



Apolipoprotein E and familial longevity

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ABSTRACT

Exceptional longevity is associated with substantial heritability. The $\epsilon 4$ allele in apolipoprotein E and the linked G allele in rs2075650 of TOMM40 have been associated with increased mortality and the $\epsilon 2$ allele with decreased mortality, although inconsistently. Offspring from long-lived families and spouse controls were recruited at 3 sites in the United States and Denmark. We used generalized estimating equations to compare the likelihood of carrying risk alleles in offspring ($n = 2307$) and spouse controls ($n = 764$), adjusting for age, sex, level of education, and family membership. The likelihood of carrying an APOE $\epsilon 4$ allele or a G allele in rs2075650 was lower (odds ratio [OR], 0.75; $p = 0.005$ and OR, 0.70; $p = 0.002$) and the likelihood of carrying an APOE $\epsilon 2$ allele was higher (OR, 1.5; $p = 0.007$) among family members in the offspring generation than among their spouse controls. Our findings support the hypothesis that both reduction in the frequency of the $\epsilon 4$ allele and increase in the frequency of the $\epsilon 2$ allele contribute to longevity.

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1. Introduction

Human exceptional longevity is the outcome of a complex interplay between genetic and environmental influences (Finch and Tanzi, 1997; McGue et al., 1993). Exceptional longevity has been noted to cluster in families and is associated with moderate heritability (De Benedictis et al., 2001; Herskind et al., 1996; Mitchell et al., 2001). In a study of centenarians and their siblings, male and female siblings of centenarians were 17 and 8 times more likely, respectively, to survive to 100 years compared with males and females in their birth cohort (Perls et al., 2002). First degree relatives of individuals who lived beyond 95 years were twice as likely to survive to the same age as were relatives of married-in controls (Gudmundsson et al., 2000; Kerber et al., 2001).

Several candidate genes have been investigated to determine their effects on life span and apolipoprotein E (APOE) has

consistently emerged as a determinant of longevity (Deelen et al., 2011; Nebel et al., 2011; Sebastiani, et al., 2012). APOE has 3 common alleles, $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$. The $\epsilon 4$ allele of APOE has been associated with early mortality and a decreased frequency of the allele in the oldest old (McKay et al., 2011; Schachter et al., 1994; Soerensen et al., 2012; Tan et al., 2004). However, the association of the $\epsilon 4$ allele with mortality risk is inconsistent and varies by population (Bader et al., 1998; Galinsky et al., 1997; Lee et al., 2001). Some studies (Ewbank, 2002, 2007) reported that the effect of the $\epsilon 4$ allele on mortality risk diminishes with increasing age, but a recent study in the Danish 1905 cohort showed an increased effect of carrying the $\epsilon 4$ alleles with increasing age (Jacobsen et al., 2010). Recent studies have also identified a variant in TOMM40, marked by the single nucleotide polymorphism (SNP) rs2075650, which is associated with longevity, but is close to and in linkage disequilibrium with rs429358, the marker for the APOE $\epsilon 4$ allele (Deelen et al., 2011; Nebel et al., 2011; Sebastiani et al., 2012).

Because longevity is heritable, a family-based study design might serve well to address the question of the relation of APOE to longevity. Mortality associated with the presence of a risk allele

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might lead to reduced frequencies of risk alleles in the parental generation. Thus, it might be more informative to examine if there is a reduced frequency of risk alleles in offspring of people achieving exceptional longevity, where mortality is unlikely to confound the association between genetic risk factors and longevity. We examined the likelihood of carrying an *APOE* $\epsilon 4$ or $\epsilon 2$ allele and distribution of the *TOMM40* SNP rs2075650 in the offspring generation of the Long Life Family Study (LLFS). We hypothesized that offspring of LLFS members would have a decreased frequency of the *APOE* $\epsilon 4$ allele, a decreased frequency of the G allele in *TOMM40* rs2075650 and an increased frequency of the *APOE* $\epsilon 2$ allele compared with similarly aged peers not selected for familial longevity.

2. Methods

Long-lived individuals, their siblings, and their offspring were recruited for an examination that characterized key intermediate phenotypes of longevity, including major chronic diseases, risk factors, and physical and cognitive function. A referent group consisting of the spouses, primarily of the offspring generation, was also recruited and examined. For this study, we restricted the analysis to the offspring generation and the examined sons, daughters, nieces, and nephews ($n = 2314$) and their spouses ($n = 773$).

2.1. Recruitment

In the United States, each field center used Center for Medicare and Medicaid Services lists to mail a recruitment brochure to people who were at least 79 years old on January 1, 2005; had no recorded date of death; did not have end-stage renal disease or were not in hospice programs; and lived within 3 hours driving distance of 1 of the 3 US study centers (Boston University, Columbia University, and the University of Pittsburgh). Mailings were performed in collaboration with Center for Medicare and Medicaid Services and the National Institute on Aging via an Intra-Agency Agreement. Study participants were also recruited from the community using Web-based media and newspaper advertisements, mailing lists obtained through local government agencies, purchased public domain lists from various commercial vendors, and community presentations at churches and senior centers. The University of Southern Denmark study site first identified individuals who would be aged 90 and older during the study recruitment period through the Danish National Register of Persons, which contains current information on names, including past names such as maiden names for women, addresses, place of birth, marriages, and vital status (Pedersen et al., 2006). Second, using information on the place of birth and the names, parish registers available in regional archives were searched to locate the parents of the elderly individuals in order to identify sibships. Based on the above information, potentially eligible families were identified and contact was made with potential probands to further assess the family's eligibility for and willingness to participate in the LLFS using criteria parallel to that used in the United States. Recruitment, informed consent, and study procedures were approved by the Institutional Review Boards of all participating sites.

2.2. Eligibility and enrollment

The Family Longevity Selection Score (FLoSS) was developed by the LLFS study in order to rank longevity among families based on birth-year cohort survival probabilities of the proband and siblings (Sebastiani et al., 2009). On screening, a FLoSS of 7 or more was required for a family to be eligible. If a proband's family was FLoSS-eligible, they also had to meet the following criteria: the proband

and at least 1 living sibling were able to give informed consent and willing to participate in the in-person interview and examination, including providing blood for serum and for extraction of DNA; and either the proband or a sibling had a living offspring willing to participate. A minimum of 2 siblings and 1 offspring was required for the key triad. Additionally, we recruited and enrolled the spouses of interested individuals, primarily in the offspring generation, to serve as a comparison group ascertained from the same source populations, but not selected for familial longevity. Spouse controls were employed to adjust for characteristics of individuals within a family which are likely to be correlated. Before examination, written informed consent was obtained from all enrollees. The Institutional Review Boards at all of the Field Centers and the Data Management and Coordinating Center (Washington University, St. Louis) in the United States reviewed and approved this project and the regional Institutional Review Board in Denmark reviewed and approved this project.

2.3. Genotyping

Among offspring and their married-in controls, we were able to genotype *APOE* for 2307 of 2371 offspring (97.3%) of probands and their siblings and 764 of 793 spouse controls (96.3%). We were able to genotype the *TOMM40* SNP rs2075650 for 2274 (95.9%) offspring and 746 married-in controls (94.1%). Of the 3071 participants in the analysis, 983 were Danish (32.0%).

Genotyping of *APOE* polymorphisms was based on SNPs rs7412 and rs429358 and was performed at the Biomedical Genomics Center at the University of Minnesota. Genotyping was performed using the Taqman genotyping platform and concordance among genotypes for both SNPs was 100% based on 51 blinded duplicates. We also sequenced DNA from 12 samples with different *APOE* genotypes to assure correct assignment of alleles. Genotyping of the *TOMM40* SNP rs2075650 was performed as part of the LLFS genome wide association study and was typed via the Illumina HumanOmni 2.5 at the Center for Inherited Disease Research at Johns Hopkins University. Participants were classified by the presence or absence of the *APOE* $\epsilon 4$ and $\epsilon 2$ alleles, and as carrying 1 or more G alleles at rs2075650.

2.4. Statistical analysis

Before association analysis, we tested all SNPs for Hardy–Weinberg Equilibrium using the Haploview program (Barrett, 2009; Barrett et al., 2005) and we did not find deviations of genotype frequencies from Hardy–Weinberg Equilibrium for any of the SNPs. To minimize population stratification, analysis was restricted to subjects of white ethnicity, resulting in the loss of 8 spouses (1%) and 5 relatives (0.2%) from the analysis. We used logistic regression procedures in generalized estimating equations to estimate the likelihood of carrying 1 or more *APOE* $\epsilon 4$ alleles, 1 or more *APOE* $\epsilon 2$ alleles, or 1 or more rs2075650 G alleles in *TOMM40*. Generalized estimating equations adjusts for the relatedness of the LLFS offspring and controls and for the possibility that the characteristics of family members are correlated by both shared genetics and shared environment, by treating family membership as a cluster. LLFS offspring were compared with spouse controls, adjusting for age, sex, level of education, and family membership (model A) and then adjusting for age, sex, level of education, family membership and a history myocardial infarction, hypertension, stroke, diabetes, and Parkinson's disease (model B). In the offspring generation, only 2 people were reported as suffering from dementia, so we did not include dementia as a covariate for these analyses. SNPs in *TOMM40* have been shown to be in linkage disequilibrium with the *APOE* $\epsilon 4$ allele and it has been suggested that rs2075650 might not have an

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