

# Apolipoprotein E (APOE) Genotypes in the Israeli population

Lior Charach MD<sup>1,2\*</sup>, Gideon Charach MD<sup>1,2\*</sup>, Eli Karniel MD<sup>1,2</sup>, Dorin Bar Ziv MD<sup>1,2</sup>, Leonid Galin MD<sup>1,2</sup>, Moshe Weintraub MD<sup>1,2</sup>, and Itamar Grosskopf MD<sup>1,2</sup>

<sup>1</sup>Department of Internal Medicine B, Meir Medical Center, Kfar Saba, Israel

<sup>2</sup>Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

## ABSTRACT

**Background:** *APOE* genotype strongly affects plasma lipid levels and risk for cardiovascular disease and cognitive decline. Studies of apo-e allelic and *APOE* genotype frequencies among several populations have revealed interesting ethnic variations that might affect cardiovascular morbidity and cognition deterioration.

**Objectives:** To evaluate apo-e allelic frequency among Israeli newborns based on known variances in *APOE* allelic frequencies in different countries.

**Methods:** We examined 498 consecutive neonates born at Tel Aviv Sourasky Medical Center. Umbilical cord blood was sampled for genotyping and lipids. Birth weights were recorded. Demographics and parental risk factors for atherosclerosis were obtained from the mothers.

**Results:** Most parents were native-born Israelis. Other countries of origin of grandparents were Morocco, Russia, and Iraq. The prevalence of *APOE* genotypes in Israel is *APOE* 2/2: 1.4%, *APOE* 2/3: 8.2%, *APOE* 3/3: 77.7%, and *APOE* 4/4: 11.8%. There were no associations of *APOE* genotype with parental country of origin. However, there was a tendency for *APOE* 3/4 to be more frequent in newborns of parents of Asian and African origin. Genotype 3/3 was more frequent in newborns whose parents came from Europe and America (78%) compared to those from Asia or Africa (69%).

**Conclusions:** It is important to determine risk factors such as *APOE* genotype for evaluation of premature atherosclerosis. Determining genetic and environmental risk factors may facilitate earlier treatment and prevent heart and brain atherosclerosis. *APOE* genotypes did not appear to affect total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or triglyceride levels in newborns.

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**KEY WORDS:** *APOE* genotype, apolipoprotein E (APOE), atherosclerosis, premature atherosclerosis

\*The first two authors contribute equally to this study

Human apolipoprotein E (APOE) is an arginine-enriched glycoprotein found as a structural component in chylomicrons, very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and high-density lipoproteins (HDL). It

plays a central role in lipoprotein metabolism including hepatic clearance of chylomicrons and VLDL remnants by binding to the LDL receptor in hepatic and extrahepatic tissues. It is also a ligand for the putative LDL receptor-related proteins [1]. *APOE* is a polymorphic gene with three common isoforms (E2, E3, and E4). Phenotypes E4/4 and E4/3 have lower affinity to the LDL receptor and to the LDLR-related protein and are associated with higher levels of pro-atherogenic lipoprotein. Phenotypes E3/2 and E2/2 have higher affinity to these receptors and are thus associated with lower levels of pro-atherogenic lipoprotein.

The role of APOE in atherosclerosis development was first demonstrated in animal models [2]. Further research found that APOE has an atherogenesis modulating effect in humans [3–6]. The E4 allele (phenotypes E4/4 and E4/3) is associated with higher low-density lipoprotein cholesterol (LDL-c) and is considered proatherogenic, whereas the E2 allele (E3/2, E2/2), is associated with lower LDL-c levels and seemed to have the opposite effect (although it may be associated with increased plasma triglycerides and lipoprotein remnants) [3]. *APOE* also modifies the reverse cholesterol efflux from cholesterol loaded macrophages and thus affects atherosclerosis plaque formation [7].

In almost all populations, the *APOE* 3/3 genotype is by far the most common. Typically, 50% to 70% of the population has the *APOE* 3/3 genotype, with the E3 allele making up 70–80% of the *APOE* gene pool [8,9]. *APOE* 2 allele frequencies are 0–13%. *APOE* 4 is 12–18%. The *APOE* polymorphism has been found to influence plasma lipid metabolism [2]. The relative frequency of the *APOE* 2 allele is increased in patients with type 3 hyperlipoproteinemia [8]. However, the *APOE* 2 allele has been associated with lower levels of plasma cholesterol and LDL-c as well as higher levels of triglyceride-rich lipoproteins compared to *APOE* 3 [3]. Conversely, *APOE* 4 is associated with higher levels of total cholesterol and LDL-c [2,3,9]. Song et al. [3] evaluated data from several studies that included Caucasian and Asian populations and found remarkably consistent patterns. Individuals with the E2/2 genotype had the lowest plasma cholesterol levels, while those with E4/4 genotype had the highest. The allele E4 has been suggested as a risk-factor for atherosclerosis [5–10], Alzheimer's, dementia, and Parkinson's disease [10,11]. *APOE*4 has an allele frequency of about 37% in

Caucasian Alzheimer's dementia patients [8,9,11]. When evaluated according to the specific genotype frequencies, *APOE* 3/4 individuals represent about 21% of the cognitively normal Caucasian population vs. about 41% of Caucasian Alzheimer's dementia patients (odds ratio [OR] 3.2) [11], whereas *APOE* 4/4 individuals have a genotype frequency of approximately 2% in the cognitively normal Caucasian population vs. about 15% in Alzheimer's dementia population. *APOE* 3/4 phenotype was found to have a frequency that was twofold higher in patients with Alzheimer's dementia compared to cognitively preserved individuals, while *APOE* 4/4 phenotype was reported to be 7-fold more frequent in Alzheimer's dementia [8-11].

Studies of patients with coronary artery disease (CAD) and those who have had myocardial infarctions yielded conflicting information as to whether *APOE* 4 imposes an increased risk of cardiovascular disease [6-8,12,13].

It was shown that *APOE* 4 is associated with CAD and thoracic and abdominal atherosclerosis. In contrast, *APOE* 2 correlates with reduced risk [7-11]. Several studies have demonstrated that *APOE* 4 is involved in higher intestinal absorption of cholesterol and increased LDL-c production [5-7]. Weintraub and colleagues [13] showed that lipoproteins containing *APOE* 2 are detected in the liver due to increased LDL receptors. In contrast, individuals with *APOE* 4/3 genotype displayed accelerated plasma clearance of intestinally derived lipoproteins and low levels of remnant lipoproteins in plasma [13].

The association of *APOE* 4 allele with increased levels of plasma total cholesterol and LDL-c has been postulated to occur secondary to a decrease in LDL receptor expression in the liver, caused by accelerated delivery of dietary cholesterol to the liver and down-regulation in the receptor [14-22].

In the current study, we determined the frequency of genetic variations in *APOE* compared with populations in other countries and investigated the effects of *APOE* polymorphism on quantitative variations in plasma lipids.

## PATIENTS AND METHODS

In this cross-sectional study, we examined 498 Israeli neonates born at the Tel Aviv Medical Center. The study was conducted from September 1996 to February 1997.

The study was approved by the Tel Aviv Medical Center Ethics Committee. All women gave written consent to donate umbilical cord blood and agreed to complete a questionnaire about demographic data, neonatal birth weight, parental family history, and risk factors for atherosclerosis.

A preliminary sample of the population taken before the study demonstrated that the study population reflected the Israeli population: 77.9% women were native Israelis, 7.0 % of the women were born in Asia or Africa, and 15.1.% were born in Europe or the United States. A total of 517 women were recruited to the study; however, only 498 consented to undergo *APOE* genotyping.

## LABORATORY METHODS

### Lipid profile

Total serum cholesterol, triglyceride and HDL-cholesterol (HDL-c) were determined by enzymatic methods using reagents from Beringer-Manheim, Germany [18,20]. HDL-c was determined by Mg2/dextran sulfate precipitation method. LDL-c level was calculated using the Friedewald formula.

### *APOE* typing

The *APOE* gene was amplified using primers and conditions described by Wenhan and colleagues [18]. After amplification [18,19], PCR product was digested with the restriction enzyme H-hal and fragments were separated by electrophoresis on 5% agarose gel. *APOE* alleles were visualized by staining with ethidium bromide.

## STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA). Nominal data were described as numbers and percentage and metric data as means and standard deviations. Statistical tests were performed accordingly: Chi-square test for qualitative variables and *t*-test or Mann-Whitney non-parametric test as appropriate (after Shapiro-Wilk test for normality distribution) for continuous parameters and one-way ANOVA with Bonferroni correction were conducted. *P*-values < 0.05 were considered statistically significant.

## RESULTS

Among 498 newborns, 281 were male and 217 were female. Of the parents, 388 (77.9%) mothers and 372 (74.7%) fathers were born in Israel. Approximately 7% of the mothers and 11% of the fathers were born in Asia or Africa, and 15% of the mothers and 14% of the fathers were of European or North American extraction. There fewer parents from Asia and Africa compared to other origins (*P* = 0.012). Grandparents were most frequently from Russia (17%), Morocco (15%), and Iraq (14%).

Table 1 depicts variations in lipid profile of the newborns according to *APOE* genotype. No difference was found in lipid profiles or *APOE* genotypes by sex.

Table 2 shows differences in *APOE* genotypes of Israeli newborns according to parental country of origin. The comparison of *APOE* according to the country of origin of the parents showed that 18.2% of couples were from different countries. Most parents (64.2%) were native Israelis.

There were no associations between *APOE* genotype and parental country of origin. However, 3/4 phenotype was the most frequent in the subgroup of newborns whose grandparents were from Asia/Africa (21.7 % vs. 13.0%), and inversely in the subgroup of newborns whose grandparents came from Asia/Africa

3/4 phenotype was most frequent. The 3/3 genotype was found more often in those of European and North American origin (21.7 % vs. 13.0%).

It is likely that we did not identify a difference in *APOE* according to country of origin because of the mixed origins of Israelis in the generation studied.

Table 3 and Figure 1 present the distribution of *APOE* genotypes in Israel and other countries. The Israeli *APOE* polymorphism differs statistically from some of the countries mentioned. *APOE* 2/2 genotype was comparable in all five countries while *APOE* 2/3 genotype was more prevalent in the United States. *APOE* 3/3 genotype was more prevalent in Israel and comparable to Japan. *APOE* 3/4 genotype prevalence was highest in Finland. *APOE* 4/4 genotype was scarce in all countries, and *APOE* 2/4 genotype prevalence was exceedingly low in all five countries.

## DISCUSSION

We discuss the importance of determining *APOE* genotype as a potential risk factor to atherosclerosis.

The classic risk factors for CAD do not seem to entirely explain cardiovascular morbidity and mortality. Therefore, ad-

ditional risk factors have been suggested. In this respect, the composition of apolipoproteins have been a major focus of interest in recent years [10-16,20-25]. It is thought [4-6, 21-25] that determining *APOE* very early in life can predict future atherosclerosis (e.g., CAD, stroke) much more accurately than measurement of lipid profile, because newborns and toddlers have very low total cholesterol, LDL-c, HDL-c, and triglyceride levels. *APOE* modulates lipoprotein transport and metabolism. Its polymorphism explains about 7% of cholesterol variation at the population level [3,20-22]. There is an obvious relationship between *APOE* and major coronary risk factors, including family history, total cholesterol, and LDL-c level.

In this study, we investigated the distribution of *APOE* alleles and its genotypes in a group that we believe represents the Israeli population, and compared this distribution to subgroups, according to parental country of origin. We found the following distribution: 1.4% (*APOE* 2/2), 8.2% (*APOE* 2/3), 77.7% (*APOE* 3/3), 0.6% (*APOE* 4/4), 0.2% (*APOE* 2/4), and 11.8% (*APOE* 3/4).

In our study, the E4 allele (E3/4) was associated with slightly higher LDL-c, total cholesterol levels [Table 2]. This corresponds with several previous studies that found a higher

**Table 1.** Variations in lipid profiles according to *APOE* genotypes of the newborns

| <i>APOE</i> genotype       | n  | E 3/2 | SD    | n   | E 3/3 | SD    | n  | E 4/3 | SD    |
|----------------------------|----|-------|-------|-----|-------|-------|----|-------|-------|
| <b>Total cholesterol</b>   |    |       |       |     |       |       |    |       |       |
| Females                    | 16 | 54.06 | 14.35 | 157 | 59.65 | 16.62 | 22 | 59.22 | 12.76 |
| Males                      | 25 | 54.88 | 14.86 | 22  | 55.95 | 16.11 | 35 | 53.25 | 13.56 |
| <b>LDL-cholesterol*</b>    |    |       |       |     |       |       |    |       |       |
| low-density                | 16 | 25.12 | 17.06 | 157 | 27.17 | 12.33 | 22 | 25.95 | 8.78  |
| lipoproteins               | 25 | 21.24 | 11.22 | 220 | 24.88 | 11.89 | 35 | 24.14 | 10.77 |
| <b>HDL-cholesterol**</b>   |    |       |       |     |       |       |    |       |       |
| Females                    | 16 | 24.12 | 8.44  | 157 | 24.96 | 9.63  | 22 | 24.27 | 8.17  |
| Males                      | 25 | 25.00 | 10.00 | 220 | 22.99 | 10.70 | 35 | 20.82 | 8.24  |
| <b>VLDL-cholesterol***</b> |    |       |       |     |       |       |    |       |       |
| Females                    | 16 | 8.68  | 3.28  | 157 | 8.41  | 3.80  | 22 | 8.68  | 2.99  |
| Males                      | 25 | 11.48 | 16.33 | 220 | 9.71  | 2.69  | 35 | 8.42  | 2.39  |
| <b>Triglycerides</b>       |    |       |       |     |       |       |    |       |       |
| Females                    | 16 | 44.06 | 17.03 | 157 | 41.26 | 17.64 | 22 | 42.81 | 14.05 |
| Males                      | 25 | 41.36 | 12.65 | 220 | 43.80 | 17.38 | 35 | 40.60 | 13.28 |

The genotypic groups E 2/2 (6), E 2/4 (1), E 4/4 (3) were omitted from analysis due to the low number of individuals

Total cholesterol: E3/2 vs. E3/3 females,  $P = 0.028$

\*LDL-cholesterol: E3/2 vs. E3/3 males,  $P = 0.025$

\*\*HDL-cholesterol: E3/2 vs. E4/3 males,  $P = 0.04$

\*\*\*VLDL-cholesterol: E3/2 vs. E3/3 males,  $P = 0.06$

HDL = high-density lipoproteins, LDL = low-density lipoproteins, VLDL = very low-density lipoproteins, SD = standard deviation

**Table 2.** Distribution of APOE genotypes according to parents' country of origin

| Country of origin | Total | %    | 4/4 | %   | 3/4 | %     | 3/3 | %    | 2/4 | %   | 2/3 | %    | 2/2 | %   |
|-------------------|-------|------|-----|-----|-----|-------|-----|------|-----|-----|-----|------|-----|-----|
| Israel            | 320   | 64.2 | 0   | 0   | 42  | 13.1  | 246 | 76.8 | 1   | 0.3 | 26  | 8.12 | 5   | 1.6 |
| Asia, Africa      | 23    | 4.6  | 0   | 0   | 5   | 21.7  | 16  | 69.6 | 0   | 0   | 2   | 8.69 | 0   | 0   |
| Europe, America   | 46    | 9.2  | 1   | 2.1 | 6   | 13.0  | 36  | 78.2 | 0   | 0   | 3   | 6.52 | 0   | 0   |
| Mixed             | 90    | 18.2 | 2   | 2.2 | 8   | 8.8   | 68  | 75.5 | 0   | 0   | 12  | 13.3 | 1   | 1.1 |
| Unknown           | 17    | 3.4  | 0   | 0   | 2   | 11.8  | 13  | 76.5 | 0   | 0   | 2   | 11.7 | 0   | 0   |
| Total             | 498   | 100  | 3   | 0.6 | 63  | 12.56 | 379 | 76.1 | 1   | 0.2 | 45  | 9.03 | 6   | 1.2 |

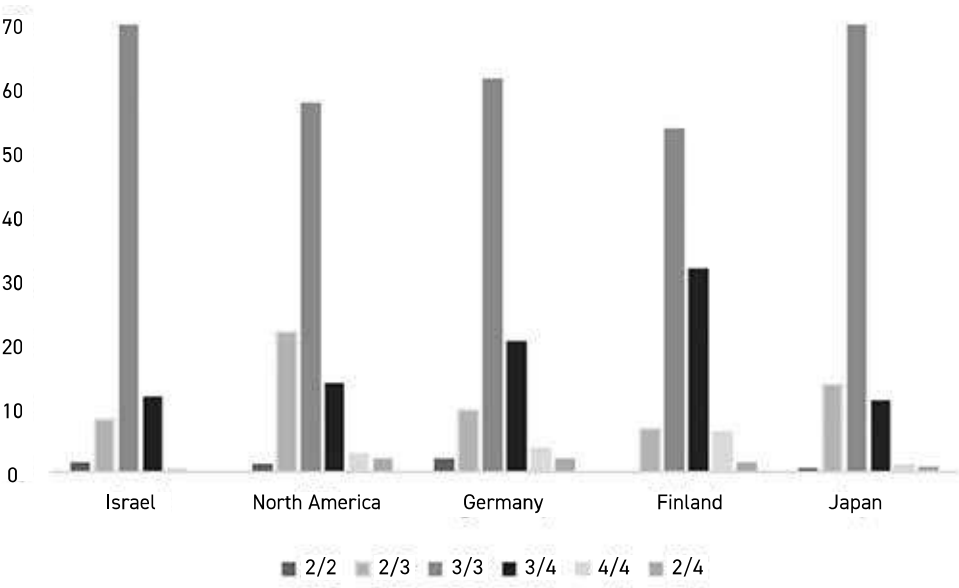
No statistical difference was found between Israel and any other country by APOE genotypes

**Table 3.** Distribution of APOE genotypes in several countries

| Type of APOE          | 2/2 | P-value* | 2/3  | P-value | 3/3  | P-value | 3/4  | P-value | 4/4 | P-value | 2/4 | P-value |
|-----------------------|-----|----------|------|---------|------|---------|------|---------|-----|---------|-----|---------|
| Israel 498 (%)        | 1.4 |          | 8.2  |         | 77.7 |         | 11.8 |         | 0.6 |         | 0.2 |         |
| United States 152 (%) | 1.3 | 0.5      | 22.0 | < 0.01  | 58.0 | < 0.01  | 14.0 | 0.5     | 3.0 | 0.02    | 2.0 | 0.04    |
| Germany 1000 (%)      | 2.0 | 0.5      | 9.8  | 0.3     | 61.8 | < 0.01  | 20.6 | < 0.01  | 3.9 | < 0.01  | 2.0 | < 0.01  |
| Finland 615 (%)       | 0.3 | 0.08     | 6.7  | 0.3     | 54.0 | < 0.01  | 31.9 | < 0.01  | 6.3 | < 0.01  | 1.5 | 0.03    |
| Japan 279 (%)         | 0.3 | 0.4      | 7.1  | 0.01    | 74.6 | 0.06    | 16.5 | < 0.01  | 1.1 | 0.4     | 0.7 | 0.3     |

\*P-value for any APOE genotype percentage in Israel compared to each one of the other four countries

**Figure 1.** Distribution of APOE genotypes in several countries



frequency of the APOE 4 allele in CAD patients, compared to healthy individuals, and more severe atherosclerosis compared with other alleles [1-11,13-17,21-25].

In Finland, the prevalence of 4/4 is higher than in other countries. Israeli APOE polymorphism is comparable to that of Japan, although it differs significantly from that reported from Finland [15,21,24,25].

The APOE genotypes were partially related to total cholesterol, LDL-c, HDL-c, or triglyceride levels in our study total cholesterol E3/2 vs. E3/3 females ( $P = 0.028$ ), LDL-c E3/2 vs. E3/3 males ( $P = 0.025$ ), HDL-c E3/2 vs. E4/3 males ( $P = 0.04$ ), VLDL-c E3/2 vs. E3/3 males ( $P = 0.06$ ). Lipid levels in newborns and young children are exceedingly low before they start to consume a standard diet around the age of 3 years [15,20,21].

The Finnish [21] study did not find a relationship between APOE and lipid profile. However, total cholesterol and LDL-c were reported to correlate with APOE 3/4 genotype compared to APOE 3/2 and 3/3. In that study, it was not clear whether elevation of total-c and LDL-c and especially HDL-c were related to diet type (e.g., eggs, fats consumption) or to a genetic predisposition in children of age 3 years [15,17,21].

More babies whose parents originated in Europe or the United States tended to have APOE 3/3 genotype. Significantly more newborns with parents of Asian and African origin had APOE 3/4. When the study was conducted, the distribution of parents of newborns according to country of origin reflected strong demographic effects of a recent wave of immigration from the former Soviet Union. Demographic studies did not show APOE differences between Sephardi and Ashkenazi groups, which can be explained by mixed marriages of immigrants from different countries of origin in the two preceding generations.

## CONCLUSIONS

The numbers of young individuals with CAD are increasing slowly. It is, therefore, important to investigate risk factors for premature CAD in addition to hypertension, diabetes, hyperlipidemia, smoking history, and family history. Determination of genetic, as well as environmental risk factors, may facilitate earlier prevention and treatment of cardiac and cerebral atherosclerosis. The APOE genotype has been a focus of interest as an emerging such risk factor. We surveyed the frequencies of APOE alleles and APOE genotypes in Israel in reference to ethnicity, blood lipids, and birth weight. Israeli APOE genotype distribution was comparable to that of Japan but varied significantly from Finland. The genotype E 3/3 was less common in newborns whose parents originated in Asia or Africa (69%) compared to Europe or United States (78%). The APOE genotypes did not appear to affect total cholesterol, LDL-c, HDL-c, or triglyceride levels in newborns. There was a tendency of lower birth weight to be associated with APOE distribution.

## Correspondence

Dr. G. Charach

Dept. of Internal Medicine B, Meir Medical Center, Kfar Saba 4428164, Israel  
email: drcharach@012.net.il

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**That is happiness; to be dissolved into something complete and great.**

Willa Cather (1873–1947), American novelist