THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2017, Vol. 72, No. 10, 1407–1410
doi:10.1093/gerona/glw206
Advance Access publication November 5, 2016

OXFORD

Brief Report

Genome-wide Association Study of Parental Life Span

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Received February 10, 2016; Accepted November 1, 2016

Decision Editor: Stephen Kritchevsky, PhD

Abstract

Background: Having longer lived parents has been shown to be an important predictor of health trajectories and life span. As such, parental life span is an important phenotype that may uncover genes that affect longevity.
Methods: A genome-wide association study of parental life span in participants of European and African ancestry from the Health and Retirement Study was conducted.
Results: A genome-wide significant association was observed for rs35715456 ($\log_{10}$BF = 6.3) on chromosome 18 for the dichotomous trait of having at least one long-lived parent versus not having any long-lived parent. This association was not replicated in an independent sample from the InCHIANTI and Framingham Heart Study. The most significant association among single nucleotide polymorphisms in longevity candidate genes (*APOE*, *MINIPP1*, *FOXO3*, *EBF1*, *CAMKIV*, and *OTOL1*) was observed in the *EBF1* gene region (rs17056207, p = .0002).
Conclusions: A promising genetic signal for parental life span was identified but was not replicated in independent samples.

Keywords: Genetics—Successful aging—Life span—Epidemiology—Public health

There is an increasing interest in understanding the factors that contribute to healthy aging and longevity. It has been demonstrated that longevity is a trait that aggregates in families, where children of long-lived parents are more likely to live longer than children with short-lived parents (1–3). In addition, parental life span is linked with lower risk for chronic diseases (1,4–8). Although alternative hypotheses are possible, offspring of longer lived parents may have enrichment of genetic variants for longer life span and health span.

Several genetic association studies on longevity in humans have been performed to date (9,10). Although several candidate loci have been identified, two loci have been consistently replicated, FOXO3a and ApoE (9,11,12). It is thought that the genetic basis of longevity is complex, and the genes identified to date only explain a small fraction of the heritable component of longevity (9). In this regard, offspring of longer lived parents may provide a unique opportunity to identify variants associated with life span. One prior genome-wide association study (GWAS) of parental life span conducted in the UK Biobank identified a variant on nicotine receptor (CHRNA3) to be associated with father's age of death (13). To identify additional loci, we performed a GWAS of parental life span in the Health and Retirement Study (HRS).

Methods

The HRS recruited a representative multiethnic sample of Americans aged 51–61 years, as documented elsewhere (14). Baseline interviews were conducted in 1992 and repeat interviews biennially through 2010. For our analyses, we used data from 10 HRS waves (1992–2010), collated in a single data set by the RAND Corporation (15). The HRS genome-wide data were accessed by the National Center

for Biotechnology Information Genotypes and Phenotypes Database (dbGaP Study Accession: phs000428.v1.p1) (16,17).

The calculation of parental age of death in the HRS has been described elsewhere (1). Briefly, parental age at death or current age (if alive) of respondents' parents was recorded. Parental Lifespan Score was created for participants whose both parents were deceased (Supplementary Material). Briefly, a normal curve using a nonlinear least square regression was used to determine the modal age (*M*) of death for each parent. They were then categorized as short lived if less than *M* – 1 *SD* (mothers: 61–76 years and fathers: 46–74 years), intermediate as *M* ± 1 *SD* (mothers: 77–91 years and fathers: 65–87 years), and long lived (mothers: older than 91 years and fathers: older than 87 years). The primary parental life span traits analyzed included one quantitative and three dichotomous traits: (i) Parental Lifespan Score, (ii) having two long-lived parents versus not having any long-lived parent, (iii) having at least one long-lived parent versus having no long-lived parent, (iv) and having at least one long-lived parent versus having at least one short-lived parent. Genome-wide genotyping of HRS was conducted using the Illumina HumanOmni2.5-4v1 array and screened using standard quality control methods (Supplementary Material). Genome-wide association analysis was conducted for unrelated HRS participants of European ancestry and African ancestry using an additive genetic model adjusting for age, sex, and first eight principal components. A linear regression as implemented in MERLIN (18) for quantitative traits and logistic regression using PLINK (http://pngu.mgh.harvard.edu/~purcell/plink/) for dichotomous traits were performed. Genome-wide significance was considered at the Bonferroni corrected *p* value for one million independent single nucleotide polymorphisms (SNPs) at a *p* value of 5×10^{-8}. A transethnic meta-analysis of results from European and African ancestry was conducted using MANTRA (Meta-Analysis of Trans-ethnic Association studies) (19). Evidence in favor of association was determined using a Bayes' factor (BF) where a $\log_{10}$BF of 6 or higher was considered genome-wide significant. To calculate combined effect sizes, we combined results using inverse-variance based meta-analysis in METAL software (http://www.sph.umich.edu/csg/abecasis/metal). Replication analysis for rs35715456 with the dichotomous trait of having at least one long-lived parent versus having no long-lived parent was conducted in the Framingham Heart Study and the InCHIANTI study (Supplementary Material).

Results

The basic characteristics of the study sample are described in Table 1. There were no genome-wide significant results from the race-specific analysis for any of the parental life span traits examined (data not shown). Genome-wide significant results were observed in the transethnic meta-analysis for the dichotomous trait of having at least one long-lived parent versus not having any long-lived parent (Supplemental Figure 1). The most significant association was observed for rs35715456 on chromosome 18 ($\log_{10}$BF = 6.3, $p = 2.89 \times 10^{-8}$; Table 2; Figure 1) within the mothers against decapentaplegic homolog 7 (*SMAD7*) gene. The association of rs35715456 with parental life span was not replicated in the InCHIANTI (β = 0.01 ± 0.20, *p* = .943; Table 2) and Framingham studies (β = 0.07 ± 0.16, *p* = .628).

As an exploratory analysis, we examined 374 independent SNPs ($r^2 < .5$) that are positioned 50 kb within previously described longevity candidate loci APOC/TOMM40/*APOE*, *MINIPP1*, *FOXO3*, *CAMKIV*, *EBF1*, and *OTOL1*. We also examined 36 independent variants ($r^2 < .5$) in the *CHRNA3* gene recently reported to be associated with paternal age of death. In the current analyses, none of the SNPs reached a multiple corrected significance threshold for 410 SNPs at *p* less than .0001 (Supplementary Table 1). The most significant association among SNPs was observed for a SNP in the *EBF1* gene region (rs17056207, *p* = .0002).

Table 1. Basic Characteristics of Health and Retirement Study Participants

	European Ancestry	African Ancestry	
	Mean (*SD*) [*n*]	Mean (*SD*) [*n*]	*p*[a]
Age (years)	57.5 (8.8)	55.9 (8.0)	<.001
%Male (*N*)	41.6% [3,599]	36.1% [548]	<.001
Mother's age of death	76.6 (14.7) [6,901]	70.4 (17.3) [1,185]	<.001
Father's age of death	71.6 (14.2) [7,529]	69.6 (15.4) [1,240]	<.001
Parental Lifespan Score [*N*][b]	[5,034]	[682]	.0292
Two short-lived parents[c]	9.9% [496]	11.4% [78]	
One short-lived parent	34.4% [1,730]	40.3% [275]	
Intermediate lived parents[d]	33.1% [1,668]	28.2% [192]	
One long-lived parent[e]	18.8% [947]	16.4% [112]	
Two long-lived parents	3.8% [193]	3.7% [25]	

Note: [a]Differences between baseline values were tested using one-way analysis of variance or chi-square test.
[b]The number of participants with information on both parents' age of death.
[c]Age range for short-lived mothers: 61–76 years, fathers: 46–64 years.
[d]Age range for intermediate lived mothers: 77–91 years, fathers: 65–87 years.
[e]Age range for long-lived mothers: older than 91 years, fathers: older than 87 years.

Table 2. Association of rs35715456 With Having at Least One Long-Lived Parent

rs35715456	*N*	Beta	*SE*	*p* Value
HRS European ancestry	5,034	0.29	0.06	1.25×10^{-7}
HRS African ancestry	682	0.49	0.27	.068
HRS meta-analysis	5,716	0.30	0.05	2.89×10^{-8}[a]
Replication				
InCHIANTI	426	0.01	0.20	.943
Framingham	1,525	0.07	0.16	.640
Overall meta-analysis				1.63×10^{-7}

Notes: HRS = Health and Retirement Study.
[a]$\log_{10}$BF = 6.3.

Discussion

We have performed a genome-wide association analysis of parental life span in participants from the HRS. Although the lack of a significant association in this study is disappointing, it is consistent with the general experience that mapping of aging genes in humans is difficult. One of the biggest challenges is the definition of aging and longevity phenotypes. Past studies have used case–control designs such as comparing centenarians with noncentenarians or those who live to a certain age (85 or 90 years) compared with those who are short lived (9). Other projects have examined aging traits such as physical function or muscle strength. In this regard, parental life span has been shown to be a powerful measure that is predictive of the life span and health span of an individual (1–8).

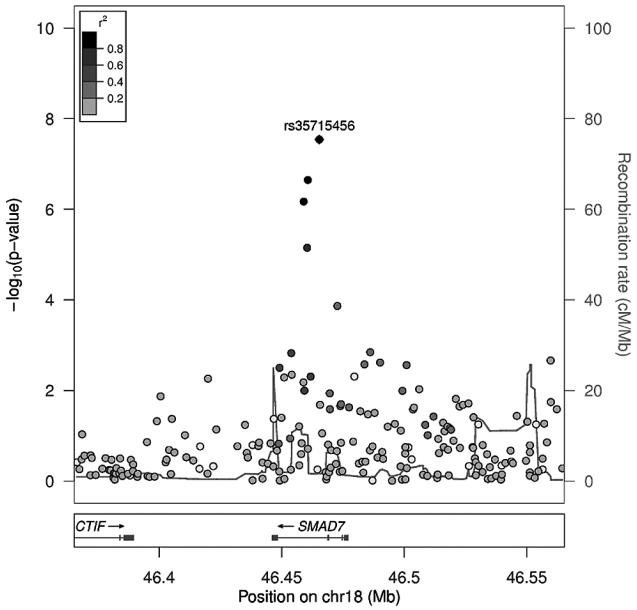

Figure 1. Associations of single nucleotide polymorphisms (SNPs) within 100 kb of SMAD7 with parental life span. The figures display $-\log_{10}$ *p* values for the association between SNPs and the dichotomous trait of parental life span of having at least one long-lived parent versus not having any long-lived parent. The SNP (rs35715456, $\log_{10}$BF = 6.3, $p = 2.89 \times 10^{-8}$) with the strongest evidence of association is indicated. The degree of linkage disequilibrium (LD; r^2) is displayed as black (high LD) to gray (low LD) reflecting the strength of LD.

Offspring of long-lived parents have been shown to have lower risk of age-related diseases (1–8). In the HRS study, increasing parental survival beyond 65 years of age was associated with 14% decline per decade in all-cause mortality and lower incidence of cancer, diabetes, heart disease, and stroke (1). These associations between parental longevity and favorable health outcomes have been reported in other cohorts such as the Framingham and Leiden Longevity study (4,6–8).These observations motivated us to examine parental life span as a novel aging trait for genetic analysis. A potential limitation of this trait is that parental age of death may not be extreme enough, and studies have suggested that genetic effects are greater for survival beyond 95 years (20). An advantage is the larger sample size achieved by using information on parental death; however, the current study may still be underpowered. One prior GWAS of parental life span in the UK Biobank (N = 75,000) reported associations with candidate longevity genes but no confirmed GWAS signals (13). Because the HRS includes individuals of both European and African descent, we can potentially identify loci that transcend across ethnic groups.

A genome-wide significant association was observed for a SNP in the *SMAD7* gene. SMAD7 is a member of a family of TGF-β effector proteins that serves as an inhibitor of TGFβ signaling with higher expression in aging tissues (21). In a recent meta-analysis of whole blood gene expression in 14,983 individuals of European descent, expression of SMAD7 was significantly increased with chronological age (22). Although the identified locus is a good candidate for association with parental life span trait, the association observed in the HRS study was neither confirmed in the InCHIANTI nor in the Framingham Heart Study.

The quest for "aging" genes has been challenging. The two most consistent loci are ApoE and FOXO3a, which were not associated with parental life span in the current analysis. The most significant SNP in the *APOE* and FOXO3a region was only marginally associated with parental age of death. Although these genes are the most replicated longevity loci, not all studies report significant associations (23,24). Of the other candidate genes tested (9,10), a SNP in the *EBF1* gene region was most significantly associated with parental life span—however, the association was not significant after adjustment for multiple comparisons. In a previous GWAS of parental age of death, the *CHRNA3* loci reached genome-wide significance but was neither replicated in the Framingham study nor in the HRS study. Larger GWAS of this trait to gain greater power to identify additional loci is warranted.

In summary, we conducted a genome-wide association analysis of parental life span in the HRS study and report a common genetic variant in the SMAD7 gene to be significantly associated with parental life span, this result was however not replicated in two independent samples. Further studies need to be conducted to confirm the reported association.

Supplementary Material

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

Funding

The Health and Retirement Study (genetic) data are sponsored by the National Institute on Aging (grant numbers U01AG009740, RC2AG036495, and RC4AG039029) and the study was conducted by the University of Michigan. The Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine were supported by the National Heart, Lung and Blood Institute's Framingham Heart Study Contract N01-HC-25195 and its contract with Affymetrix, Inc for genotyping services (Contract N02-HL-6-4278). The Framingham Study phenotype–genotype analyses were supported by the National Institute of Aging grant number R01AG029451. The InCHIANTI study baseline (1998–2000) was supported as a "targeted project" (ICS110.1/RF97.71) by the Italian Ministry of Health and in part by the U.S. National Institute on Aging (Contracts 263 MD 9164 and 263 MD 821336).

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