

No Association between the Mitochondrial Genome and Prostate Cancer Risk: The Multiethnic Cohort

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Abstract

Background: Mitochondria are involved in many processes that are central to the life and death of a cell. Oxidative phosphorylation (OXPHOS), in particular, is known to be altered in carcinogenesis, leading to an increase in the production of reactive oxidative species and glycolysis, one of the hallmarks of cancer cells. Because of this, genetic variation in the mitochondrial genome, which encodes for part of the OXPHOS pathway, has been suggested to play a role in many cancers, including prostate cancer.

Methods: We comprehensively examined the role of the mitochondrial genome and prostate cancer risk in 4,086 prostate cancer cases and 3,698 controls from the Multiethnic Cohort (MEC), testing 350 mitochondrial SNPs (mtSNPs) in five racial/ethnic populations—Africans, Asian Americans, Europeans, Latinos, and Native Hawaiians. Logistic regression was

conducted to examine single mitochondrial SNP and haplogroup associations. The sequence kernel association test was conducted for gene and pathway analysis.

Results: Eleven mtSNPs and haplogroup N were nominally associated with overall prostate cancer risk at $P < 0.05$. The mitochondrial DNA-encoded OXPHOS pathway, complexes, and genes were not associated with prostate cancer risk. No significant associations were identified after multiple testing corrections (all FDR $q > 0.20$).

Conclusions: The mitochondrial genome was not associated with prostate cancer risk in our study of 7,784 subjects from the MEC.

Impact: Our comprehensive study does not support the role of the mitochondrial genome in the risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev*; 25(6); 1001–3. ©2016 AACR.

Introduction

Prostate cancer is the most common cancer in U.S. men. Mitochondrial DNA (mtDNA), 16 kb pairs of circular, double-stranded, maternally inherited DNA, consists of 37 genes involved in numerous cellular processes, including cell apoptosis and the oxidative phosphorylation (OXPHOS) pathway. Mutations in the mitochondria of cancer cells have been shown to inhibit OXPHOS and increase anaerobic glycolysis, one of the hallmarks of cancer growth (1). Thirteen proteins encoded by the mtDNA are

involved in the OXPHOS pathway, and variants in this region may alter OXPHOS and promote the production of reactive oxidative species. Previous studies suggested that genetic variation in the mitochondrial genome and the OXPHOS pathway may be associated with increased risk of several cancers, including prostate cancer (2, 3). Here, we conducted a large nested case-control study within the Multiethnic Cohort (MEC) to evaluate the association between the mitochondrial genome and its associated OXPHOS pathway, complexes, genes, and haplogroups in relation to prostate cancer risk.

Materials and Methods

Our study population consisted of 4,086 prostate cancer cases and 3,698 controls nested within the MEC, a large population-based cohort of more than 215,000 men and women from Hawaii and Los Angeles (4). Age, family history of prostate cancer, and self-declared maternal race/ethnicity are described in Table 1. Of all cases, 1,456 were classified as aggressive (Gleason score of 7 or higher or advanced stage) and 2,341 were nonaggressive (Gleason score <7 and localized stage).

A total of 350 mitochondrial SNPs (mtSNPs), distributed across the 13 mtDNA genes that comprise the four complexes of the OXPHOS pathway and the tRNA and rRNA subunits, were pooled from the Exome and Sequenom genotyping platforms [described elsewhere (5, 6)]. The average individual call rate was 99.8%, the average mtSNP call rate was 99.8%, and the average mtSNP concordance rate for 20% replicated samples was 99.3%.

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

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Table 1. Study characteristics of 4,086 cases and 3,698 controls by maternal race/ethnicity

	African Americans		Asian Americans		European Americans		Latinos		Native Hawaiians	
	Cases (n = 1,004)	Controls (n = 1,003)	Cases (n = 1,009)	Controls (n = 999)	Cases (n = 836)	Controls (n = 825)	Cases (n = 1,099)	Controls (n = 739)	Cases (n = 138)	Controls (n = 132)
Age, mean (SD)	69.46 (7.24)	70.13 (7.84)	71.43 (7.38)	71.32 (8.24)	69.23 (7.56)	70.47 (8.43)	69.16 (6.58)	68.50 (7.21)	68.91 (6.67)	68.85 (7.13)
Family history of prostate cancer, n (%)	118 (13.32)	110 (12.32)	94 (10.27)	46 (4.83)	106 (14.52)	70 (9.27)	110 (11.12)	39 (5.57)	13 (10.4)	7 (5.6)
Disease aggressiveness ^a										
Aggressive, n (%)	300 (32.93)	—	462 (48.84)	—	299 (37.90)	—	331 (32.42)	—	64 (49.23)	—
Nonaggressive, n (%)	611 (67.07)	—	484 (51.16)	—	490 (62.10)	—	690 (67.58)	—	66 (50.77)	—

^aCases were classified as "aggressive" when the Gleason score was 7 or higher or cancer stage was advanced or higher, "nonaggressive" when Gleason score was less than 7 and cancer stage was localized and either well or moderately differentiated.

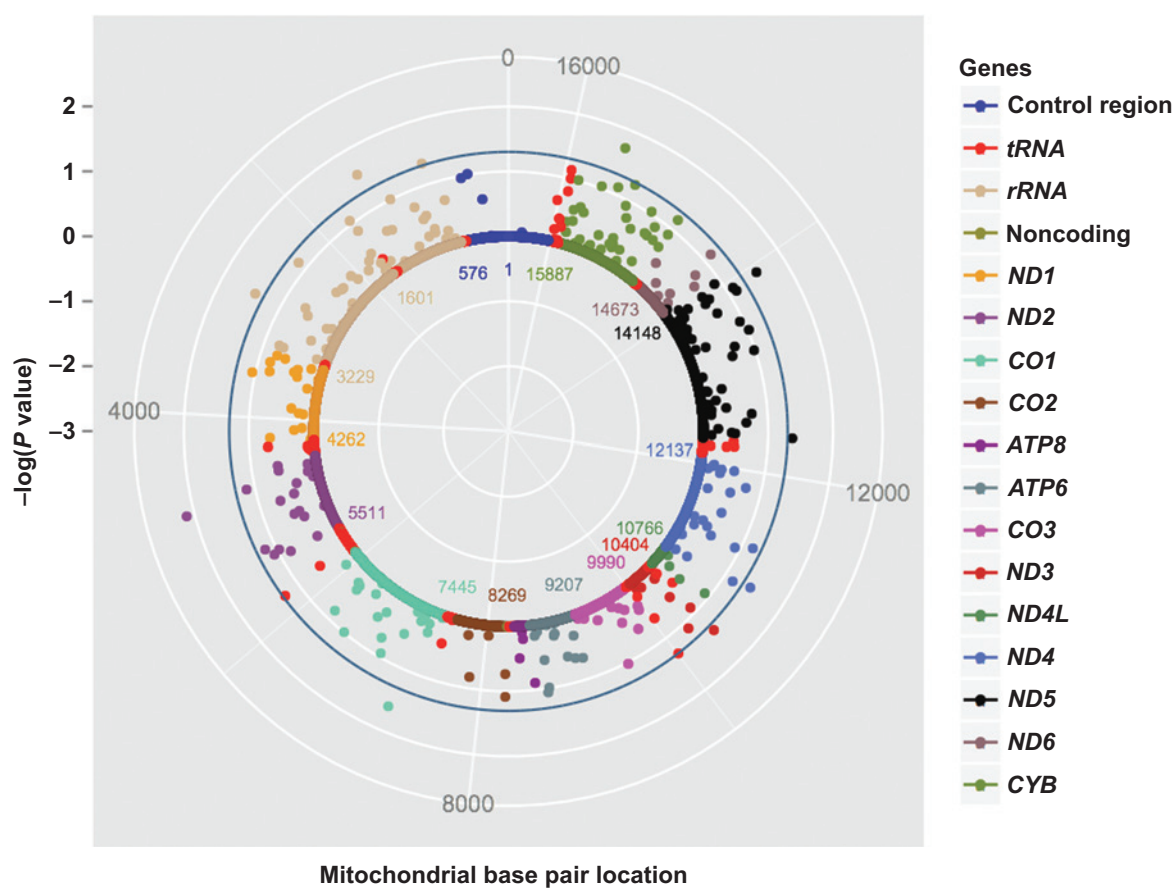
To estimate haplogroups, we used the HaploGrep software based on PhyloTree Build 16 (6).

Single mtSNP and haplogroup associations were assessed through unconditional logistic regression and adjusted for age, the first five principal components of genetic ancestry, and self-declared maternal race/ethnicity. Mitochondrial pathway and set-based analysis were conducted using the sequence kernel association test available through the R package SKAT (7) and adjusted for the same covariates. Stratified analyses were conducted by maternal race/ethnicity and disease aggressiveness. All analyses and figures were run using the R statistical platform ([https://cran.](https://cran.r-project.org/)

[r-project.org/](https://cran.r-project.org/)). To account for multiple hypothesis testing, FDR (8) was used, and statistical significance was defined as the proportion of false discoveries $q < 0.2$.

Results

Eleven of the 350 mtSNPs tested were associated with overall prostate cancer risk at the nominal P value of <0.05 (Fig. 1; Supplementary Table S1). The most significant overall association was with mt4820, located in mitochondrially encoded NADH dehydrogenase 2 (*MT-ND2*) gene [minor allele frequency

**Figure 1.**

From outside to inside, the three gray circles correspond to the P values of 10^{-3} , 10^{-2} , and 10^{-1} . Teal circle, $P = 0.05$. Each dot represents the mtSNP association P value with prostate cancer, color coded by mitochondrial gene.

(MAF) = 0.07; OR = 0.94; 95% confidence interval (CI), 0.90–0.98; $P = 0.008$; $q = 0.784$], which did not reach our threshold of statistical significance. When stratifying by maternal race/ethnicity, the strongest nominal association was in African Americans with a noncoding variant, mt15314 (MAF = 0.01; OR = 0.74; 95% CI, 0.59–0.92; $P = 0.007$; $q = 0.98$; Supplementary Table S1). When considering mtDNA globally as a whole, grouped into the OXPHOS pathway, four separate mitochondrial complexes (I, III, IV, and V), or 13 mitochondrial genes and tRNA, rRNA subunits, there were no statistically significant associations with prostate cancer risk ($q > 0.2$; Supplementary Table S2). Haplogroup N was nominally associated with prostate cancer risk in Asian Americans (frequency = 0.07; OR = 0.91; 95% CI, 0.85–0.99; $P = 0.026$; $q = 0.445$; Supplementary Table S3), Europeans (frequency = 0.03; OR = 0.85; 95% CI, 0.74–0.98; $P = 0.029$; $q = 0.445$; Supplementary Table S3), and in all race/ethnicities combined (frequency = 0.03; OR = 0.90; 95% CI, 0.83–0.98; $P = 0.02$; $q = 0.445$; Supplementary Table S3) and did not reach a $q < 0.2$. Similar patterns of associations were observed for aggressive and nonaggressive disease.

Discussion

Our study had 80% power to detect an OR of 1.35 for mtSNPs with MAF 5% at a significance level of 1.42×10^{-4} . A previous study of 260 European and African American prostate cancer patients and 54 controls found a higher frequency of somatic mutations in the mitochondrially encoded cytochrome oxidase subunit I (*MT-COI*) gene (12%) compared with controls (1.9%; ref. 2). In our current study, which included 1,661 European and 2,007 African American subjects, we found *MT-COI* mtSNP mt6253 to be nominally protective ($P = 0.02$; Supplementary Table S1). In another study of 221 North American white prostate cancer cases and 246 controls, haplogroup U was associated with prostate cancer risk (OR = 1.95; $P = 0.019$; ref. 3). We observed in our larger study no association with haplogroup U in European Americans (OR = 0.97; $P = 0.387$; Supplementary Table S3). Our study found a nominal association with haplogroup N in European ($P = 0.029$; Supplementary Table S3) and Asian American populations ($P = 0.026$; Supplementary Table S3) and among all racial/ethnic groups combined ($P = 0.02$; Supplementary Table S3). In summary, we did not find strong evidence of

associations between the mitochondrial genome and prostate cancer risk. This is in line with previous GWAS studies, which have found no nuclear component of OXPHOS to be associated with prostate cancer risk.

Disclosure of Potential Conflicts of Interest

R. Saxena has ownership interest (including patents) in AstraZeneca and Surface Oncology. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Writing, review, and/or revision of the manuscript: E.E. Giorgi, Y. Li, K.B. Beckman, A. Lum-Jones, C.A. Haiman, L. Le Marchand, D.O. Stram, R. Saxena, I. Cheng
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