

Two Percent of Finnish Prostate Cancer Patients Have a Germ-line Mutation in the Hormone-binding Domain of the Androgen Receptor Gene¹

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ABSTRACT

Mutations of the androgen receptor (AR) gene have been reported in prostate cancer, usually from tumor tissue specimens from late-stage, androgen-independent cancer. Occasionally, germ-line mutations have been found, but a link between AR mutations and predisposition to human prostate cancer has not been firmly established. Recently, two independent studies reported the same germ-line mutation at codon 726 in exon E (CGC to CTC) in two apparently unrelated Finnish prostate cancer patients. This arginine to leucine substitution was reported to alter the transactivational specificity of the AR protein. In the present study, the R726L mutation was analyzed by allele-specific oligohybridization in DNA specimens from 418 consecutive prostate cancer patients who reported a negative family history (sporadic group) and from 106 patients with a positive family history (hereditary group). The population frequency of the R726L mutation in blood donors was 3 of 900 (0.33%). In contrast, eight (1.91%) mutations (odds ratio = 5.8; $P = 0.006$) were found in the sporadic group, and two (1.89%) mutations were found in the hereditary group (odds ratio = 5.8; $P = 0.09$). Suggestive evidence of the segregation of the mutation with prostate cancer was seen in these two families. The present study indicates that the R726L substitution in the AR may confer an up to 6-fold increased risk of prostate cancer and may contribute to cancer development in up to 2% of Finnish prostate cancer patients. These results warrant additional large-scale studies of the significance of rare mutations and polymorphisms in candidate genes along the androgen signaling pathway as risk factors for prostate cancer.

INTRODUCTION

In many Western countries, prostate cancer is the most common malignancy among men, who have a cumulative lifetime risk of 1 in 10 or greater (1). Prostate cancer is believed to arise as a result of an interplay of genetic factors, endogenous hormones, and environmental influences, with the strongest known risk factors being age, ethnic origin, and positive family history (2–7). Male relatives of prostate cancer patients have a 2–5-fold elevated risk of cancer. Up to 5–10% of all prostate cancers may result from an inherited predisposition. Up to seven genetic predisposition loci for prostate cancer have been found in genetic linkage studies (8–14). These include three predisposition loci on chromosome 1: (a) *HPC1* (8) at 1q24–q25; (b) *HPC2* at 1q42 (9); and (c) a putative prostate-brain tumor (*CAPB*) locus at 1p36 (10). Other chromosomal regions suggested to harbor prostate cancer susceptibility loci include Xq27–q28 (*HPCX*; Ref. 11), 11p (12), 16q (13), and 20q13 (14). All of these loci are suspected to harbor rare gene mutations conferring a

high risk for prostate cancer development. Other genetic features suggested to be involved in prostate cancer include mutations in the *BRCA1* (15) and *BRCA2* genes (16), as well as common polymorphisms of a number of candidate genes, such as 5- α reductase, vitamin D receptor, and the *AR*³ gene (17–19).

Because AR protein is a key mediator of growth signaling in the prostate, many investigators have considered AR as a candidate prostate cancer susceptibility gene. The AR gene contains two polymorphic trinucleotide repeat regions in exon A: (a) a CAG repeat (coding for polyglutamine); and (b) a GGC repeat (polyglycine). The length of the CAG repeat sequence is inversely correlated with the transactivational activity of the AR. Irvine *et al.* (20) proposed that men with short CAG repeats would have an increased risk of prostate cancer. Subsequently, Giovannucci *et al.* (21) and Stanford *et al.* (22) conducted a case-control study and found an association between a low number of AR gene CAG repeats and an increased risk of prostate cancer. In particular, short CAG repeat sequence was strongly associated with cancers characterized by extraprostatic extension, distant metastases, or poor histological differentiation. However, not all authors have been able to confirm these findings (23, 24).

Numerous specific mutations of the AR gene have also been reported in human prostate cancer patients (see the Androgen Receptor Gene Mutations Database⁴). Many of these mutations occur in regions of the gene coding for the ligand- or DNA-binding domains of the AR, and functional studies have indicated that such mutations often alter the specificity of the transcriptional response of the AR to androgens, anti-androgens, and other steroids. In many cases, the mutations have only been studied from the tumor tissue, with the highest prevalence of AR mutations reported in metastases of patients with hormone-refractory disease (25, 26). The germ-line origin of such mutations has been established in only two reports (27, 28), but the role of such mutations in the genetic predisposition to prostate cancer has not been firmly established.

Elo *et al.* (27) described an R726L germ-line mutation of the AR gene in a prostate cancer patient from Northern Finland. We recently found the same mutation in another Finnish prostate cancer patient when screening for AR mutations by single-strand conformational polymorphism in six patients whose cancers appeared during finasteride treatment for benign prostatic hyperplasia (29). The R726L mutation affects the hormone-binding region in exon E and was reported to lead to activation of the AR not only by dihydrotestosterone and testosterone but also by estradiol (27). The fact that this mutation has not been found in any published study of the AR gene suggests that it may represent a unique Finnish mutation. Here we analyzed the frequency of the R726L mutation in over 1400 specimens from blood donors, consecutive prostate cancer patients with no family history of prostate cancer, and patients with a positive family history of prostate cancer to explore the frequency of this mutation in the Finnish population, as well as its association with prostate cancer.

Received 3/27/00; accepted 9/15/00.

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¹ Supported by the Medical Research Fund of Tampere University Hospital, the Sigrid Juselius Foundation, the Lahtikari Foundation, the Finnish Cancer Institute (P. A. K.), Duodecim (Finnish College of Physicians; P. A. K.), the Dutch Cancer Society (J. T.), Pirkanmaa Cancer Society, and Maud Kuistila Foundation. The prostate cancer family collection was supported in part by a contract from the National Human Genome Research Institute, NIH (NO1-HG-55389).

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³ The abbreviations used are: AR, androgen receptor; ASO, allele-specific oligonucleotide; OR, odds ratio; TAUH, Tampere University Hospital.

⁴ <http://www.mcgill.ca/androgendb>.

Table 1 R726L mutation in Finnish prostate cancer patients and families

	No. of mutations (%)	Total no. of AR alleles	<i>p</i>	OR	95% Confidence interval
Controls	3 (0.33)	900		1.0	
Sporadic	8 (1.91)	418	0.006	5.8	1.5–22.1
Familial	2 (1.89)	106	0.09	5.8	0.95–34.8

MATERIALS AND METHODS

Patients. We collected blood samples from 418 consecutive sporadic prostate cancer patients at TAUH between 1996 and 1999, 106 patients with a positive family history of prostate cancer from the whole of Finland, and 778 healthy blood donors (656 men and 122 women) from the Tampere region.

During the sample collection, 559 new prostate carcinomas were diagnosed at TAUH. Twenty-five percent of the patients were excluded from the present study because of a positive family history for prostate cancer or their refusal to participate in the study. One hundred and six prostate cancer families with two or more affected cases were identified through referrals from physicians, family questionnaires sent to patients, and newspaper, radio, and television advertisements. A sample from one randomly chosen affected case from each family was screened for the R726L mutation.

Written informed consent was obtained from all patients and their family members, and research protocols were approved by the Ethical Committee of TAUH. Diagnoses of all prostate cancer patients were confirmed through medical records or the Finnish Cancer Registry. The patients' family histories for malignancies were documented from family questionnaires completed by the patients. Prostate cancer was considered "sporadic" when the patient reported no first- or second-degree relatives with prostate cancer.

The population frequency of the R726L mutation was established by analyzing DNA specimens from 778 anonymous, unselected healthy blood donors from the Tampere region (656 men and 122 women). Together, these specimens allowed us to scan for the allele frequency of the R726L mutation on 900 X chromosomes.

ASO Hybridization to Detect R726L. Genomic DNA was amplified using primers 5'-CCCAACAGGGAGTCAGACTTA-3' and 5'-CCTGGAGT-TGACATTGGTGA-3'. One hundred ng of DNA was amplified by 35 cycles of PCR in reactions containing 200 nM of both primers, 200 μM of each deoxynucleotide triphosphate, 50 mM KCl, 10 mM Tris-HCl (pH 8.3), 1.75 mM MgCl₂, 0.001% (w/v) gelatin, and 2.5 units of AmpliTaqGold DNA polymerase (Perkin-Elmer, Norwalk, CT). After an initial denaturation step of 10 min at 95°C, the cycle parameters were as follows: 95°C for 30 s, 57°C for 1 min, and 72°C for 1 min, with a 5-min extension at 72°C after the last cycle. Mutation detection was done using ASO hybridization as described by Friedman *et al.* (30) with the following exceptions: (a) filters were prewet and wells were washed with 0.4 M Tris-HCl (pH 7.5); (b) probes were end-labeled with ³²P at 37°C for 3 h by terminal deoxynucleotidyl transferase (Amersham Life Science Inc., Cleveland, OH); and (c) hybridizations were performed at 54°C. ASOs used in hybridizations were 5'-AGGCTTCGCAACTTACA-3' (wild type) and 5'-AGGCTTCCTCAACTTACA-3' (mutation). A mutation positive control as well as a negative control of the PCR reaction was included in each ASO hybridization. All samples with R726L mutation as well as 42 randomly chosen samples negative for mutation were sequenced with ABI PRISM 310 Genetic Analyzer (Perkin-Elmer) as recommended by the manufacturer. Primers used in sequencing were the same as those used for PCR.

Analysis for CAG Repeats in the AR. To explore whether the R726L mutation had a common origin, we analyzed the length of the AR CAG repeat in all mutation carriers. If the R726L mutation represented an ancient founder mutation, one would expect to find that neighboring genetic markers on the X chromosome, such as the CAG repeat, would also be shared between the mutation carriers. The distribution of CAG repeats in the R726L carriers was compared with CAG repeats of 811 Finnish blood donors.⁵ The fragment containing the CAG repeat was amplified by PCR using previously published primers (20), with the exception that the other inner primer was labeled with 5'-6-6-carboxyfluorescein. Electrophoresis was performed using the ABI 310

Genetic Analyzer (Perkin-Elmer) according to the manufacturer's instructions. Run results were analyzed by use of the Genescan 2.1 and Genotyper 2.0 (Perkin-Elmer) computer programs.

Statistical Analyses. Statistical analyses were performed using GraphPad InStat version 2.04a (GraphPad Software, San Diego, CA). Correlations were made with the two-tailed Fisher's exact test, χ^2 test, and χ^2 test for linear trend. Comparison of the ages was made using the two-tailed Student's *t* test. In addition, the OR and 95% confidence intervals were calculated.

RESULTS

Germ-line R726L AR mutation was found in 8 of 418 (1.91%) consecutive prostate cancer patients collected at TAUH between 1996 and 1999 (Table 1). All of these patients reported a negative family history for prostate cancer. On the basis of the analysis of blood donors from the same hospital region, the carrier frequency of R726L was established as 3 of 900 people (0.33%), which is significantly less than the frequency of the R726L mutation among the prostate cancer patients (OR = 5.8; *P* = 0.006).

The R726L mutation was also found in 2 of the 106 patients (1.89%) with a positive family history for prostate cancer (OR = 5.8; *P* = 0.09). Analysis of additional affected and unaffected cases from these two families indicated that the mutation was systematically present in all affected cases, whereas unaffected male individuals were not carriers.

Because the R726L mutation was also found in eight prostate cancer patients who reported no family history of prostate cancer, we constructed extended pedigrees from their families based on family questionnaires sent to the patients. Two of these patients turned out to have a maternal relative with prostate cancer.

Clinical features of the R726L mutation-positive prostate cancers were compared with those of noncarriers (Table 2). There were no significant differences in tumor stage, metastasis stage, or tumor grade between these groups. The average age at prostate cancer diagnosis was slightly lower in patients harboring the R726L mutation (65.5 ± 7.0 years; range, 59–79 years) as compared with the rest of the prostate cancer patients (68.4 ± 8.3 years; range, 48–92 years), but this difference was not statistically significant (*P* = 0.25).

To explore whether the R726L mutations shared the same origin, we studied the distribution of the adjacent AR CAG repeat in the 13 mutation carriers. Strong evidence of linkage disequilibrium was observed between the two different loci at the same gene. Eleven cases (85%) had 26 CAG repeats, and the remaining two cases had 25 and 27 repeats. As compared with the distribution of the CAG repeat lengths in the general Finnish population, the CAG repeat length of 26 is rather long. In the unselected Finnish population, the average CAG repeat length is 21.6 ± 2.6.⁵ Only 2.7% of men have 26 CAG repeats,

Table 2 Tumor characteristics of the R726L mutation carriers compared to sporadic prostate cancer patients

	R726L mutation <i>n</i> = 13 (%)	No. mutations <i>n</i> = 410 (%)	<i>P</i>
Tumor-stage			0.58 ^a
1 + 2	6 (46)	225 (55)	
3 + 4	7 (54)	185 (45)	
Metastasis-stage			0.53 ^b
0	7 (54)	281 (69)	
I	3 (23)	62 (15)	
Unknown	3 (23)	67 (16)	
WHO grade			0.46 ^c
I	3 (23)	100 (24)	
II	6 (46)	238 (58)	
III	4 (31)	72 (18)	

^a Fisher's exact test.

^b χ^2 test.

⁵ N. Mononen, M. Matikainen, J. Schleutker, P. A. Koivisto, T. L. J. Tammela, and O-P. Kallioniemi. The AR CAG repeat and its relationship to prostate cancer, manuscript

a significant difference as compared with R726L mutation carriers (OR = 197.3; 95% confidence interval, 41.2–943.8; $P < 0.0001$). The two mutation-positive cases with 25 and 27 CAG repeats could represent new mutations in this unstable trinucleotide tract. This strong linkage disequilibrium between the two markers, as well as the homogeneous distribution of CAG repeat lengths in the cases, suggests that the R726L mutation originates from a single ancestral event. Two repeat lengths (25 and 27 nucleotides) that differed in the mutation carriers may represent the inherent instability of the trinucleotide repeats, especially over many, perhaps dozens, of generations.

DISCUSSION

In this study, we report a comprehensive analysis of the frequency and significance of the R726L germ-line mutation of the *AR* gene in Finnish prostate cancer patients. Several findings substantiate the hypothesis that the R726L mutation contributes to the development of prostate cancer.

First, the mutation was seen in approximately 2% of the samples from the prostate cancer patients, whereas the population frequency of this allele in blood donors was 0.3%. The results suggest an almost 6-fold overrepresentation of the R726L mutation in the prostate cancer cases as compared with ethnically and geographically matched population controls. Second, the mutation was found in two patients with a positive family history for prostate cancer. Family members of the mutation-positive cases were also screened for the R726L mutation, and the R726L mutation was shared between the prostate cancer patients. Third, the R726L germ-line mutation in the coding region of the *AR* gene changes an evolutionarily exceptionally well-conserved amino acid in the protein (from a positively charged amino acid to a nonpolar amino acid). In addition, there is prior evidence that the R726L mutation may change the functional characteristics of the AR protein. Elo *et al.* (27) demonstrated that the R726L mutation did not alter the ligand binding specificity of the AR protein, but its transactivational activity in the presence of estradiol was increased. Although estradiol itself is unlikely to be the target of the mutant receptor, this finding suggests that the transactivational response of the mutated *AR* gene is altered in response to the ligands. This, in turn, may explain its association with prostate cancer. Additional studies are needed to establish the exact biological significance of the R726L mutation.

Eighty-five percent of the R726L mutation carriers had 26 CAG repeats in the *AR* gene. The average *AR* CAG repeat length in the Finnish population is 22, with a wide range from 8 to 30. The population frequency of the 26 CAG repeat length is only 2.7%,⁵ suggesting that there is a strong linkage disequilibrium between the R726L mutation and the CAG repeat within the *AR* gene. The 25 and 27 *AR* CAG repeats seen in two mutation carriers may be explained by the instability of the CAG repeats (20–24). Together, the results suggest that the R726L mutation carriers originate from a single ancestral founder.

In conclusion, we have demonstrated an up to 6-fold increased frequency of the *AR* R726L germ-line mutation in sporadic as well as family-positive prostate cancers. Additional studies are required to elucidate the potential role of the R726L mutation as a marker of genetic predisposition for prostate cancer or as a modifier locus. These kinds of infrequent but potentially cancer-associated variants of the *AR* gene provide an example of the importance of rare disease-associated single-nucleotide polymorphisms that are often overlooked in single-nucleotide polymorphism-based genetic studies. The role of such events along the AR signaling pathway deserves further study in prostate cancer.

ACKNOWLEDGMENTS

We are grateful to the participating subjects and their families. We thank Kaisa Vaherto for help with data collection and pedigree files and Minna

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The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

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Cancer Res 2000;60:6479-6481.

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