4%)	2 (7.7%)	
Secondary	66 (53.2)	52 (53.1%)	14 (53.8%)	
Tertiary	26 (21.0)	20 (20.4%)	6 (23.1%)	
Postgraduate	4 (3.2)	2 (2%)	2 (7.7%)	0.339
Past Smoker*	16 (12.26)	6 (6.1%)	10 (38.5%)	<0.01
Current smoker	2 (1.6)	2 (2.0%)	0 (0.0%)	0.623

*Significant at p<0.05. Variables are represented as n (%)

Table 2 describes the clinical characteristic of the study participants. Among the study participants, 16 (12.26%) were known hypertensive and 8 (6.3%) had past CVD events. There were 18 (14.2%) participants who reported a family history of CVD and there were 2 (1.6%) participants with diabetes mellitus. There was a significant difference in BMI across gender (females vs males, 26.44 (5.71) Vs 23.53 (3.36), p-value <0.01).

Table 2 Clinical characteristics of the study participants

Variables	Total	Female	Male	p-value
Height (m)*	1.64 (0.09)	1.62 (0.09)	1.71 (0.06)	0.003
Weight (kg)	69.05 (14.75)	68.93 (15.65)	69.52 (10.95)	0.820
BMI (kg/m^2)*	25.83 (5.42)	26.44 (5.71)	23.53 (3.36)	0.007
Systolic BP (mmHg)	130.61 (21.54)	130.86 (22.70)	129.69 (16.77)	0.770
Diastolic BP (mmHg)	80.97(14.15)	80.84 (13.54)	81.46 (16.53)	0.860
Known Hypertensive	16 (12.26)	10 (10.2%)	6 (23.1%)	0.084
Past History of CVD	8 (6.3)	6 (6.1%)	2 (7.7%)	0.530
Family history of CVD	18 (14.2)	14 (14.3%)	4 (15.4%)	0.550
Diabetes mellitus	2 (1.6)	2 (2.0%)	0 (0.0%)	0.623

*Significant at p<0.05. Variables are represented as mean (SD)

Figure 1 shows the ApoE genotype among the study participants, the most common ApoE genotype observed was E3/E3. This genotype was present in 52 (41.9%) of the participants. At least one allele of ApoE2, ApoE3, and ApoE4 was present in 28(22.5%), 102 (82.2%), and 50 (40.3) of the study participants respectively.

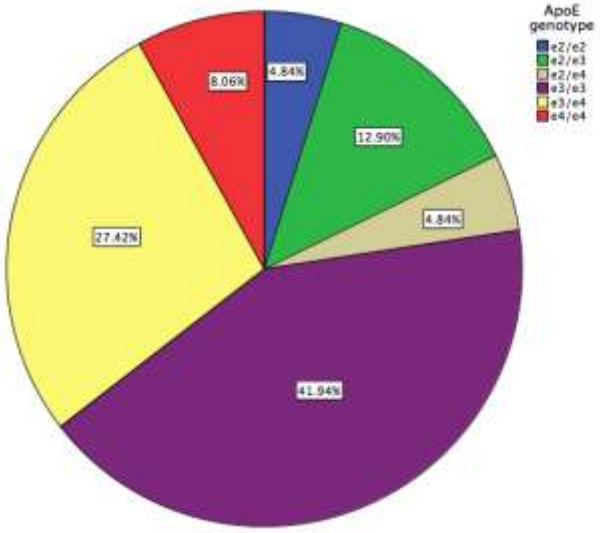

Figure 1: Apo E genotype of study participants

Discussion

This study identified the allele frequencies of human apolipoprotein E. The majority of the study participants 98 (79%) were females and only 26 (21%) were males. This is similar to studies done by Kuti et. al. and Mafigiri et. al (10, 11) in a similar study population of patients attending HIV clinics (12). The majority of the female participants 54(54.5) had their ages between 40 and 49 years, while the majority of the male participants 16 (61.6) were between ages 40 and 59. Most of the study participants had formal education with 52 (53.1) females and 14 (53.8) males having at least a secondary school education. This finding supports those seen by Hegdahl et. al that, HIV prevalence in urban areas is more in females, within the age group 25-49 years. However, there was no difference in HIV prevalence by education Hegdahl *et al* (12)**.**

Although 16 (12.26%) of the participants had smoked in the past, only 2 (1.6%) were current smokers. The majority (98.4%) of the study participants were non-smokers (Table 2). Among the study participants, 16 (12.26%) were known hypertensive and 8 (6.3%) had past CVD events. There were 18 (14.2%) participants who reported a family history of CVD and there were 2 (1.6%) participants with diabetes mellitus. These findings negate those of Sasha et al, Murphy et al, and Kwarisiima et al who reported that HIV-infected adults on ART have a higher prevalence of hypertension and smoking history when compared with HIV-uninfected individuals (13, 14, 15). But it is supported by the studies of Davis K et al who reported that high blood pressure is less common among people with HIV in sub-Saharan Africa compared to the rest of the world population, a systematic review presented at HIV Glasgow 2020 (16)**.**

In this study, the ApoE genotype E3/E3 was observed to be the most dominant genotype. This is in keeping with previous studies by Atadzhanov et al in Zambia, other African populations, and in African-Americans reported by Ziki et al (17, 18). The ApoE3 allele is the most common allele seen in more than half of the population and it binds LDL-C receptor with high affinity. This is because apoE3 possesses both the requisite lipid-binding ability and affinity for LDLR to mediate appropriate lipolysis and endocytosis of TG-rich lipoprotein remnant particles (4). The ApoE genotype E3/E4 was the second dominant genotype. This also supports the findings of Seperhnia et al and Ziki et al on the prevalence of ApoE polymorphisms in a different Nigerian population (15, 16). Previous findings in Nigerian populations by Seperhnia et al reported that the prevalence of APO E polymorphism is in general agreement with those reported in other world populations (19). Some studies have demonstrated that the apoE3/E3 genotype may be cardioprotective, especially for those on protease inhibitor therapy as hypertriglyceridemia was significant in non-carriers of the E3/E3 genotype who were on ritonavir-boosted HAART regimen (8, 9). Ritonavir-boosted HAART remains a significant 2nd line of therapy for the management of HIV in Nigeria (20).

Furthermore, in the grouping of the frequencies of the polymorphisms, we observed that at least

one allele of- E3, E4, and E2 was present in 82.3%, 40.3%, and 22.5% of the study participants respectively. The order of representation was similar to studies on the prevalence of ApoE. Srinivasan et al in a study demonstrated the relative frequency of the E3 allele was most common in white than black children; while the E3/3 genotype was the most frequent phenotype, and E2/2 was the least (21). The apo E phenotype distribution and allele frequency showed a significant race difference. ($P < 0.01$) A lower frequency of the E3 allele in blacks, as compared with whites, was associated with higher frequencies of both E2 and E4 alleles. They also demonstrated that there was no sex difference in apo E phenotype distribution patterns (16, 17).

In this study, there was a high frequency of the ApoE4 allele. This supports findings of a higher ApoE4 allele in people of African descent especially of Nigerian ancestry (21, 22) as against those of Caucasian descent (21, 22, 23). while a study in brazil found no significant associations between the various apoE allele and cognitive disorders (24), a large meta-analysis observed that possessing the E4 allele confers a 42% increase in cardiovascular risk, the apoE4 allele has also been closely linked with the development of neurocognitive disorders, premature brain aging, lipid disorders and the presence of debilitating opportunistic infection in the HIV populace. Since ApoE4 is higher in the African population and has been associated with adverse effects in the HIV population, there may be a need to determine individual genotypes before commencing the HAART regimen to limit these adverse effects in predisposed individuals (7, 8, 9, 25).

There are a few limitations to the study, study participants were adults attending the antiretroviral outpatient clinic, and this study may be done in the community as this would ensure a larger sample size more representative of the study population.

In conclusion, this study helps determine the various polymorphisms in the apoE genotype, an important gene in understanding the genetic basis of certain cardiovascular and neurological diseases.

List of Abbreviations

AACE: American Association of Clinical Endocrinology
ACEK American College of Endocrinology
ApoE: Apolipopreotein E
ART: Antiretroviral therapy
ARV: Antiretroviral
BMI: Body Mass Index
CVD: Cardiovascular Disease
DNA: Deoxyribonucleic acid
DPO: Dual Priming Oligonucleotide
EDTA: Ethylenediaminetetraacetic acid
HDL: High-Density Lipoproteins
HIV: Human Immunodeficiency Virus
HSPG: Heparan Sulphate Proteoglycans
IDL: Intermediate Density Lipoproteins
LDLRs: LDL receptors
LRP1: lipoprotein receptor-related protein 1
mRNA: Messenger Ribonucleic Acid
PCR: Polymerase Chain Reaction
SD: Standard Deviation
UCH: University College Hospital, Ibadan
UI: University of Ibadan
VLDL: Very Low-Density Lipoproteins

Declarations

Ethics approval, and Consent to Participate

Ethical approval for study implementation was obtained from the UI/UCH ethical review committee (ethical review reference number 18/0328). Each participant was allowed to sign a consent form through which their confidentiality was also ascertained. Verbal consent was also taken before every sample collection and the procedure was explained to the participants in the language they understand. A letter of permission was written to the Principal Investigator, HIV program, Infectious Disease Institute, the University of Ibadan toward recruiting the patients attending the adult antiretroviral clinic of the University College Hospital, Ibadan for this study. The study adhered to the proper conduct of research with human subjects.

Consent for publication

All the authors gave consent for the publication of the work under the creative commons Attribution-Non-Commercial 4.0 license.

Availability of data and materials

The data and materials associated with this research will be made available by the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

BOT: Organized the research group, wrote the result, and discussion of the manuscript
OO: did the statistical analysis
EM and AJO: were involved in data collection and writing the manuscript
NN, BJ, and OOl: were involved in sample collection and laboratory analysis of the samples
MA: Conceptualized and supervised the research work.
All authors revised the draft and approved the final version.

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