Review Article
Ethnical disparities of prostate cancer predisposition: genetic polymorphisms in androgen-related genes

Jie Li1,2, Emma Mercer2, Xin Gou1, Yong-Jie Lu2

1Department of Urology, the First Affiliated Hospital of Chongqing Medical University, China; 2Centre for Molecular Oncology, Barts Cancer Institute, Queen Mary University of London, Barts and The London School of Medicine and Dentistry, London UK

Received February 16, 2013; Accepted March 3, 2013; Epub April 3, 2013; Published April 13, 2013

Abstract: Prostate cancer (PCa) is the most commonly diagnosed male malignancy and the second biggest cause of cancer death in men of the Western world. Higher incidences of PCa occur in men from North America, Oceania and Western countries, whereas men from Asia and North Africa have a much lower PCa incidence rate. Investigations into this population disparity of PCa incidence, in order to identify potential preventive factors or targets for the therapeutic intervention of PCa, have found differences in both environmental and genetic variations between these populations. Environmental variations include both diet and lifestyle, which vary widely between populations. Evidence that diet comes into play has been shown by men who immigrate from Eastern to Western countries. PCa incidence in these men is higher than men in their native countries. However the number of immigrants developing PCa still doesn’t match native black/white men, therefore genetic factors also contribute to PCa risk, which are supported by familial studies. There are a number of genetic polymorphisms that are differentially presented between Western and Eastern men, which are potentially associated with PCa incidence. Androgen and its receptor (AR) play a major role in PCa development and progression. In this study, we focus on genes involved in androgen biosynthesis and metabolism, as well as those associated with AR pathway, whose polymorphisms affect androgen level and biological or physiological functions of androgen. While many of the genetic polymorphisms in this androgen/AR system showed different frequencies between populations, contradictory evidences exist for most of these genes investigated individually as to the true contribution to PCa risk. More accurate measurements of androgen activity within the prostate are required and further studies need to include more African and Asian subjects. As many of these genetic polymorphisms may contribute to different steps in the same biological/physiological function of androgen and AR pathway, an integrated analysis considering the combined effect of all the genetic polymorphisms may be necessary to assess their contribution to PCa initiation and progression.

Keywords: Prostate cancer, ethnical disparity, risk factors, genetic polymorphism, androgen, androgen receptor

Introduction
Prostate cancer (PCa) is the most common male malignancy and the second leading cause of cancer mortality among men in Western countries [1]. However, there is significant disparity between the incidence and mortality of the disease among different countries and races. People in North America, Oceania, North and Western Europe have a much higher disease incidence than Asian and North African populations [1]. There are evidences to show that PCa development is due to multiple factors, such as environmental exposure, diet and genetic variation; and these factors, differentially present in different populations, may be associated with prostate carcinogenesis through the induction of certain somatic genomic alterations, which are detected at different frequencies between populations [2-4]. Important evidence that diet and environmental factors contribute to PCa include studies on Asian immigrants in North America and Europe, who have a significantly higher incidence of PCa than residents in Asia [5, 6]. Fat consumption is higher in the Western population than Asian, and is associated with around 2-fold increased PCa risk [7]. In contrast to the elevated PCa risk by saturated fat intake, soy products and green tea, which are more popular in Asian men, were
shown to associate with decreasing PCa risk [8-12]. However, although Asian immigrants in North America and Europe have a higher incidence of PCa than residents in Asia, it is still lower than white and black men in those regions [5, 13, 14]. Immigrant studies in the US also showed that, even under the same environmental conditions and medical care system, there were significant differences in mobility and mortality of PCa between white and African American men [15]. Asian American men presented with lower clinical stage PCa but a more adverse biopsy grade than Caucasian and African American men [16, 17]. These data suggest that genetic factors also play an important role in the racial and regional difference in PCa incidence and mortality. In addition, evidence of the importance of the genetic contribution to PCa is supplied by the study of familial disease, which accounts for approximately 10-15% of PCa cases. A meta-analysis study found that first degree family members of PCa patients are at a 2.53-fold lifetime risk of developing the disease [18]. Another review also showed that the risk of developing PCa is about 15% if a first line relative has suffered, this risk increases to 20% if a father or brother under the age of 60 have suffered from the disease [19]. While it can be argued that family members have a similar life style and environmental exposure, twin studies have provided more convincing evidence of the genetic effect of PCa. Monozygotic twins, who are genetically identical, were found to have a higher risk of developing PCa than dizygotic twins, who only share 50% of their genes [20-22].

We will review the ethnical disparities of genetic polymorphism and its association with differences in PCa incidence or progression. As androgen and androgen receptor (AR) play a critical role in both normal prostate and PCa growth [23, 24], in this article we will focus on genes involved in androgen biosynthesis and metabolism, as well as those associated with AR pathways, whose polymorphisms affect androgen level and androgen biological or physiological functions.

Androgen in prostate cancer development and ethnic differences in androgen levels

The growth of normal prostate epithelial cells or PCa cells depends on androgen. PCs is extremely rare in men castrated before puberty [25] and androgen deprivation is currently still the standard therapy for advanced PCa. Androgens have also been implicated in the occurrence of the TMPRSS: ERG fusion gene. This fusion gene has been found at different frequencies between populations, occurring in 50% of PCa samples from Western men, in comparison to around 10% in Chinese men [2]. This fusion gene can be induced in the PCa cell line LNCaP following treatment for 24h with DHT and in non-cancer cell line PNT1A and PNT2 following long term exposure to DHT [26-29]. Therefore, androgen levels may be an important factor in PCa risk.

Some studies have reported variation in the serum levels of androgen between different ethnic backgrounds, consistent with variation in PCa incidence between different ethnicities. They reported black men had higher serum levels of testosterone, free testosterone and dihydrotestosterone (DHT) than white men [30, 31], and DHT to testosterone ratios were highest in African-American, intermediate in white, and lowest in Asian-American men [31, 32]. This indicates that a high androgen level is a risk for PCa. However, studies stratified by age found that the difference in serum testosterone only exists in young men. Ellis et al [33] compared 525 African American men and 3654 non-Hispanic white men in different age categories. In the 31 to 34 year-old group, African-American men had a 6.6% higher mean serum testosterone level than white men, yet in the 40 to 50 year-old group, the difference was only 0.5%. Kubricht et al [34] reported that African American and white men aged over 40 had comparable serum testosterone levels. Moreover, some studies found no racial differences in circulating testosterone and DHT [35, 36].

Regarding the association between androgen level and PCa, most case-control studies did not support that serum androgen levels contribute to PCa development [37-53], only two studies reported positive association between PCa and circulating testosterone level [54, 55]. A large pooled analysis including 18 prospective studies also reported that PCa risk is not associated with serum levels of testosterone, free testosterone, or DHT [56]. Although the pooled analysis showed a negative result, Hsing et al [57] indicated circulating levels of testosterone might not reflect androgen action in the pros...
Androgen-associated ethnical differences and prostate cancer

In the serum, the concentration of DHT, which has a higher affinity for AR was far less than the concentration of testosterone, whereas the concentration of DHT in prostate tissue was several times higher than that of testosterone [57, 58]. Due to technical limitation, it is difficult to directly measure the androgen level of prostate tissue, particularly in the healthy population. There is only one study reporting androgen level analysis in prostate tissue. The study found that black men had a higher tissue concentration of sex hormone-binding globulin (SHGB) and androstenedione than white men, but the testosterone and DHT levels in prostate tissue are similar in black and white men [59]. Recent studies of androgen induced gene proximity and fusion genes [26-29] indicate that high androgen levels at a certain physiological developmental stage, is a risk factor for inducing genomic alterations in prostate cells, and consequently increases the risk of PCa. The conflicting results either support the association between androgen level and PCa risk, or oppose it in different studies using different research approaches. This may be due to the complexity in measuring the real effective androgen or associated protein levels. The ideal way to measure the impact of androgens on PCa should be the DHT levels within the prostate tissue from the period of puberty, when there is a boost of androgen levels, to age 50 or 60, when PCa occurs. However, currently it is technically difficulty to do this. Novel techniques to repeatedly measure tissue androgen levels in an individual through a long period are urgently required. For now we have to estimate the action of androgen in the prostate by other means.

Genes involved in androgen synthesis and metabolism

While it is difficult to identify the form of androgen that potentially contributes to prostate carcinogenesis and difficult to quantitatively measure the active form of androgen in the prostate, many studies have focused on genes involved in androgen synthesis and metabolism.

Many of these genes have been found to harbour genetic polymorphisms. These polymorphisms can potentially change androgen levels in prostate tissue, and therefore, may give a better idea of the action androgen is playing in prostate tissue than measuring levels of circulating androgen. Here we summarize the reported genetic polymorphisms in these pathways (Figure 1), which have been reported at differential racial frequencies and implicated in variations of PCa risk between different populations (Table 1).

**CYP11A1**

CYP11A1 gene on 15q23-q24 encodes the P450scc enzyme, which is the first and also rate-limiting step of biosynthesis for both testosterone and estrogen, it catalyzes cholesterol to pregnenolone. There is a pentanucleotide (TAAAA)_n repeat located in the 5'UTR of the gene, ranging from 4 to 10-repeat sequences [60]. Although the association between (TAAAA)_n repeat and androgen level is unclear, population studies have found higher prevalence of a 6-repeat allele in Japanese populations compared with the higher prevalence of a 4-repeat allele in European and African populations [60, 61]. Japanese PCa patients without the 4-repeat allele had an increased risk of metastatic PCa compared to those with the 4-repeat allele [61]. However, a positive association with PCa risk was not identified from a few studies of European populations [62-66].

**CYP17**

CYP17 gene is located on chromosome 10 and encodes the cytochrome P450 17 enzyme (17a-hydroxylase/17, 20-lyase). This enzyme catalyzes two reactions in the biosynthesis of testosterone in the gonad and adrenal glands. The first step is conversion of pregnenolone to 17-hydroxypregnenolone (hydroxylase activity), and the second step is the subsequent conversion to dehydroepiandrosterone (lyase activity) [67, 68]. The 5'-untranslated promoter region of the CYP17 gene contains a single nucleotide polymorphism, a T to C substitution, that gives rise to A1 (T) and A2 (C) alleles (rs743572). This T to C transition creates a potential Sp1 binding site (CCACC box) or promoter region, which was suspected to increase the transcription of the CYP17 gene [69]. However contradictory results were reported from a later study [70]. Frequency of the A2 allele was highest in Asian, intermediate in Caucasian and lowest in Black men [71, 72]. However, case-control studies for association between the A2 allele and PCa risk were inconsistent. More than half of the stud-
ies indicated that the A2 allele may be associated with an increasing PCa risk [73-80]. However, a number of studies suggested no association [81-84] and a few studies even showed a possible increased risk of PCa from the A1 allele [85-87]. It is a paradox that the Asian population, with a higher frequency of the A2 allele, have a lower incidence of PCa than Black and white populations. Results from two meta-analysis studies may partially explain this contradiction. They found that a significant association between A2 polymorphism and PCa risk only existed in the black population, but not in Caucasian or Asian populations [71, 88]. Therefore, the A2 type of CYP17 may cooperate with other genetic or environmental factors existing in the black population to contribute to the risk of PCa.

SRD5A2
Steroid 5α-reductase irreversibly converts testosterone into DHT. Two forms of steroid 5α-reductase exist, steroid 5α-reductase type 1 (SRD5A1) and steroid 5α-reductase type 2 (SRD5A2). SRD5A1 is expressed more abundantly in extra-prostatic tissues, such as the skin and SRD5A2 is exclusively expressed in the prostate [89]. 5α-reductase activity was lower in Asian than white and black men [90, 91].

The SRD5A2 enzyme is encoded by the SRD5A2 gene, which is located on chromosome 2p23. A substitution polymorphism A49T (rs9282858) results in replacement of an alanine (A) residue at codon 49 with threonine (T), which has been
Table 1. Genetic polymorphisms in genes associated with androgen biosynthesis/metabolism and AR which show differential racial frequencies and potential association with prostate cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>Racial frequency difference</th>
<th>Association with prostate cancer risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP11A1</td>
<td>(TAAA)n repeat</td>
<td>More 6-repeats in Japanese, 4-repeats in European and African</td>
<td>IC IC IC</td>
</tr>
<tr>
<td>CYP17</td>
<td>T&gt;C (rs743572)</td>
<td>Highest in Asians, intermediate in Caucasians, lowest in Blacks</td>
<td>No No Yes</td>
</tr>
<tr>
<td>SRD5A2</td>
<td>A49T</td>
<td>Sparse in whites and blacks, not detected in Asians</td>
<td>IC IC IC</td>
</tr>
<tr>
<td>V89L</td>
<td>(TA)n repeat</td>
<td>Higher in Asians than Caucasians and Blacks</td>
<td>IC IC IC</td>
</tr>
<tr>
<td>HSD3B1</td>
<td>N367T (rs1047303)</td>
<td>Higher frequency in Caucasians, middle in African Americans and lower in Asians</td>
<td>Yes Yes NA</td>
</tr>
<tr>
<td>HSD3B2</td>
<td>(TG)n(TA)n(CA)n repeat</td>
<td>Most common alleles occurred at different frequencies</td>
<td>NA Yes No</td>
</tr>
<tr>
<td>HSD3B2</td>
<td>rs1819698 and</td>
<td>Higher in African-Americans than Caucasians</td>
<td>NA No Yes</td>
</tr>
<tr>
<td>CYP19A1</td>
<td>rs2470164</td>
<td>Higher in Caucasians than African Americans</td>
<td>NA Yes No</td>
</tr>
<tr>
<td></td>
<td>Arg264Cys (rs700519)</td>
<td>Higher frequency in Indians than African Americans and Caucasians</td>
<td>Yes IC No</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>A&gt;G (rs2740574)</td>
<td>Short repeat (A1) at high frequency in Asians</td>
<td>IC IC IC</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>CYP3A5*3C (rs10249369)</td>
<td>More in Caucasians than Africans</td>
<td>NA Yes No</td>
</tr>
<tr>
<td>CYP3A43</td>
<td>CYP3A43*3 (rs680055)</td>
<td>More in African Americans than Caucasians</td>
<td>NA No Yes</td>
</tr>
<tr>
<td>HSD17B1</td>
<td>Haplotype CAGC</td>
<td>More in whites and blacks than Asians</td>
<td>Yes No No</td>
</tr>
<tr>
<td>AKR1C1</td>
<td>A&gt;G (rs3763676)</td>
<td>More in Caucasians than Asians</td>
<td>NA Yes NA</td>
</tr>
<tr>
<td>SHBG</td>
<td>D356N</td>
<td>More in whites than blacks</td>
<td>NA IC IC</td>
</tr>
<tr>
<td>AR</td>
<td>GGN repeat</td>
<td>Longest in Asians, intermediate in whites, shortest in blacks</td>
<td>IC IC IC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UGT2B15</td>
<td>D85Y</td>
<td>More 85D allele in Asians than Caucasians</td>
<td>IC IC IC</td>
</tr>
</tbody>
</table>

NA: no report in the population; IC: Inconclusive.

reported to increase the activity of 5α-reductase 5-fold, both in vitro and in vivo [92]. The prevalence of the T allele was 2-2.8% and 1% in control subjects of European and African descent. It is absent in men of Asian descent [93-95]. The association between A49T and PCA risk has been extensively investigated, but the results are controversial. Three meta-analyses for this polymorphism have been published. In a study by Ntais et al [95] (7 studies with a total of 1594 cases and 2137 controls), the T allele has shown a modest effect on PCA susceptibility. However, the meta-analysis results from Li et al [94] (24 studies with a total of 4,998 cases and 5,451 controls) indicated A49T was probably not associated with PCA risk. A recent meta-analysis including 31 association studies with 14,726 PCA cases and 15,802 controls also found that the T allele had no significant effect on the overall PCA risk, but the T allele significantly elevated the risk of high stage (Stages III-IV) disease [93]. The prevalence of the T allele is sparse in the general population, with a frequency of T/T homozygosity of only 0.5% in healthy Caucasians, who have a relatively higher frequency of the T allele than other populations [93]. This rarity of T allele cases may also contribute partly to the inconclusive results for the association between A49T and PCA risk.

The V89L (rs523349) polymorphism results in a valine (V) to leucine (L) substitution at codon 89, which decreases 5α-reductase activity [96]. Men with the LL genotype had almost a 30% reduction of activity of 5α-reductase than men with VL or VV genotypes [96]. The L allele was more commonly found in Asian (46.9-50%) than Caucasian (28.1-37.5%) and African men (25-33.5%) [93-95]. The V89L variant was also
Androgen-associated ethnical differences and prostate cancer

common in men in Greenland who had a low risk of PCa [97]. These studies suggested that the V89L substitution may be a protective factor for PCa, but some recent case-control stud-
ies did not find significant association between the V89L polymorphism and PCa risk [87, 98, 99]. All meta-analysis studies also excluded such an association in all ethnic groups [93-
95], except one, which found a small increase in PCa risk in Europeans with the L allele [100].

The TA dinucleotide repeat polymorphism is present in the 3’ untranslated region of SRD5A2. It has three main polymorphisms with different numbers of TA-dinucleotide repeats, (TA)0, (TA)9 and (TA)18 [101]. The frequencies of (TA)0 and (TA)9 alleles were 14% and 9% in healthy subjects of European and Asian descent, respectively [95], but 32% in African American men [102]. (TA)18, in particular, is present in a much higher frequency in African American than Caucasian and Asian American populations, where this allele is rare [95, 102]. Although it is expected that the longer TA alleles, presenting more frequently in the high PCa risk African American group, may increase cancer risk. Interestingly, meta-analysis studies (4 studies, 1109 cases and 1378 controls) presented the opposite result, the longer alleles were associated with a modest PCa risk reduction in Caucasian men [95]. Case-control studies in Chinese and Indian men (191 and 157 cases respectively) also reported that homozygous (TA) leads to higher PCa risk than longer alleles [99, 103]. It is not clear whether the longer repeat alleles also have a protective role in the Black population, due to lack of case-control studies in men of African descent.

HSD3B family

The HSD3B1 and HSD3B2 genes, located on 1p13.1, encode 3β-hydroxysteroid dehydroge-

nase/∆5-∆4 isomerase 1 and 2 isoenzymes (3β-HSD types 1 and 2). The proteins are bi-
functional enzymes that catalyze androstenedione production in steroidogenic tissues and convert the active DHT into inactive metabo-
lites in steroid target tissues [104].

A N367T (AAC>ACC, rs1047303) polymorphism in HSD3B1 has been reported to present at a high frequency in Caucasian (31%), inter-
med-ium frequency in African American (11.7%) and low frequency in Asian men (8.5%), although the variant has a similar activity to the wild type [105]. Chang et al [106] reported that the N type variant increased PCa risk moderately in Caucasian men, but this was not supported by further studies [64, 107].

A complex (TG)n(TA)n(CA)n dinucleotide repeat polymorphism was found in intron 3 of the HSD3B2 gene [108]. The common alleles occurred at very variable frequencies in different racial populations, with the longer alleles more commonly found in Asian men [109, 110]. The longer the allele length, the more stable the hairpin structures they formed and subsequently, the faster the degradation rate of DHT. Short alleles have been found to be associated with an increased PCa risk in Caucasian but not in African American men [109].

Beuten et al [111] found that two SNPs in HSD3B2, rs1819698 and rs1538989, were more common in African American than Caucasian men and increased PCa risk in African American but not Caucasian men.

The interaction between HDS3B1 and HSD3B2 polymorphisms has also been investigated. Although the N367T polymorphism in HSD3B1 is only weakly associated with PCa risk, the combination with HSD3B2 rs1819698 greatly enhanced the association [106].

CYP19A1

The CYP19A1 gene, located on chromosome 15q21.1, encodes the enzyme aromatase, which catalyzes the irreversible conversion of C19 androgens, androstenedione and testosterone, to the C18 estrogens, estrone and estradiol respectively. More than 30 SNPs have been detected in different populations. Several SNPs (rs2470152, rs749292, rs727479) were confirmed to be associated with serum estradiol of men [112, 113].

Beuten et al [111] explored polymorphisms of CYP19 by genotyping 2,452 samples from Caucasian and African American men, some of these polymorphisms (rs2470152, rs12439137, rs3751592, rs2470164) were associated with PCa risk and had different racial distributions. Particularly rs2470164, which was reported to increase PCa risk in Caucasian men, had a dramatically different frequency among healthy Caucasian (50%) and African American men (5.6%).
The tetranucleotide repeat (TTTA), is located in intron 4 of CYP19A1, TTTA repeat numbers range from 7 to 13 and are designated as A1 to A7 according to the repeat number. Most studies for this polymorphism were among Asian men. A1 was found to occur more frequently (about 50% of the population) than all other alleles in Asian men [114, 115]. Suzuki et al [116] reported that the shorter repeat (A1 and A2 alleles) significantly increased familial PCa risk in Japanese men. Huang et al [115] found the homozygous A1 genotype had a significantly greater risk of developing PCa in Taiwanese. However, in conflict with their results, another study in Japanese men found a longer repeat was significantly associated with increased PCa risk [114]. Latil et al [82] reported that some specific repeat lengths were associated with PCa risk in men of White French ethnographic origin, but studies among US men reported no association with PCa [64].

The polymorphism Arg264Cys substitution (rs700519) was found at a higher frequency in Indian men (27%) [117] in comparison to African American (16.8%) and Caucasian men (4-8.1%) [107, 111, 118]. Studies among Caucasian and Indian men showed a tendency for this polymorphism to increase risk [117, 118], but large case studies failed to confirm the results in Caucasian men [107, 111, 113].

CYP3A family

Cytochrome P450 3A (CYP3A) enzymes hydroxylate testosterone and dehydroepiandrosterone to less active metabolites. The CYP3A locus consists of four genes in humans, CYP3A4, CYP3A5, CYP3A7 and CYP3A43, all of which reside in a 231 kb region of chromosome 7q21-22.1 [119].

CYP3A4 is involved in the oxidative deactivation of testosterone, an A to G mutation (CYP3A4*1B, rs2740574) was reported to decrease CYP3A4 protein activity, thus increase the availability of testosterone [120]. CYP3A4*1B has a higher frequency in men from African descent than Caucasian and is absent in Asian men [121-125], but case-control studies didn’t find an association between CYP3A4*1B and PCa risk in men of African descent who had a high frequency of the variant [78, 111, 124, 126]. In addition, reports in Caucasian men were contradictory [111, 124, 127]. Studies for the association between CYP3A4*1B and the progression of PCa were also inconclusive, some studies reported CYP3A4*1B is associated with aggressive PCa in Caucasian and African American men [122, 123, 125, 127, 128], however others studies disagreed [129-131].

CYP3A5 catalyzes 6β-hydroxylation of testosterone, it has been suggested that CYP3A5 is expressed at high levels in the non-tumoral prostate tissue, specifically in the basolateral cells, and that this expression does not occur in the tumor. An A to G transition (A6986G) within intron 3 leads to a variant in the CYP3A5 mRNA expression in human prostatic tissue [132]. The allele CYP3A5*1 (A allele) produces a correctly spliced transcript leading to high levels of full-length CYP3A5 mRNA and protein [125, 133]. The allele CYP3A5*3 (rs776746, G allele) creates a cryptic splice site leading to the inclusion of a novel exon, and ultimately a premature stop codon [133]. CYP3A5*3/+3 decreases CYP3A5 mRNA content 13-fold compared to CYP3A5*1/+3 [132]. CYP3A5*1 has a higher frequency in African American individuals than Caucasian or Asian men [133]. CYP3A5*1 was suggested to show obvious linkage disequilibrium with CYP3A4*1B in Caucasian and African men [127, 133, 134], and the CYP3A4*1B/CYP3A5*1 haplotype was inversely associated with risk among Caucasian men with less aggressive disease [125]. Studies in Japanese men whose CYP3A4*1B was absent may help confirm that the CYP3A5*1 allele is associated with PCa risk, however cannot exclude that CYP3A4*1B may also be a risk factor. They reported CYP3A5*1/+1 men had lower risk of developing a low-grade localized PCa than CYP3A5*3/+3 men [135]. On the other hand, although CYP3A5*3 was reported not to associate with PCa in either white or African men [126], the CYP3A4*1B/CYP3A5*3 haplotype is significantly associated with increasing PCa risk in European American but not in African American men [125, 136]. Moreover, CYP3A5 is also reported to interact with SRD5A2 or KLK3 which could influence development of PCa [137].

CYP3A43 is predominantly expressed in the prostate [138]. The CYP3A43*3 allele (rs680055) frequency was significantly higher in African American than Caucasian men [127, 139]. There was a 2.6-fold increase in PCa risk
Androgen-associated ethnical differences and prostate cancer

among individuals with the CYP3A43*3 homozygous genotype compared with those with the CYP3A43*1 homozygous genotype in African American, but not in Caucasian men [127, 139].

There are very few studies on CYP3A7, Simense et al [140] found the CYP3A7*1C (rs11568825) G allele decreased levels of estrone sulphate, dehydroepiandrosterone sulfate, androstenedione and estrone, however no significant association was observed for CYP3A7 genotypes with PCa risk.

**HSD17B family**

The 17β-hydroxysteroid dehydrogenases (17β-HSDs) are involved in regulation of estrogens and androgens by catalyzing the reduction of 17-ketosteroids or the oxidation of 17β-hydroxysteroids.

17β-HSD1, encoded by HSD17B1 on 17q21 plays a role in estrogen and testosterone biosynthesis. Cunningham et al [64] reported a polymorphism of HSD17B1 (Ser313Gly, rs605059), detected in 40% of patients, mainly Caucasian men, had a possible association with either familial or sporadic cases of PCa. However, large numbers of multi-ethnic studies (The Breast and Prostate Cancer Cohort Consortium, BPC3) have since found no association [141]. BPC3 detected four common SNPs (rs676387, rs605059, rs598126, rs2010750). Although none were found to be associated with PCa risk, they reported some haplotypes that consisted of the four SNPs had varying frequencies between different races. The haplotype CAAC was only common in African American men, CAGC was more prevalent in white and black than Asian men, and CAGC was inversely associated with PCa risk in Latino and Japanese American but not in African American, Native Hawaiian, or white men [141].

17β-HSD2 encoded by HSD17B2 on 16q24 is involved in the conversion of active androgens into their less active forms. SNPs in HSD17B2 (rs1424151) were found to have significant associations between plasma testosterone level in Caucasian men [142], but no association with PCa was detected [64, 142].

17β-HSD3 encoded by HSD17B3 on 9q22 catalyzes androstenedione to testosterone. The frequency of the G289S polymorphism (rs2066479) of HSD17B3, was 4.3-7.3% in Caucasian men and was reported to significantly increase PCa risk in Italian men [143], but studies in Finnish and Swedish men found no positive associations [107, 144].

The HSD17B4 gene on 5q21 encodes androgen/estrogen inactivating enzyme 17β-HSD4. It was reported to be associated with the outcome of PCa patients [145, 146].

Human 17β-HSD5 belongs to the aldo-keto reductase (AKR) superfamily and is formally known as AKR1C3 encoded by the AKR1C3 gene on 10p14-p15, it catalyzes the conversion of androstenedione to testosterone and DHT to androstanediol. An A to G substitution was identified in exon 2 that confers a Glu77 Gly (rs41306308) change, this occurred in 4.8% of Caucasian men but was completely absent in Asian men, and the Glu77Gly polymorphism was associated with lower testosterone levels in serum [147]. Furthermore a promoter polymorphism (A to G, rs3763676) of AKR1C3 is more prevalent in Asian men [147] and men with the A allele have a borderline significant decreased risk of PCa [148].

**UGT2B15**

UGT2B15 is a member of UDP-glucuronosyltransferases (UGTs) family which glucuronidate steroids and many endogenous chemicals, encoded by the UGT2B15 gene located on 14q13- q21.1. It has a high capacity to glucuronidate 3α- androstenediol and a moderate capacity for DHT. A nonsense mutation in codon 85 (aspartate>tyrosine, D85Y, Asp85Tyr) has been identified in the UGT2B15 gene. The 85Y variant associates with a 2-fold increase in activity for 3α- androstenediol and DHT, it is likely to lead to lower androgen exposure compared with 85D. A study found that Asians had a higher 85D allele frequency than Caucasians [149]. Case-control studies are inconclusive, several studies reported the 85D allele increased PCa risk [150-153], but another two studies reported no association with PCa [64, 154].

**Sex hormone binding globulin**

Sex hormone-binding globulin (SHBG) gene is located on 17p12-p13 and encodes a steroid
Androgen-associated ethnical differences and prostate cancer

binding protein that is a major regulator of free plasma androgens. It also mediates androgen and estrogen signaling at the cell membrane via cyclic adenosine monophosphate. Most studies found black men who had higher PCa risk had higher plasma SHBG level than white and Asian men [155-157]. Black men were also found to have higher levels of SHBG in their prostate tissue than white men [59]. Interestingly, although the higher risk population have a higher SHBG level, a collaborative analysis of 18 prospective studies found the fifth highest serum SHBG levels had a relative PCa risk reduction of 14% when compared with the fifth lowest [56].

A common polymorphism in the SHBG gene, D356N, encodes for an additional N-glycosylation consensus site, which may reduce its clearance from circulation and alter its binding to membrane receptors [158]. Berndt et al [129] carried out a multicenter study and found the SHBG D356N heterozygotic polymorphism had a higher frequency in white men (17%) than black men (7.8%). The D356N heterozygote is associated with increasing PCa risk in non-Hispanic white but not in black men. Studies carried out in British and US men reported no association between PCa and SHBG polymorphisms [64, 159].

Androgen receptor gene (AR gene) polymorphism

AR gene is located at Xq11.2-q12, the open reading frame is separated over eight exons that encode for AR. AR comprises of four functional domains including the amino-terminal transcriptional activation domain, the DNA binding domain, a hinge region, and the carboxyl-terminal ligand binding domain [160]. Expression of AR protein was found to be higher both in benign prostate tissue and PCa tissue in black men compared with white men [161, 162]. The amino-terminal transcriptional activation domain, encoded by exon one, includes two high frequency polymorphic repeats, CAG and GGN [163]. AR expression level and function were found to have an inverse association with the length of CAG or GGN repeat in in vitro studies [164, 165].

The length of CAG repeats ranges from 8 to 35 repeats in the normal population. Hispanic men have been reported to have the longest average CAG repeat length (23-25). The Chinese population have longer CAG repeats (average between 22-23) than that of the Caucasian population (average between 21-22), and the black population have the shortest average CAG repeats (average between 19-20) [35, 97, 166-175]. Several studies reported testosterone levels were significantly elevated in men with greater CAG repeat length [167, 176, 177], but other studies found no correlation between CAG repeat length and serum testosterone levels [178-180]. Studies of polymorphic CAG repeats associating with PCa risk were also inconsistent, several studies found the shorter CAG repeats associated with increasing PCa risk [171, 181-188], a meta-analysis reported the association was different in different populations, longer repeat carriers (>/= 20 repeats) had 11% decreased risk in populations from USA, 53% decreased from Europe, and 20% decreased from Asia [189], however recently several projects, including two multiple-center, large-sample studies didn’t find association between CAG repeat length and PCa risk [166-168, 170, 175, 190-194]. A few studies among the East Asian population even observed that longer than average CAG repeat length is more common in PCa cases compared to the controls [195, 196]. Instead of studying longer or shorter CAG repeat length, one study focused on some specific CAG repeat numbers, Ding et al [164] reported 17 CAG-repeats was much more common in PCa patients (8.5%) than in the general European and American populations (1.3%).

The biological role of GGN trinucleotide repeats is less clear, polymorphisms in the normal population range from 10 to 31 repeats, present as a (GGT)3GGG(GGT)2(GGC)n motif. Similar to CAG repeat variation in different populations, black men have shorter GGN repeats than white and Asian men [197, 198]. Most studies to evaluate the relationship between PCa and GGN repeat length were carried out in Caucasian men. Case-control studies were also controversial among Caucasian and Asian men. A shorter GGN repeat length was found to be associated with PCa risk in several studies [172, 199-201]. One study found that PCa risk was higher in American men with 23 GGN repeats than all other repeat numbers [202]. However, more studies found no association between GGN repeats and PCa risk [168, 181, 182, 193,
Androgen-associated ethnic differences and prostate cancer

Unlike the inconclusive results in white and Asian men, the only two studies including black men consistently reported no associations between PCa risk and GGN polymorphism [168, 182].

The size or composition of a GGN repeat was reported to have no correlation with the length of the CAG repeat [163], however, there may be interaction between them. When a subgroup with two short repeats (CAG <22; GGN <or =16) was compared with those in which both alleles were long (CAG > or =22; GGN >16), increasing PCa risk was observed in Caucasian men [199], but the result couldn’t be replicated in a later study which found the haplotype with short CAG (<22) and short GGC repeats (<or =17) didn’t increase PCa risk [193].

Other genetic polymorphisms associated with prostate cancer predisposition

Besides these genes related to androgen, some other genetic polymorphisms have also shown population differences and have been implicated for possible association with PCa, as they play important roles in cellular proliferation, differentiation and apoptosis (Table 2). The epidermal growth factor receptor (EGFR) gene is located at 7p12. EGFR, encoded by EGFR gene is a cell surface protein that binds to epidermal growth factor. A dinucleotide (CA)_n repeat polymorphism, ranging from 14 to 21 repeats, was suggested to regulate EGFR expression. The frequency of longer alleles is significantly higher in Asian men than Caucasian and African men [206]. Although there is no direct evidence to suggest the polymorphism is associated with PCa, the longer allele with 21 repeats showed an 80% reduction of gene expression compared with the shorter allele with 16 repeats [206, 207]. EGFR protein over expression was found in 36% of the prostate tumor samples [208]. Another candidate gene RNASE L is located in the hereditary PCa 1 (HPC1) gene region (1q24-25). The polymorphism Arg462Gln in RNASEL has a higher frequency in Caucasian than African American men and is associated with increasing PCa risk in these men [209, 210], but a study among Japanese men reported the Gln462 allele decreased the risk of familial PCa [211]. Homozygous Asp541 in RNASE L is significantly less frequent in Asian than Caucasian and Africans [211-214]. The Asp541 allele is associated with decreasing PCa risk in African American men but increasing risk in Japanese men [211, 212]. The ELAC homolog-2/hereditary PCa (ELAC2/HPC2) gene at 17p11 is involved in DNA inter strand crosslink repair and mRNA editing, it has a possible role in the regulation of cell cycle progression. The polymorphisms Leu217 and Thr541 in ELAC2 were more prevalent in Caucasian than in Asian and black men [212, 215]. A meta-analysis reported the Leu217 allele and Thr541 polymorphisms significantly increased PCa risk in Asian men but moderately affected Caucasian men [215]. Leu217 could also significantly increase PCa risk in African American men [212].

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>Racial frequency difference</th>
<th>Association with prostate cancer risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>CA repeat</td>
<td>Longer in Asians than whites and blacks</td>
<td>NA NA NA</td>
</tr>
<tr>
<td>RNASEL</td>
<td>Arg462Gln</td>
<td>More in Caucasians than Asians and African-Americans</td>
<td>IC IC IC</td>
</tr>
<tr>
<td>RNASEL</td>
<td>Asp541Glu</td>
<td>Less Asp allele homozygote in Asians than Caucasians and Africans</td>
<td>IC IC IC</td>
</tr>
<tr>
<td>ELAC2</td>
<td>Ser217Leu</td>
<td>More in Caucasians than Asians and blacks</td>
<td>Yes No Yes</td>
</tr>
<tr>
<td>ELAC2</td>
<td>Ala541Thr</td>
<td>More in Caucasians than Asians and blacks</td>
<td>Yes No No</td>
</tr>
<tr>
<td>XRCC1</td>
<td>G&gt;A (rs25487)</td>
<td>Similar in Asian and Whites, but higher than African descents</td>
<td>Yes No No</td>
</tr>
<tr>
<td>CDH1</td>
<td>−160 C/A</td>
<td>Higher in whites and blacks than Asians</td>
<td>IC IC No</td>
</tr>
<tr>
<td>VDR</td>
<td>TaqI</td>
<td>Lowest in Asians</td>
<td>IC IC IC</td>
</tr>
<tr>
<td>VDR</td>
<td>Apal</td>
<td>More in Asians than Caucasians and Africans</td>
<td>IC IC IC</td>
</tr>
<tr>
<td>VDR</td>
<td>Poly(A)</td>
<td>Lowest in Asians</td>
<td>No No No</td>
</tr>
<tr>
<td>VDR</td>
<td>BsmI</td>
<td>Lower in Asians than other populations</td>
<td>IC IC IC</td>
</tr>
<tr>
<td>VDR</td>
<td>FokI</td>
<td>More in Asians than Caucasians and Africans</td>
<td>IC IC Yes</td>
</tr>
</tbody>
</table>

NA: no report in the population; IC: Inconclusive.
repair cross-complementing group 1 (XRCC1) is an important DNA repair gene located at 19q13.2-13.3. The polymorphism Arg399Gln correlates with DNA repair activity. Meta-analysis found Gln399 associated with higher PCA risk in Asian men but not Caucasian men [216, 217]. E-cadherin (CDH1) gene encoding an adhesion glycoprotein, located at 16q22.1, has a -160C/A polymorphism in the promoter region. The A allele has approximately 68% decreased transcriptional activity compared with the C allele [218]. Most studies showed the A allele increased the risk of PCa among Caucasians [219-223], but did not affect men from African descent [222, 223]. Studies in Asian men reported inconclusive results [224-226].

There are several common allelic variants in the vitamin D receptor (VDR) encoding gene VDR, located on chromosome 12q13-q14, including Bsml (rs1544410), Apal (rs 7975232), TaqI (rs731236), FokI (rs10735810) and a poly(A) in the 3′UTR region. They are in strong linkage disequilibrium with each other in white individuals except FokI. The frequency of the FokI allele and the Apal A allele is higher in Asians than Caucasians and Africans, whereas the frequency of the Bsml B allele is much lower in the Asian population compared to other populations. The TaqI and poly (A) polymorphisms occur at a similar ratio, with the lowest percentage in Asians [227]. 1,25 (OH) 2D3, the active form of vitamin D, inhibits the proliferation of epithelial cells derived from normal and malignant prostatic tissues [228]. The vitamin D receptor (VDR) is a crucial mediator for the cellular effects of vitamin D and interacts with other cell-signaling pathways that influence cancer development. However, the case-control studies looking at the association between VDR polymorphisms and PCa risk are inconsistent. An earlier meta-analysis, including 26 studies suggested that none of these VDR polymorphisms are related to PCa risk [229], whereas most recent studies reported positive associations [190, 230-236]. The study design may be an imporant factor to influence the results.

With the development of SNP array technology, a genome wide association study (GWAS) emerged for identifying small and moderate risk SNPs. The first two GWAS studies identified a 3.8 Mb interval on chromosome 8q24 as significantly associated with susceptibility to PCa in 2006 [237, 238]. Today GWAS have been remarkably successful in identifying dozens of common genetic variants or loci associated with PCa [239-241]. Most of those PCa predisposition SNP loci were initially identified in Western populations and half of them are not associated with PCa risk in the East Asian population [239, 240]. Two SNPs located at chromosome 4 have also been reported to show specific ethnical association with PCa risk [242]: rs12500426, which exhibited an association in Europeans but not in Asian or African American men and rs7679673, which was associated with disease in European and Asian populations but not in African American men. A replication study of five PCa loci initially identified in an Asian population (rs13385191, rs12653946, rs1983891, and rs339331, rs9600079) found that one SNP (rs9600079) was not associated with PCa risk in European populations [243].

**Conclusions**

Most studies for androgen-related genes showed a trend that the alleles leading to higher androgen levels are more common in high risk populations, although a few studies reported the opposite results, such as the A2 allele of CYP17, which potentially increases androgen synthesis and has the highest frequency in Asian men, middle in Caucasian and lowest in African [71, 88] and CYP3A5*1, which may decrease testosterone activity but is more prevalent in men of African descent than Caucasian and Asian men [133]. However, the evidences show that the resultant androgen level difference among populations is contradictory. This may be caused by several factors. 1. Androgen and DHT concentration is affected by both androgen synthesis and metabolism, which are controlled by multiple genes, most of them with polymorphisms that play a role in this pathway. Polymorphisms in some genes may be compensated by other genes and, therefore, the total effect on the change in androgen levels is small. 2. Androgen action is determined by cooperation of androgen and AR. Populations with a longer CAG repeat polymorphism of AR, which leads to higher plasma androgen levels to compensate for lower AR transactivity [167, 176, 177], usually have more genetic polymorphisms leading to lower androgen concentration. These opposing genetic
effects may also minimize the population disparity of androgen levels. 3. There are different forms of androgens and the androgen level in plasma and the prostate tissue is not correlated. It is not surprising that previous studies measuring different forms of androgens generate different results. Unfortunately, accurately measuring DHT levels in the prostate tissue, which may be the most effective indicator of androgen activity in the prostate and may be closely associated with the role of androgen in prostate carcinogenesis, is currently difficult. 4. Due to the complexity and limited effects of each of the genetic factors in determining androgen levels and the potential subtle difference among populations of androgen levels, population studies with a large number of individuals from each population are required, but yet have rarely been achieved in previous studies.

Regarding the association between those polymorphisms and PCa risk, case-control studies for most genetic polymorphisms were inconclusive and some SNPs were only found to be associated with disease in a particular population. In addition to the above explanation, which may affect androgen level and PCa risk in complex ways, gene-gene interaction or gene-environment interaction may contribute to these controversial conditions. Some SNPs are found to have no association with PCa individually, but several adjacent loci could increase PCa risk. As a haplotype, some genes on different chromosomes or in different pathways were also reported to interact with and increase PCa risk. An example of this is the SRD5A2 V89L VV genotype, which interacts with VDR Fok1 TT/CT genotypes in non-Hispanic white men to increase PCa risk [233]. Interestingly, the interactions of genetic polymorphisms with other factors have also presented racial differences. Barnholtz-Sloan et al [136] reported that the CYP3A4 genotype displays a distinct hierarchy of gene-environment and gene-gene interactions. In European American men it is associated with PCa risk in combination with a history of benign prostate hypertrophy, a familial history of PCa and age at consent. However, in African American men, the CYP3A4/CYP3A5 haplotype of this gene is associated with PCa risk in combination with a familial history of PCa, a higher individual proportion of European ancestry and the number of GGC AR repeats. Inconclusive results may also be due to the majority of previous studies, especially large numbers of case-control studies, having been carried out in white men. Limited case numbers of Asian and African men, result in studies lacking sufficient power to confirm results. Besides the limited case numbers, Kittles et al [124] indicated other characteristics in studies on men of African descent. The African American population was genetically heterogeneous because of its African ancestry and subsequent admixture with European Americans, so strong population stratification happened among African Americans. The results of their study revealed the potential for confusion in association studies including African American men.

In summary, due to the complex nature of the AR pathway, there are many different ways that genetic polymorphisms can contribute to the deregulation of this pathway and PCa risk. Future studies need to include an integrated analysis of the combined effect of these polymorphisms on the AR pathway, as well as androgen metabolism/biosynthesis in addition to more accurate measurements of prostatic DHT levels. Analysis of these polymorphisms also becomes more problematic due to racial disparities in the research data. Future studies should include more African and Asian subjects and take into account all the factors considered when judging the PCa risk. While these are currently difficult to achieve, functional confirmation of those genetic factors in affecting carcinogenic molecular or biological features may help to establish their contribution to PCa development.

Address correspondence to: Dr. Yong-Jie Lu, Centre for Molecular Oncology, Barts Cancer Institute, QMUL, John Vane Science Centre, Charterhouse Square, London, EC1M 6BQ, UK. Tel: +44 (0) 20 7882 3597; Fax: +44 (0) 20 7882 3884; E-mail: y.j.lu@qmul.ac.uk

References


Androgen-associated ethnical differences and prostate cancer

populations suggest alternative pathways of prostate carcinogenesis. Cancer Res 2010 Jul 1; 70: 5207-12.


Androgen-associated ethnical differences and prostate cancer


Androgen-associated ethnical differences and prostate cancer


[69] Ross RK, Pike MC, Coetzee GA, Reichardt JK, Yu MC, Feigelson H, Stanczyk FZ, Kolonel LN,
Androgen-associated ethnical differences and prostate cancer


Androgen-associated ethnic differences and prostate cancer

in three racial/ethnic groups: implications for prostate cancer risk. Prostate 1997 Sep 15; 33: 9-12.


Androgen-associated ethnical differences and prostate cancer


[144] Rasiah KK, Gardiner-Garden M, Padilla EJ, Möller G, Kench JG, Alles MC, Eggleton SA, Stricker PD, Adamski J, Sutherland RL, Hen-
Androgen-associated ethnical differences and prostate cancer


Androgen-associated ethnical differences and prostate cancer


[184] Ashtiani ZO, Hasheminasab SM, Ayati M, Goulian BS, Modarressi MH. Are GSTM1, GSTT1 and CAG repeat length of androgen receptor gene polymorphisms associated with risk of
Androgen-associated ethnical differences and prostate cancer


Androgen-associated ethnical differences and prostate cancer


Androgen-associated ethnical differences and prostate cancer
