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, 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 correction (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 Multiethnic Cohort.

Impact: Our comprehensive study does not support the role of the mitochondrial genome in the risk of prostate cancer.
Introduction

Prostate cancer (PC) is the most common cancer in U.S. men. Mitochondrial DNA (mtDNA)—16 kilobase 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 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 PC [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 PC risk.

Materials and Methods

Our study population consisted of 4,086 PC 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 PC, 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 non-aggressive (Gleason score <7 and localized stage).
A total of 350 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%. 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.r-project.org/). To account for multiple hypothesis testing, a false discovery rate (FDR) [8] was used and statistical significance was defined as the proportion of false discoveries q<0.2.

Results

Eleven of 350 mtSNPs tested were associated with overall PC risk at the nominal p value of < 0.05 (Fig. 1, Suppl. Table 1). The most significant overall association was with mt4820, located in mitochondrially encoded NADH dehydrogenase 2 (MT-ND2) gene (MAF=0.07; OR=0.94; 95% 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 non-coding variant, mt15314 (MAF=0.01; OR=0.74; 95% CI=0.59-0.92; p=0.007; q=0.98; Suppl. Table 1). When considering mtDNA globally as a whole, grouped into the OXPHOS pathway, into four separate mitochondrial complexes (I, III, IV and V), or into 13 mitochondrial genes and tRNA, rRNA subunits, there were no statistically significant associations with PC risk (q>0.2; Suppl. Table 2). Haplogroup N was nominally associated with PC risk in Asian Americans (frequency=0.07; OR=0.91; 95% CI=0.85-0.99; p=0.026; q=0.445; Suppl. Table 3), Europeans (frequency=0.03; OR=0.85; 95% CI=0.74-0.98; p=0.029; q=0.445; Suppl. Table 3), and in all race/ethnicities combined (frequency=0.03; OR=0.90; 95% CI=0.83-0.98; p=0.02; q=0.445; Suppl. Table 3), and did not reach a q<0.2. Similar patterns of associations were observed for aggressive and non-aggressive disease.

Discussion

Our study had 80% power to detect an OR of 1.35 for mtSNPs with MAF 5% at a significance level of 1.42x10^-4. A previous study of 260 European and African American PC patients and 54 controls found a higher frequency of somatic mutations in the mitochondrially encoded cytochrome oxidase subunit I (MT-COI) gene (12%) compared to controls (1.9%) [2]. In our present 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; Suppl. Table 1). In another study of 221 North American white PC cases and 246 controls, haplogroup U was associated with
PC risk (OR=1.95; p=0.019) [3]. We observed in our larger study no association with haplogroup U in European Americans (OR=0.97; p=0.387; Suppl. Table 3). Our study found a nominal association with haplogroup N in European (p=0.029; Suppl. Table 3) and Asian American populations (p=0.026; Suppl. Table 3) and among all racial/ethnic groups combined (p=0.02; Suppl. Table 3). In summary, we did not find strong evidence of associations between the mitochondrial genome and PC risk. This is in line with previous GWAS studies, which have found no nuclear component of OXPHOS to be associated with PC risk.
References


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

<table>
<thead>
<tr>
<th></th>
<th>African Americans</th>
<th>Asian Americans</th>
<th>European Americans</th>
<th>Latinos</th>
<th>Native Hawaiians</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n=1004)</td>
<td>Controls (n=1003)</td>
<td>Cases (n=1009)</td>
<td>Controls (n=999)</td>
<td>Cases (n=1099)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>69.46 (7.24)</td>
<td>70.13 (7.84)</td>
<td>71.43 (7.38)</td>
<td>71.32 (8.43)</td>
<td>69.23 (6.58)</td>
</tr>
<tr>
<td>Family history of prostate cancer, n (%)</td>
<td>118 (13.32)</td>
<td>110 (12.32)</td>
<td>94 (10.14)</td>
<td>70 (9.27)</td>
<td>110 (11.12)</td>
</tr>
<tr>
<td>Disease aggressiveness*</td>
<td>300 (32.93)</td>
<td>--</td>
<td>462 (48.84)</td>
<td>--</td>
<td>299 (37.90)</td>
</tr>
<tr>
<td>aggressive, n (%)</td>
<td>611 (67.07)</td>
<td>--</td>
<td>484 (51.16)</td>
<td>--</td>
<td>490 (62.10)</td>
</tr>
<tr>
<td>non-aggressive, n (%)</td>
<td>--</td>
<td>--</td>
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</tbody>
</table>

* Cases were classified as aggressive when the Gleason score was 7 or higher or the stage was 2 or higher; non-aggressive when the stage was localized and either well or moderately differentiated.

Table 1. Study subject characteristics of cases and controls, by maternal race/ethnicity.
**Figure 1 Legend**
From outside to inside, the three grey circles correspond to the P value of $10^{-3}$, $10^{-2}$ and $10^{-1}$. The teal circle represents a p-value of 0.05. Each dot represents the mtSNP association p-value with PC, color-coded by mitochondrial gene.
Figure 1

Mitochondrial Base Pair Location

-log(p-value)

Genes
- Control Region
- tRNA
- rRNA
- Non-Coding
- ND1
- ND2
- CO1
- CO2
- ATP8
- ATP6
- CO3
- ND3
- ND4L
- ND4
- ND5
- ND6
- CYB

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