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Review

Genetic variation: effect on prostate cancer ☆

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ABSTRACT

The crucial role of androgens in the development of prostate cancer is well established. The aim of this review is to examine the role of constitutional (germline) and tumor-specific (somatic) polymorphisms within important regulatory genes of prostate cancer. These include genes encoding enzymes of the androgen biosynthetic pathway, the androgen receptor gene, genes that encode proteins of the signal transduction pathways that may have a role in disease progression and survival, and genes involved in prostate cancer angiogenesis. Characterization of deregulated pathways critical to cancer cell growth have lead to the development of new treatments, including the CYP17 inhibitor abiraterone and clinical trials using novel drugs that are ongoing or recently completed [1]. The pharmacogenetics of the drugs used to treat prostate cancer will also be addressed. This review will define how germline polymorphisms are known affect a multitude of pathways, and therefore phenotypes, in prostate cancer etiology, progression, and treatment.

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Contents

1. Introduction

Prostate cancer is the most frequently diagnosed cancer, and the second leading cause of death from cancer among men in the United States. The disease is more frequent in older men and is associated with a higher incidence in certain racial/ethnic backgrounds. African

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Americans have the highest frequency of prostate cancer worldwide, while Caucasians, Hispanics, and Asians respectively have the next highest risk in the United States [2]. Native Asian men historically have the lowest prostate cancer incidence in the world [3] although much of this difference may be due to differences in detection strategies used in various countries [4]. Racial identity is a strong predictor of an individual's risk of prostate cancer, and migration to Western countries further increases risk within racial groups [5]. Using epidemiological data, it appears that there is a significant influence of genetic background in prostate carcinogenesis, and the genetic impact is most important in the context of environmental/lifestyle influences [6].

As there are many factors that influence disease etiology, inherited prostate cancer risk is often difficult to ascertain. Over the past decade, disease susceptibility and aggressiveness loci have been reported, and the risk of developing prostate cancer is significantly increased in certain families. However, rare highly penetrant loci explain only a small percentage of the overall number of cases of prostate cancer, with most cases being of a sporadic nature (~75% of prostate cancers) [7]. Rather common low-penetrance alleles in multiple genes may be even more important in determining prostate cancer risk in most individuals, and might also be related to familial prostate cancer [8,9]. The androgen biosynthetic pathway, the androgen receptor (AR), and downstream AR effector pathways (Fig. 1) are genetically polymorphic, and many such polymorphisms have been linked to prostate cancer etiology and treatment. Moreover, somatic mutations in prostate cells also increase the ability of prostate cancer to increase in aggressiveness and ultimately evade treatment. The aim of this review is to examine the role of constitutional (germline), and tumor-specific (somatic) polymorphisms (including single nucleotide polymorphisms (SNPs) at or within candidate genes for prostate cancer, genes that encode enzymes of the androgen biosynthetic pathway, the AR gene and proteins of the signal transduction pathway which may have a role in disease progression and survival.

2. Androgen biosynthetic pathways and the androgen receptor

Although many factors may contribute to the underlying biology and clinical course of prostate cancer [10], it is thought that genetic variation in androgen biosynthesis and signaling genes most likely influence the eventual outcome of the disease. This section will summarize investigations into inherited inter-individual variability in the most studied androgen biosynthesis genes: *CYP17*, *SRD5A2*, and *AR*.

2.1. CYP17

Localized within the liver, testis, and adrenal cortex, CYP17 catalyzes the formation of several products in the androgen biosynthetic pathway (Fig. 1). It converts pregnenolone into 17α-hydroxypregnenolone and 17α-hydroxyprogesterone (17α-hydroxylase activity) and both of these products into dehydroepiandrostanedione (DHEA) and androstanedione, the major circulating steroid hormone precursors (17,20-lyase activity). Abiraterone, TOK-001, TAK-700, and ketoconazole all inhibit this pathway.

Individuals with prostate disease comprising many different racial backgrounds have been genotyped for various *CYP17* alleles, although most studies have focused on the A1/A2 allele (rs743572). The A1/A2 allele encodes a T > C transition that results in the formation of a CCACC Sp-1 promoter site 34 base pairs upstream of *CYP17* that changes a *Msp1a* restriction site designating either the 'A1' or 'A2' alleles [11]. However, the nucleotide change in the Sp-1 promoter site does not

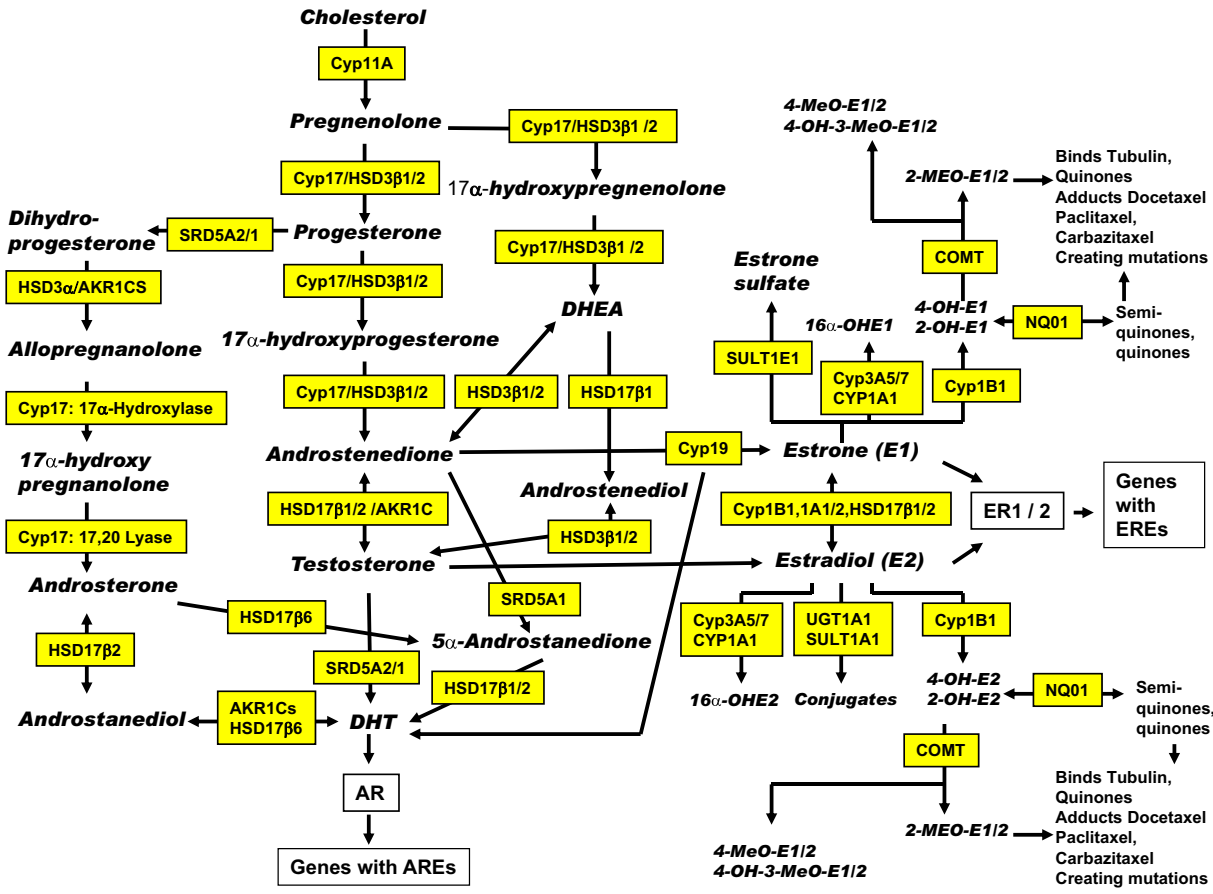

Fig. 1. Sex hormone biosynthesis and degradation pathway.

influence Sp-1 binding [12], and the functionality of the A1/A2 allele is unclear. Only a single study has determined that CYP17 variants are associated with circulating testosterone concentrations [13] with others finding no relationship [14–18]. Still others have evaluated SNPs in the promoter and 5′UTR, exons, introns, and the 3′UTR [19–24]. Given that there is strong linkage in the *CYP17* region some have also evaluated *CYP17* haplotypes comprised of tagging SNPs and risk alleles [20,21,25]. The phenotypic consequences of these latter SNPs are also unclear.

Several studies have found that the A1 allele was actually associated with prostate cancer risk [25–28], or that individuals with heterozygous A1/A2 genotypes had increased risk [23]. A recent meta-analyses on nine studies revealed that African Americans may be at higher risk of prostate cancer if they carry the A2 allele [29]. This is supported by an earlier study in African Americans [23]; however, another study on white men draws an association between the A2 allele and an increased risk of prostate cancer in first-degree relatives [41]. Four other large studies found an association with risk and other CYP17 SNPs [19,23,25,30]. There is also no apparent consistency in the literature regarding the association of *CYP17* alleles with age, clinico-pathological characteristics, or prostate-anatomical variability [16,17,21,22,26,27,31–41], although two studies have determined that CYP17 alleles are related to overall survival following diagnosis [42,43]. In spite of these many efforts, the effects of *CYP17* variants in prostate disease remain unclear. Given the clear role of CYP17 inhibitors in the treatment of prostate cancer, it is logical that CYP17 alleles should have predictive value. Other studies have found that the A2 allele was associated with increased risk of prostate cancer [16,34,37,44–50], but most found no association [17,20–22,24,30,33,36,39,41,51–63], including a recent meta-analysis of 25 studies [64].

2.2. SRD5A2

The 5α-reductase enzymes, SRD5A1 and SRD5A2, convert testosterone into dihydrotestosterone (DHT), the most active form of testosterone (Fig. 1). SRD5A1 may have a more important role in androgen disposition by catalyzing the formation of androstanedione in castration-resistant prostate cancer [65], but few studies have been completed on important SNPs in this gene. SRD5A2 is primarily expressed within the prostate and testes and plays a major role in prostate function and disease etiology. For this reason, SRD5A2 inhibitors (i.e., finasteride and dutasteride) have been developed to manage benign prostatic hyperplasia (BPH) and potentially prevent prostate cancer [66,67]. *SRD5A2* is highly polymorphic with some variants being associated with functional differences in testosterone metabolism, conferring risk towards prostate cancer, inter-individual variation in prostate cancer prognosis, and genetic variation in 5α-reductase inhibitors (e.g. finasteride and dutasteride). A summary of the association of genetic variants of SRD5A2 with prostate cancer risk and prognosis is reported in Table 1.

Three *SRD5A2* variants may be related to SRD5A2 metabolism of testosterone into DHT. Dinucleotide repeat polymorphisms are present in the 3′ untranslated region of *SRD5A2*, and might alter mRNA stability [68]. The *SRD5A2* A49T (rs9282858) allelic variant has been shown to be associated with an increased *in vitro* Vmax towards testosterone metabolism to DHT, and an increased Ki for finasteride and dutasteride inhibition [69,70]. Finally, the *SRD5A2* V89L (rs523349) variant has been related to a lower activity of SRD5A2 [71], lower concentrations of free and total testosterone [15], and lower circulating concentrations of the DHT breakdown product 3α-androstanediol-glucuronide (3α-diol-G) [72]. Others found no relationship between these polymorphisms versus circulating hormone levels or anatomical variability [14,15,35,72–75], whereas the A49T variant was related to unexpected decreases in 3a-diol-G levels [73].

Polymorphisms in *SRD5A2* have been studied as potential genetic markers of prostate cancer risk and prognosis. Of the studies that have related the A49T allele to prostate cancer risk, only three studies have found an association [70,72,76] while no relationship was found in most studies [20,32,37,47,51,52,56,58,77–85]. Four meta-analyses have confirmed that the A49T SNP is not a relevant genetic marker in the assessment of prostate cancer risk and that some studies in this regard might have been flawed [83,86–88]. Other studies have shown that the T allele may confer an increased risk of early onset prostate cancer [85], high-stage disease, or BPH [87,89–91]. However, results associating prostate cancer prognostic factors to the A49T SNP have not always been consistent [72,84,92,93]. The V89L polymorphism has been associated with increased risk [20,51,53,56,76,84,90,94,95], but other studies have found no relation with V89L and prostate cancer risk [16,23,32,37,39,47–49,52,58,72,75,77,78,80,81,96–98]. Moreover, the 89 V allele was associated with increased risk [99], while the 89 L was associated with decreased risk [100–102]. However, meta-analyses demonstrated that there is no association [86–88]. Only two studies found that the $(TA)_{9/9}$ SNP was associated with decreased risk of prostate cancer [77,102] whereas most studies in this regard have found no relationship [32,56,58,79,80,84,97]. Similarly no consistent results have been observed relating to prognostic factors, BPH, or age of onset with the V89L or $(TA)_n$ dinucleotide repeat [51,53,58,72,84,85,89–93,100]. However one recent study has shown positive associations of several SRD5A1 and SRD5A2 variations as independent predictors of biochemical recurrence after radical prostatectomy [103].

2.3. Androgen receptor

The androgen receptor (AR) gene is composed of eight exons that encode four functional domains: the amino-terminal transcription activation (transactivation) domain, the DNA-binding domain, a hinge

Table 1
Role of SRD5A2 polymorphisms in prostate cancer (CaP).

Polymorphism	Effect	Reference
3′UTR (TA)n	mRNA stability	[64]
	Decreased CaP risk	[73,98]
	No relationship with CaP risk	[13,20,27–30,35,41,44,56,68,71,73,74,76,77,92–94]
	No association with tumor aggressiveness or risk	[34,36,41,68,80,81,85–89,96]
A49T (c.145G > A, rs9282858)	Association with CaP risk	[66,68,72]
	No association with CaP risk	[17,27,28,34,35,39,41,56,73–81]
	Increased *in vitro* Vmax of testosterone conversion to DHT; increased Ki for 5α-reductase inhibitors	[65,66]
	Prognostic factor for early onset or high-stage CaP or BPH	[83,85–87]
	No consistent association with prognosis	[68,80,88,89]
V89L (rs523349)	Increased risk of CaP	[17,34,36,39,72,80,86,90,91,95–98]
	No association with CaP risk	[13,20,27–30,35,41,44,56,68,71,73,74,76,77,92–94]
	Lower activity of SRD5A2	[67]
	Lower free and total testosterone levels	[12]
	Lower levels of the DHT metabolite 3α-androstanediol-glucuronide	[68]
	No relationship with hormon levels	[11,12,57,68–71]

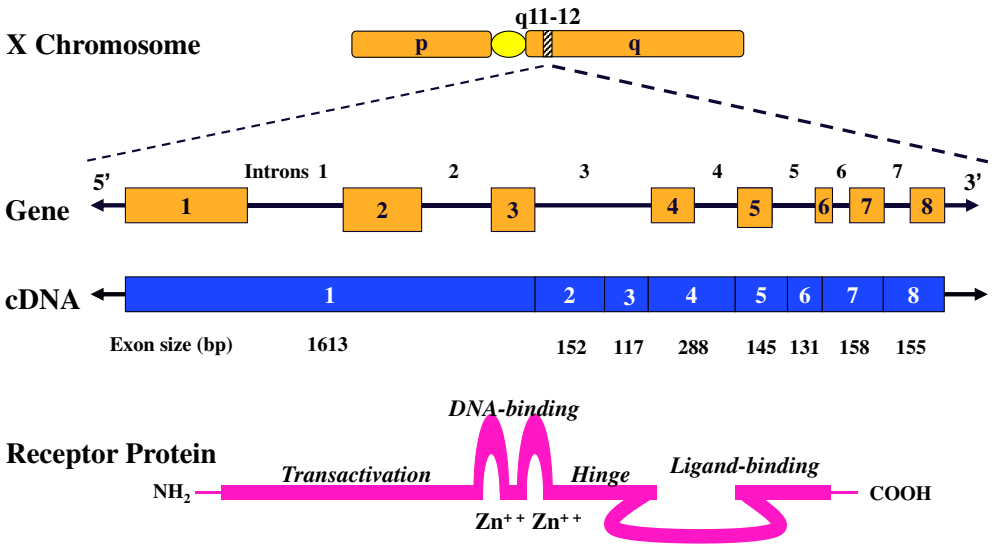

Fig. 2. Structures of the androgen receptor gene, cDNA, and protein product.

region, and the carboxy-terminal ligand-binding domain (Fig. 2). As of 2012, there are 1,029 reported mutations within the AR, and 159 reported from prostate cancer tissue, almost all of these are somatic single-base substitutions [104].

The AR has been extensively studied in attempts to elucidate its role in the development and progression of prostate cancer. It is a nearly ubiquitous protein acting as a ligand-activated transcription factor that regulates tissue specific genes. The AR is the vehicle through which androgens, particularly testosterone and dihydrotestosterone (DHT), accomplish the regulation of prostate cellular proliferation and differentiation. Without these androgens, the prostate undergoes apoptosis and significant atrophy. Standard treatment of prostate cancer utilizes androgen deprivation therapy (ADT), a combination of AR antagonism and pharmacological or surgical suppression of androgen production. Unfortunately, in many cases, therapy fails even with castrate levels of androgens and it is thought that the high levels of AR expression may be due to AR gene amplification, increased expression of necessary cofactors, activation of growth factors, or a selection of somatic mutations within the AR [105]. It has been reported that antiandrogen activated ARs may occur due to mutations selected by drug treatment [106]. Human AR mutations were evaluated both from autopsy samples of patients treated with common antiandrogens, and from lymph node metastases excised from hormone naïve patients. Mutations within the AR occurred at low levels in all specimens. Missense mutations found within the NH2- terminal domain occurred in multiple tumors, while those found in the ligand binding domain (LBD) of the AR were case specific. Mutations were further investigated to unravel potential mechanisms that help evade treatment and cause resistance to therapy. In three metastases from an antiandrogen (flutamide)-treated patient, the promiscuous receptor variant V716M was found. Other examples of treatment induced gain of function AR mutations were W435L that was located in the AR N-terminal domain in a motif involved in promoter-selective, cell dependent transactivation, and E255K located in a domain that interacts with an E3 ubiquitin ligase leading to increased protein stability and nuclear localization in the absence of ligand [106]. The identification of splice variants as an alternative mechanism of AR reactivation after androgen deprivation therapy complicates the potential of the AR as a drug target [107,108].

Comprising more than half of the AR, the amino-terminal transactivation domain, is encoded by a single exon. Within this exon are three microsatellite trinucleotide repeats, two of which are polymorphic in length. The variability of the transactivation domain implicates it as an important determinant of gene activation specificity. The CAG repeat within exon 1 has a normal range of 8–35 repeats, with shorter CAG repeats being associated with increased AR transactivation activity [109] and benign prostatic hyperplasia [110]. Since the initial suggestion that variations in CAG repeat length are associated with prostate cancer [111], many groups have evaluated the association of CAG repeat length and risk of prostate cancer. Price et al., reported the results of the analysis of AR CAG repeat length within the Prostate Cancer Prevention Trial, a randomized, placebo controlled trial testing the a 5a-reductase inhibitor finasteride as a preventative agent for prostate cancer [112]. Unlike all previous studies evaluating the association between CAG repeat length and prostate cancer risk, cases in this study were taken from men with biopsy proven prostate cancer minimizing potential bias and error to due latent, undetected prostate cancer in the study population. The results from this nested case control study of 1159 cases and 1353 controls showed that the mean CAG repeat length did not differ between cases and controls, and there were no significant associations of CAG repeat length with prostate cancer risk when either stratified by treatment arm or combined. There was also no association of CAG repeat length and the risk of low or high grade prostate cancer, and that the AR CAG length provides no clinically useful information to predict risk of prostate cancer [112]. A summary of the association of genetic variants of AR with prostate cancer risk and prognosis is reported in Table 2.

In spite of the multitude of studies that have ascertained the relationship between genetic variants in androgen synthesis genes and prostate cancer biology and clinical progression, there have been inconsistent results. While there are several plausible reasons behind these discrepancies, we suggest that since prostate cancer is a very heterogeneous disease with many different clinic-pathological stages and

Table 2
Role of AR polymorphisms in CaP.

Polymorphism	Effect	Reference
V716M, W435L, E255K, splice variants	Resistance to AR antagonists	[102–104]
CAG repeats	Increased AR transactivation activity and BPH risk	[105,106]
	Association with CaP risk	[107]
	No association with CaP risk or tumor grade	[108]

treatments, future studies must carefully define more specific populations prior to evaluating how polymorphic variation affects prostate disease. There is increasing evidence that intratumoral synthesis and transport of androgens drives prostate cancer, thereby separating the tumor from regulation by systemic synthesis of hormones, and it is unlikely that many of the studies that have ascertained testosterone disposition in the blood are accurate with respect to the true effects of these polymorphisms on androgen phenotype *in situ*. Much has been learned about prostate cancer over the past 10 years, and future studies must utilize this information to develop and test more specific hypotheses in order to apply genetic testing of androgen biosynthesis and signaling genes in the setting of personalized medicine.

3. Genes involved in signal transduction and angiogenesis pathways

3.1. EGFR pathway

The epidermal growth factor receptor (EGFR) is a 170 kDa transmembrane receptor that plays an important role in the differentiation and proliferation of epithelial cells [113]. Binding of the epidermal growth factor (EGF), transforming growth factor-alpha (TGF-α) or amphiregulin to the receptor results in its activation and in the initiation of a cascade of reactions that ultimately result in DNA replication and cell division [114]. Activation of EGFR can occur via autocrine, paracrine, or juxtacrine mechanisms [115]. On ligand binding, EGFR dimerizes with neighboring receptors and is auto-phosphorylated at three major tyrosine residues [116]. As a consequence, the receptor interacts with a number of proteins that are elements of signal transduction pathways, including phospholipase Cγ, phosphatidylinositol-3′-kinase, growth factor receptor-binding protein 2, Src family kinases, and components of the Jak/STAT pathway [117,118]. EGFR is known to participate in the pathogenesis or maintenance of several human cancers. It is implicated in the malignant transformation of epithelial cells, and high levels of EGFR mRNA and protein have been found in solid organ malignancies [119,120]. EGF/EGFR (HER-1) and HER-2/neu may contribute to the proliferation and growth of prostate cancer [121]. Indeed, 39% to 47% of prostate cancers are positive for EGFR [122], and increased expression has been observed during progression to advanced androgen independent stages [123]. In prostate cancer cells, EGFR ligands are frequently elevated and EGFR itself is commonly overexpressed [124]. A germline functional G > A SNP at position +61 in the 5′ untranslated region (5′UTR) of the EGF gene in patients with prostate cancer has been identified [125]. In vitro studies showed that patients with a G at this position have increased EGF production in peripheral blood mononuclear cells, glioblastoma, and breast cancer cells [125–128]. The investigation of the potential prognostic and predictive role of EGF SNP +61G > A in 123 patients with prostate cancer given anti-androgen therapy and 152 healthy controls demonstrated an association between the G allele on the time to relapse during ADT ($P = 0.018$), supporting the involvement of EGF as an alternative pathway in castrate resistant prostate cancer (CRPC) [125]. Studies have demonstrated that a subset of prostate cancers shows an unexplained depletion of EGFR and an overexpression of the EGFRvIII variant. In a retrospective study, prostate tissues from benign hyperplasia (19 patients) and cancer (38 patients) were examined for EGFRvIII mRNA and protein levels. The results demonstrated that EGFRvIII was not present in hyperplastic prostatic glands and the expression levels of this variant protein increased progressively with the transformation of the tissues to the malignant phenotype. This suggests a role for this mutant receptor in the initiation and progression of malignant prostatic growth [120]. A study on 212 patients with prostate cancer found a statistically significant association between the variant genotype AA of the SNP rs884419 (g.194556G > A) and high risk of prostate cancer recurrence [129]. Table 3 summarizes the impact of the various EGFR variants with prostate cancer biology and clinical outcome.

Table 3
Role of EGFR polymorphisms in CaP.

Polymorphism	Effect	Reference
+61G > A	Longer time to relapse	[121]
EGFRvIII	High expression in CaP compared to BPH	[116]
g.194556G > A (rs884419)	Higher risk of CaP recurrence	[125]

3.2. VEGF and VEGF receptors

Vascular endothelial growth factor (VEGF) is an angiogenic factor that stimulates endothelial cell growth and enhances vascular permeability by binding of this factor to the cell surface receptors: VEGFR-1, VEGFR-2 and VEGFR-3. The VEGF gene is located on chromosome 6 at location 6p21.1 and VEGF exists in 5 different isoforms generated by alternate splicing of a single gene and 5 different polypeptides [130]. The vascular endothelial growth factor (VEGF) ligand and receptor family have been implicated in the growth and spread of prostate cancer via activation of the blood vasculature and lymphatic systems. A study conducted on 15 ex vivo prostate cancer specimens, obtained from patients undergoing radical retropubic prostatectomy, selected to contain both cancer and BPH tissue, showed significant levels of VEGF in prostate cancer, but not in BPH or normal prostate cells [131]. Other studies conducted on 30 well, moderately and poorly differentiated stage D2 prostate cancer specimens and 20 BPH specimens, observed widespread expression of VEGF in both BPH specimens and prostate cancer [132]. A correlation study between down-regulation of VEGF and selective ablation of immature blood vessels in prostate tumors conducted on patients undergoing androgen-ablation therapy showed that, upon VEGF withdrawal, blood vessels in both xenografts and primary human tumors contained a sizable fraction of immature blood vessels that had not yet recruited periendothelial cells [133]. In human prostate cancer, the constitutive production of VEGF by the glandular epithelium was suppressed as a consequence of androgen-ablation therapy and VEGF loss led to selective apoptosis of endothelial cells in vessels devoid of periendothelial cells. These results suggest that the unique dependence on VEGF of blood vessels lacking periendothelial cells can be exploited to reduce an existing tumor vasculature, suggesting a role for testosterone in the regulation of VEGF [133]. Various studies have been conducted investigating VEGF variants versus prostate cancer risk, and these are summarized in Table 4. The 5′- and 3′-UTR of the VEGF gene contain key regulatory elements sensitive to hypoxia and contributes to high variability in VEGF production among tissues [134,135]. A study conducted on predictive risk of prostate cancer examined the effect of four SNPs of pro-angiogenic factors (VEGF −1154G > A; VEGF −634G > C; MMP9 1562C > T and TSP1 8831A > G). Significant gene–dosage effects for increasing numbers of potential high-risk genotypes were found. Gene–gene interaction of VEGF and TSP1 polymorphisms increased risk of prostate cancer, but the TSP1 polymorphism was not associated with risk. The analysis of the synergistic effect of these polymorphisms in relation to prostate cancer prognosis revealed potential higher order gene–gene interactions between VEGF and TSP1 polymorphisms in

Table 4
Role of VEGF, MMP9 and TSP1 polymorphisms in CaP.

Polymorphism	Effect	Reference
VEGF -1154G > A and -634G > C, MMP9 1562C > T, TSP1 8831A > G	Increased risk of CaP or higher tumor grade	[132,133]
VEGF -1154G > A	Reduced risk of CaP	[134]
VEGF -460C > T	Increased risk of CaP	[135]
VEGF -634G > C	No correlation with CaP risk	[137]

increasing the risk of developing an aggressive phenotype disease [136]. Other studies have evaluated the role of functional VEGF polymorphisms as genetic markers for prostate cancer susceptibility and prognosis. Patients with prostate cancer (101 subjects) and controls (100 subjects) were found to have a negative association between VEGF −1154G > A genotype and prostate cancer risk. Furthermore, the presence of the VEGF −1154A allele appears to be associated with an increased risk of higher tumor grade, and a significant increased risk of prostate cancer was associated with the VEGF -634 (GC + CC) combined genotype. [137]. A case-control study on 247 patients with prostate cancer and 263 controls examined SNPs in 5 cytokines including the VEGF −1154 G > A and demonstrated that the −1154 AA genotype had reduced risk of prostate cancer [138]. However, this SNP was not related with prognosis (i.e., clinical stage and pathological tumor grade) and response to hormonal therapy [139]. Thus, the VEGF −1154 A allele appears to predict reduced prostate cancer risk [137,138] and imparts protection against high-grade tumor and tumor aggressiveness [137]. A recent meta-analysis using 16 published case-control studies did not find any association between the VEGF -1154G > A and overall cancer risk [140]. The −634C allele was predictive of increased risk and high tumor grades in Tunisian subjects [137], but had no relation with risk in a study on 702 Austrian patients with prostate cancer, and 702 age-matched control subjects [141]. This is supported by the results of a meta-analysis that showed no significant association between any other VEGF polymorphism and prostate cancer risk or clinical outcome [142]. More recently, a study published that examined cancerous and adjacent benign prostate tissue from 52 subjects representing various grades of prostate cancer found that in epithelial cells, VEGF-A and VEGFR-1 expression was higher in tumor tissue compared with benign tissue, and VEGF-D and VEGFR-3 expression was significantly higher in benign tissue compared to tumor in the stroma and the endothelium of lymphatic and blood vessels. In addition, the frequency of lymphatic vessels was lower in tumor tissue compared with benign tissue, suggesting that in carcinoma cells activation of VEGFR-1 by VEGF-A, and activation of lymphatic endothelial cell VEGFR-3 by VEGF-D within the adjacent benign stroma may be important for the progression and subsequent metastatic spread of prostate cancer [143].

4. Candidate gene vs genome wide association studies

Candidate-gene research interrogates a limited number of variants with known mechanistic importance; therefore, it is not surprising that the majority of candidate gene studies have focused on known androgen synthesis-, angiogenesis-, and TKI-pathway genes. On the other hand, GWAS platforms are designed to account for tag SNPs with significant linkage disequilibrium among multiple variants, rather than focusing on functional polymorphisms with known mechanistic importance. For this reason, GWAS studies have generally found different variants in association with PCa risk and outcome, and these same variants typically have a rather unclear mechanistic relationship with known disease etiology. Additional factors also confound studies of genetic markers given that genetic penetrance is often low in disease etiology and progression, and numerous other multi-factorial complexities are taken for granted. Prostate cancer is a heterogenous disease with a multigenic origin, so these complexities are likely to confound studies of prostate cancer in particular. Both candidate-gene and GWAS approaches also have their own statistical limitations. For instance, candidate gene studies typically have a high rate of false positives and overestimated effect sizes, while genome-wide approaches typically have a high rate of false negatives due to multiple testing. It is therefore challenging to ascertain which type of study is more valid, and it is more likely that the answer lies in between – that we need to be focused on ascertaining the true importance of candidate gene findings while ascertaining the mechanism of properly-conducted GWAS studies (personal communication with Dr. Howard McLeod).

5. Germline Variants Identified in GWAS

With the arrival of high throughput genotyping techniques for whole genomes, many germline variants have been discovered that are significantly associated with prostate cancer susceptibility (recently reviewed by Nakagawa) [144]. While the use of genome wide association studies (GWAS), next-generation sequencing (NGS), whole exome sequencing (WES), and RNA sequencing (RNA-Seq) has allowed for the comprehensive analysis of prostate cancer genomes, it has also given an indication of the complexity and heterogeneous nature of prostate cancer.

The use of these new tools has led to the identification of multiple chromosome loci, prostate-, metabolism- and inflammation-specific genes, somatic alterations of prostate cancer genomes, fusion transcripts and gene fusions. Over seventy different variants or loci have been identified by GWAS studies in prostate cancer [144]. Meta-analysis using combined GWAS cohorts containing more than 50,000 samples have added to the total of identified prostate cancer susceptibility variants and genes [145,146]. One common result of GWAS has been the identification of 8q24[147–149], but unfortunately, no gene of biological significance has been identified in this region. Recent studies have identified loci at 19q13[150], 10q11 [150], 8p21 [145], and 5p15 [151] that all demonstrate prostate-specific genes that are associated with prostate development and carcinogenesis. Both a Japanese GWAS and a GWAS on Chinese men with prostate cancer identified a susceptibility locus at 19q13.4. The Japanese GWAS mapped the SNP to the *FOXP4* gene which encodes a transcription factor essential for T-cell development [152], while the Chinese GWAS identified a SNP linked to a deletion in *LILRA3* that induced loss of this leukocyte immunoglobulin-like receptor in T-cells [153]. Both of these findings suggest a role in the immune response in prostate cancer.

GWAS has identified over 50 variants or loci that have been shown to be significantly associated with the risk of prostate cancer. Unfortunately due to the modest effect by these markers, their use in prostate cancer risk assessment is limited (reviewed by Nakagawa) [144]. Also limiting the use of GWAS and other high-throughput technology is the sample size of most current studies due to cost and sample acquisition, the complexity of the prostate cancer genome, and the ethnic and racial group differences in results. Interpreting the results of the enormous amount of GWAS data and applying the findings to the clinic remains a challenge as most of the identified loci currently lack biological significance. This problem will be overcome in the future as better bioinformatic approaches become available to help define the biology behind these associations.

6. Pharmacogenetics of drugs used to treat prostate cancer

In the last few years, five new treatment options for prostate cancer have emerged. Sipleucel-T immunotherapy, a first-line option for metastatic castration-resistant prostate cancer (CRPC), cabazitaxel in the second-line setting, abiraterone, an androgen-deprivation treatment showing survival benefit in CRPC [1,154], enzalutimide [155], and Radium-223 chloride all gained FDA approval. While advances in prostate cancer treatment seem to be promising, not all patients receive the same benefit. Variability in response and toxicity, combined with a narrow therapeutic window, calls for better prediction of outcomes. Of all prostate cancer therapies, docetaxel pharmacogenetics is the most widely studied. For this reason, this section will summarize what is currently known about the pharmacogenetics of docetaxel. Emerging research on the pharmacogenetics of other therapies will also be introduced.

6.1. Androgen Deprivation Therapy

Individuals presenting with advanced-stage, hormone-sensitive prostrate cancer receive an initial treatment of androgen deprivation therapy (ADT). The therapy seeks to enhance the duration of disease

control although the disease typically progresses at which point the patient is said to be "castration resistant". This time to progression or TTP as it is more commonly known, can vary from a months to several years with a median time ranging from 18 to 30 months. There is considerable inter-individual variation in the response to androgen deprivation therapy, and it is likely that genetic variation contributes significantly to this heterogeneity.

So far, candidate gene studies have focused on germline variants in genes that regulate steroid hormone synthesis, uptake, and signaling. Polymorphisms in HSD3B1/2, CYP17A1, AKR1C3, HSD3B1, HSD17B2, and HSD17B4 have been previously associated with ADT therapy outcomes [156–158]. For the most part, genes that favor hormone synthesis are associated with disease progression. *SLCO1B3* and *SLCO2B1* (encoding the uptake transporters, OATP1B3 and OATP2B1) have been associated with ADT response in several studies [158,159]. Both transporters are expressed in prostate tumors and are involved in steroid hormone uptake; therefore it is thought that polymorphisms alter the ability of these tumors to accumulate steroid hormones that promote disease progression. Several have also investigated hormone signaling through the AR, ER, AR-interacting pathways (e.g., TGFB signaling), and genes that harbor androgen receptor elements (e.g., ARRDC3 and FBXO32) [160–162]. Surprisingly, genetic variation in the androgen receptor has not been linked to ADT response although other hormone signaling factors appear to be related. Other candidate gene studies have focused on the vitamin D receptor [163], RNASEL [164] and IL18 [165] with mixed results.

Large-scale and genome-wide approaches have also been conducted. Findings include polymorphisms in genes encoding: BNC2, TACC2, ALPK1, KIF3C, CDON, IFI30, PALLD, GABRA1, SYT9, MSMB, MYCN, PSMD7, CCL17, MON1B, CASP3, BMP5, IRS2, TRMT11, PRMT3, and HSD17B2 [165–172]. Results from these studies suggest that the most important predictors of a poor response to ADT are not necessarily within androgen-related genes; however, the genetic variants identified in these studies have not been sufficiently validated from a mechanistic standpoint. Therefore, in spite of recent progress in studies of germline variants and associations with ADT, additional research is needed.

6.2. Docetaxel

The inter-individual variation of docetaxel treatment outcomes is seen in an approximate 10% difference in docetaxel clearance [173], wide variability in systemic exposure [174], alterations in toxicity [175,176], and alterations in progression and survival [177,178]. Several gene products are involved in docetaxel metabolism and elimination and these are summarized in Table 5. Docetaxel is hydroxylated by CYP3A4/5 [179], and transported with its metabolites across biological barriers by ABCB1 [180], ABCC2 [181], and OATP1B3 (encoded by the gene *SLCO1B3*)[182]. The current literature suggests that docetaxel is taken into the liver by OATP1B3, inactivated by CYP3A4/5, eliminated through hepatobilliary secretion by ABCB1 and ABCC2, and undergoes enterohepatic recirculation mediated by ABCB1 [183]. CYP1B1 metabolism may interfere with docetaxel-microtubule interactions as well as binding covalently to docetaxel itself [177,184]. Pharmacogenetic studies have examined genetic variation in the above genes.

Several studies have evaluated *CYP3A4* polymorphisms in relation to docetaxel pharmacokinetics. Most studies in this regard have been negative [185–191], although recent evidence suggests that some SNPs may be important when considering the *CYP3A4/5* haplotype [192,193]. Carriers of a haplotype consisting of *CYP3A4*1B* and *CYP3A5*1A* alleles, named *CYP3A4/5*2*, were found to have a 64% higher clearance of docetaxel [192]. The haplotype structure of *CYP3A4/5* is likely an important factor in docetaxel pharmacokinetics in Caucasians. However, it is important to note that the haplotype is organized differently in non-Caucasians. Future investigations must take interracial genetic variation into account.

CYP1B1 has also been related to docetaxel response and toxicity. CYP1B1 was found highly expressed in the prostate [194]. Four studies have indicated that the *CYP1B1* L432V (*CYP1B1*3*) allele might be negatively associated with docetaxel treatment efficacy in prostate cancer [177,195–197]. Another study that genotyped 95 breast cancer patients being treated with a taxane (74% of whom were treated with docetaxel), found a significant reduction in hypersensitivity reactions with the CYP1B1*3 allele [198]. These effects are likely due to higher metabolism of estrogen, resulting in increased levels of reactive estrogen metabolites that antagonize docetaxel (Fig. 1)[177]. However, in a study of docetaxel-resistant prostate cancer cells, CYP1B1 transcription was upregulated upon treatment, but gene silencing did not affect resistance [199]. Further studies are required to validate these findings.

The membrane transporter *ABCB1* is the most-studied transporter in docetaxel pharmacogenetics. Earlier studies found that *ABCB1* polymorphisms were associated with docetaxel clearance [185,187] and toxicity [193]. Still other studies found no relationship [190,193]. Since Kimchi-Sarfaty and collaborators showed that *ABCB1* haplotypes are more strongly related to protein folding and expression than any individual SNP alone, two studies have investigated the combined effect of ABCB1 SNPs at the 1236C > T, 2677G > T/A, and 3435C > T loci on docetaxel treatment [200].

The first investigated *ABCB1* 1236C > T, 2677G > T/A, 3435C > T SNPs alone and in diplotype in patients with CRPC treated with docetaxel. It was found that patients carrying 1236C-2677G-3435C linked alleles had improved overall survival. However, patients carrying the 2677 T-3435 T diplotype had shorter median survival after treatment, and were more likely to have higher grade neutropenia during treatment and on-study PSA. No relationship with docetaxel clearance was seen. This study suggests that *ABCB1* SNPs contribute to survival and toxicity differences in men with CRPC, and again demonstrates that haplotype analysis is important to determine associations with polymorphisms [176].

A second study investigated variation in both individual genotypes and common haplotypes within *ABCB1* (1236C > T, 2677G > T/A, 3435C > T), *ABCC2* (-1019A > G, -24C > T, 1249G > A, IVS26 -34C > T, 3972C > T, 4544G > A), and *SLCO1B3* (334 T > G, 439A > G, 699G > A, 767G > C, 1559A > C, 1679 T > C) against docetaxel clearance data in Caucasian patients with various malignancies, including 24 patients with prostate cancer. Consistent with the first study, none of the genotypes or haplotypes were related to docetaxel pharmacokinetics [192].

Table 5
Role of drug metabolising enzymes and transporters in docetaxel activity and pharmacokinetics.

Polymorphism	Effect	Reference
CYP3A4/5*2	Higher clearence of docetaxel	[161]
CYP1B1*3 (L432V)	Lower docetaxel efficacy and fewer hypersensitivity reactions	[146,164–167]
CYP1B1	Enzyme up regulation has no effect on drug resistance	[168]
ABCB1 1236C > T, 2677G > T/A, 3435C > T	Improved overall survival and increased risk of neutropenia	[145]
ABCB1 1236C > T, 2677G > T/A, 3435C > T	No correlation with pharmacokinetics	[161]
ABCC2 -1019A > G, -24C > T, 1249G > A, IVS26-34C > T, 3972C > T, 4544G > A SLCO1B3 334 T > G, 439A > G, 699G > A, 767G > C, 1559A > C, 1679 T > C		
ABCC2 (g.52425235C > G, rs12762549)	Higher risk of neutropenia	[159,161]
ABCG2 421C > A	Lower transporter expression and improved survival	[157]

A few studies evaluated other known docetaxel transporters. The *ABCC2* rs12762549 SNP has been linked to docetaxel-induced neutropenia in the Asian population [190], although no associations have been found between *ABCC2* polymorphisms and docetaxel pharmacokinetics [192]. Similar results were found for SNPs in *SLCO1B3*. The ABCG2 421C > A (Q141K) variant has been attributed to lowered expression of ABCG2 [201–205]. This polymorphism was associated with improved survival following treatment with combination docetaxel and vinorelbine or combination docetaxel and estramustine in CRPC [188]. The authors concluded that the survival increase was related to drug efflux pump inefficiency. However, since docetaxel is not an ABCG2 substrate [206], it is likely that the SNP mediates docetaxel efficacy or cancer progression through another substrate.

6.3. Pharmacogenetics of other therapies in prostate cancer

Cabazitaxel, a semisynthetic taxane, was approved by the FDA in 2010 for patients with metastatic CRPC who have failed docetaxel treatment. A major difference between cabazitaxel and docetaxel is that cabazitaxel has a low affinity for the drug-efflux gene ABCB1, perhaps explaining its activity in docetaxel-resistant CRPC [207]. However, SNPs in CYP3A4 and CYP3A5 may affect cabazitaxel clearance and toxicity [208], and further studies on the pharmacogenetics of this new taxane are warranted.

Mitoxantrone is a chemotherapeutic agent with palliative benefit in CRPC. Transporters including ABCG2 extrude mitoxantrone from cells [209,210]. The Q141K polymorphism causes an approximate 2–5-fold increase in drug-sensitivity towards mitoxantrone in vitro as compared to the wild-type protein in 4 separate studies [201,211–213].

Pharmacogenetic studies have shown that a SNP in the membrane transporter gene SLCO1B3 increases testosterone uptake and decreases time to resistance on androgen deprivation therapy and overall survival [214]. More studies are needed to verify if this or other polymorphisms have an effect on ADT pharmacology and response.

An exciting development in the methods of pharmacogenetics is the use of high-throughput genotyping platforms, such as the drug-metabolizing enzyme and transporter (DMET) chip by Affymetrix. This platform tests for SNPs in close to 200 metabolism genes, and has great exploratory value. It has been used to generate hypotheses from a study of docetaxel and thalidomide treatment of CRPC [215].

Given that treatments for prostate cancer have a narrow therapeutic window and high risk of toxicity, inter-individual variation in pharmacokinetics and clinical outcome must be better explored to identify optimal dosing and treatment. Such studies will be utilized to improve therapy for prostate cancer and eventually lead to the design of superior therapeutic options.

6.4. Future perspectives on pharmacogenomics

Risk studies on germline SNPs have been ongoing in the literature for decades whereas pharmacogenomics is an emerging field, especially in prostate cancer, and there are numerous key issues that remain to be studied.

Firstly, prostate cancer has recently experienced a renaissance in therapeutic development with numerous new therapeutics recently coming to market (e.g. enzalutamide, abiraterone, cabazitaxel, radium 223 chloride, and sipleucel-T) and more likely still to come. There are currently no studies relating to the pharmacogenomics of these drugs. As with any new therapy, the clinical pharmacology community is currently exploring additional pathways of drug metabolism, transport, PK/PD, and toxicity and it is expected that pharmacogenomics studies of these pathways (and those listed in the package inserts) will be published soon. Moreover, optimal patient selection and drug sequencing are also currently under investigation. With this in mind, pharmacogenomic pathways may be crucial to improve dosing and sequencing of these drugs, and such studies should be collecting DNA to utilize for pharmacogenetics endpoints.

Secondly, resistance mechanisms to these drugs are only recently coming to light. Although it is more likely that resistance will occur due to somatic mutations and microenvironment changes rather than germline DNA variance, germline polymorphisms should still be ascertained. This is especially true for abiraterone and enzalutamide, which inhibit both tumoral and non-tumoral androgen biosynthesis and response.

Finally, the field of pharmacogenomics has already demonstrated utility in ascertaining patient populations that are at increased risk of having excessive toxicity or lack of efficacy. This is likely going to also be the case for prostate cancer therapies even though the therapeutic window appears to be wider for many up-and-coming drug therapies that are not cytotoxic.

In summary, germline pharmacogenomics approaches will be useful to optimize dose and sequencing, select appropriate patient populations, negotiate drug resistance, and mitigate toxicity. It is therefore crucial that ongoing studies collect DNA for pharmacogenomics analysis.

References

[1] G. Attard, et al., Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven, J. Clin. Oncol. 26 (28) (2008) 4563–4571.
[2] R. Siegel, D. Naishadham, A. Jemal, Cancer statistics, 2013, CA Cancer J. Clin. 63 (1) (2013) 11–30.
[3] M.M. Center, et al., International variation in prostate cancer incidence and mortality rates, Eur. Urol. 61 (6) (2012) 1079–1092.
[4] H. Shimizu, R.K. Ross, L. Bernstein, Possible underestimation of the incidence rate of prostate cancer in Japan, Jpn. J. Cancer Res. 82 (5) (1991) 483–485.
[5] K. Ito, Prostate cancer in Asian men, Nat. Rev. Urol. 11 (4) (2014) 197–212.
[6] G.P. Haas, W.A. Sakr, Epidemiology of prostate cancer, CA Cancer J. Clin. 47 (5) (1997) 273–287.
[7] P.C. Walsh, A.W. Partin, Family history facilitates the early diagnosis of prostate carcinoma, Cancer 80 (9) (1997) 1871–1874.
[8] A. Gsur, E. Feik, S. Madersbacher, Genetic polymorphisms and prostate cancer risk, World J. Urol. 21 (6) (2004) 414–423.
[9] V. Nwosu, et al., Heterogeneity of genetic alterations in prostate cancer: evidence of the complex nature of the disease, Hum. Mol. Genet. 10 (20) (2001) 2313–2318.
[10] A.W. Hsing, S.S. Devesa, Trends and patterns of prostate cancer: what do they suggest? Epidemiol. Rev. 23 (1) (2001) 3–13.
[11] A.H. Carey, et al., Polycystic ovaries and premature male pattern baldness are associated with one allele of the steroid metabolism gene CYP17, Hum. Mol. Genet. 3 (10) (1994) 1873–1876.
[12] V. Nedelcheva Kristensen, et al., CYP17 and breast cancer risk: the polymorphism in the 5′ flanking area of the gene does not influence binding to Sp-1, Cancer Res. 59 (12) (1999) 2825–2828.
[13] H. Kakinuma, et al., Serum sex steroid hormone levels and polymorphisms of CYP17 and SRD5A2: implication for prostate cancer risk, Prostate Cancer Prostatic Dis. 7 (4) (2004) 333–337.
[14] R.M. Lunn, et al., Prostate cancer risk and polymorphism in 17 hydroxylase (CYP17) and steroid reductase (SRD5A2), Carcinogenesis 20 (9) (1999) 1727–1731.
[15] N.E. Allen, M.S. Forrest, T.J. Key, The association between polymorphisms in the CYP17 and 5alpha-reductase (SRD5A2) genes and serum androgen concentrations in men, Cancer Epidemiol. Biomark. Prev. 10 (3) (2001) 185–189.
[16] C.A. Haiman, et al., The relationship between a polymorphism in CYP17 with plasma hormone levels and prostate cancer, Cancer Epidemiol. Biomark. Prev. 10 (7) (2001) 743–748.
[17] M.P. Madigan, et al., CYP17 polymorphisms in relation to risks of prostate cancer and benign prostatic hyperplasia: a population-based study in China, Int. J. Cancer 107 (2) (2003) 271–275.
[18] G. Severi, et al., The rs743572 common variant in the promoter of CYP17A1 is not associated with prostate cancer risk or circulating hormonal levels, BJU Int. 101 (4) (2008) 492–496.
[19] J.A. Douglas, et al., Identifying susceptibility genes for prostate cancer–a family-based association study of polymorphisms in CYP17, CYP19, CYP11A1, and LH-beta, Cancer Epidemiol. Biomark. Prev. 14 (8) (2005) 2035–2039.
[20] S. Lindstrom, et al., Systematic replication study of reported genetic associations in prostate cancer: Strong support for genetic variation in the androgen pathway, Prostate 66 (16) (2006) 1729–1743.
[21] A. Loukola, et al., Comprehensive evaluation of the association between prostate cancer and genotypes/haplotypes in CYP17A1, CYP3A4, and SRD5A2, Eur. J. Hum. Genet. 12 (4) (2004) 321–332.
[22] N. Mononen, et al., Profiling genetic variation along the androgen biosynthesis and metabolism pathways implicates several single nucleotide polymorphisms and their combinations as prostate cancer risk factors, Cancer Res. 66 (2) (2006) 743–747.

[23] A.V. Sarma, et al., Genetic polymorphisms in CYP17, CYP3A4, CYP19A1, SRD5A2, IGF-1, and IGFBP-3 and prostate cancer risk in African-American men: the Flint Men's Health Study, Prostate 68 (3) (2008) 296–305.
[24] V.W. Setiawan, et al., CYP17 genetic variation and risk of breast and prostate cancer from the National Cancer Institute Breast and Prostate Cancer Cohort Consortium (BPC3), Cancer Epidemiol. Biomark. Prev. 16 (11) (2007) 2237–2246.
[25] S. Lindstrom, et al., Germ-line genetic variation in the key androgen-regulating genes androgen receptor, cytochrome P450, and steroid-5-alpha-reductase type 2 is important for prostate cancer development, Cancer Res. 66 (22) (2006) 11077–11083.
[26] C. Antognelli, et al., Association of CYP17, GSTP1, and PON1 polymorphisms with the risk of prostate cancer, Prostate 63 (3) (2005) 240–251.
[27] T. Habuchi, et al., Increased risk of prostate cancer and benign prostatic hyperplasia associated with a CYP17 gene polymorphism with a gene dosage effect, Cancer Res. 60 (20) (2000) 5710–5713.
[28] M. Wadelius, et al., Prostate cancer associated with CYP17 genotype, Pharmacogenetics 9 (5) (1999) 635–639.
[29] E. Taioli, et al., Polymorphisms in CYP17 and CYP3A4 and prostate cancer in men of African descent, Prostate 73 (6) (2012) 668–676.
[30] J. Beuten, et al., Single and multigenic analysis of the association between variants in 12 steroid hormone metabolism genes and risk of prostate cancer, Cancer Epidemiol. Biomark. Prev. 18 (6) (2009) 1869–1880.
[31] M. Tajtakova, et al., Serum level of IGFBP3 and IGF1/IGFBP3 molar ratio in addition to PSA and single nucleotide polymorphism in PSA and CYP17 gene may contribute to early diagnostics of prostate cancer, Neoplasma 57 (2) (2010) 118–122.
[32] A.R. Azzouzi, et al., Impact of constitutional genetic variation in androgen/oestrogen-regulating genes on age-related changes in human prostate, Eur J Endocrinol 147 (4) (2002) 479–484.
[33] B. Chang, et al., Linkage and association of CYP17 gene in hereditary and sporadic prostate cancer, Int. J. Cancer 95 (6) (2001) 354–359.
[34] R.A. Kittles, et al., Cyp17 promoter variant associated with prostate cancer aggressiveness in African Americans, Cancer Epidemiol. Biomark. Prev. 10 (9) (2001) 943–947.
[35] S. Larre, et al., Genetic impact on prostate anatomical variability during ageing: role of CYP17, SRD5A2 and androgen receptor genes polymorphisms, BJU Int. 100 (3) (2007) 679–684.
[36] C.C. Lin, et al., CYP17 gene promoter allelic variant is not associated with prostate cancer, Urol. Oncol. 21 (4) (2003) 262–265.
[37] R.M. Lunn, et al., Prostate cancer risk and polymorphism in 17 hydroxylase (CYP17) and steroid reductase (SRD5A2), Carcinogenesis 20 (9) (1999) 1727–1731.
[38] C. Ntais, A. Polycarpou, J.P. Ioannidis, Association of the CYP17 gene polymorphism with the risk of prostate cancer: a meta-analysis, Cancer Epidemiol. Biomark. Prev. 12 (2) (2003) 120–126.
[39] H. Okugi, et al., Association of the polymorphisms of genes involved in androgen metabolism and signaling pathways with familial prostate cancer risk in a Japanese population, Cancer Detect. Prev. 30 (3) (2006) 262–268.
[40] G. Schatzl, et al., Association of vitamin D receptor and 17 hydroxylase gene polymorphisms with benign prostatic hyperplasia and benign prostatic enlargement, Urology 57 (3) (2001) 567–572.
[41] J.L. Stanford, et al., A polymorphism in the CYP17 gene and risk of prostate cancer, Cancer Epidemiol. Biomark. Prev. 11 (3) (2002) 243–247.
[42] A. Hamada, et al., Effect of SLCO1B3 haplotype on testosterone transport and clinical outcome in caucasian patients with androgen-independent prostatic cancer, Clin. Cancer Res. 14 (11) (2008) 3312–3318.
[43] J.L. Wright, et al., CYP17 polymorphisms and prostate cancer outcomes, Prostate 70 (10) (2010) 1094–2101.
[44] A. Gsur, et al., A polymorphism in the CYP17 gene is associated with prostate cancer risk, Int. J. Cancer 87 (3) (2000) 434–437.
[45] R.C. Sobti, et al., Role of hormonal genes and risk of prostate cancer: gene-gene interactions in a North Indian population, Cancer Genet. Cytogenet. 185 (2) (2008) 78–85.
[46] R.C. Sobti, et al., CYP17 gene polymorphism and its association in north Indian prostate cancer patients, Anticancer Res. 29 (5) (2009) 1659–1663.
[47] I.H. Onen, et al., The association of 5alpha-reductase II (SRD5A2) and 17 hydroxylase (CYP17) gene polymorphisms with prostate cancer patients in the Turkish population, DNA Cell Biol. 26 (2) (2007) 100–107.
[48] R.C. Sobti, et al., CYP17, SRD5A2, CYP1B1, and CYP2D6 gene polymorphisms with prostate cancer risk in North Indian population, DNA Cell Biol. 25 (5) (2006) 287–294.
[49] Y. Yamada, et al., Impact of genetic polymorphisms of 17-hydroxylase cytochrome P-450 (CYP17) and steroid 5alpha-reductase type II (SRD5A2) genes on prostate-cancer risk among the Japanese population, Int. J. Cancer 92 (5) (2001) 683–686.
[50] E. Taioli, et al., Polymorphisms in CYP17 and CYP3A4 and prostate cancer in men of African descent, Prostate 73 (6) (2013) 668–676.
[51] M.S. Cicek, et al., Association of prostate cancer risk and aggressiveness to androgen pathway genes: SRD5A2, CYP17, and the AR, Prostate 59 (1) (2004) 69–76.
[52] J.M. Cunningham, et al., Evaluation of genetic variations in the androgen and estrogen metabolic pathways as risk factors for sporadic and familial prostate cancer, Cancer Epidemiol. Biomark. Prev. 16 (5) (2007) 969–978.
[53] O. Cussenot, et al., Combination of polymorphisms from genes related to estrogen metabolism and risk of prostate cancers: the hidden face of estrogens, J. Clin. Oncol. 25 (24) (2007) 3596–3602.
[54] A. dos Santos, et al., No association of the 5′ promoter region polymorphism of CYP17 gene with prostate cancer risk, Prostate Cancer Prostatic Dis. 5 (1) (2002) 28–31.
[55] R.M. dos Santos, et al., PSA and androgen-related gene (AR, CYP17, and CYP19) polymorphisms and the risk of adenocarcinoma at prostate biopsy, DNA Cell Biol. 27 (9) (2008) 497–503.
[56] M.S. Forrest, et al., Association between hormonal genetic polymorphisms and early-onset prostate cancer, Prostate Cancer Prostatic Dis. 8 (1) (2005) 95–102.
[57] S. Gunes, et al., Prostate-specific antigen and 17-hydroxylase polymorphic genotypes in patients with prostate cancer and benign prostatic hyperplasia, DNA Cell Biol. 26 (12) (2007) 873–878.
[58] A.G. Latil, et al., Prostate carcinoma risk and allelic variants of genes involved in androgen biosynthesis and metabolism pathways, Cancer 92 (5) (2001) 1130–1137.
[59] S. Lindstrom, et al., Inherited variation in hormone-regulating genes and prostate cancer survival, Clin. Cancer Res. 13 (17) (2007) 5156–5161.
[60] H. Tigli, H. Yazici, N. Dalay, Cyp17 genetic polymorphism in prostate cancer and benign prostatic hyperplasia, Res. Commun. Mol. Pathol. Pharmacol. 113–114 (2003) 307–314.
[61] Z. Vesovic, et al., Role of a CYP17 promoter polymorphism for familial prostate cancer risk in Germany, Anticancer Res. 25 (2B) (2005) 1303–1307.
[62] J. Yang, et al., Polymorphisms of metabolic enzyme genes, living habits and prostate cancer susceptibility, Front. Biosci. 11 (2006) 2052–2060.
[63] M. Risio, et al., Genetic polymorphisms of CYP17A1, vitamin D receptor and androgen receptor in Italian heredo-familial and sporadic prostate cancers, Cancer Epidemiol. 35 (4) (2011) e18–e24.
[64] L. Cai, W. Huang, K.C. Chou, Prostate cancer with variants in CYP17 and UGT2B17 genes: a meta-analysis, Protein Pept. Lett. 19 (1) (2012) 62–69.
[65] N. Sharifi, The 5alpha-androstanedione pathway to dihydrotestosterone in castration-resistant prostate cancer, J. Investig. Med. 60 (2) (2012) 504–507.
[66] I.M. Thompson, et al., The influence of finasteride on the development of prostate cancer, N. Engl. J. Med. 349 (3) (2003) 215–224.
[67] I.M. Thompson Jr., et al., Long-term survival of participants in the prostate cancer prevention trial, N. Engl. J. Med. 369 (7) (2013) 603–610.
[68] J.K. Reichardt, et al., Genetic variability of the human SRD5A2 gene: implications for prostate cancer risk, Cancer Res. 55 (18) (1995) 3973–3975.
[69] N. Makridakis, J.K. Reichardt, Pharmacogenetic analysis of human steroid 5 alpha reductase type II: comparison of finasteride and dutasteride, J. Mol. Endocrinol. 34 (3) (2005) 617–623.
[70] N.M. Makridakis, et al., Association of mis-sense substitution in SRD5A2 gene with prostate cancer in African-American and Hispanic men in Los Angeles, USA, Lancet 354 (9183) (1999) 975–978.
[71] N. Makridakis, et al., A prevalent missense substitution that modulates activity of prostatic steroid 5alpha-reductase, Cancer Res. 57 (6) (1997) 1020–1022.
[72] V.M. Hayes, et al., 5alpha-Reductase type 2 gene variant associations with prostate cancer risk, circulating hormone levels and androgenetic alopecia, Int. J. Cancer 120 (4) (2007) 776–780.
[73] N.E. Allen, et al., Association between two polymorphisms in the SRD5A2 gene and serum androgen concentrations in British men, Cancer Epidemiol. Biomark. Prev. 12 (6) (2003) 578–581.
[74] I. Boger-Megiddo, et al., V89L polymorphism of the 5alpha-reductase Type II gene (SRD5A2), endogenous sex hormones, and prostate cancer risk, Cancer Epidemiol. Biomark. Prev. 17 (2) (2008) 286–291.
[75] P.G. Febbo, et al., The V89L polymorphism in the 5alpha-reductase type 2 gene and risk of prostate cancer, Cancer Res. 59 (23) (1999) 5878–5881.
[76] Y.L. Giwercman, et al., The 5alpha-reductase type II A49T and V89L high-activity allelic variants are more common in men with prostate cancer compared with the general population, Eur. Urol. 48 (4) (2005) 679–685.
[77] S. Rajender, et al., Longer (TA)n repeat but not A49T and V89L polymorphisms in SRD5A2 gene may confer prostate cancer risk in South Indian men, J. Androl. 30 (6) (2009) 703–710.
[78] B.L. Chang, et al., Evaluation of SRD5A2 sequence variants in susceptibility to hereditary and sporadic prostate cancer, Prostate 56 (1) (2003) 37–44.
[79] P.W. Kantoff, et al., A polymorphism of the 5 alpha-reductase gene and its association with prostate cancer: a case-control analysis, Cancer Epidemiol. Biomark. Prev. 6 (3) (1997) 189–192.
[80] N. Lamharzi, et al., Polymorphic markers in the 5alpha-reductase type II gene and the incidence of prostate cancer, Int. J. Cancer 105 (4) (2003) 480–483.
[81] K. Margiotti, et al., Evidence for an association between the SRD5A2 (type II steroid 5 alpha-reductase) locus and prostate cancer in Italian patients, Dis. Markers 16 (3–4) (2000) 147–150.
[82] N. Mononen, et al., A missense substitution A49T in the steroid 5-alpha-reductase gene (SRD5A2) is not associated with prostate cancer in Finland, Br. J. Cancer 84 (10) (2001) 1344–1347.
[83] C.L. Pearce, et al., No association between the SRD5A2 gene A49T missense variant and prostate cancer risk: lessons learned, Hum. Mol. Genet. 17 (16) (2008) 2456–2461.
[84] M.T. Salam, et al., Associations between polymorphisms in the steroid 5-alpha reductase type II (SRD5A2) gene and benign prostatic hyperplasia and prostate cancer, Urol. Oncol. 23 (4) (2005) 246–253.
[85] T. Soderstrom, et al., 5alpha-reductase 2 polymorphisms as risk factors in prostate cancer, Pharmacogenetics 12 (4) (2002) 307–312.
[86] J. Li, et al., Steroid 5-{alpha}-reductase Type 2 (SRD5a2) gene polymorphisms and risk of prostate cancer: a HuGE review, Am. J. Epidemiol. 171 (1) (2010) 1–13.
[87] X. Li, et al., Meta-analysis of three polymorphisms in the steroid-5-alpha-reductase, alpha polypeptide 2 gene (SRD5A2) and risk of prostate cancer, Mutagenesis 26 (3) (2011) 371–383.
[88] Q. Li, et al., Steroid 5-alpha-reductase type 2 (SRD5A2) V89L and A49T polymorphisms and sporadic prostate cancer risk: a meta-analysis, Mol. Biol. Rep. 40 (5) (2013) 3597–3608.

[89] T.R. Rebbeck, et al., Joint effects of inflammation and androgen metabolism on prostate cancer severity, Int. J. Cancer 123 (6) (2008) 1385–1389.
[90] M.H. Vaarala, et al., The interaction of CYP3A5 polymorphisms along the androgen metabolism pathway in prostate cancer, Int. J. Cancer 122 (11) (2008) 2511–2516.
[91] J.M. Jaffe, et al., Association of SRD5A2 genotype and pathological characteristics of prostate tumors, Cancer Res. 60 (6) (2000) 1626–1630.
[92] R.O. Roberts, et al., Polymorphisms in the 5alpha reductase type 2 gene and urologic measures of BPH, Prostate 62 (4) (2005) 380–387.
[93] A. Shibata, et al., Polymorphisms in the androgen receptor and type II 5 alpha-reductase genes and prostate cancer prognosis, Prostate 52 (4) (2002) 269–278.
[94] J.K. Scariano, et al., The SRD5A2 V89L polymorphism is associated with severity of disease in men with early onset prostate cancer, Prostate 68 (16) (2008) 1798–1805.
[95] C. Neslund-Dudas, et al., SRD5A2 and HSD3B2 polymorphisms are associated with prostate cancer risk and aggressiveness, Prostate 67 (15) (2007) 1654–1663.
[96] S.I. Berndt, et al., Variant in sex hormone-binding globulin gene and the risk of prostate cancer, Cancer Epidemiol. Biomark. Prev. 16 (1) (2007) 165–168.
[97] A.W. Hsing, et al., Polymorphic markers in the SRD5A2 gene and prostate cancer risk: a population-based case-control study, Cancer Epidemiol. Biomark. Prev. 10 (10) (2001) 1077–1082.
[98] C.L. Pearce, et al., Steroid 5-alpha reductase type II V89L substitution is not associated with risk of prostate cancer in a multiethnic population study, Cancer Epidemiol. Biomark. Prev. 11 (4) (2002) 417–418.
[99] K.C. Torkko, et al., VDR and SRD5A2 polymorphisms combine to increase risk for prostate cancer in both non-Hispanic White and Hispanic White men, Clin. Cancer Res. 14 (10) (2008) 3223–3229.
[100] Z. Li, et al., Association of V89L SRD5A2 polymorphism with prostate cancer development in a Japanese population, J. Urol. 169 (6) (2003) 2378–2381.
[101] R.K. Nam, et al., V89L polymorphism of type-2, 5-alpha reductase enzyme gene predicts prostate cancer presence and progression, Urology 57 (1) (2001) 199–204.
[102] C. Yang, et al., A49T, V89L and TA repeat polymorphisms of steroid 5alpha-reductase type II and breast cancer risk in Japanese women, Breast Cancer Res. 4 (4) (2002) R8.
[103] E. Audet-Walsh, et al., SRD5A polymorphisms and biochemical failure after radical prostatectomy, Eur. Urol. 60 (6) (2011) 1226–1234.
[104] B. Gottlieb, et al., The androgen receptor gene mutations database: 2012 update, Hum. Mutat. 33 (5) (2012) 887–894.
[105] B.J. Feldman, D. Feldman, The development of androgen-independent prostate cancer, Nat. Rev. 1 (1) (2001) 34–45.
[106] M.P. Steinkamp, et al., Treatment-dependent androgen receptor mutations in prostate cancer exploit multiple mechanisms to evade therapy, Cancer Res. 69 (10) (2009) 4434–4442.
[107] Z. Guo, Y. Qiu, A new trick of an old molecule: androgen receptor splice variants taking the stage?! Int. J. Biol. Sci. 7 (6) (2011) 815–822.
[108] S. Haile, M.D. Sadar, Androgen receptor and its splice variants in prostate cancer, Cell. Mol. Life Sci. 68 (24) (2011) 3971–3981.
[109] S. Rajender, L. Singh, K. Thangaraj, Phenotypic heterogeneity of mutations in androgen receptor gene, Asian J. Androl. 9 (2) (2007) 147–179.
[110] E. Giovannucci, Is the androgen receptor CAG repeat length significant for prostate cancer? Cancer Epidemiol. Biomark. Prev. 11 (10 Pt 1) (2002) 985–986.
[111] G.A. Coetzee, R.K. Ross, Re: Prostate cancer and the androgen receptor, J. Natl. Cancer Inst. 86 (11) (1994) 872–873.
[112] D.K. Price, et al., Androgen receptor CAG repeat length and association with prostate cancer risk: results from the prostate cancer prevention trial, J. Urol. 184 (6) (2010) 2297–2302.
[113] D.M. Thompson, G.N. Gill, The EGF receptor: structure, regulation and potential role in malignancy, Cancer Surv. 4 (4) (1985) 767–788.
[114] W.J. Gullick, Type I growth factor receptors: current status and future work, Biochem. Soc. Symp. 63 (1998) 193–198.
[115] V. Kumar, S.A. Bustin, I.A. McKay, Transforming growth factor alpha, Cell Biol. Int. 19 (5) (1995) 373–388.
[116] J. Boonstra, et al., The epidermal growth factor, Cell Biol. Int. 19 (5) (1995) 413–430.
[117] G.J. Kelloff, et al., Epidermal growth factor receptor tyrosine kinase inhibitors as potential cancer chemopreventives, Cancer Epidemiol. Biomark. Prev. 5 (8) (1996) 657–666.
[118] K. Malarkey, et al., The regulation of tyrosine kinase signalling pathways by growth factor and G-protein-coupled receptors, Biochem. J. 309 (Pt 2) (1995) 361–375.
[119] R. Derynck, et al., Synthesis of messenger RNAs for transforming growth factors alpha and beta and the epidermal growth factor receptor by human tumors, Cancer Res. 47 (3) (1987) 707–712.
[120] E.O. Olapade-Olaopa, et al., Evidence for the differential expression of a variant EGF receptor protein in human prostate cancer, Br. J. Cancer 82 (1) (2000) 186–194.
[121] A.S. Neto, et al., Molecular oncogenesis of prostate adenocarcinoma: role of the human epidermal growth factor receptor 2 (HER-2/neu), Tumori 96 (5) (2010) 645–649.
[122] C.M. Rocha-Lima, et al., EGFR targeting of solid tumors, Cancer Control 14 (3) (2007) 295–304.
[123] G. Di Lorenzo, et al., Expression of epidermal growth factor receptor correlates with disease relapse and progression to androgen-independence in human prostate cancer, Clin. Cancer Res. 8 (11) (2002) 3438–3444.
[124] C. Vicentini, et al., Prostate cancer cell proliferation is strongly reduced by the epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 in vitro on human cell lines and primary cultures, J. Cancer Res. Clin. Oncol. 129 (3) (2003) 165–174.
[125] A.L. Teixeira, et al., Genetic polymorphism in EGF is associated with prostate cancer aggressiveness and progression-free interval in androgen blockade-treated patients, Clin. Cancer Res. 14 (11) (2008) 3367–3371.
[126] D.A. Bhowmick, et al., A functional polymorphism in the EGF gene is found with increased frequency in glioblastoma multiforme patients and is associated with more aggressive disease, Cancer Res. 64 (4) (2004) 1220–1223.
[127] B.M. Costa, et al., Association between functional EGF + 61 polymorphism and glioma risk, Clin. Cancer Res. 13 (9) (2007) 2621–2626.
[128] M. Shahbazi, et al., Association between functional polymorphism in EGF gene and malignant melanoma, Lancet 359 (9304) (2002) 397–401.
[129] C.A. Perez, et al., The EGFR polymorphism rs884419 is associated with freedom from recurrence in patients with resected prostate cancer, J. Urol. 183 (5) (2010) 2062–2069.
[130] E. Tischer, et al., The human gene for vascular endothelial growth factor. Multiple protein forms are encoded through alternative exon splicing, J. Biol. Chem. 266 (18) (1991) 11947–11954.
[131] F.A. Ferrer, et al., Expression of vascular endothelial growth factor receptors in human prostate cancer, Urology 54 (3) (1999) 567–572.
[132] M.W. Jackson, J.M. Bentel, W.D. Tilley, Vascular endothelial growth factor (VEGF) expression in prostate cancer and benign prostatic hyperplasia, J. Urol. 157 (6) (1997) 2323–2328.
[133] L.E. Benjamin, et al., Selective ablation of immature blood vessels in established human tumors follows vascular endothelial growth factor withdrawal, J. Clin. Invest. 103 (2) (1999) 159–165.
[134] A. Minchenko, et al., Hypoxia regulatory elements of the human vascular endothelial growth factor gene, Cell. Mol. Biol. Res. 40 (1) (1994) 35–39.
[135] A. Schultz, et al., Interindividual heterogeneity in the hypoxic regulation of VEGF: significance for the development of the coronary artery collateral circulation, Circulation 100 (5) (1999) 547–552.
[136] S. Sfar, et al., Combined effects of the angiogenic genes polymorphisms on prostate cancer susceptibility and aggressiveness, Mol. Biol. Rep. 36 (1) (2009) 37–45.
[137] S. Sfar, et al., Association of VEGF genetic polymorphisms with prostate carcinoma risk and clinical outcome, Cytokine 35 (1–2) (2006) 21–28.
[138] S.L. McCarron, et al., Influence of cytokine gene polymorphisms on the development of prostate cancer, Cancer Res. 62 (12) (2002) 3369–3372.
[139] C.C. Lin, et al., Vascular endothelial growth factor gene-460 C/T polymorphism is a biomarker for prostate cancer, Urology 62 (2) (2003) 374–377.
[140] T.T. Hong, et al., Polymorphism of vascular endothelial growth factor -1154G > A (rs1570360) with cancer risk: a meta-analysis of 16 case-control studies, Mol. Biol. Rep. 39 (5) (2012) 5283–5289.
[141] T. Langsenlehner, et al., Single nucleotide polymorphisms and haplotypes in the gene for vascular endothelial growth factor and risk of prostate cancer, Eur J Cancer 44 (11) (2008) 1572–1576.
[142] L. Jain, et al., The role of vascular endothelial growth factor SNPs as predictive and prognostic markers for major solid tumors, Mol. Cancer Ther. 8 (9) (2009) 2496–2508.
[143] D.J. Woollard, et al., Differential expression of VEGF ligands and receptors in prostate cancer, Prostate 3 (6) (2013) 563–572.
[144] H. Nakagawa, Prostate cancer genomics by high-throughput technologies: genome-wide association study and sequencing analysis, Endocr. Relat. Cancer 20 (4) (2013) R171–R181.
[145] R.A. Eeles, et al., Identification of seven new prostate cancer susceptibility loci through a genome-wide association study, Nat. Genet. 41 (10) (2009) 1116–1121.
[146] R.A. Eeles, et al., Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array, Nat. Genet. 45 (4) (2013) 385–391 (391e1-2).
[147] J. Gudmundsson, et al., Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24, Nat. Genet. 39 (5) (2007) 631–637.
[148] C.A. Haiman, et al., Multiple regions within 8q24 independently affect risk for prostate cancer, Nat. Genet. 39 (5) (2007) 638–644.
[149] M. Yeager, et al., Genome-wide association study of prostate cancer identifies a second risk locus at 8q24, Nat. Genet. 39 (5) (2007) 645–649.
[150] R.A. Eeles, et al., Multiple newly identified loci associated with prostate cancer susceptibility, Nat. Genet. 40 (3) (2008) 316–321.
[151] H.H. Nguyen, et al., IRX4 at 5p15 suppresses prostate cancer growth through the interaction with vitamin D receptor, conferring prostate cancer susceptibility, Hum. Mol. Genet. 21 (9) (2012) 2076–2085.
[152] R. Takata, et al., Genome-wide association study identifies five new susceptibility loci for prostate cancer in the Japanese population, Nat. Genet. 42 (9) (2010) 751–754.
[153] J. Xu, et al., Genome-wide association study in Chinese men identifies two new prostate cancer risk loci at 9q31.2 and 19q13.4, Nat. Genet. 44 (11) (2012) 1231–1235.
[154] M. Salem, J.A. Garcia, Abiraterone acetate, a novel adrenal inhibitor in metastatic castration-resistant prostate cancer, Curr. Oncol. Rep. 13 (2) (2011) 92–96.
[155] S.K. Pal, C.A. Stein, O. Sartor, Enzalutamide for the treatment of prostate cancer, Expert. Opin. Pharmacother. 14 (5) (2013) 679–685.
[156] R.W. Ross, et al., Inherited variation in the androgen pathway is associated with the efficacy of androgen-deprivation therapy in men with prostate cancer, J. Clin. Oncol. 26 (6) (2008) 842–847.
[157] T. Yamada, et al., Genetic polymorphisms of CYP17A1 in steroidogenesis pathway are associated with risk of progression to castration-resistant prostate cancer in Japanese men receiving androgen deprivation therapy, Int. J. Clin. Oncol. 18 (4) (2013) 711–717.
[158] C.C. Yu, et al., Molecular markers in sex hormone pathway genes associated with the efficacy of androgen-deprivation therapy for prostate cancer, PLoS ONE 8 (1) (2013) e54627.

[159] M. Yang, et al., SLCO2B1 and SLCO1B3 may determine time to progression for patients receiving androgen deprivation therapy for prostate cancer, J. Clin. Oncol. 29 (18) (2011) 2565–2573.
[160] E.C. Connolly, J. Freimuth, R.J. Akhurst, Complexities of TGF-beta targeted cancer therapy, Int. J. Biol. Sci. 8 (7) (2012) 964–978.
[161] E. Levesque, et al., Molecular markers in key steroidogenic pathways, circulating steroid levels, and prostate cancer progression, Clin. Cancer Res. 19 (3) (2013) 699–709.
[162] A.L. Teixeira, et al., Improvement of a predictive model of castration-resistant prostate cancer: functional genetic variants in TGFbeta1 signaling pathway modulation, PLoS ONE 8 (8) (2013) e72419.
[163] J.B. Pao, et al., Vitamin D receptor gene variants and clinical outcomes after androgen-deprivation therapy for prostate cancer, World J. Urol. 31 (2) (2013) 281–287.
[164] J.D. Schoenfeld, et al., A single nucleotide polymorphism in inflammatory gene RNASEL predicts outcome after radiation therapy for localized prostate cancer, Clin. Cancer Res. 19 (6) (2013) 1612–1619.
[165] J.M. Liu, et al., Effect of IL-18 gene promoter polymorphisms on prostate cancer occurrence and prognosis in Han Chinese population, Genet. Mol. Res. 12 (1) (2013) 820–829.
[166] B.Y. Bao, et al., Significant associations of prostate cancer susceptibility variants with survival in patients treated with androgen-deprivation therapy, Int. J. Cancer 130 (4) (2012) 876–884.
[167] B.Y. Bao, et al., Polymorphisms inside microRNAs and microRNA target sites predict clinical outcomes in prostate cancer patients receiving androgen-deprivation therapy, Clin. Cancer Res. 17 (4) (2011) 928–936.
[168] A. Dahlman, et al., Effect of androgen deprivation therapy on the expression of prostate cancer biomarkers MSMB and MSMB-binding protein CRISP3, Prostate Cancer Prostatic Dis. 13 (4) (2010) 369–375.
[169] C.N. Huang, et al., Genetic polymorphisms in oestrogen receptor-binding sites affect clinical outcomes in patients with prostate cancer receiving androgen-deprivation therapy, J. Intern. Med. 271 (5) (2012) 499–509.
[170] S.P. Huang, et al., Genetic variants in CASP3, BMP5, and IRS2 genes may influence survival in prostate cancer patients receiving androgen-deprivation therapy, PLoS ONE 7 (7) (2012) e41219.
[171] S.P. Huang, et al., Genetic variants in nuclear factor-kappa B binding sites are associated with clinical outcomes in prostate cancer patients, Eur. J. Cancer 49 (17) (2013) 3729–3737.
[172] M. Kohli, et al., Germline predictors of androgen deprivation therapy response in advanced prostate cancer, Mayo Clin. Proc. 87 (3) (2012) 240–246.
[173] S.D. Baker, A. Sparreboom, J. Verweij, Clinical pharmacokinetics of docetaxel: recent developments, Clin. Pharmacokinet. 45 (3) (2006) 235–252.
[174] R. Bruno, et al., Alpha-1-acid glycoprotein as an independent predictor for treatment effects and a prognostic factor of survival in patients with non-small cell lung cancer treated with docetaxel, Clin. Cancer Res. 9 (3) (2003) 1077–1082.
[175] R. Bruno, et al., Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies in patients with cancer, J. Clin. Oncol. 16 (1) (1998) 187–196.
[176] T.M. Sissung, et al., ABCB1 genetic variation influences the toxicity and clinical outcome of patients with androgen-independent prostate cancer treated with docetaxel, Clin. Cancer Res. 14 (14) (2008) 4543–4549.
[177] T.M. Sissung, et al., Association of the CYP1B1*3 allele with survival in patients with prostate cancer receiving docetaxel, Mol. Cancer Ther. 7 (1) (2008) 19–26.
[178] C. Veyrat-Follet, et al., Clinical trial simulation of docetaxel in patients with cancer as a tool for dosage optimization, Clin. Pharmacol. Ther. 68 (6) (2000) 677–687.
[179] M. Shou, et al., Role of human cytochrome P450 3A4 and 3A5 in the metabolism of taxotere and its derivatives: enzyme specificity, interindividual distribution and metabolic contribution in human liver, Pharmacogenetics 8 (5) (1998) 391–401.
[180] H.A. Bardelmeijer, et al., Low systemic exposure of oral docetaxel in mice resulting from extensive first-pass metabolism is boosted by ritonavir, Cancer Res. 62 (21) (2002) 6158–6164.
[181] M.T. Huisman, et al., MRP2 (ABCC2) transports taxanes and confers paclitaxel resistance and both processes are stimulated by probenecid, Int. J. Cancer 116 (5) (2005) 824–829.
[182] N.F. Smith, et al., Identification of OATP1B3 as a high-affinity hepatocellular transporter of paclitaxel, Cancer Biol. Ther. 4 (8) (2005) 815–818.
[183] L. van Zuylen, et al., Role of intestinal P-glycoprotein in the plasma and fecal disposition of docetaxel in humans, Clin. Cancer Res. 6 (7) (2000) 2598–2603.
[184] T.M. Sissung, et al., Association of ABCB1 genotypes with paclitaxel-mediated peripheral neuropathy and neutropenia, Eur J Cancer 42 (17) (2006) 2893–2896.
[185] T.M. Bosch, et al., Pharmacogenetic screening of CYP3A and ABCB1 in relation to population pharmacokinetics of docetaxel, Clin. Cancer Res. 12 (19) (2006) 5786–5793.
[186] F.K. Engels, et al., Influence of ketoconazole on the fecal and urinary disposition of docetaxel, Cancer Chemother. Pharmacol. 60 (4) (2007) 569–579.
[187] B.C. Goh, et al., Explaining interindividual variability of docetaxel pharmacokinetics and pharmacodynamics in Asians through phenotyping and genotyping strategies, J. Clin. Oncol. 20 (17) (2002) 3683–3690.
[188] N.M. Hahn, et al., Hoosier Oncology Group randomized phase II study of docetaxel, vinorelbine, and estramustine in combination in hormone-refractory prostate cancer with pharmacogenetic survival analysis, Clin. Cancer Res. 12 (20 Pt 1) (2006) 6094–6099.
[189] S.Y. Hor, et al., PXR, CAR and HNF4alpha genotypes and their association with pharmacokinetics and pharmacodynamics of docetaxel and doxorubicin in Asian patients, Pharmacogenomics J. 8 (2) (2008) 139–146.
[190] K. Kiyotani, et al., Association of genetic polymorphisms in SLCO1B3 and ABCC2 with docetaxel-induced leukopenia, Cancer Sci. 99 (5) (2008) 967–972.
[191] L.D. Lewis, et al., A comparison of the pharmacokinetics and pharmacodynamics of docetaxel between African-American and Caucasian cancer patients: CALGB 9871, Clin. Cancer Res. 13 (11) (2007) 3302–3311.
[192] S.D. Baker, et al., Pharmacogenetic pathway analysis of deocetaxel elimination, Clin. Pharmacol. Ther. 85 (2) (2009) 155–163.
[193] A. Tran, et al., Pharmacokinetics and toxicity of docetaxel: role of CYP3A, MDR1, and GST polymorphisms, Clin. Pharmacol. Ther. 79 (6) (2006) 570–580.
[194] D.M. Carnell, et al., Target validation of cytochrome P450 CYP1B1 in prostate carcinoma with protein expression in associated hyperplastic and premalignant tissue, Int. J. Radiat. Oncol. Biol. Phys. 58 (2) (2004) 500–509.
[195] D.J. Woollard, et al., Differential expression of VEGF ligands and receptors in prostate cancer, Prostate 3 (6) (2013) 563–572.
[196] W.D. Figg, et al., Pre-clinical and clinical evaluation of estramustine, docetaxel and thalidomide combination in androgen-independent prostate cancer, BJU Int. 99 (5) (2007) 1047–1055.
[197] I. Pastina, et al., Cytochrome 450 1B1 (CYP1B1) polymorphisms associated with response to docetaxel in Castration-Resistant Prostate Cancer (CRPC) patients, BMC Cancer 10 (2010) 511.
[198] R. Rizzo, et al., Association of CYP1B1 with hypersensitivity induced by taxane therapy in breast cancer patients, Breast Cancer Res. Treat. 124 (2) (2010) 593–598.
[199] F. Desarnaud, et al., Gene expression profiling of the androgen independent prostate cancer cells demonstrates complex mechanisms mediating resistance to docetaxel, Cancer Biol. Ther. 11 (2) (2011) 204–212.
[200] C. Kimchi-Sarfaty, et al., Ethnicity-related polymorphisms and haplotypes in the human ABCB1 gene, Pharmacogenomics 8 (1) (2007) 29–39.
[201] Y. Imai, et al., C421A polymorphism in the human breast cancer resistance protein gene is associated with low expression of Q141K protein and low-level drug resistance, Mol. Cancer Ther. 1 (8) (2002) 611–616.
[202] D. Kobayashi, et al., Functional assessment of ABCG2 (BCRP) gene polymorphisms to protein expression in human placenta, Drug Metab. Dispos. 33 (1) (2005) 94–101.
[203] D. Kolwankar, et al., Expression and function of ABCB1 and ABCG2 in human placental tissue, Drug Metab. Dispos. 33 (4) (2005) 524–529.
[204] C. Kondo, et al., Functional analysis of SNPs variants of BCRP/ABCG2, Pharm. Res. 21 (10) (2004) 1895–1903.
[205] A. Sparreboom, et al., Diflomotecan pharmacokinetics in relation to ABCG2 421C > A genotype, Clin. Pharmacol. Ther. 76 (1) (2004) 38–44.
[206] Y. Bessho, et al., Role of ABCG2 as a biomarker for predicting resistance to CPT-11/SN-38 in lung cancer, Cancer Sci. 97 (3) (2006) 192–198.
[207] M.D. Galsky, et al., Cabazitaxel, Nat. Rev. Drug Discov. 9 (9) (2010) 677–678.
[208] J.S. de Bono, et al., Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial, Lancet 376 (9747) (2010) 1147–1154.
[209] L.A. Doyle, et al., A multidrug resistance transporter from human MCF-7 breast cancer cells, Proc. Natl. Acad. Sci. U. S. A. 95 (26) (1998) 15665–15670.
[210] K. Miyake, et al., Molecular cloning of cDNAs which are highly overexpressed in mitoxantrone-resistant cells: demonstration of homology to ABC transport genes, Cancer Res. 59 (1) (1999) 8–13.
[211] S. Mizuarai, N. Aozasa, H. Kotani, Single nucleotide polymorphisms result in impaired membrane localization and reduced atpase activity in multidrug transporter ABCG2, Int. J. Cancer 109 (2) (2004) 238–246.
[212] K. Morisaki, et al., Single nucleotide polymorphisms modify the transporter activity of ABCG2, Cancer Chemother. Pharmacol. 56 (2) (2005) 161–172.
[213] A. Tamura, et al., Re-evaluation and functional classification of non-synonymous single nucleotide polymorphisms of the human ATP-binding cassette transporter ABCG2, Cancer Sci. 98 (2) (2007) 231–239.
[214] N. Sharifi, et al., A polymorphism in a transporter of testosterone is a determinant of androgen independence in prostate cancer, BJU Int. 102 (5) (2008) 617–621.
[215] J.F. Deeken, et al., A pharmacogenetic study of docetaxel and thalidomide in patients with castration-resistant prostate cancer using the DMET genotyping platform, Pharmacogenomics J. 10 (3) (2010) 191–199.