GWAS of Longevity in CHARGE Consortium Confirms APOE and FOXO3 Candidacy

Linda Broer,1,2,3 Aron S. Buchman,4 Joris Deelen,2,5 Daniel S. Evans,6 Jessica D. Faul,7 Kathryn L. Lunetta,8,9 Paola Sebastiani,8 Jennifer A. Smith,10 Albert V. Smith,11,12 Toshiko Tanaka,13 Lei Yu,4 Alice M. Arnold,14 Thor Aspelund,11,12 Emelia J. Benjamin,9,15,16 Philip L. De Jager,17,18,19 Gudny Eiriksdottir,11 Denis A. Evans,20 Melissa E. Garcia,21 Albert Hofman,1,2 Robert C. Kaplan,22 Sharon L. R. Kardia,10 Douglas P. Kiel,18,23,24 Ben A. Oostra,1,2 Eric S. Orwoll,25 Neeta Parimi,4 Bruce M. Psaty,26,27,28,29 Fernando Rivadeneira,1,2,3 Jerome I. Rotter,30 Sudha Seshadri,8,31 Andrew Singleton,32 Henning Tiemeier,1,2,33 André G. Uitterlinden,1,2,3 Wei Zhao,10 Stefania Bandinelli,34 David A. Bennett,35 Luigi Ferrucci,13 Vilmundur Gudnason,11,12 Tamara B. Harris,21 David Karasik,23,36 Lenore J. Launer,21 Thomas T. Perls,37 P. Eline Slagboom,25 Gregory J. Tranah,6,38 David R. Weir,7 Anne B. Newman,39,* Cornelia M. van Duijn,1,2,* and Joanne M. Murabito9,40,*

1Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands.
2Netherlands Consortium for Healthy Ageing, Leiden University Medical Center, The Netherlands.
3Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands.
4Rush Alzheimer’s Disease Center, Rush University Medical Center, Chicago, Illinois.
5Department of Molecular Epidemiology, Leiden University Medical Center, The Netherlands.
6California Pacific Medical Center Research Institute, San Francisco.
7Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor.
8Department of Biostatistics, Boston University School of Public Health, Massachusetts.
9NHBLI’s and Boston University’s Framingham Heart Study, Massachusetts.
10Department of Epidemiology, University of Michigan, Ann Arbor.
11Icelandic Heart Association, Kopavogur, Iceland.
12Department of Medicine, University of Iceland, Reykjavik.
13Translational Gerontology Branch, National Institute on Aging, Baltimore, Maryland.
14Department of Biostatistics, University of Washington, Seattle.
15Department of Medicine, Sections of Preventive Medicine and Cardiology, Boston University School of Medicine, Massachusetts.
16Department of Epidemiology, Boston University School of Public Health, Massachusetts.
17Program in Translational NeuroPsychiatric Genomics, Institute for the Neurosciences, Departments of Neurology and Psychiatry, Brigham and Women’s Hospital, Boston, Massachusetts.
18Harvard Medical School, Boston, Massachusetts.
19Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts.
20Rush Institute for Healthy Ageing and Department of Internal Medicine, Rush University Medical Center, Chicago, Illinois.
21Laboratory of Epidemiology and Population Sciences, National Institute on Aging, Bethesda, Maryland.
22Department of Epidemiology and Population Health, Albert Einstein College, Bronx, New York.
23Institute for Aging Research, Hebrew SeniorLife, Harvard Medical School Department of Medicine, Boston, Massachusetts.
24Division of Gerontology, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts.
25School of Medicine, Oregon Health and Science University, Portland.
26Department of Medicine, University of Washington, Seattle.
27Department of Epidemiology, University of Washington, Seattle.
28Department of Health Services, University of Washington, Seattle.
29Group Health Research Institute, Group Health Cooperative, Seattle, Washington.
30Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute and Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, California.
31Department of Neurology, Boston University School of Medicine, Massachusetts.
32Laboratory of Neurogenetics, National Institute on Aging, Bethesda, Maryland.
33Department of Child and Adolescent Psychiatry, Erasmus MC and Sophia Children’s Hospital, Rotterdam, The Netherlands.
34Geriatric Unit, Azienda Sanitaria Firenze, Florence, Italy.
35Rush Alzheimer’s Disease Center, Rush University Medical Center, Chicago, Illinois.
36Faculty of Medicine in The Galilee, Bar-Ilan University, Safed, Israel.
37Section of Geriatrics, Boston University School of Medicine and Boston Medical Center, Massachusetts.
38Department of Epidemiology and Biostatistics, University of California, San Francisco.
39Department of Epidemiology, University of Pittsburgh, Pennsylvania.
40Department of Medicine, Section of General Internal Medicine, Boston University School of Medicine, Massachusetts.

*These authors contributed equally to this work.
**Background.** The genetic contribution to longevity in humans has been estimated to range from 15% to 25%. Only two genes, APOE and FOXO3, have shown association with longevity in multiple independent studies.

**Methods.** We conducted a meta-analysis of genome-wide association studies including 6,036 longevity cases, age ≥90 years, and 3,757 controls that died between ages 55 and 80 years. We additionally attempted to replicate earlier identified single nucleotide polymorphism (SNP) associations with longevity.

**Results.** In our meta-analysis, we found suggestive evidence for the association of SNPs near CADM2 (odds ratio [OR] = 0.81; p value = 9.66 × 10⁻⁷⁷) and GRIK2 (odds ratio = 1.24; p value = 5.09 × 10⁻⁵⁰) with longevity. When attempting to replicate findings earlier identified in genome-wide association studies, only the APOE locus consistently replicated. In an additional look-up of the candidate gene FOXO3, we found that an earlier identified variant shows a highly significant association with longevity when including published data with our meta-analysis (odds ratio = 1.17; p value = 1.85 × 10⁻⁸⁰).

**Conclusions.** We did not identify new genome-wide significant associations with longevity and did not replicate earlier findings except for APOE and FOXO3. Our inability to find new associations with survival to ages ≥90 years because longevity represents multiple complex traits with heterogeneous genetic underpinnings, or alternatively, that longevity may be regulated by rare variants that are not captured by standard genome-wide genotyping and imputation of common variants.

**Key Words:** Longevity—GW AS—FOXO3—APOE.

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**There** is ample evidence that genetic factors are involved in extreme longevity both in humans and in other organisms. In model organisms, ranging from *Caenorhabditis elegans* to *Mus musculus*, mutations in the insulin/IGF-1 signaling (IIS) pathway have been shown to substantially increase lifespan (1–6). Other suggested mechanisms involve stress resistance as mediated by heat shock proteins (7,8), cellular senescence as mediated by telomere length (9) and inflammation/immune function (10). The genetic contribution to longevity in humans has been estimated to range from 15% to 25% (11–13).

Although many human candidate longevity genes have been investigated, only two genes have been widely replicated. The first consistent association reported was APOE (14). It was subsequently replicated in both candidate gene and genome-wide association studies (GWAS) with genome-wide significant evidence (15–20). The second longevity gene, identified in American male centenarians of Japanese descent and replicated in other candidate gene studies that included both men and women across ethnicities, was FOXO3, although this gene was not identified in GWAS (21–25).

Early GWAS have failed to identify novel longevity genes as reviewed by Murabito and coworkers (26). In 2010, the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium published a meta-analysis of 1,836 longevity (90+) cases and a comparison group of 1,955 individuals who died between 55 and 80 years of age (27). A total of 24 independent SNPs were identified, though none reached genome-wide significance. Finally, a recent GWAS by Deelen and coworkers identified one new longevity locus on 5q33.3 (28).

The key to success to GWAS has proven to be large sample sizes. Since the original CHARGE longevity GWAS (27) additional members of each cohort have reached or exceeded age of 90 years and additional studies have joined the consortium, permitting an expanded meta-analysis of longevity. Using the much expanded sample of 6,036 longevity cases and 3,757 controls and the same study design as the original CHARGE longevity study, we attempted to produce robust new associations and replicate earlier identified associations for longevity coming from several earlier studies.

**Methods**

**Participants**

The participants in our study were of European ancestry and included cohorts from the CHARGE Consortium (29). All cohorts periodically assess the vital status of their participants. Although some of the cohorts include multiple ethnic groups, only data from Caucasian participants were used. Informed written consent was obtained from all participants, and appropriate institutional approvals were obtained. A brief description of each population is given in the Supplementary Material.

**Longevity Phenotype**

Longevity was defined as reaching age ≥90 years. A more extreme longevity threshold of age 100 years was considered. However, the sample size was deemed insufficiently powered. Genotyped participants who died between the
ages of 55 and 80 years were used as the control group. The control group was limited to deceased participants to ensure that no control individuals could subsequently achieve longevity. The minimum age at death was set to match the minimum age at enrollment in the Rotterdam Study. The maximal age at death was set arbitrarily at the age of 80 years to include the majority of deaths and to exclude those participants who survived far beyond the average life expectancy for their respective birth cohort. Across the discovery cohorts, there were 6,036 participants who achieved longevity and the control group had 3,757 participants.

We did not have direct replication cohorts; however, we performed a look-up of our strongest associations in three independent studies with similar phenotypes, one of which is a published GWAS on longevity (30).

**Genotyping and Imputation**

As different genotyping platforms were used across studies, we imputed to ~2.5 million SNPs using the HapMap 22 CEU (Build 36) genotyped samples as a reference. Details on the study-specific quality control procedures for genotyping and imputation are found in Supplementary Table 1. Although genotyping between different studies was performed on different genotyping platforms, genotyping of cases and controls within studies was performed on the same genotyping platform in each study.

**Statistical Analysis**

We used logistic regression to test each SNP for association with longevity using an additive model adjusting for sex and principal components to adjust for population stratification. Fixed-effects inverse-variance meta-analysis was performed using METAL. The p values were corrected for genomic control. Associations with a p value < 5 × 10^{-8} were considered genome-wide significant, whereas associations with a p value < 1 × 10^{-5} were considered suggestive and taken forward to the look-up phase.

Detailed analysis of cohorts participating in the look-up phase and additional analyses can be found in the Supplementary Material. Conditional analysis of the FOXO3 locus was performed using the GCTA tool which analyzes aggregate, not individual level data (31,32). We further attempted to replicate earlier identified SNP associations with longevity. Finally, we used gene networks available at www.genenetworks.nl as a bioinformatics resource to further investigate significant findings.

**RESULTS**

General characteristics of discovery and look-up cohorts are found in Tables 1 and 2, respectively. Between 0.0% and 70.3%, varying per cohort, of those achieving longevity were still alive at the time that longevity status was ascertained. Among those who had died, the distribution of causes of death differed between longevity cases and the comparison group. While 1.0%–17.3% of those achieving longevity died of cancer, 10.1%–50.3% of deaths in the control group could be attributed to cancer.

None of the SNP-longevity associations reached the genome-wide significance threshold of 5 × 10^{-8} in the discovery phase (Supplementary Figure 1), although the strongest association was borderline significant for rs1416280 located 369 kb from GRIK2 (odds ratio [OR] = 1.24; p value = 5.09 × 10^{-8}). In total, seven loci passed the threshold for suggestive association (<1 × 10^{-5}) and were included in the look-up phase (Table 3). For look-up, we also included the most significant SNP in the current study from the known candidate longevity gene, FOXO3 (p value = 8.56 × 10^{-5}). Forest plots of all eight SNPs can be found in Supplementary Figure 2. Although none of the SNPs reached Bonferroni adjusted significance in any of the look-up cohorts, consistent results considering direction of effect were found for FOXO3 across discovery and look-up cohorts (Table 3). Association results for CADM2 and, to a lesser degree, GRIK2 were consistent across cohorts.

In pathway analysis using the gene networks tool, both CADM2 and GRIK2 genes were found to be involved in neuronal pathways (Supplementary Table 2).

Of the 24 SNPs identified as suggestively associated in the original CHARGE longevity GWAS (27), the p value for only one of these (GRIK2; rs954551) improved in the current study (Supplementary Table 3). One additional region (RGS7) from the earlier study appeared among the strongest associations in the current study, but the association was not strengthened in the look-up phase of this study.

Next, we aimed to replicate the GWAS of Sebastiani and coworkers conducted on centenarians (Supplementary Table 4) (20). Two hundred and eighty-one SNPs were reported using four different genetic models (20). Six out of the 281 SNPs were reported to have a p value <1 × 10^{-5} in the additive model. We attempted to replicate these six SNPs, and only the SNP at the APOE locus replicated at the Bonferroni corrected significance level (OR = 1.20; p value = 4.8 × 10^{-4}). Similarly, of the four regions identified with linkage analysis of longevity sib-pairs (age ≥90 years ) (33) we also replicated only the APOE locus (Supplementary Table 5).

Finally, in a candidate gene approach, we examined the original SNP reported for the FOXO3 gene (rs2802292) in the current study and added our current study (each discovery cohort individually) to the published studies reporting on the same FOXO3 SNP (Supplementary Table 6) (21–25,30). In the current study, rs2802292 reached a p value of .012 (OR = 1.09). When including the published studies, both candidate gene and GWAS, in the meta-analysis rs2802292 reached a p value of 1.85 × 10^{-10} (OR = 1.17). The Linkage Disequilibrium (LD) as measured by r^2 between this SNP and the top FOXO3 SNP in the current study (rs10457180) was .64. In conditional analyses of the discovery phase.
GWAS LONGEVITY

Table 1. General Characteristics of Discovery Cohorts

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Women (%)</th>
<th>Alive (%)</th>
<th>Cause of Death (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotterdam Study 1 (RS1) 90+ cases</td>
<td>899</td>
<td>79.0</td>
<td>23.6</td>
<td>31.4 7.9 60.7 0.0</td>
</tr>
<tr>
<td>Comparison</td>
<td>1,192</td>
<td>41.3</td>
<td>0.0</td>
<td>32.2 40.1 27.7 0.0</td>
</tr>
<tr>
<td>Rotterdam Study 2 (RS2) 90+ cases</td>
<td>69</td>
<td>60.9</td>
<td>69.6</td>
<td>33.3 14.3 52.4 0.0</td>
</tr>
<tr>
<td>Comparison</td>
<td>161</td>
<td>37.3</td>
<td>0.0</td>
<td>23.6 50.3 26.1 0.0</td>
</tr>
<tr>
<td>Study of Osteoporotic Fractures (SOF)‡</td>
<td>1,720</td>
<td>100.0</td>
<td>54.4</td>
<td>16.8 3.6 21.5 0.0</td>
</tr>
<tr>
<td>Cardiovascular Health 90+ cases</td>
<td>124</td>
<td>100.0</td>
<td>0.0</td>
<td>37.9 28.2 33.9 0.0</td>
</tr>
<tr>
<td>Study (CHS)</td>
<td>560</td>
<td>53.2</td>
<td>0.0</td>
<td>35.6 39.3 27.0 0.2</td>
</tr>
<tr>
<td>Osteoporotic Fractures in Men Study (MrOS)†</td>
<td>670</td>
<td>0.0</td>
<td>43.6</td>
<td>19.9 6.9 21.8 3.1</td>
</tr>
<tr>
<td>Framingham Heart 90+ cases</td>
<td>320</td>
<td>66.9</td>
<td>0.0</td>
<td>24.1 11.6 51.9 12.5</td>
</tr>
<tr>
<td>Study (FHS)</td>
<td>484</td>
<td>34.3</td>
<td>0.0</td>
<td>24.6 43.8 25.2 6.4</td>
</tr>
<tr>
<td>Health and Retirement 90+ cases</td>
<td>384</td>
<td>67.5</td>
<td>0.0</td>
<td>3.0 15.0 12.6 69.5</td>
</tr>
<tr>
<td>Study (HRS)</td>
<td>401</td>
<td>45.6</td>
<td>0.0</td>
<td>12.1 10.1 16.2 61.6</td>
</tr>
<tr>
<td>Age, Gene/Environment 90+ cases</td>
<td>541</td>
<td>61.2</td>
<td>0.0</td>
<td>27.3 8.4 16.2 48.1</td>
</tr>
<tr>
<td>SusceptibilityReykjavik Study (AGES)‡</td>
<td>145</td>
<td>49.0</td>
<td>0.0</td>
<td>28.2 35.5 18.4 18.0</td>
</tr>
<tr>
<td>Religious Orders Study and Rush</td>
<td>468</td>
<td>75.2</td>
<td>0.0</td>
<td>0.0 0.0 100.0 0.0</td>
</tr>
<tr>
<td>Memory and Aging Project (RADC)</td>
<td>78</td>
<td>48.7</td>
<td>0.0</td>
<td>0.0 0.0 100.0 0.0</td>
</tr>
<tr>
<td>Invecchiare nel Chianti (InCHIANTI)‡</td>
<td>101</td>
<td>72.3</td>
<td>0.0</td>
<td>8.9 3.0 79 80.2</td>
</tr>
<tr>
<td>Baltimore Longitudinal Study of Ageing (BLSA)</td>
<td>128</td>
<td>49.2</td>
<td>0.0</td>
<td>6.7 20.0 4.0 69.3</td>
</tr>
<tr>
<td>Comparison</td>
<td>42</td>
<td>26.2</td>
<td>0.0</td>
<td>9.5 19.0 2.3 69.1</td>
</tr>
</tbody>
</table>

Notes: *In cases the % of all deaths is reported.
† In SOF, the vital status is not known for all individuals.
‡ In MrOS, the vital status is not known for all individuals.

Table 2. General Characteristics of Look-Up Cohorts

<table>
<thead>
<tr>
<th>Study</th>
<th>NECS Cases (100+)</th>
<th>NECS Comparison</th>
<th>LLFS Survival Analysis</th>
<th>EU longevity Cases (90+); Comparison (&lt;65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>801</td>
<td>914</td>
<td>4,567</td>
<td>5,409; 16,121</td>
</tr>
<tr>
<td>Age at DNA draw (median [range])</td>
<td>95 (95–119)</td>
<td>73 (54–90)</td>
<td>67 (25–110)</td>
<td>NA</td>
</tr>
<tr>
<td>Follow-up (median [range])</td>
<td>NA</td>
<td>3 (0–7)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Women, %</td>
<td>72.0</td>
<td>56.0</td>
<td>55.0</td>
<td>NA</td>
</tr>
<tr>
<td>Alive, %</td>
<td>3.0</td>
<td>0.0</td>
<td>83.0</td>
<td>NA</td>
</tr>
</tbody>
</table>

Notes: LLFS = Long Life Family Study; NECS = New England Centenarian Study. No study specific information for the EU longevity consortium was available. Causes of death were not available in the look-up cohorts.

cohorts, including both SNPs, only rs10457180 remained significant at nominal p value (OR = 0.94; p value = 5.53 × 10^-4).

**DISCUSSION**

In this investigation of 6,036 longevity cases and 3,757 controls, we found suggestive evidence for the involvement of SNPs near CADM2 and GRIK2. We further confirmed the associations of APOE and FOXO3 with longevity. FOXO3 is a known candidate gene for longevity and part of the well-characterized IIS pathway (6). Although originally identified in candidate gene studies, it did not earlier reach genome-wide significance (21–25). In this study, the strongest signal in the FOXO3 gene was found for rs10457180 which is in LD (r^2 = .64) with the earlier identified SNP rs2802292. Pooling our data with that of independent studies from literature yielded a p value of 1.85 × 10^-10. Although we included all studies reporting on FOXO3 association with longevity from the literature as well as contacted authors of earlier published GWAS for information on FOXO3 in their study (19), publication bias, which is common in candidate gene studies, may be influencing the results of this analysis. In a conditional analysis of the discovery phase cohorts, only rs10457180 remained significant, which suggests that rs10457180 may be a better tagging SNP for the true causal variant. A point of notice is that FOXO3 has 99% sequence homology in its exonic regions with its pseudogene (ZNF286B), which could complicate the calling of genetic variants for this gene (34,35). However, the investigated variants (rs2802292 and
Table 3. Association Results for Longevity: Discovery and Look-Up

<table>
<thead>
<tr>
<th>SNP</th>
<th>Chr</th>
<th>Gene</th>
<th>Distance (kb)</th>
<th>EA</th>
<th>EAF</th>
<th>p Value</th>
<th>OR</th>
<th>95% CI</th>
<th>Direction</th>
<th>p Value</th>
<th>OR</th>
<th>95% CI</th>
<th>Direction</th>
<th>p Value</th>
<th>rs9377361</th>
<th>1/HR</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1416290</td>
<td>6</td>
<td>GRIK2</td>
<td>369</td>
<td>C</td>
<td>0.75</td>
<td>$5.09 \times 10^{-4}$</td>
<td>1.24</td>
<td>1.15–1.34</td>
<td>+</td>
<td>.276</td>
<td>rs9377361</td>
<td>1.00</td>
<td>0.98</td>
<td>.833</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs9841144</td>
<td>3</td>
<td>CADM2</td>
<td>-236</td>
<td>A</td>
<td>0.79</td>
<td>$9.66 \times 10^{-7}$</td>
<td>0.81</td>
<td>0.74–0.88</td>
<td>+</td>
<td>.825</td>
<td>rs9822731</td>
<td>0.96</td>
<td>1.03</td>
<td>.726</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs4611001</td>
<td>1</td>
<td>RGS7</td>
<td>-28</td>
<td>A</td>
<td>0.97</td>
<td>$1.84 \times 10^{-4}$</td>
<td>1.79</td>
<td>1.41–2.27</td>
<td>+?---------</td>
<td>.207</td>
<td>rs7536260</td>
<td>0.68</td>
<td>0.65</td>
<td>.013</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs11023737</td>
<td>11</td>
<td>SOX6</td>
<td>-28</td>
<td>A</td>
<td>0.32</td>
<td>$3.64 \times 10^{-6}$</td>
<td>0.83</td>
<td>0.77–0.90</td>
<td>+</td>
<td>.684</td>
<td>rs2196961</td>
<td>0.27</td>
<td>1.03</td>
<td>.668</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs11753077</td>
<td>6</td>
<td>MBOAT1</td>
<td>-76</td>
<td>T</td>
<td>0.64</td>
<td>$7.51 \times 10^{-4}$</td>
<td>1.17</td>
<td>1.09–1.26</td>
<td>+</td>
<td>.995</td>
<td>rs7763815</td>
<td>0.87</td>
<td>1.04</td>
<td>.572</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs10875746</td>
<td>12</td>
<td>PFKM</td>
<td>Intron</td>
<td>A</td>
<td>0.76</td>
<td>$7.3 \times 10^{-4}$</td>
<td>1.20</td>
<td>1.11–1.30</td>
<td>+</td>
<td>.240</td>
<td>rs2228500</td>
<td>0.74</td>
<td>1.03</td>
<td>.796</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs10007810</td>
<td>4</td>
<td>LIMCH1</td>
<td>Intron</td>
<td>A</td>
<td>0.23</td>
<td>$8.08 \times 10^{-6}$</td>
<td>1.20</td>
<td>1.11–1.30</td>
<td>+</td>
<td>.979</td>
<td>Same</td>
<td>1.00</td>
<td>0.98</td>
<td>.841</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs10457180</td>
<td>6</td>
<td>FOXO3</td>
<td>Intron</td>
<td>A</td>
<td>0.70</td>
<td>$8.56 \times 10^{-3}$</td>
<td>0.87</td>
<td>0.81–0.93</td>
<td>-</td>
<td>.023</td>
<td>rs2153960</td>
<td>0.89</td>
<td>0.98</td>
<td>.822</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: EA = effect allele; EAF = effect allele frequency; "+" = effect allele over-represented in cases; "−" = effect allele underrepresented in cases; "?" = not tested in this cohort. The p values < .05 in replication are represented in bold. The p values < .05 in replication are represented in bold. EU_longevity: European consortium investigating the genetics of longevity with similar phenotype to discovery (cases: 90+; controls: < 65 y old); Centenarians (NECS, New England Centenarian Study): centenarian cases compared to younger controls; Survival (LLFS, Long Life Family Study): all-cause mortality Cox-regression analysis, 1/HR shown for direct comparison of the direction of the effect. In NECS and LLFS, imputation is not available. Study order for direction column: RS1, RS2, SOF, CHS, MrOS, FHS, HRS, AGES, RADC, InCHIANTI, BLSA.

*Linkage disequilibrium with discovery SNP.
rs10457180) are both intronic, which are not present in ZNF286B. Therefore, we believe our results are not affected by this phenomenon.

Although our look-up for both CADM2 and GRIK2 did not show consistent associations, these genes are interesting candidate genes for longevity. Both genes are involved in neuronal pathways, in particular in neuron cell–cell adhesion and regulation of glutamatergic synaptic transmission (www.genenetworks.nl). Neuronal pathways have been implicated earlier in all-cause mortality in a formal pathway analysis (36).

We did not replicate other earlier reported associations with longevity, except for FOXO3 and APOE. Although many attempts to unravel the genetic contribution to the longevity phenotype have been undertaken, it has proven difficult to find robust associations (26). Genome-wide association studies have identified the genetic architecture of many complex traits with great success, even when the heritability of the trait is modest, as is the case for longevity. Yet the longevity phenotype remains elusive to uncovering new genetic associations.

As with any chosen methodology GWAS has its pitfalls. The most obvious pitfall of a GWAS is the low \( p \) value of significance required to call a variant significantly associated. There are many potential sources of Type I and II errors in GWAS, including case–control misclassification, nongenetic covariates, and population stratification, which can only partly be accounted for in the design of the study (37). We have used the standard approach of considering \( p \) values < \( 5 \times 10^{-8} \) as significant to prevent false positive findings. As a result, we accept the presence of false negative findings. Recently, we have shown that the number of false positive findings increases exponentially when higher \( p \) values are used in GWAS setting, further justifying the use of a stringent cut-off (38). We do not believe that case–control misclassification is a big issue in our study as we have very clear cut-offs for being included as a case (≥90 years) or control (deceased between 55 and 80 years). The potential influence of nongenetic covariates is more difficult to ascertain. However, these are assumed to be independent of genotypes and are therefore unlikely to be confounders. In addition, it has been shown that the power of meta-analysis is not optimal for SNPs with small to modest effect sizes (39). However, it is common practice in GWAS to perform large-scale meta-analyses as the sample size required to detect variants at such low \( p \) values is not sufficient in any one study. Increasing the sample size of the current study may help identify new variants.

There are several potential explanations for why longevity has proven difficult to dissect genetically. First, the longevity phenotype simply could be too complex and heterogeneous for successful identification of longevity genes. Achieving longevity may require a great number of “protective” genes all with small effects (20). Although in highly heritable traits, like height, genes with very small effects have been uncovered, in a trait like longevity it may be challenging to identify individual genetic variants given the numbers of available genotyped individuals reaching longevity. In addition, the complexity of the longevity phenotype is made more challenging due to its interaction with a number of age-related diseases, that is, cancer, cardiovascular disease, and dementia, all of which have independent genetic risk variants. Although it has been shown that currently identified variants for age-related diseases do not strongly associate with longevity (40), suggesting that there are longevity-specific variants remaining to be discovered, this genetic and phenotypic heterogeneity of longevity makes it very challenging to identify genetic variants for longevity.

Using biomarkers that explain (a part of) longevity might be a more fruitful pursuit for finding associations with longevity itself. Unfortunately, no good biomarkers of aging currently exist, although many have been proposed (41). Telomere length, a marker of senescence, could be an interesting biomarker of aging and, GWAS have already proven successful in identifying genes for this trait (42). An alternative approach could be the development of novel phenotypes like the healthy aging index, which incorporates information across physiologic systems and predicts mortality better than age itself (43).

The second potential reason for not finding any genome-wide significant associations with the longevity phenotype is that GWAS targets common variants. As longevity in the general population is quite rare, but common in specific long-lived families, it could be that rare variants, rather than common variants are involved in the longevity phenotype (44). Such variants are not likely to be picked up in GWAS, but may be uncovered with rare variant association analysis, which requires sequencing technology (45).

Another avenue that deserves consideration for future studies is the identification of joint genetic effects (epistasis) (46). Epistasis has been demonstrated to be an important contributor to age-related diseases such as cardiovascular disease (47). Methods for identifying epistasis are improving and becoming feasible for genome-wide studies (48).

Finally, it is possible that epigenetic changes could influence the expression of genetic variations leading to longevity. Epigenetic modifications such as DNA methylation and histone modification are essential for development and differentiation, but can also arise later in life (49). Age-related changes in DNA methylation have been implicated in senescence and longevity (50). Such changes may be a major contributor to longevity that might make it difficult to find associations with common genetic variants. A known phenomenon in longevity is that the majority of individuals reaching longevity are female. Whether this has a genetic or epigenetic basis is unknown and should be investigated in future studies.

A limitation of our phenotype is our definition of longevity, namely, living to age ≥90 years may not be “extreme” enough as a case definition. We considered more extreme
longevity cut-offs, including centenarian status; however, we found that the sample size for such currently was not enough to have sufficient power to detect association in GWAS. Similarly, the definition of dying before 80 years might be too liberal for the definition of controls since they survived far beyond the average life expectancy for their respective birth cohort. Furthermore, more extreme cut-offs would have resulted in a too small sample size for GWAS.

In conclusion, we confirmed the association of FOX3 and APOE with longevity, but did not find any new associations, aside from the suggestive evidence for CADM2 and GRIK2. Notably, variants in neuronal pathway genes were confirmed to play a role in longevity. Future genetic studies should consider: (i) using more extreme age definitions for longevity, (ii) performing rare variant association analyses, (iii) analyzing epistasis, (iv) exploring epigenetic changes associated with longevity, (v) sex-specific analysis, and (vi) increasing the sample sizes of both cases and controls.

Supplementary Material

Supplementary material can be found at: https://academic.oup.com/biomedgerontology/article-abstract/70/1/110/294766

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References


