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Genetic Variability of the Human SRD5A2 Gene: Implications for Prostate Cancer Risk

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Abstract

Elevated dihydrotestosterone levels have been suggested to increase the risk of prostate cancer. The human SRD5A2 gene encodes the type II steroid 5α-reductase, which converts testosterone to the more bioactive compound dihydrotestosterone. We have determined the distribution of a dinucleotide repeat in low-risk Asian-Americans, high-risk African-Americans, and intermediate-risk non-Hispanic Whites. We found this marker to be more polymorphic than previously reported, with some alleles being specific to African-Americans. Genetic variants of the SRD5A2 gene may play a role in predisposition to prostate cancer and in explaining the substantial racial/ethnic variability in risk.

Introduction

Prostate cancer in the United States will be diagnosed in some 240,000 men during this year, and more than 45,000 will die of this disease (1). This cancer is characterized by marked variations in incidence among U.S. population groups: African-American men have a 70% increase in risk, while Asian-American men (of either Chinese or Japanese ancestry) have an approximately 60% decrease in risk when compared to non-Hispanic White males (2). We have previously suggested that elevated testosterone levels and, more particularly, intraprostatic DHT levels may be responsible for some of these variations in risk (3). The molecular basis for these striking differences is presently unknown. Furthermore, molecular studies thus far have revealed few mutations responsible for predisposition to prostate cancer and early tumor progression (4, 5).

Testosterone is converted to the more active intracellular metabolite, DHT, by steroid 5α-reductase with NADPH as the cofactor (6). DHT binds to the AR, and the DHT-AR complex transactivates a number of genes with AR-responsive elements (6). Two isozyme forms of steroid 5α-reductase have been reported: the type I enzyme encoded by the SRD5A1 gene, which is expressed mostly in newborn scalp and in skin and liver (7). The type II enzyme is primarily expressed in genital skin and the prostate, and is encoded by the SRD5A2 gene (7). These data suggest that the type I enzyme is primarily responsible for virilization and male pattern baldness, whereas the type II enzyme is involved in prostate development and growth.

The human SRD5A2 gene was cloned independently by two groups and shown to map to a single band on the short arm of chromosome 2 (2p23) spanning over 40 kb of genomic DNA (8, 9). Mutations in the SRD5A2 gene cause a rare human disorder, male pseudohermaphrodism. Males with this disorder are phenotypically female at birth, but develop male musculature and other secondary sex characteristics at puberty (7). The prostate, however, remains highly underdeveloped, and DHT levels are low despite a rise in testosterone at puberty (7). Thigpen et al. (9) and others have described mutations in the SRD5A2 gene responsible for male pseudohermaphroditism. These mutations, however, do not appear to be involved in prostatic diseases in adults.

Davis and Russell (10) reported a polymorphic three-allele system for the SRD5A2 gene that can be detected by PCR. The variable region is found in the transcribed 3' untranslated region of the type II steroid 5α-reductase gene and consists primarily of variable numbers of TA dinucleotide repeats. The most common allele, accounting for 96% of the chromosomes examined, was reported as a (TA)6 allele, i.e., a chromosome lacking TA dinucleotide repeats in the amplified region (10). Two other alleles, (TA)6 and (TA)9 repeats, were also described on the few remaining chromosomes (10).

We examined the hypothesis that SRD5A2 is a candidate gene for prostate cancer by genotyping males from three population groups at different risks for prostate cancer: high-risk African-American, intermediate-risk non-Hispanic White, and low-risk Asian men. We report here significant polymorphism in the SRD5A2 gene, with some alleles restricted to African-Americans.

Materials and Methods

Samples. We have genotyped 199 healthy controls to date: 94 African-Americans, 37 Asian-Americans (16 of Chinese and 21 of Japanese ancestry), and 68 non-Hispanic Whites ("Whites"). The control subjects in this report are derived from three sources. Sixty-one subjects (45 African-Americans and 16 Whites) are participants of an ongoing multiethnic cohort study of diet and cancer involving populations in Hawaii and Los Angeles. In the Los Angeles component, approximately 29,000 healthy African-American and 12,300 White men and women between the ages of 45 and 74 years have been recruited during the past 2 years from lists of residents of Los Angeles County. Participants completed a detailed health and dietary questionnaire and are now being traced primarily through a population-based cancer registry of Los Angeles for occurrence of all incident cancers. We also routinely collect blood and urine specimens from a 3% random sample of cohort members and all incident cancer cases of selected sites (including prostate). Another 117 control subjects (44 African-Americans, 36 Whites, and 37 Asian-Americans) were participants of a cross-sectional survey conducted during 1990–1991 among male residents of Los Angeles County who were ages 35–74 years (11). The remaining 21 subjects (5 African-Americans and 16 Whites) were detected from a pool of male subjects who had been recruited as control subjects for various case-control studies of cancer conducted by University of Southern California epidemiologists. These controls were all residents of Los Angeles County and were ages 50–74 years.

SRD5A2 Genotyping. Genomic DNA was extracted from buffy coat by purifying high molecular weight DNA with proteinase K digestion, phenol/chloroform extraction, and ethanol precipitation (12). Primers for PCR amplification were modified from those used by Davis and Russell (10): 3s (GAAAACGTG-CAGCGAAA) and 3s (GGCGAAAAGGACGAC). Syntheses of primers were performed in 30 nmol scales on a Beckman Oligo 1000 (Fullerton,...
The results of this study show that certain genetic variations in the SRD5A2 gene are associated with an increased risk of prostate cancer. The most common allele in the population is 87 bp, which is found in 67% of African-Americans, 78% of Asians, and 81% of non-Hispanic Whites. However, there is a significant difference in the prevalence of certain alleles by race, with African-Americans having a higher prevalence of the 87-bp allele and a lower prevalence of the 105-bp allele compared to Asians and non-Hispanic Whites.

**Table 1: Distribution of SRD5A2 alleles in three U.S. population groups**

<table>
<thead>
<tr>
<th>Population</th>
<th>Allele (bp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>African-American</td>
<td>87</td>
</tr>
<tr>
<td>(n = 94)</td>
<td>63</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>103</td>
</tr>
<tr>
<td>(n = 68)</td>
<td>55</td>
</tr>
<tr>
<td>Asian-American</td>
<td>105</td>
</tr>
<tr>
<td>(n = 37)</td>
<td>29</td>
</tr>
</tbody>
</table>

*Only the rare allele is given for people who are heterozygous. Two control individuals were homozygous for alleles other than the common 87 bp allele. The three families of alleles are 87 bp, 103-107 bp, and 121-131 bp. The prevalence of the 121-131 bp family of alleles is statistically different in African-Americans from that in Asian-Americans and Whites (two-sided, P < 0.00005; Ref. 13)."

**Discussion**

We report here an improved method for genotyping the previously reported TA dinucleotide repeat polymorphism in the 3' untranslated region of the human SRD5A2 gene (10). Our data indicate (a) that this gene is more polymorphic than previously reported, and (b) that certain polymorphisms are restricted to African-Americans (Table 1). There appear to be three families of alleles as described by Davis and Russell (10). However, our data indicate that two of the families are much more diverse than previously reported. The 87-bp allele, which probably corresponds to the (TA)$_n$ chromosome described earlier (10), is the predominant allele in all three populations examined: African-Americans, Asian-Americans, and non-Hispanic Whites (Fig. 1 and Table 1). The (TA)$_n$ family (10) appears to be heterogeneous: it is comprised of three alleles of 103, 105, and 107 bp (Fig. 1 and Table 1). The 121-131-bp allele family, which probably includes the previously described (TA)$_n$ repeat (10), is very diverse and apparently found exclusively in African-Americans (Table 1).

We have previously proposed that the difference in racial/ethnic incidence of prostate cancer (2) may be determined by different levels of testosterone and more specifically its intraprostatic metabolite DHT (3). This difference was particularly noticeable between African-Americans who are at very high risk for prostate cancer and lower risk Whites and Japanese (3). The present study provides a possible molecular genetic basis for our hypothesis. The statistically significant finding of SRD5A2 TA repeat alleles that are present only in high-risk African-Americans and not in lower risk Whites and Asians (Table 1) supports our initial study (2). Thus, we propose that certain steroid 5a-reductase enzyme variants encoded by SRD5A2 genes marked by particular TA repeat alleles may result in an elevation of enzyme activity, resulting in an increased prostatic level of DHT. Elevated levels of this hormone would then increase the risk for developing prostate cancer.

We have begun genotyping incident prostate cancer cases occurring among African-American participants of the multiethnic cohort study described in “Materials and Methods.” A preliminary analysis of the first 54 cancer cases with race- and age-matched control subjects revealed an excess of 121-131-bp alleles among cases relative to controls (relative risk, 1.8 with respect to the 87-bp allele). In another preliminary study of 59 White subjects with prostate cancer and an equal number of race- and age-matched controls, we have detected a
relative risk of 1.9 for prostate cancer associated with the 103–107-bp family of alleles as compared to the 87-bp allele (data not shown). None of these associations achieves statistical significance due to the relatively small number of cases and controls studied. We recognize that these preliminary findings require confirmation with adequate sample size. Nonetheless, our data are compatible with the hypothesis that the SRD5A2 gene plays a role in the racial/ethnic variation in prostate cancer risk.

The present study has provided a plausible molecular rationale for the difference in prostate cancer risk linked to androgen metabolism, and in particular DHT levels (3), in African-Americans on the one hand and Asian-Americans and Whites on the other.

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References

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