

Brief Report

Genome-wide Association Study of Parental Life Span

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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*, *MINIP1*, *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 $M \pm 1 SD$ (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 ($\beta = 0.01 \pm 0.20$, $p = .943$; Table 2) and Framingham studies ($\beta = 0.07 \pm 0.16$, $p = .628$).

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*, *MINIPPI*, *FOXO3*, *CAMKIV*, *EBF1*, and *OTOL1*. We also examined 36 independent variants ($r^2 < .5$) in the *CHRNA3* gene recently reported to be

Table 1. Basic Characteristics of Health and Retirement Study Participants

	European Ancestry	African Ancestry	p^a
	Mean (SD) [n]	Mean (SD) [n]	
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: ^aDifferences between baseline values were tested using one-way analysis of variance or chi-square test.

^bThe number of participants with information on both parents' age of death.

^cAge range for short-lived mothers: 61–76 years, fathers: 46–64 years.

^dAge range for intermediate lived mothers: 77–91 years, fathers: 65–87 years.

^eAge 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^{-8a}
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.

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, $p = .0002$).

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).

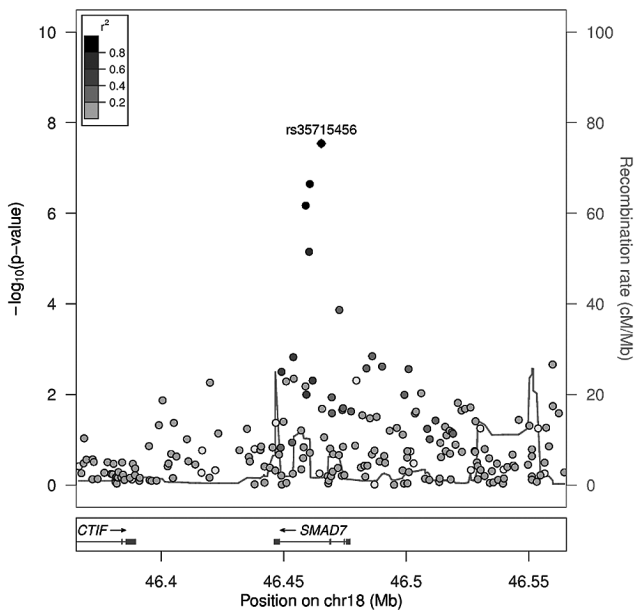


Figure 1. Associations of single nucleotide polymorphisms (SNPs) within 100 kb of SMAD7 with parental life span. The figures display $-\log_{10} p$ values for the association between SNPs and the dichotomous trait of parental life span of having at least one long-lived parent versus not having any long-lived 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 TGF β 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.

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References

1. Dutta A, Henley W, Robine JM, Langa KM, Wallace RB, Melzer D. Longer lived parents: protective associations with cancer incidence and overall mortality. *J Gerontol A Biol Sci Med Sci.* 2013;68:1409–1418. doi:10.1093/gerona/glt061
2. Adams ER, Nolan VG, Andersen SL, Perls TT, Terry DF. Centenarian offspring: start healthier and stay healthier. *J Am Geriatr Soc.* 2008;56:2089–2092. doi:10.1111/j.1532-5415.2008.01949.x
3. Terry DF, Wilcox MA, McCormick MA, et al. Lower all-cause, cardiovascular, and cancer mortality in centenarians’ offspring. *J Am Geriatr Soc.* 2004;52:2074–2076. doi:10.1111/j.1532-5415.2004.52561.x
4. Murabito JM, Beiser AS, Decarli C, Seshadri S, Wolf PA, Au R. Parental longevity is associated with cognition and brain ageing in middle-aged offspring. *Age Ageing.* 2014;43:358–363. doi:10.1093/ageing/af175
5. Dutta A, Henley W, Robine JM, et al. Aging children of long-lived parents experience slower cognitive decline. *Alzheimer Dement.* 2014;10:S315–S322. doi:10.1016/j.jalz.2013.07.002
6. Wijsman CA, Rozing MP, Streefland TC, et al. Familial longevity is marked by enhanced insulin sensitivity. *Aging Cell.* 2011;10:114–121. doi:10.1111/j.1474-9726.2010.00650.x
7. Westendorp RG, van Heemst D, Rozing MP, et al. Nonagenarian siblings and their offspring display lower risk of mortality and morbidity than sporadic nonagenarians: The Leiden Longevity Study. *J Am Geriatr Soc.* 2009;57:1634–1637. doi:10.1111/j.1532-5415.2009.02381.x
8. Terry DF, Evans JC, Pencina MJ, et al. Characteristics of Framingham offspring participants with long-lived parents. *Arch Intern Med.* 2007;167:438–444. doi:10.1001/archinte.167.5.438

9. Murabito JM, Yuan R, Lunetta KL. The search for longevity and healthy aging genes: insights from epidemiological studies and samples of long-lived individuals. *J Gerontol A Biol Sci Med Sci*. 2012;67:470–479. doi:10.1093/gerona/gls089
10. Deelen J, Beekman M, Uh HW, et al. Genome-wide association meta-analysis of human longevity identifies a novel locus conferring survival beyond 90 years of age. *Hum Mol Genet*. 2014;23:4420–4432. doi:10.1093/hmg/ddu139
11. Schachter F, Faure-Delanef L, Guenet F, et al. Genetic associations with human longevity at the APOE and ACE loci. *Nat Genet*. 1994;6:29–32. doi:10.1038/ng0194-29
12. Willcox BJ, Donlon TA, He Q, et al. FOXO3A genotype is strongly associated with human longevity. *Proc Natl Acad Sci USA*. 2008;105:13987–13992. doi:10.1073/pnas.0801030105
13. Pilling LC, Atkins JL, Bowman K, et al. Human longevity is influenced by many genetic variants: evidence from 75,000 UK Biobank participants. *Aging*. 2016;8:547–563. doi:10.18632/aging.100930
14. Sonnega A, Faul JD, Ofstedal MB, Langa KM, Phillips JW, Weir DR. Cohort Profile: the Health and Retirement Study (HRS). *Int J Epidemiol*. 2014;43:576–585. doi:10.1093/ije/dyu067
15. Clair SC, Bugliari D, Campbell N, et al. *RAND HRS Documentation, Version K*. Santa Monica, CA: RAND Corporation; 2011.
16. Mailman MD, Feolo M, Jin Y, et al. The NCBI dbGaP database of genotypes and phenotypes. *Nat Genet*. 2007;39:1181–1186. doi:10.1038/ng1007-1181
17. Tryka KA, Hao L, Sturcke A, et al. NCBI's Database of Genotypes and Phenotypes: dbGaP. *Nucleic Acids Res*. 2014;42:D975–D979. doi:10.1093/nar/gkt1211
18. Abecasis GR, Cherny SS, Cookson WO, Cardon LR. Merlin—rapid analysis of dense genetic maps using sparse gene flow trees. *Nat Genet*. 2002;30:97–101. doi:10.1038/ng786
19. Morris AP. Transethnic meta-analysis of genomewide association studies. *Genet Epidemiol*. 2011;35:809–822. doi:10.1002/gepi.20630
20. Sebastiani P, Nussbaum L, Andersen SL, Black MJ, Perls TT. Increasing sibling relative risk of survival to older and older ages and the importance of precise definitions of “aging,” “life span,” and “longevity”. *J Gerontol A Biol Sci Med Sci*. 2016;71:340–346. doi:10.1093/gerona/glv020
21. Han KH, Choi HR, Won CH, et al. Alteration of the TGF-beta/SMAD pathway in intrinsically and UV-induced skin aging. *Mech Ageing Dev*. 2005;126:560–567. doi:10.1016/j.mad.2004.11.006
22. Peters MJ, Joehanes R, Pilling LC, et al. The transcriptional landscape of age in human peripheral blood. *Nat Commun*. 2015;6:8570. doi:10.1038/ncomms9570
23. Bader G, Zuliani G, Kostner GM, Fellin R. Apolipoprotein E polymorphism is not associated with longevity or disability in a sample of Italian octo- and nonagenarians. *Gerontology*. 1998;44:293–299.
24. Heijmans BT, Slagboom PE, Gussekloo J, et al. Association of APOE epsilon2/epsilon3/epsilon4 and promoter gene variants with dementia but not cardiovascular mortality in old age. *Am J Med Genet*. 2002;107:201–208.