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LETTER TO THE EDITOR

# Influence of Genes on the Lifespan of Long- and Short-Lived Families

**KEYWORDS**
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CETP;
ACE

There is enormous personal concern regarding lifespan. Investigation of the biological basis of human lifespan, is warranted due to the long lifespan of humans. Genetic studies have identified a limited number of loci associated with human longevity by examining the phenotype of age at death or survival to advanced age. Long-lived people are defined as those who live at least 90 years.[1] Long-lived people overcome or avoid some of the most deadly diseases, such as cancer and atherosclerosis, or develop stabilized disease.[2] Many genes are related to the risk of progression of such deadly diseases, such as cholesteryl ester transfer protein (*CETP*), apolipoprotein E (*ApoE* ), angiotensin converting enzyme (*ACE* ), and adiponectin (*ADIPOQ*).[1] Genes possibly involved in cancer pathology include insulin-like growth factor (*IGF* ), *p53*, and Fork-head box O3A.[3] This study focused on 5 variants of each of the following genes: *CETP*, *AIPOQ*, *IGFBP3*, and *ACE*. *CETP* polymorphisms, such as *TaqIB* (*rs708272*) and *I405 V* (*rs5882*), were found to be associated with atherosclerosis, left main coronary disease[4] and longevity.[5] The *ACE* gene, particularly the *rs1799752* polymorphism, has been evaluated in the pathogenesis of hypertension, coronary artery disease (CAD), heart failure, and, more recently, longevity.[6] ADIPOQ is a determinant of insulin sensitivity that exerts anti-inflammatory and anti-atherogenic effects. A common variant of the *ADIPOQ* gene (+45T>G, *rs2241766*) is associated with the risk of CAD. The *IGF-1* gene appears to be negatively related to age.[7] Moreover, the *rs2854744* (A-202C) variant of the IGF-binding protein-3 (*IGFBP3*) gene was found to be associated with circulating IGFBP-3 levels and a higher risk of early stage cancer.[8] We evaluated 5 longevity- or disease-associated variants of 4 genes in 62 families of Greek descent (152 individuals): 28 long-lived families for 3 consecutive generations (LON families,) and 34 short-lived families for 2 consecutive generations [early death of parents (75 years of age or less), EAD families]. The oldest individual in each LON family was aged $\geq$90 years (P), and each LON family also included one of P's offspring (FL1) and one of FL1's offspring (FL2). Each EAD family had no history of individuals living >90 years and consisted of one middle-aged individual (FD1) and one of FD1's offspring (FD2). The study was designed and performed in agreement with the recommendations for human genotype-phenotype association studies published by the National Cancer Institute-National Human Genome Research Institute (NCI-NHGRI) Working For Replication in Association Studies with consideration of time period and location of subject recruitment and DNA acquisition success rate and the use of internal control samples (from the same DNA) and sample tracking methods. The study protocol was approved by the institutional ethics committee (Onassis Cardiac Surgery Center and Harokopio University, Athens, Greece) and was performed in accordance with the Declaration of Helsinki for Human Research. All participants were of Caucasian origin. The extraction of genomic DNA was performed using the standard method of the FlexiGene® DNA kit (Qiagen). The gene variants being studied were detected using polymerase chain reaction (PCR) and restricted fragment length polymorphism (RFLP) analysis. Categorical variables were statistically analyzed using chi-square and Fisher's exact criteria. All data were analyzed using the statistical software package SPSS 19.0 (SPSS Inc, Chicago, IL, USA). Demographic and biochemical differences between the studied families are presented in Table 1. In the LON families, the *B1B1* genotype was less frequent in P individuals than FL1 individuals ($p = 0.007$) and FL2 individuals ($p = 0.06$). The *B1B1* genotype was more frequent in FL1 individuals (53.6%) than FD1 individuals (20.6%) ($p = 0.02$, Table 2). The *B1B2*

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**Table 1** Comparison of biochemical data of Longevity and Early Death groups.

| Characteristics | Longevity group (LON) | | | p-value (P-FL1, FL1-FL2, P-FL2) | Early Death group (EAD) | | | LON vs EAD |
|---|---|---|---|---|---|---|---|---|
| | P (n = 28) | FL1 (n = 28) | FL2 (n = 28) | | FD1 (n = 34) | FD2 (n = 31) | p-value (FD1-FD2) | p-value (FL1-FD1, FL2-FD2) |
| Age (years) | 93 (90–96) | 63.5 (58.3–66.7) | 31.0 (26.3–39.0) | **<0.001**<br>**<0.001**<br>**<0.001** | 58.5 (51.7–66.3) | 33.0 (26–38) | **<0.001** | **0.02**<br>0.72 |
| Sex M | 11 (39) | 11 (39) | 14 (50) | 1.00 | 16 (47) | 15 (48) | 0.79 | 0.54 |
| F | 17 (61) | 17 (61) | 14 (50) | 0.42<br>0.42 | 18 (53) | 16 (52) | | 0.90 |
| BMI (kg/m$^2$) | 23 (22–27) | 27 (24–30) | 23 (21–26) | **0.009**<br>**0.003**<br>0.62 | 27 (25–30) | 23 (21–26) | **0.005** | 0.96<br>0.58 |
| TC (mg/dL) | 185 (144–214) | 192 (149–226) | 173 (155–206) | 0.36<br>0.19<br>0.78 | 195 (160–238) | 183 (135–209) | 0.07 | 0.56<br>0.81 |
| TGs (mg/dL) | 77 (62–129) | 75 (54–130) | 44 (31–68) | 0.70<br>**0.002**<br>**0.001** | 101 (72–151) | 53 (39–72) | **0.001** | 0.23<br>0.68 |
| HDL (mg/dL) | 44 (35–52) | 45 (36–71) | 55 (50–61) | 0.28<br>0.28<br>**0.02** | 51 (33–58) | 51 (41–61) | 0.23 | 0.30<br>0.21 |
| LDL (mg/dL) | 116 (85–1150) | 119 (81–154) | 101 (94–124) | 0.74<br>0.34<br>0.51 | 119 (87–151) | 111 (72–146) | 0.21 | 0.59<br>0.92 |
| UA (mg/dL) | 4.7 (4–6) | 4.4 (3–6) | 4.1 (3–5) | 0.23<br>0.48<br>**0.06** | 4.6 (3–6) | 4.1 (3–5) | **0.02** | 0.28<br>0.62 |
| Gl (mg/dL) | 103 (89–123) | 98 (88–113) | 88 (82–97) | 0.44<br>**0.04**<br>**0.002** | 101 (97–114) | 90 (83–96) | **<0.001** | 0.74<br>0.55 |
| CETP (μg/mL) | 1.97 (1.7–2.3) | 2.2 (1.9–2.5) | 2.2 (1.9–2.7) | **0.03**<br>0.93<br>**0.03** | 1.9 (1.7–2.4) | 1.7 (1.5–2.3) | 0.78 | 0.22<br>0.13 |
| ACE (ng/mL) | 140 (113–158) | 157 (131–169) | 136 (127–170) | 0.14<br>0.55<br>0.26 | 145 (105–168) | 126 (110–154) | 0.32 | 0.29<br>0.10 |
| IGF-1 (ng/mL) | 57 (36–74) | 83 (67–107) | 123 (101–160) | **<0.001**<br>**<0.001**<br>**<0.001** | 72 (65–93) | 123 (92–188) | **<0.001** | 0.19<br>0.82 |
| ADIPO (μg/mL) | 15 (9–21) | 7 (4–11) | 8 (6–133) | **0.001**<br>0.69<br>**0.004** | 6 (3–9) | 6 (4–11) | 0.65 | 0.40<br>0.12 |
| Statin use, yes | 9 (32) | 12 (43) | 0 (0) | 0.40<br>–<br>– | 21 (62) | 2 (6) | <0.001 | 0.18<br>– |

LON: Longevity, EAD: Early Death, P: older individuals, FL1: 1st generation of longevity group, FL2: 2nd generation of longevity group, FD1: 1st generation of EAD group, FD2: 2nd generation of EAD group. M: Male, F: Female BMI: Body mass index, HDL: High density lipoprotein, LDL: Low density lipoprotein, UA: Uric acid, Gl: Glucose, CETP: Cholesterol ester transfer protein, ACE: Angiotensin converting enzyme, IGF-1: Insulin-like growth factor-1. ADIPOQ: Adiponectin.
Data are presented as medians (25-75 percentiles) or n (%).
Bold means the statistical significance with p-value < 0.005.

genotype was more frequent in FD1 individuals (61.8%) than FL1 (28.6%) individuals (p = 0.02, Table 2).

The *B1B1* genotype of the *CETP TaqIB* polymorphism may be negatively associated with human lifespan, since it was less frequent in families with longer lifespans. No association with human lifespan was observed for the *ADIPOQ*, *IGFBP3*, *ACE* or *CETP I405 V* gene polymorphisms. The *B1* allele was observed to be associated with CAD and could be

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