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Distribution of *APOE* gene variations in the Jordanian population: Association with longevity

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ABSTRACT

APOE gene common variants, known as ε2, ε3 and ε4, can modulate the risk of several age- associated diseases in human. The aim of the current investigation was to investigate the distribution of *APOE* gene variations and their contribution to human longevity in Jordan. The genotypes of the *APOE* gene were identified in 203 subjects (101 young and 102 older adults) using polymerase chain reaction. Allele frequencies of *APOE* variants were: 0.03, 0.925 and 0.045 for ε2, ε3 and ε4 respectively. The ε4 frequency was more abundant in young (0.045) than in older adults (0.005, $p < 0.01$). The *APOE* gene polymorphism might be associated with longevity phenotype in Jordanian population.

1. Introduction

Apolipoprotein E (apoE) is a member of apolipoprotein family that mediates several functions inside the body. It exists as a constituent of chylomicrons, chylomicron remnants, and high- very low- and intermediate-density lipoproteins (HDL, VLDL, and IDL respectively). ApoE is involved in lipid metabolism (Rasmussen, 2016) via the regulation of uptake of remnant lipoproteins by the liver and facilitation of cholesterol efflux from foam cells (Greenow et al., 2005). In addition, apoE contributes to the inflammation (Gonzalez et al., 2017) by regulation of macrophages and suppression of T cell proliferation (Liu et al., 2016). High expression of apoE has been reported in the brain, liver and retina (Elshourbagy et al., 1985). In the brain, apoE is among the players that mediate the central nervous system response to injury and oxidative stress pathways (Handattu et al., 2013; Verghese et al., 2011).

The gene that encode apoE (*APOE*) contains 4 exons and 3 introns and is located 19q (Smith et al., 1988). Three different variations (ε2, ε3 and ε4) have been reported in the *APOE* gene that code for three isoforms (Schachter et al., 1994). The three isoforms of *APOE* differ at amino acids of the protein sequence (at position 112 and position 158). ε3 isoform has cystein and arginine at these positions, whereas ε4 has arginine at both sites, and ε2 has cysteines at both sites. Compared with ε3, individuals with ε4 isoform have high levels of LDL, whereas ε2 individuals have low levels of LDL (Mahley, 2016). Several diseases have been shown to be associated with *APOE* isoforms. For example, *APOE* ε4 variant has been shown to play a role in the pathogenesis of Alzheimer's disease (Limon-Sztencel et al., 2016; Liu et al., 2013), head trauma (Olivecrona and Koskinen, 2017) ischemic stroke (Chauhan and Debette, 2016), coronary artery disease (Ciftdogan et al., 2012), PD (Li et al., 2004; Lopez et al., 2007) and diabetic neuropathy (Ng et al., 2006). In addition, a strong association has been reported between *APOE* ε4 variant and decline in cognition in multiple sclerosis patients, particularly in the domains of learning and memory (Mazurek and Shi, 2008). Previous studies showed differences in the *APOE* ε4 allele among different ethnic populations and to be varied with latitude as higher frequencies of ε4 allele were reported in countries of the equator and in the northern polar regions (Hu et al., 2011; Kern et al., 2015; Lucotte et al., 1997).

Due to the involvement of apoE in the body metabolism, immune response and oxidative stress, *APOE* gene has been suggested to be a good candidate that might impact human longevity (Raichlen and Alexander, 2014; Tindale et al., 2017). In fact,

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genome-wide association studies (GWAS) identified the *APOE* allele ε4 as a strong determinant of human mortality before age 90 (Deelen et al., 2011; Fortney et al., 2015; Nebel et al., 2011). In this study, we aimed at examining the distribution of *APOE* gene variants in the Jordanian population. In addition, the association between *APOE* variants and longevity was examined.

2. Materials and methods

2.1. Study population

Two hundred and three unrelated subjects were recruited from Northern Jordan to participate in the study. Participants were recruited into two groups based on their age: older adults group (>85 yrs, mean age 91.4 yrs, n = 102: 67 male and 35 female) and young group (20–50 yrs, mean age 31.8 yrs, n = 101: 64 male 37 female). Since specialized aging centers are absent in Jordan, recruitment was performed by advertising through the university e-mail directory and via asking in the neighborhoods in the Northern part of Jordan. Since men are usually more known in the neighborhoods than women, this could explain the relatively higher number of male participants recruited in the study. Thus, the sample might not reflect the actual distribution of both genders in older adult population in Jordan. The study design and selection criteria were according to previous longevity investigations reviewed in (Glatt et al., 2007). In addition, the age range of the young group was selected based on the reported Jordanians mortality rate that starts gradually increasing from the early fifties and reach a maximum in the late seventies (Khoury et al., 1999). According to statistics, life expectancy in Jordan is 74.1 years and death rate is 3.4 deaths/1000 population (Alloubani et al., 2016). Accordingly, persons who are >85 years are rare in the country (Khabour et al., 2010) with an estimated percentage of less than 0.3% of the population distribution of the year 2016 (Jordan in Figures, department of statistics, http://dosweb.dos.gov.jo/product/jordan-in-figures-2016/) All participants gave written informed consent as required by the IRB (Institutional Review Boards) of King Abdulla University Hospital/ Jordan University of Science and Technology.

2.2. DNA isolation

Blood (3 ml) from each participant was obtained from cubital vein in EDTA collection tubes. Genomic DNA was extracted from white blood cells using the Promega DNA extraction kit as shown in the kit manual (Promega, Madison, USA). After extraction, concentration of DNA was determined using Nanodrop Spectrophotometer (2000c, Thermo Scientific, Wilmington, DE, USA) and then DNA was stored at −35 °C.

2.3. APOE genotyping

The *APOE* variations were determined using polymerase chain reaction followed by restriction digestion of amplified fragment (Wenham et al., 1991). The template DNA fragment (227 bp) was amplified using the following primers (Forward: 5′CCAAGGAGCTGCAGGCGGCGCA3′) and a reverse primer (Reverse: 5′ACAGAATTCGCCCCGGCCTGGTACAC-3′) (Alpha DNA). The reaction volume of 20 μl contained 50 ng of DNA, 0.30 mM of each dNTP, 0.30 μM of each primer, 5% dimethyl sulfoxide, 1X Gotaq green buffer, and 0.5 u of DNA polymerase (Promega, Madison, USA). The reaction was denatured at 95 °C for 6 min, followed by 31 cycles of 94 °C for 35 s, 60.5 °C for 30 s, and 72 °C for 90 s. Then the reaction was subjected to 7 min final extension at 72 °C. Amplification was carried out using a BioRad thermocycler model C1000 (Philadelphia, PA, USA). The amplified 227 bp gene fragment was restricted with 4 u of *HhaI* (Fermentas, Germany) at 37 °C for 4 h. The restricted DNA fragment was then separated using 10% polyacrylamide gel and vertical electrophoresis tank obtained from Bio Rad (Philadelphia, PA, USA). DNA bands were detected by ethidium bromide staining. The PCR product with the ε3 allele was digested to six fragments (16, 18, 21, 33, 48 and 91 bp), ε4 allele to seven fragments (16, 18, 19, 21, 33, 48 and 72 bp) and ε2 allele to five fragments (16, 18, 21, 81 and 91 bp). DNA ladder of 10–150 bp was used as a marker to estimate the sizes of the restricted DNA fragments (Fig. 1).

2.4. Statistical analysis

The *APOE* allelic and genotype frequencies were analyzed using Chi square/ Fisher's exact tests as appropriate. A *P* value of less than 5% was considered significant.

3. Results

Demographic characteristics of participants are shown in Table 1. The average age of the young group was 31.8 years and of the older adults was 91.4 years. The distribution of the sample with respect to gender and smoking status between older adults and young was similar ($P > 0.05$).

The allelic and genotypic frequencies of the *APOE* variations in the studied sample are shown in Table 2. Three genotypes were detected and their frequencies were ε3/ε3: 85.1%, ε3/ε2: 5.6%, ε3/ε4: 8.5%. Thus, allele ε3 is very common in the Jordanian population with a frequency that reaches 92.5%. On the other hand, allele ε2 and ε4 occur in very low frequency (3% and 4.5% respectively). This distribution of *APOE* alleles was within the range observed in other populations (Table 3).

The genotypes of *APOE* were different between the young and older adults ($P < 0.05$). Similarly, the allelic distribution between the two groups were significantly different ($P < 0.012$). Thus, *APOE* polymorphism might be related to life span in the studied population.

4. Discussion

The aim of this case-control study was to examine the distribution of *APOE* variations and their contribution to human longevity in Jordan. Strong association was found between *APOE* variations and longevity phenotype in the studied population.

The clinical importance of *APOE* variations promotes the researcher to investigate their distribution among different populations. In this study, the results showed that the frequency of ε3 allele in Jordan is 92.5%, which considered among the highest globally (Table 3). Similar frequencies were also detected in neighboring countries like Lebanon, Oman and Turkey (Al-Yahyaee et al., 2005; Almawi et al., 1999; Ilhan et al., 2007). However, a slightly lower abundance of the ε3 was reported in countries like Brazil, Serbia, Spain and China with a range: 66–81% (Alvim et al., 2010; Guan et al., 2011; Haddy et al., 2002; Topic et al., 2008). On the other hand, the prevalence of ε2 and ε4 is very low among Jordanians with frequencies of 3% and 4.5% respectively. These frequencies are within the range of neighboring countries, but are slightly lower than that in countries far from Jordan (Table 3). Thus, Jordan belongs to the countries with the lowest *APOE* ε4 allele frequency, which seems characteristic for the countries from the Middle East (Al-Muhanna et al., 2008; Alloubani et al., 2016). The present distribution of *APOE* isoforms in Jordan is also in concordance with global pattern that shows relatively high frequency of ε4 allele in countries of the equator and in the northern polar regions (Hu

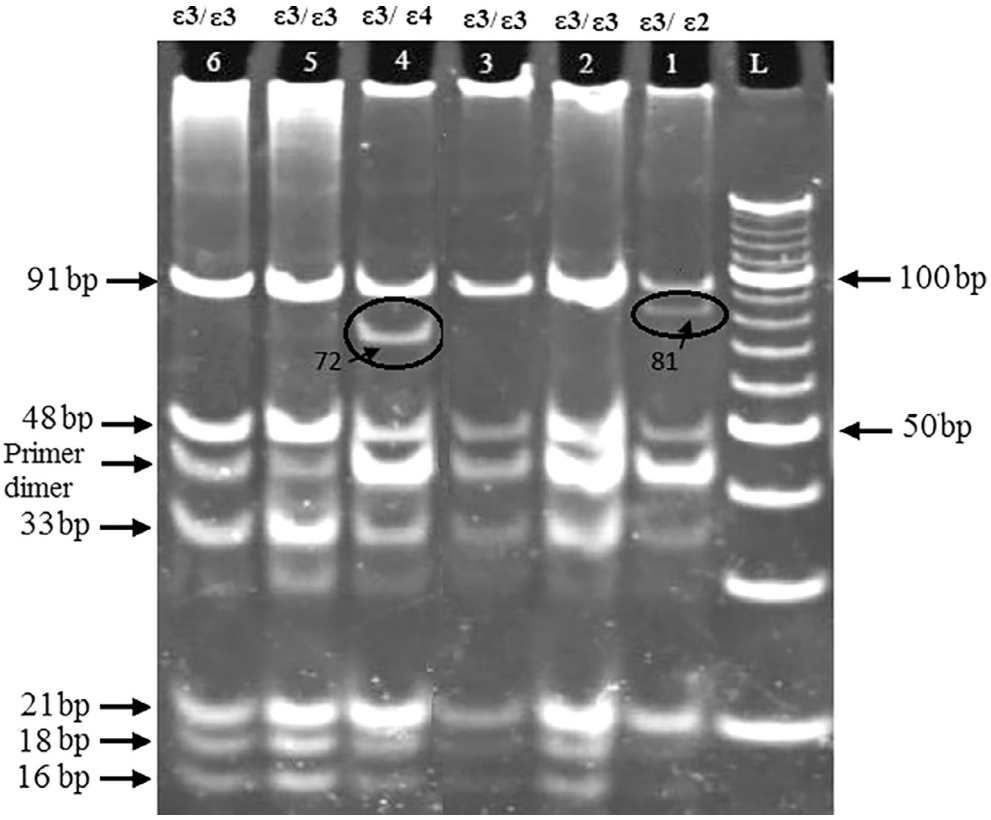

Fig. 1. Gel electrophoresis of *APOE* isoforms. Lanes 1–6 are treated samples with *Hhal* enzyme. Sample in lane 1 represents ε3/ε2 genotype. Sample in lane 4 represents ε3/ε4 genotype. Samples in lanes 2, 3, 5, 6 represent ε3/ε3 genotype. L represents 10 bp DNA ladder. Digestion of the PCR product with the ε3 gives six fragments (16, 18, 21, 33, 48 and 91 bp) whereas ε4 allele gives seven fragments (16, 18, 19, 21, 33, 48 and 72 bp) and ε2 allele gives five fragments (16, 18, 21, 81 and 91 bp). The prominent band between 33 and 48 bp appeared in all PCR reactions and from its size is expected to be for primer dimers.

Table1
Characteristics of the studied population.

	Older adults N = 102	Controls N = 101	P value
Age (mean ± SEM)	90.06 ± 1.2	31.8 ± 5.4	<0.001
Gender			
Male	67 (66%)	64 (63%)	0.405
Female	35 (34%)	37 (37%)	
% of smokers	30.5%	28.2%	0.775
Presence of first/second degree relatives >85 years	70.3%	59.8%	0.013

Table 2
Genotype and allele frequencies of *APOE* variations in the studied population.

Genotypes and Alleles	Older adults N (percentage)	Young N (percentage)	P value [a]
ε3/ε3	89 (87.3)	86 (85.1)	0.013
ε3/ε2	12 (11.8)	6 (5.9)	
ε3/ε4	1 (1)	9 (8.9)	
Allele ε3	191 (93.6)	187 (92.5)	0.012
Allele ε2	12 (5.9)	6 (3.0)	
Allele ε4	1 (0.5)	9 (4.5)	

[a] Based on the Fisher's exact test.

et al., 2011; Kern et al., 2015; Lucotte et al., 1997; Morelli et al., 1996; Sklavounou et al., 1997). Despite these population variance in the distribution of *APOE* isoforms, in the majority ε3 is the common allele followed by ε4 and then ε2.

The findings of the current study revealed a strong association between *APOE* and longevity in Jordanian population. Data showed that *APOE* ε4 is associated with reduction in life span. This result is in agreement with several studies done in many populations such as Finland, Ireland, Denmark, Japan, China, Sweden and USA (Reviewed in (Ang et al., 2008). In addition, GWAS identified the *APOE* allele ε4 as a strong determinant of human mortality before age 90 (Deelen et al., 2011; Fortney et al., 2015; Nebel et al., 2011). In contrast, few reports were unable to show such association between *APOE* and longevity (Galinsky et al., 1997; Liu et al., 2017).

The *APOE* ε4 might affect lifespan in different ways. Many studies showed that ε4 contributes to the risk of many age related conditions such as Alzheimer's disease, head trauma, stroke; PD; diabetic neuropathy and cognitive impairment (Ciftdogan et al., 2012; Crawford et al., 2002; Li et al., 2004; Lopez et al., 2007; Mazurek and Shi, 2008; Olivecrona and Koskinen, 2012; Rassas et al., 2012; Takei et al., 2009; Wang et al., 2009). Other reports found that presence of *APOE* ε4 might affect the oxidative stress status inside the body (Stephens et al., 2008). In addition, the antioxidant effectiveness of apoE lipoproteins against cytotoxicity of H_2O_2 was ε2 > ε3 > ε4 (Jolivalt et al., 2000). Moreover, levels of circulatory lipid peroxides are higher in ε4 isoform carriers compared to ε2 ones (Fernandes et al., 1999; Smith et al., 1998). Furthermore, lipoproteins in the plasma from mice deficient in *APOE* gene are more prone to oxidative stress than the ones from normal animals (Stephens et al., 2008). The last pathway by which ε4 might impact longevity is via its effect on promoting inflammation by causing macrophage dysfunction, and on enhancing apoptosis via endoplasmic reticulum stress induction (Dose et al., 2016).

It is worth to mention that longevity is a multifactorial trait that can be affected by genetic as well as environmental factors. Among the other loci that have been shown to affect longevity are adiponectin, tyrosine hydroxylase, *IL-6* and, haemochromatosis,

Table 3
Summary of the distribution of *APOE* variations among various populations.

Region/country	Sample size	ε2 allele	ε3 allele	ε4 allele
Middle East				
Jordan (this study)	203	0.030	0.925	0.045
Omani Al-Yahyaee et al. (2005)	162	0.052	0.886	0.062
Lebanese Almawi et al. (1999)	155	0.071	0.881	0.048
Saudis Al-Muhanna et al. (2008)	62	0.030	0.840	0.130
Asia				
Chinese Guan et al. (2011)	746	0.162	0.698	0.150
Europe				
Serbian Topic et al. (2008)	326	0.083	0.766	0.152
Turkey Ilhan et al. (2007))	108	0.043	0.935	0.022
Spanish Haddy et al. (2002)	1009	0.077	0.812	0.111
Greek Sklavounou et al. (1997)	216	0.053	0.882	0.065
South America				
Brazilian Alvim et al. (2010)	1493	0.123	0.661	0.266
Argentinean Morelli et al. (1996)	101	0.059	0.787	0.153

interferon-gamma and *APOC-I* (Glatt et al., 2007; Khabour et al., 2010). None genetic (environmental) factors might include diet, pollution and life styles (Christen, 2003). The contribution of genetic factors to human longevity is estimated to be close to 25%, while 75% is attributed to environmental factors (Snejdrlova et al., 2011).

In this study, we assumed that the initial *APOE* allelic distribution in the young and older adults are not different, and the mortality risk due to the different genotypes of *APOE* is not affected by the year of birth. However, a review study that was conducted on fifteen investigations of *APOE* has shown variation in *APOE* allele frequencies between geographically proximate populations and changes in *APOE* related causes of death over time (Lewis and Brunner, 2004). The current study was conducted in Jordan, which is a small country in the Middle East. About 98% of the current population are Arab (Khabour et al., 2010). In addition, the distribution of the common *APOE* alleles among Jordanians is similar to that of neighboring countries. Moreover, older adults and young were from the same neighborhood and thus the sample is considered homogeneous. However, the finding that *APOE* related causes of death changes over the years (Lewis and Brunner, 2004) is considered as a confounding factor that might affect the conclusion drawn from the study. Another possible confound factor could be the high frequency of consanguineous marriage in Jordan.

In conclusion, the results of the current investigation indicate that *APOE* gene might be associated with longevity in Jordanian population.

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