THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2017, Vol. 72, No. 10, 1401–1406
doi:10.1093/gerona/glw198
Advance Access publication October 5, 2016

OXFORD

Research Article

Replication of Genome-Wide Association Study Findings of Longevity in White, African American, and Hispanic Women: The Women's Health Initiative

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Received May 10, 2016; Accepted September 18, 2016

Decision Editor: Stephen Kritchevsky, PhD

Abstract

Background: No study has evaluated whether genetic factors are associated with longevity in African Americans or Hispanics, and it is unclear whether genetic factors are associated with healthy aging.

Methods: In this prospective study, we determined whether 14 genetic variants previously associated with longevity in genome-wide association studies were associated with survival to ages 85 and 90 in 11,053 postmenopausal white, African American, and Hispanic women from the Women's Health Initiative. The associations of these variants with healthy aging, defined as survival to age 85 without chronic diseases or disability, were also determined.

Results: Among white women, three single nucleotide polymorphisms (SNPs) (rs2075650 [*TOMM40*], rs4420638 [*APOC1*], and rs429358 [*APOE*]) were significantly associated with survival to 90 years after correction for multiple testing ($p < .001$); rs4420638 and rs429358 were also significantly associated with healthy aging ($p = .02$). In African American women, no SNP was associated with longevity. In Hispanic women, 7 SNPs in linkage disequilibrium with a novel SNP, rs2149954, recently identified as being associated with increased longevity in a European population, were significantly associated with decreased survival to age 85 for carriers of the T versus C allele ($p = .04$). The association with decreased longevity was explained by higher risk of coronary heart disease in carriers of the T allele. There were no associations between *FOXO3A* SNPs and longevity in the analyses. In a meta-analysis, rs2075650 and rs429358 were significantly associated with longevity.

Conclusions: Future studies are needed to identify novel loci associated with longevity in African American and Hispanic women to determine biologic pathways regulating life span in these groups.

Keywords: Gene—Aging—Successful aging—Minority

By 2060, it is expected that approximately 12 million women will be aged 85 and older, commonly referred to as the "oldest-old" age group (1). Although attaining longevity is becoming increasingly common, healthy aging, or reaching old age free of morbidity and disability, is more important from a public health perspective. However, factors contributing to longevity and healthy aging in women are not completely understood.

Heritability estimates for longevity range from 25% to 30% (2). In previous candidate gene association studies, only variants of apolipoprotein E (*APOE*) and forkhead box O3A (*FOXO3A*) genes, which are involved in Alzheimer's disease risk and insulin-signaling pathways, respectively, have been consistently associated with longevity (2–11). Although several longevity genome-wide association studies (GWAS) and meta-analyses of GWAS have been performed (12–16), only variants near the *APOE* locus have consistently achieved genome-wide significant associations with longevity (13–16). However, prior GWAS were conducted among populations of European descent, and no study has evaluated associations of genetic variants with longevity in African Americans or Hispanics.

We determined whether genetic variants previously associated with longevity in prior GWAS among European populations were associated with survival to ages 85 and 90 and healthy aging in postmenopausal white, African American, and Hispanic women from the Women's Health Initiative (WHI).

Methods

Study Population

The WHI is a large, prospective study investigating major determinants of chronic diseases in 161,808 postmenopausal women (17,18). Details of the study, including the use of existing genetic data for this study and data collection, are discussed in greater detail in the Supplementary Methods. All participants provided written informed consent, and Institutional Review Board approval was received by all participating institutions.

This study was exclusive to women with genetic data who were born on or before August 29, 1929 and thus could survive to age 85 during follow-up ending August 29, 2014, representing up to 21 years of follow-up (Supplementary Figure 1). All women were from a similar birth cohort, minimizing bias due to varying lifetime exposures. Only those whose survival status could be ascertained were included. After quality control procedures, the final sample size consisted of 11,053 women (8,656 white, 1,858 African American, and 539 Hispanic women).

SNP Selection

Single nucleotide polymorphisms (SNPs) significantly associated with longevity at the genome-wide level ($p < 5 \times 10^{-8}$) in previous GWAS, replication of GWAS findings, and meta-analyses of GWAS published through January 2015 were selected (5–7,10–16). All GWAS were conducted in populations of European ancestry. The two SNPs that define the three isoforms of *APOE* and SNPs significantly associated with longevity in candidate gene studies for *FOXO3A* were also selected; candidate gene studies were all conducted in European populations except for one (11) that was conducted in Japanese Americans. For candidate gene studies, SNPs were selected if statistically significant after correction for multiple testing (eg, Bonferroni correction). Henceforth, SNPs selected from previous studies will be referred to as "index SNPs." In total, 14 index SNPs were chosen (5–7,10–16): rs2075650 (*TOMM40*); rs4420638 (*APOC1*); rs7412 and rs429358 (*APOE*); rs2149954 (on chromosome 5); and rs10457180, rs2764264, rs13217795, rs2802292, rs9400239, rs3800231, rs479744, rs1935949, and rs4946935 (*FOXO3A*).

Individuals from different genetic ancestries exhibit divergent linkage disequilibrium (LD) and allele frequency patterns. Index SNPs associated with longevity in prior studies may thus not be in LD with functional variants among African Americans or Hispanics, and previous associations may be population specific. Therefore, for African Americans and Hispanics, proxy SNPs in LD with the index SNPs were chosen to fully explore replication of prior findings in these groups (see Supplementary Material).

Study Outcomes

Women were classified as having survived to age 85 or died before age 85, and in a separate outcome, as having survived to age 90 or died before age 90. The use of a dead comparison group from the same birth cohort was important to be certain that these participants never reached advanced old age. Death was confirmed by trained physician adjudicators based on hospital records, autopsy or coroner's reports, or death certificates. Periodic linkage to the National Death Index was performed for all participants, including those lost to follow-up. Approximately 89% of women eligible for inclusion in this study had complete survival status ascertainment.

Healthy aging was defined as survival to age 85 years or older without a history of major age-related diseases and with no impairment of physical function or assistance in activities of daily living (ADL). Physical function and ADL were assessed during study follow-up using the RAND 36-item Health Survey (19). Good physical function for healthy aging was defined as not reporting any of these limitations (20): limited at least "a little" on moderate activities (moving a table, vacuuming, bowling, or golfing; climbing one flight of stairs; walking more than one mile; walking several blocks; or bathing or dressing) or limited "a lot" on difficult performance items (running, lifting heavy objects, or strenuous sports; lifting or carrying groceries; climbing several flights of stairs; or bending, kneeling, or stooping). Being able to perform all six ADL (feeding, dressing and undressing, getting in and out of bed, taking a bath or shower, doing own grocery shopping, and keeping track of and taking medicines) without any help was also a criterion for healthy aging. This resulted in three categories: healthy survivors, usual survivors, and nonsurvivors.

Statistical Analysis

Comparisons of survivors and nonsurvivors on baseline characteristics were performed using χ^2 tests for categorical variables and two-sample *t* tests or Wilcoxon's rank-sum tests for normally distributed and non-normally distributed continuous variables, respectively. Comparisons of healthy aging categories were performed using χ^2 tests for categorical variables and analysis of variance or Kruskal–Wallis tests for continuous variables.

For all SNPs, count and reference alleles were defined. Separate analyses were conducted in white, Hispanic, and African American women. Logistic regression models assuming a log-additive genetic effect were used to assess associations of SNPs with survival to age 85. For SNPs that were directly genotyped, SNP data were coded as 0/1/2 (indicating the number of count alleles present), and for imputed SNPs, the mean dosage of the count allele (a value between 0 and 2) was used. In the models, SNPs were used as continuous variables. All models adjusted for the top five principal components to control for population stratification. Models also adjusted for potential confounders including baseline age, WHI study component, education, marital status, body mass index, physical activity, alcohol consumption, smoking behavior, and history of age-related diseases (see Supplementary Methods). Analyses were repeated with survival to age 90 as the outcome in white and African American women only, as a limited number of Hispanic women survived to age 90. Multinomial logistic regression models were used to examine

associations of SNPs with healthy aging in white women, using nonsurvivors as the reference category. Similar variable inclusion criteria as previously described were used. Healthy aging analyses were not performed in African American or Hispanic women due to lower sample sizes of aging categories in these groups. Because of varying patterns of missing data in covariates, multivariable logistic regression models had lower sample sizes resulting from the complete case analysis. Thus, models only adjusting for age and the first five principal components were also fit to make use of all of the available genetic data. Results are reported as odds ratios and 95% confidence intervals. The odds ratios represent the change in the odds of longevity for each additional copy of the count allele. A trans-ethnic meta-analysis using a random-effects model was conducted to calculate odds ratios combining white, African American, and Hispanic women (see Supplementary Material for more detailed methods).

p Values were corrected for multiple testing using the Benjamini–Hochberg procedure (21), which controls for the false discovery rate and is a more powerful and less conservative approach than Bonferroni correction. *p* Values were two tailed and considered nominally statistically significant at *p* less than .05 after correction. Analyses were conducted using Statistical Analysis Software (SAS), Version 9.3 (SAS Institute, Cary, NC) and METASOFT for the meta-analysis.

Results

Comparisons of survivors and nonsurvivors on baseline characteristics are shown in the Supplementary Material and Supplementary Tables 1–6. In white women, no index SNP was significantly associated with survival to age 85 after correction for multiple testing (Supplementary Table 7). However, in an analysis comparing women who lived to age 90 with those who died before this age, 3 of 14 SNPs were replicated after correction for multiple testing (Table 1). The SNPs rs2075650 and rs4420638, which tag the longevity effects of *APOE*, were significantly associated with survival to age 90 ($p < .001$). Of the two SNPs that define the three *APOE* isoforms, only rs429358 was significantly associated with survival to age 90 ($p < .001$). To determine whether associations of rs2075650 and rs4420638 with survival to age 90 were independent of *APOE*, models additionally adjusting for rs7412 and rs429358 were fit. After adjustment for these SNPs, rs2075650 and rs4420638 were no longer significantly associated with survival to age 90 (data not shown). Other SNPs, including rs2149954 on chromosome 5, and SNPs located at *FOXO3A*, failed to replicate in white women (Supplementary Table 8). Findings were similar in models only adjusting for age and population stratification, and rs7412 was also significantly associated with survival to age 90 in this analysis (Supplementary Tables 9 and 10).

In African American women, no SNP was significantly associated with longevity (Supplementary Tables 11–13). In Hispanic women, no SNP was significantly associated with survival to age 85 after correction for multiple testing in the fully adjusted models (Supplementary Table 14); analyses for survival to age 90 were not performed due to inadequate sample size. However, in models only adjusting for age and population stratification, only seven SNPs in LD with rs2149954 were significantly associated with survival to age 85 after correction for multiple testing ($p = .037$; Table 2 and Supplementary Table 15). Carriage of the T versus C allele was associated with decreased survival to age 85. To determine potential mechanisms that may explain the link between these SNPs and longevity, associations with age-related diseases, hypertension, and diastolic and systolic blood pressures were evaluated (Supplementary Tables 16 and 17). There were significant associations between SNPs in LD with rs2149954 and increased risk of coronary heart disease ($p < .001$) for carriers of the T allele. Associations with other phenotypes were not observed.

Analyses for healthy aging were only performed in white women due to small sample sizes of survival categories in the other ethnic groups. Of the 14 SNPs, rs4420638 and rs429358 were significantly associated with healthy aging (Table 3 and Supplementary Table 18; $p = .021$ and $p = .021$, respectively). After adjustment for rs7412 and rs429358, rs4420638 was no longer significantly associated with healthy survival (data not shown). In analyses adjusting only for age and population stratification, findings were similar (Supplementary Table 19).

In a meta-analysis among white, African American, and Hispanic women, rs2075650 ($p = .04$) and rs429358 ($p = .04$) were significantly associated with survival to age 85 (Supplementary Table 20). Furthermore, rs2149954 showed evidence of heterogeneity ($I^2 = 75$; *p* value for heterogeneity = .02). In a meta-analysis among white and African American women, rs2075650 ($p = .001$), rs4420638 ($p = .006$), rs7412 ($p = .02$), and rs429358 ($p < .001$) were significantly associated with survival to age 90 (Supplementary Table 21).

In sensitivity analyses, findings were similar when comparing women who survived to age 85 with those who died before age 80

Table 1. Associations of Significant Loci From Previous Studies With Longevity in Postmenopausal White Women From the Women's Health Initiative

SNP	Chromosome	Position	Count Allele/Reference Allele (count allele frequency)	OR (95% CI) Survived to 90 vs. Died Before 90[a]	Uncorrected *p* Value	Corrected *p* Value
TOMM40[b]						
rs2075650	19	45395619	G/A (0.13)	0.75 (0.63–0.87)	<.001	**<.001**
APOC1[b]						
rs4420638	19	45422946	G/A (0.16)	0.72 (0.61–0.85)	<.001	**<.001**
APOE[b]						
rs7412	19	45412079	T/C (0.08)	1.27 (1.04–1.54)	.020	.069
rs429358	19	45411941	C/T (0.13)	0.68 (0.57–0.80)	<.001	**<.001**

Notes: CI = confidence interval; OR = odds ratio; SNP = single nucleotide polymorphism.

Bold *p* values are significant at $p < .05$ after correction for multiple testing using the Benjamini-Hochberg procedure.

[a]Multivariable model adjusts for age, study membership, body mass index, physical activity, education, marital status, alcohol consumption, smoking behavior, history of age-related diseases, and population stratification ($N = 3,380$).

[b]Gene.

and women who survived to age 90 with those who died before age 80. Findings persisted after adjustment for genotyping source in the models (data not shown).

Discussion

This was the first study to determine whether genetic factors associated with longevity in previous studies replicate in African American and Hispanic women. No index SNP or SNP in LD with any index SNP was significantly associated with longevity in African American women. In Hispanic women, SNPs in LD with a novel locus (rs2149954) identified as being associated with longevity in a recent meta-analysis of GWAS of Europeans (14) were associated with survival to age 85. Among white women, three SNPs were associated with survival to age 90: rs2075650, located at *TOMM40*; rs4420638, located at *APOC1*; and rs429358, one of two SNPs defining the three *APOE* isoforms. In a meta-analysis among all ethnic groups, rs2075650 and rs429358 were significantly associated with survival to age 85.

In previous GWAS among European populations, only genetic variants near *APOE* have reached genome-wide significance (13–16). Among white women, we observed that rs2075650 and rs4420638 were no longer significantly associated with survival to age 90 after adjusting for the two *APOE* SNPs, indicating that *TOMM40* and *APOC1* do not have independent effects on exceptional survival but rather tag variation at *APOE* (13). Index SNPs were not associated with survival to age 85 in white women, supporting the observation that genetic factors may be of greater importance at more advanced ages such as 90 years and older (2).

In the current study, rs4420638 and rs429358 were significantly associated with healthy aging in white women. However, effect sizes for healthy survival and usual survival were similar in magnitude, suggesting that the association may be driven by survival to age 85 and not healthy aging per se. Limited genetic studies of healthy aging have been conducted (2,22). Mechanisms allowing exceptional survivors to markedly delay or avoid disease and disability entirely are currently unknown, but it is possible that genetic factors may play a role. A previous study showed that nonagenarians carry the same number of risk alleles for chronic diseases including cardiovascular disease, type 2 diabetes, and cancer as younger controls, suggesting that there may be genetic variants specifically promoting longevity, healthy aging, and a delay in disease (23).

Table 2. Associations of SNPs With Longevity in Postmenopausal Hispanic Women From the Women's Health Initiative

SNP	Chromosome	Position	Count allele/Reference allele (count allele frequency)	OR (95% CI) Survived to 85 vs. Died before 85[a]	Uncorrected *p* Value	Corrected *p* Value
rs2149954	5	157820602	T/C (0.31)	0.69 (0.52–0.93)	.015	.053
rs7721599	5	157819991	T/C (0.31)	0.69 (0.52–0.93)	.015	.053
rs7724836	5	157826281	A/G (0.35)	0.64 (0.48–0.85)	.002	**.037**
rs4704775	5	157824556	A/G (0.27)	0.80 (0.59–1.08)	.142	.368
rs7701003	5	157824481	G/A (0.33)	0.71 (0.53–0.95)	.022	.070
rs13163917	5	157832300	G/A (0.35)	0.64 (0.48–0.85)	.002	**.037**
rs17694395	5	157851580	T/C (0.35)	0.67 (0.50–0.90)	.007	**.037**
rs9313775	5	157856776	A/G (0.35)	0.68 (0.51–0.91)	.008	**.037**
rs10044792	5	157861839	T/C (0.35)	0.67 (0.50–0.90)	.007	**.037**
rs10037337	5	157862392	G/T (0.35)	0.67 (0.50–0.90)	.007	**.037**
rs12716344	5	157876908	G/C (0.36)	0.65 (0.49–0.88)	.005	**.037**

Notes: CI = confidence interval; OR = odds ratio; SNP = single nucleotide polymorphism.
Bold *p* values are significant at $p < .05$ after correction for multiple testing using the Benjamini-Hochberg procedure.
[a]Multivariable model adjusts for age and population stratification ($N = 539$).

Table 3. Associations of SNPs With Healthy Aging in Postmenopausal White Women From the Women's Health Initiative

SNP	Chromosome	Position	Count Allele/Reference Allele (count allele frequency)	OR (95% CI) Healthy Survival vs. Died Before 85[a]	OR (95% CI) Usual Survival vs. Died Before 85[a]	Uncorrected *p* Value	Corrected *p* Value
TOMM40[b]							
rs2075650	19	45395619	G/A (0.13)	0.83 (0.70–0.97)	0.84 (0.72–0.98)	.027	.094
APOC1[b]							
rs4420638	19	45422946	G/A (0.16)	0.78 (0.66–0.93)	0.80 (0.68–0.93)	.003	**.021**
APOE[b]							
rs7412	19	45412079	T/C (0.08)	1.16 (0.94–1.45)	1.15 (0.95–1.41)	.236	.661
rs429358	19	45411941	C/T (0.13)	0.76 (0.64–0.90)	0.79 (0.68–0.93)	.002	**.021**

Notes: CI = confidence interval; OR = odds ratio; SNP = single nucleotide polymorphism.
Bold *p* values are significant at $p < .05$ after correction for multiple testing using the Benjamini-Hochberg procedure.
[a]Multivariable model adjusts for age, study membership, body mass index, physical activity, education, marital status, alcohol consumption, smoking behavior, and population stratification ($N = 4,517$).
[b]Gene.

In the current study, variants at *FOXO3A*, which is involved in the insulin/insulin-like growth factor 1 signaling pathway, were not replicated in any ethnic group and were not significant in the meta-analyses. The association of *FOXO3A* with longevity has been shown to be stronger in persons aged 95 and older and especially in centenarians (6,11), which may partially explain the lack of associations between *FOXO3A* SNPs and longevity in our study.

SNPs previously associated with longevity did not reach statistical significance among African American women, and the majority did not reach significance among Hispanic women. Lack of significance may be due to smaller sample size and lower power to detect previous effect sizes compared with whites in these groups (Supplementary Tables 22–24). Among whites, power was more than 99% for almost all SNPs. However, among African Americans, power estimates ranged from 11.2% to 99.9% and were 80% or more for *TOMM40*, *APOC1*, and some *FOXO3A* SNPs. Among Hispanics, power was less than 80% for almost all SNPs. However, effect sizes for SNPs among African Americans and Hispanics were similar to those among white women and in the meta-analysis, rs2075650 and rs429358 were significantly associated with survival to age 85. These findings suggest that *APOE* may also be associated with longevity in African American and Hispanic women. Although no study has evaluated genetic factors in relation to longevity in African Americans or Hispanics, GWAS and replication studies of phenotypes such as type 2 diabetes, cancer, and obesity have revealed that there are ethnic variations in SNP associations with various health outcomes (24–26). They have also revealed novel loci associated with these phenotypes, suggesting that there may also be other, unknown genes and mechanisms that may influence longevity in these populations.

In analyses only adjusting for age and population stratification, several SNPs in LD with rs2149954, located on chromosome 5 downstream of *EBF1* (11), were significantly associated with longevity among Hispanic women. Furthermore, in the meta-analysis, rs2149954 showed evidence of heterogeneity. A study in more than 12,000 European nonagenarians and younger controls observed that carriage of the T allele at rs2149954 was significantly associated with increased odds of longevity at the genome-wide level (14). However, we observed that carriage of the T allele was associated with decreased likelihood of longevity among Hispanic women. This previous study also observed that the T allele at rs2149954 was associated with lower cardiovascular mortality risk. However, our findings were explained by increased risk of coronary heart disease. Collectively, these findings support ethnic variations in the association of rs2149954 with longevity.

This study has several limitations. There was lower power to detect effect sizes reported in previous studies among African Americans and Hispanics in our study due to smaller sample sizes in these groups (Supplementary Tables 22–24). Women who enrolled for additional follow-up were more likely to be white, educated, and healthier at baseline than those who withdrew, thus our findings may be biased by selective attrition. It is possible that those who dropped out were more likely to be cognitively impaired, which may have biased *APOE* findings.

Strengths of this study include a large, multiethnic sample of women. This study was novel in that it was the first to evaluate the association of genetic factors with exceptional survival in African American and Hispanic women. Additional strengths include the prospective design with up to 21 years of follow-up, high retention of study participants over time, and adjudicated outcome ascertainment. Finally, our population had a narrow age range, limiting birth cohort bias.

Longevity is a complex phenotype that may be regulated by multiple pathways (2). Recent studies are uncovering novel genes that may be associated with longevity in different populations (27,28). In our study, variation at *APOE* was significantly associated with survival to age 90 among postmenopausal white women. In Hispanic women, SNPs in LD with a novel SNP recently identified as being associated with longevity in Europeans were significantly associated with decreased survival to age 85. Additional studies will be important in identifying novel loci and biologic pathways regulating life span in African American and Hispanic women. In the future, when there are sufficient numbers of long-lived ethnic minorities from different studies, data from multiple cohorts should be combined to evaluate genetic factors associated with longevity in these groups.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biomedical Sciences and Medical Sciences* online.

Funding

This work was supported by the National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services (contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C).

Acknowledgments

Role of the Sponsor: The National Heart, Lung, and Blood Institute has representation on the WHI Steering Committee, which governed the design and conduct of the study, the interpretation of the data, and preparation and approval of manuscripts.

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Conflict of Interest

None declared.

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