Y Chromosome Haplotypes and Prostate Cancer in Sweden

Sara Lindström,[1] Hans-Olov Adami,[1,3] Jan Adolfsson,[2] and Fredrik Wiklund[1]

Abstract

Purpose: Certain Y-chromosomal lineages have been suggested to predispose individuals to prostate cancer in the Japanese population; in other ethnic groups, however, the importance of the Y chromosome is poorly understood.

Experimental Design: To assess the possible Y-chromosomal contribution to prostate cancer risk and prognosis, we analyzed five binary Y-chromosomal markers in 1,447 prostate cancer cases and 983 population controls from the Swedish population. Together, these five markers capture the vast majority of chromosome Y haplogroup diversity in the Swedish population. Individual lineages were tested for association with both prostate cancer risk and cancer-specific death. We replicated observed associations in an independent Swedish prostate cancer case-control study comprising 1,452 cases and 779 controls.

Results: One rare lineage (I1c) was associated with an increased risk of developing prostate cancer [odds ratio (OR), 2.9; 95% confidence interval (CI), 1.4-5.8; $P = 0.001$]. However, confirmatory analysis of this lineage in the independent case-control study revealed no association with prostate cancer risk (OR, 0.65; 95% CI, 0.4-1.2, $P = 0.17$). We observed no association between chromosome Y variation and prostate cancer–specific death.

Conclusions: This study provides strong evidence against an important role of the Y chromosome in the initiation or outcome of prostate cancer in the Swedish population.

There is strong support for a role of inherited genetic variation in prostate cancer, and recent genome-wide efforts, using high-density single nucleotide polymorphism markers, have been successful in identifying several prostate cancer susceptibility loci (1–5). A general limitation in these scans, however, has been a complete lack of chromosome Y coverage. The importance of chromosome Y in prostate cancer has been suggested by cytogenic findings, with loss of chromosomal Y segments being the most common chromosomal change observed in prostate cancer tissue (6, 7). Moreover, aberrant expression and loss of chromosome Y–specific genes has been observed in prostate cancer (8–10). In particular, *SRY*, the sex-determining gene on chromosome Y, is down-regulated in prostate cancer. This gene has been shown to be a negative regulator of the androgen receptor (11), suggesting a casual link between chromosomal Y loss and cancer growth.

Specific genetic features apply to the Y chromosome. Except for a small pseudoautosomal region, all loci on the paternally transmitted Y chromosome are haploid and paternally transmitted (12). As a result, Y-linked alleles have been successfully used to establish phylogeny (13, 14), thus providing a powerful resource for genetic association studies.

To date, only a few small studies have suggested that specific Y-chromosomal lineages are associated with prostate cancer risk in the Japanese population (15, 16), but no association has been found in other ethnic populations (16, 17). Therefore, we explored the possible role of Y-chromosomal haplogroups in prostate cancer development and prognosis in a large population-based case-control study of Swedish men.

Subjects and Methods

Case-control study. The study population has been described in detail elsewhere (18). Briefly, we identified and recruited prostate cancer cases from four of the six regional cancer registries in Sweden. These registries encompass approximately two thirds of the Swedish population. The inclusion criterion was biopsy-confirmed or cytologically verified adenocarcinoma of the prostate, diagnosed between July 2001 and October 2003. Among the 3,648 identified subjects with prostate cancer, 3,161 (87%) agreed to participate. DNA samples from blood, TNM stage, Gleason grade, and prostate-specific antigen levels at time for diagnosis were available for 2,893 subjects (92%).

Control subjects, who were recruited concurrently with case subjects, were randomly selected from the Swedish Population Registry and matched according to the expected age distribution of cases (groups of 5-year intervals) and geographic region. A total of 2,149 of 3,153 control subjects (68%) who were invited subsequently agreed to participate in the study. DNA samples from blood were available for 1,781 control subjects (83%). Recruitment of the study population was completed in two

Authors' Affiliations: [1]Department of Medical Epidemiology and Biostatistics and [2]Oncologic Center, CLINTEC, Karolinska Institutet, Stockholm, Sweden; and [3]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts

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Requests for reprints: Sara Lindström, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobels väg 12 A, P.O. Box 281, SE-171 77 Stockholm, Sweden. Phone: 617-432-5896; Fax: 617-432-1722; E-mail: slindstr@hsph.harvard.edu.

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Translational Relevance

With this study, we show that it is highly unlikely that inherited chromosome Y variation from father to son affects the risk of developing prostate cancer. In addition, we conclude that chromosome Y variation does not affect the aggressiveness of disease or the clinical outcome with prostate cancer – specific death as primary end-point. Chromosome Y variation has been previously hypothesized to be involved in prostate cancer development, but very few epidemiologic studies have addressed this question. This study is the first that investigates how inherited chromosome Y variation in Caucasians affects prostate cancer risk on a large-scale basis. Because all recently conducted genome-wide scans have excluded the male-specific chromosome Y, this study provides an important contribution to ongoing research by filling a significant gap in the exhaustive search for prostate cancer loci throughout the genome. Moreover, this study clearly illustrates the importance of replicating initial promising findings in genetic association studies. Despite a strong association in our large screening population (>2,000 individuals), we were not able to replicate these results in a follow-up study. This shows that false positive findings occur also in large, well-powered populations and that replication is always required to claim a true association.

phases, each with a similar number of subjects; the first phase (CAPS1) ended on October 31, 2002, the second phase (CAPS2) on November 1, 2003.

In this study, we first analyzed DNA from 1,447 cases and 983 controls recruited in the second phase (CAPS2), henceforth denoted the screening population. In addition, we replicated significant associations in 1,452 cases and 779 controls recruited in the first phase (CAPS1), henceforth denoted the replication population. Table 1 presents the clinical characteristics of the study subjects. Each subject provided written informed consent. The study received institutional approval from the ethical board of Karolinska Institutet.

Follow-up. With the use of each study participant's unique national registration number, vital status was assessed from the date of blood draw up until March 1, 2007 through record linkage to the Swedish Population Registry, and prostate cancer – specific survival was obtained through linkage with the Cause of Death Registry up to December 31, 2004. A review of death certificates, done by an oncologist, established cause of death for individuals deceased after December 31, 2004. At end of follow-up, a total of 140 men in the screening population and 218 in the replication population had died with prostate cancer as the underlying cause of death.

SNP selection and genotyping. Based on a recent study of chromosome Y diversity in the Swedish population (19), we selected five binary markers, i.e., M253, M223, M46 (Tat), M17, and M269 (Fig. 1), for genotyping in the screening population. Together, these markers account for >95% of the Swedish male lineages (19). M46 failed in genotyping due to technical problems with primer design and was replaced by M9, which resulted in collapsing four specific lineages into one haplogroup (Fig. 1). However, because the estimated population frequencies of the K*(xN3,P), P*(xR1a,Rb3), and R1a* lineages (1.6%, 3.3%, and 0.3%, respectively) are relatively small compared with the N3 lineage (9.5%), this collapsing had a minor effect on the attained genetic coverage. Markers found to be significantly associated with the risk (M223) or prognosis (M17) of prostate cancer were also genotyped in the independent replication population.

Genotyping details have been described earlier (20). Shortly we used matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Sequenom Inc.; ref. 21). PCR assays and associated extension reactions were designed using the SpectroDESIGNER software (Sequenom, Inc.). Primer sequences are available on request.

Statistical methods. For each lineage, a covariate was created, coded as "1" if the individual carried the specific lineage and "0" if otherwise. Association between prostate cancer risk and each lineage was assessed using a likelihood ratio test based on an unconditional logistic regression model as implemented in the publicly available R software (22). We adjusted all analyses for age and geographic region.

We did time-to-event analysis using death from prostate cancer as outcome. Survival time was censored at time of death for patients dying from causes other than prostate cancer. Association between a specific lineage and prostate cancer death was assessed by a likelihood ratio test based on the Cox proportional hazards model as implemented in R. All *P* values are based on two-sided tests.

Results

By combinations of the five binary markers, Y chromosomes were classified into six haplogroups, i.e., I1a*, R1a1, N3 K* P* R1a*, R1b3, I1c, and untagged, according to the nomenclature of the Y chromosome consortium (ref. 23; Fig. 1). Quality control of genotyping results based on 51 blind replicate samples revealed no discordant genotypes, and the average genotyping success rate was 95% (range, 86-99%). The clinical characteristics of the screening and replication populations are presented in Table 1. Due to limited prostate-specific antigen screening in Sweden, our study populations comprise high proportions (>40%) of clinically advanced prostate cancer (defined as tumors meeting at least one of the following criteria: T_3/T_4, N+, M+, Gleason score of 8 to 10 or prostate-specific antigen level $\geq$50 ng/mL).

Prostate cancer risk. Carriers of the I1c lineage had an almost 3-fold increased risk of developing prostate cancer [odds ratio (OR), 2.87; 95% confidence interval (CI), 1.4-5.8; *P* = 0.001; Table 2], and the magnitude of this association was increased after stratifying for advanced disease (OR, 3.53; 95% CI, 1.6-7.6; *P* = 0.0007) and early age of onset (< 65 years; OR, 3.47; 95% CI, 1.2-10.1; *P* = 0.001). Stratifying the analysis on cases that had a father with prostate cancer (204 individuals) did not alter the results. No other lineage or haplogroup was associated with prostate cancer risk. To validate the increased risk associated with the I1c lineage, additional samples from 1,452 cases and 779 controls from the replication population were genotyped for the M223 marker that defines the I1c lineage. In this independent population, however, we observed no association between the I1c lineage and prostate cancer risk (OR, 0.65; 95% CI, 0.4-1.2; *P* = 0.17). The combined OR in the two populations was 1.26 (95% CI, 0.8-1.9; *P* = 0.29).

Table 1. Characteristics for prostate cancer cases and controls enrolled in the CAPS study

Characteristics*	Screening population		Replication population	
	Cases (%)	Controls (%)	Cases (%)	Controls (%)
	n = 1,447	*n* = 983	*n* = 1,452	*n* = 779
Age, y				
≤59	350 (24.2)	184 (18.7)	290 (20,0)	104 (13.4)
60-69	720 (49.8)	424 (43.1)	640 (44.1)	326 (41.8)
≥70	377 (26.1)	375 (38.1)	522 (36.0)	349 (44.8)
Prostate-specific antigen levels, ng/mL				
<4	75 (5.3)	821 (83.6)	73 (5.2)	632 (81.1)
4-9.99	527 (37.5)	127 (12.9)	475 (33.6)	115 (14.8)
10-19.99	330 (23.5)	22 (2.2)	326 (23.1)	19 (2.4)
20-49.99	229 (16.3)	9 (0.9)	234 (16.6)	11 (1.4)
50-99.99	97 (6.9)	2 (0.2)	134 (9.5)	1 (0.1)
≥100	149 (10.6)	1 (0.1)	171 (12.1)	1 (0.1)
T stage				
T_0/T_X	48 (3.3)		34 (2.3)	
T_1	568 (39.3)		517 (35.6)	
T_2	431 (29.9)		470 (32.4)	
T_3	343 (23.7)		382 (26.3)	
T_4	56 (3.9)		49 (3.4)	
N stage				
N_0/N_X	1,398 (96.6)		1,405 (96.8)	
N_1-N_3	49 (3.4)		47 (3.2)	
M stage				
M_0/M_X	1,312 (90.7)		1,309 (90.2)	
M_1	135 (9.3)		143 (9.8)	
Gleason score				
≤4	52 (3.9)		54 (3.7)	
5	134 (9.9)		158 (10.9)	
6	521 (38.6)		469 (32.3)	
7	404 (29.9)		385 (26.5)	
8	126 (9.3)		133 (9.2)	
9	99 (7.3)		88 (6.1)	
10	14 (1.0)		11 (0.8)	
Differential grade				
GI/GX	1,021 (70.6)		965 (66.5)	
GII	257 (17.8)		335 (23.1)	
GIII	169 (11.7)		152 (10.5)	
Prostate cancer stage †				
Localized	850 (58.7)		814 (56.1)	
Advanced	597 (41.3)		638 (43.9)	
Status at follow-up				
Alive	1,243 (85.9)		1,133 (78)	
Dead from causes other than prostate cancer	64 (4.4)		101 (7.0)	
Dead due to prostate cancer	40 (9.7)		218 (15.0)	

*Characteristics were not available for all study participants.
† Case subjects were classified as advanced cases if they met at least one of the following criteria: T_3/T_4, N+, M+, Gleason score of 8-10 or PSA level ≥50 ng/mL.

Prostate cancer–specific death. During an average follow-up time of 3.3 years (range, 0.04-5.9 years), 204 (14%) of the 1,447 patients died and of those, 140 (10%) had prostate cancer classified as the underlying cause of death. Overall, Y-chromosomal variation showed no association with prostate cancer–specific death, although carriers of the R1a1 lineage had a suggestive worse prognosis (hazard ratio, 1.48; 95% CI, 0.99-2.22, P = 0.07; Table 3). Stratifying for stage, Gleason score, prostate-specific antigens, metastasis, or treatment did not alter the results (data not shown). To further explore this suggestive finding, additional samples from 1,452 cases from the replication population, of which 218 had died from prostate cancer during follow-up, were genotyped for the M17 marker that defined the R1a1 lineage. Pooling the two cohorts, however, did not reveal any significant association between the R1a1 lineage and prostate cancer–specific death (hazards ratio, 1.25; 95% CI, 0.97-1.63; P = 0.09).

Discussion

In this study, we evaluated the question of whether inherited variation on the male-specific Y chromosome modulates the initiation or prognosis of prostate cancer in a large population-based Swedish case-control study. Initially, we identified a rare lineage (population frequency, 1%) that increased the risk of developing prostate cancer almost 3-fold; however, we were not able to replicate this result in an independent study, indicating a false positive association in the primary analysis. Assessment

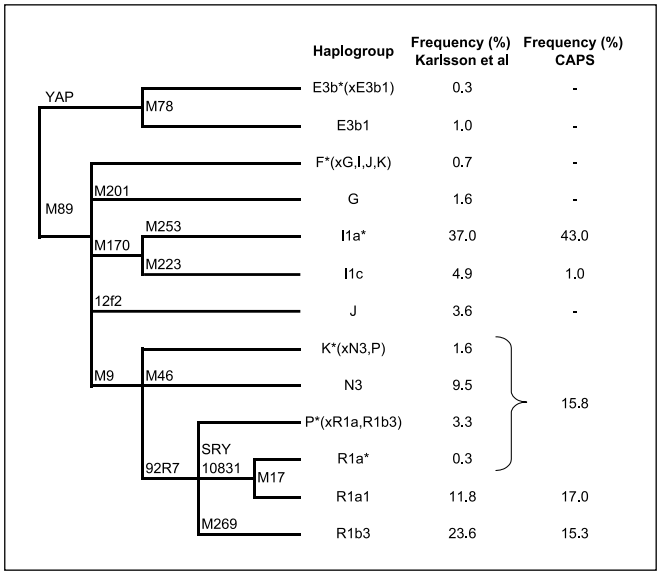

Fig. 1. Y-chromosomal haplogroups in the Swedish population defined by 16 binary markers as described by Karlsson and colleagues (19). The haplogroup frequencies in the study by Karlsson et al. and in CAPS controls are shown. *, The sum of the frequencies in CAPS do not add up to 1 as all lineages not including any of the typed markers are not considered.

of the association between chromosome Y haplogroups and prostate cancer–specific survival did not reveal any significant findings. Except for a suggestive association with one lineage, which attenuated in an extended population sample, no haplogroup among our prostate cancer cases showed any association with disease outcome. Considering the large size and population-based design of our study population, these results provide strong support against a role of chromosome Y in prostate cancer etiology in Sweden.

There is a wide variability in prostate cancer incidence worldwide (24), which in part may be explained by population-specific genetic diversity. As chromosome Y haplogroup frequencies vary significantly among different ethnic groups (12), chromosome Y variation constitutes a plausible risk factor for prostate cancer. To date, only a few studies have investigated the possible role of chromosome Y variation on prostate cancer. Paracchini and colleagues analyzed 118 binary markers in a study population including 930 prostate cancer cases and 1,208 controls from four different ethnic groups (African-American, White, Latino, and Japanese; ref. 15). They found that haplogroup O-M122–derived lineages, present almost exclusively in their Japanese samples, were associated with significant predisposition to prostate cancer. In contrast, no association with prostate cancer was observed with any of the haplogroups observed in their African-American, White, or Latino study populations. Ewis et al. (14) also reported significant association between chromosome Y haplogroups and prostate cancer in a Japanese population: the D/E-YAP haplogroup was significantly associated with increased prostate cancer risk whereas the O-SRY haplogroup was associated with a decreased disease risk.

Because the above lineages reported to be associated with prostate cancer development are exclusively found in populations of Asian origin, we could therefore not assess them in our Swedish study population. However, in a recent study from the Korean population, a population with close genetic relationship to the Japanese population (25), Kim et al. observed no statistically significant association between any Y-chromosomal haplogroup and prostate cancer risk, suggesting that the reported findings in the Japanese population may be explained by genetic effects only seen in an environment specific to the Japanese population, or by false positive associations.

Interestingly, the magnitude of the association reported by Paracchini and co-workers was increased among cases with advanced disease (defined as a Gleason sum of =8, and/or regional or metastatic stage), suggesting a role of chromosome Y in prostate cancer progression and prognosis. We were not able to observe any association between Y-chromosomal haplogroups specific to the Swedish population and prostate cancer prognosis. Thus, further studies in Asian populations, preferably using prostate cancer–specific mortality as outcome, are necessary to validate the suggested importance of Asian-specific chromosome Y lineages in prostate cancer prognosis.

Our study represents by several magnitudes the largest study ever assessing the role of chromosomal-Y structure in prostate cancer etiology. The strengths of our study include its large sample size (providing excellent statistical power to detect even

Table 2. Association between chromosome Y lineages and prostate cancer risk

Lineage*	Frequency (%)		OR (95% CI)	*P*	Advanced cases	
	Cases	Controls			OR (95% CI)	*P*
I1a*	790 (58.2)	527 (57.0)	0.96 (0.81-1.15)	0.68	0.87 (0.70-1.09)	0.23
	567 (41.8)	397 (43.0)				
R1a1	1,189 (83.7)	802 (83.0)	0.95 (0.76-1.19)	0.66	1.02 (0.78-1.35)	0.87
	232 (16.3)	164 (17.0)				
N3,K*,P*,R1a	1,226 (86.5)	811 (84.2)	0.85 (0.67-1.07)	0.16	0.77 (0.57-1.04)	0.09
	191 (13.5)	152 (15.8)				
R1b3	1,174 (82.5)	820 (84.7)	1.17 (0.93-1.47)	0.17	1.23 (0.93-1.62)	0.15
	249 (17.5)	148 (15.3)				
I1c	1,396 (97.0)	971 (99.0)	2.87 (1.43-5.79)	0.001	3.51 (1.63-7.53)	0.0008
	43 (3.0)	10 (1.0)				

NOTE: Prostate cancer risk was assessed with an unconditional logistic regression adjusted for age and geographic region.
*Each lineage was tested using all other lineages as reference.

Table 3. Association between chromosome Y lineages and prostate cancer-specific survival

Lineage*	No. events	HR (95% CI)	*P*
I1a	51	0.90 (0.63-1.27)	0.54
R1a1	31	1.48 (0.99-2.22)	0.07
N3,K*,P*,R1a	20	1.13 (0.71-1.81)	0.60
R1b3	23	0.89 (0.57-1.41)	0.62
I1c	3	0.71 (0.23-2.23)	0.53

NOTE: Hazard ratios and corresponding confidence intervals for survival analysis was done with Cox regression.
Abbreviation: HR, hazard ratio.
*Each lineage was tested using all other lineages as reference.

rare low-penetrant susceptibility genes), population-based design, complete follow-up, and profound clinical end point. Considering the large number of individuals in this study, the possibility that our results represent false negative findings is small. Assuming a dominant inheritance model with an allele frequency of 1% (as for the M223 marker), our combined study population has an 80% power to detect an OR of 2.1.

A limitation in this study is the failure to analyze the M46 binary marker, which resulted in collapsing four specific lineages into one haplogroup. However, three of the four collapsed lineages were rare in the Swedish populations as determined by Karlsson et al. (19). Therefore, we argue that this grouping of three rare and one common lineage into one haplogroup will be of less concern in interpreting our results. A possible limitation in the CAPS population is the differential participation rate between cases (87%) and controls (68%), reflected by an observed difference in age distribution between cases and controls, which could introduce selection bias. However, because all analyses comparing cases with controls were adjusted for age and it is implausible that specific genotypes would influence individuals' willingness to participate in the study, we find it unlikely that selection bias is an issue in our study.

In conclusion, we found no evidence supporting a role of chromosome Y in predisposition to or in the prognosis of prostate cancer in the Swedish population. Additional studies in the non-European population are necessary to further explore the putative role of chromosome Y in prostate cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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