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Molecular basis for prostate cancer racial disparities

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Abstract

Prostate cancer (PCa) remains the most common cancer in American men. African-American (AA) men continue to have higher PCa prevalence and mortality rates compared to men in other populations. In addition to socioeconomic factors and lifestyle differences, molecular alterations contribute to this discrepancy. We summarize molecular genetics research results interrelated with the biology of PCa racial disparity. Androgen and androgen receptor (AR) pathways have long been associated with prostate growth. Racial differences have also been found among variants of genes of the enzymes involved in androgen biosynthesis and metabolism. Growth factors and their receptors are a potential cause of the disparity in PCa. Recent molecular and biotechnological approaches in the field of proteomics and genomics will greatly aid the advancement of translational research on racial disparity in PCa, which may help, in finding new prognostic markers and novel therapeutic approaches for the treatment of PCa in AA.

Keywords

Prostate Cancer; Androgen Receptors (AR); Racial Disparity

2. INTRODUCTION

Prostate cancer (PCa) is the second most common cause of death from malignancy in American men. The incidence of PCa varies widely between ethnic populations and countries. In 2015, approximately 220,800 cases of prostate cancer was newly diagnosed; 27,540 PCa deaths were estimated in the United States. PCa is the most commonly diagnosed cancer among African American (AA) men. In AA, there is a higher incidence of PCa at a younger age with poor prognosis than men of other ethnicities (1–3). It is estimated that one in five AA men will be diagnosed with prostate cancer in their lifetime (4). Along with positive family history and older age, African ancestry has long been recognized as an important risk factor for PCa (5, 6). The underlying reasons for this disparity are not well understood, although existing evidence implicates important genetic components. While it has been argued that racial variation may be largely due to lifestyle, dietary, socioeconomic (7, 8), or clinical factors, these cannot fully explain the discrepancy (1–3, 9) or the results of migration studies, and consequently, genetic parameters may be important. Studies of the

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pathology and recurrence of tumors in AA and Caucasian American (CA) men have suggested that racial differences in the biology of PCa tumors may explain observed differences in outcome (10, 11).

Although there are some effective treatment approaches for clinically localized PCa through surgery and radiotherapy, however, the metastatic PCa remains incurable. The metastatic potential of tumor cells and its possible dissemination to secondary sites are critical factors related to its mortality rates. In spite of the high incidence and mortality rates, the molecular mechanisms involved in oncogenesis and progression to PCa are still poorly understood, especially related to the progression to the metastatic form. PCa etiology remains obscure and its tumors vary from indolent forms with low progression rates to extremely aggressive with rapid growth rates. Several methods have been used for the study of oncogenes expression, characterization, chromosomal aberrations and heredity loci in this neoplastic disease (12, 13). In the current review, we are highlighting recent research on differential androgen levels in prostate cancer development in ethnic population.

3. DIFFERENTIAL ANDROGEN LEVELS IN PROSTATE CANCER DEVELOPMENT IN ETHNIC POPULATION

Androgens and the androgen receptor pathway constitute the most intensely studied field in PCa. Several aspects of the pathway are related to the racial disparity of PCa.

3.1. Androgen receptors (AR)

Prostate cells require androgen stimulation in the form of testosterone and 5α-dihydrotestosterone (DHT-A) for normal growth and maintenance. The AR is the key receiver of androgen signal. After formation of the complex AR- androgen, it translocated to the nucleus and acts in the transcription of androgen response genes (14). AR- androgen complex regulates the expression of genes necessary for the growth and development of both normal and malignant prostate tissue. Immunohistochemical studies of malignant and benign prostate tissue from AA and Caucasian American (CA) men who underwent radical prostatectomy for PCa, showed expression of AR protein was 22% higher in the benign prostate and 81% higher in PCa of AA patients (15). This suggests that differences in androgenic stimulation may play an important role in racial disparity.

The AR gene is over 90 kb in length, located within chromosome Xq11–12 and has eight exons. Exon 1 encodes the N-terminal (transactivation) domain, which controls transcriptional activation of the receptor as well as two polymorphic trinucleotide repeats (CAG and GGC), which code for polyglutamine and polyglycine tracts, respectively, in the N-terminal domain. Studies have shown that CAG repeat varies in length from 11 to 31 repeats in normal men (16), and an inverse relationship has been demonstrated between CAG repeat length and AR transcriptional activation ability (17). Short CAG and GGC repeat lengths are associated with an increased risk of developing PCa (18–20), specifically individuals with CAG repeat length less than 20 and GGC repeat length less than 16 (18, 20–22). AA men populations have significantly shorter repeat length than CA men (17, 23, 24).

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Prostate cancer may occur at a younger age and progress more rapidly in AA than CA because of racial differences in androgenic stimulation of the prostate. CWR-22 xenograft model of androgen regulated genes include CDK1 and CDK2, cyclin A and B1 (25); α-enolase, α-tubulin, IκBα, IGFBP-5 (26), PSA, *h*K-2, Nkx3.1., ARA-70 (27); EF-1α, tomoregulin, TRX-R1, and M*xi*-1 are expressed at higher levels in recurrent and androgen-dependent tumors with higher proliferation rate in PCa (27, 28).

3.2. Serum androgen levels

Although there is no clear relationship between circulating androgen levels and PCa (29–31), high levels of androgens have long been considered as risk factor (29, 32). Racial differences in maternal androgens during gestation, serum androgens and time of puberty during adolescence may imprint the AA prostate to respond more to similar levels of androgenic stimulation in adulthood. AA men (aged 31 to 50) have higher mean serum testosterone level (15%) (33) than CA men (34). However, elevated testosterone and dihydrotestosterone (DHT) have not been persuasively shown to increase the risk of PCa (35).

3.3. Tissue androgens

Testosterone is the major circulating androgen, and DHT is 1/10 the concentration of testosterone in serum. DHT is the major intra-prostatic androgen. In prostate tissues 5α-reductase converts testosterone to DHT. DHT is a preferred ligand for the AR, since AR–DHT complex is more stable than the AR–testosterone complex. Also androgen levels are measured for radical prostatectomy from clinically localized PCa (37).

Steroid hormones analysis from snap frozen tissue obtained intra-operatively from radical prostatectomy specimens from AA and CA showed similar levels of testosterone, DHT, dehydroepiandrosterone, dehydroepiandrosterone sulfate, and PSA. However, AA had higher androstenedione (ASD) and sex hormone-binding globulin (SHBG) levels. Age, BMI, PSA, and pathologic gleason sum and stage (nonparametric rank analysis) make the racial differences between ASD and SHBG. A higher ASD tissue level in AA is not the result of higher levels of testosterone whereas higher serum levels of SHBG have been postulated to be protective against prostate cancer. SHBG decreases bioavailable testosterone for androgen receptor ligand activation. Although AA has been reported to have higher serum levels of SHBG than CA (36), but SHBG serum levels have not correlated significantly with risk of prostate cancer (37, 38).

More recently, SHBG has been demonstrated to be produced in the human PCa cell lines (LNCaP, DU-145, and PC3), and in cultured human prostate epithelial and stromal cells (27). SHBG binds to a membrane receptor in prostate (39), which was reported to initiate an intracellular signal that increased cAMP levels and modulated androgen action in the prostate (40). Immunostaining revealed heterogeneous expression of SHGB protein, primarily in the epithelium of both benign prostate (27) and prostate cancer (41). Also *in situ* hybridization of adjacent sections confirmed local synthesis of SHBG (27). Higher tissue levels of SHBG may enhance androgen action in prostate tissue (42) of AA through cAMP-dependent pathways.

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4. GENES INVOLVED IN ANDROGEN BIOSYNTHESIS

Variants in the genes involved in androgen biosynthesis and metabolism are compelling candidates for susceptibility factors in PCa pathogenesis. Many of these genes have been found to harbor genetic polymorphisms. These polymorphisms can potentially change androgen levels in prostate tissue. Genetic polymorphisms in these pathways are summarized in Figure 1.

4.1. *CYP11A1*

CYP11A1 gene is the first rate-limiting step for biosynthesis of both testosterone and estrogen, located on 15q23–q24 chromosome encodes for the enzyme P450scc, and has pentanucleotide (TAAAA) n repeat range (4 to 10-repeat sequences) at 5′-untranslated region (UTR) (60), which catalyzes cholesterol to pregnolone. Population based 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 (43, 44). Interestingly, Japanese PCa patients without the 4-repeat allele have an increased risk of metastatic tiPCa compared to those with the 4-repeat allele (44). However, a positive association with PCa risk was not identified in the European populations (45).

4.2. *CYP17*

CYP17 gene is located on chromosome 10, encodes the cytochrome P450c17a enzyme (46), which mediates both 17α-hydroxylase and 17,20-lyase activities in testosterone biosynthesis in the gonads and adrenals (46). The 5′-untranslated promoter region of *CYP17* contains a polymorphic T-to-C substitution that gives rise to A1 (T) and A2 (C) alleles (47). Previous studies reported that the A2 allele may be associated with an increased risk of PCa (48–53); however, other results have either been inconclusive (54, 55) or showed a possible increased risk from the A1 allele (56, 57). The results of a meta-analysis suggest that *CYP17* polymorphisms may have a role in PCa susceptibility in AA but not CA men (58). The A2 allele was slightly less frequent in AA versus CA men, but a different study had the opposite finding (59). Ultimately, there may be little difference in A2 frequency and a null effect of the *CYP17* polymorphism on androgen levels.

4.3. *SRD5A2*

Intra-prostatic DHT levels may be integral to racial variations in risk (60). Steroid 5α-reductase irreversibly converts testosterone into DHT. Two forms of steroid 5α-reductase exist, steroid 5α-reductase type1 (*SRD5A1*) and steroid 5α-reductase type 2 (SRD5A2). *SRD5A1* is expressed more abundantly in extra-prostatic tissues (e.g., skin), whereas *SRD5A2* is exclusively expressed in the prostate (61). Activity of 5α-reductase was reported lower in Asian than in white and black men (60, 62). This gene is more polymorphic in AA men than previously assumed (63), though *SRD5A2* TA repeats alleles are only present in high-risk AA men and not in lower risk CA and Asian men (60, 62). Thus, it has been proposed that certain steroid 5α-reductase enzyme variants encoded by *SRD5A2* genes marked by particular TA repeat alleles may result in an elevation of enzyme activity, leading to an increased prostatic level of DHT, which may increase the risk for developing PCa. Furthermore, the V89L and A49T variants of *SRD5A2* gene have been shown to alter the

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conversion of testosterone to DHT (64, 65). While the V89L polymorphism is decreased the production of DHT (66) and A49T variant increases its production, particularly in AA and Hispanic men (67)

4.4. *HSD3B* family

The *HSD3B1* and *HSD3B2* genes are located on 1p13.1., and encode 3β-hydroxysteroid dehydrogenase/Δ5-Δ4 isomerase 1 and 2 isoenzymes (3β-HSD types 1 and 2). The proteins are bifunctional enzymes that catalyze androstendione production in steroidogenic tissues and convert the active DHT into inactive metabolites in steroid target tissues (68). A *N367T* (AAC>ACC, rs1047303) polymorphism in *HSD3B1* has been reported to present at a high frequency in Caucasian (31%), inter-medium frequency in AA (11.7.%) and low frequency in Asian men (8.5.%), although the variant has a similar activity to the wild type (69). A complex (TG)n (TA)n(CA)n dinucleotide repeat polymorphism is found in intron 3 of the *HSD3B2* gene (70). The common alleles occurred at variable frequencies in different racial populations. The longer allele formed more stable hairpin structures with faster degradation rate of DHT. Longer alleles commonly found in Asian men (71, 72), whereas short alleles have been found to be associated with an increased PCa risk in Caucasian but not in AA men (71). There are two SNPs in *HSD3B2*, rs1819698 and rs1538989 reported which is more common in AA than CA and increased the risk of PCa in AA but not CA (77). The interaction between *HSD3B1* and *HSD3B2* polymorphisms has also been investigated. Although the N367T polymorphism in *HSD3B1* is weakly associated with PCa risk, but the combination with *HSD3B2* rs1819698 is greatly enhanced the association (73).

4.5. *CYP19A1*

The *CYP19A1* gene is located on chromosome 15q21.1., and 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) are confirmed to be associated with serum estradiol of men (74, 75). The polymorphisms of *CYP19* gene in Caucasian and AA men (rs2470152, rs12439137, rs3751592, rs2470164) are associated with PCa risk (77). Particularly, the rs2470164 was reported to increase PCa risk in Caucasian men with different frequency among healthy Caucasian (50%) and AA men (5.6.%). The tetranucleotide repeat (TTTA) n is located in intron 4 of *CYP19A1*. The 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 are among Asian men. In Asian men, A1 is found more frequently (~50% of the population) than all other alleles (76, 77). Several studies have shown that TTTA repeat length is associated with PCa risk (57, 80, 81, 82), however, TTTA repeat length is not associated with the American population (80). The polymorphism Arg264Cys substitution (rs700519) is found at a higher frequency in Indian men (27%) (78) in comparison to AA (16.8.%) and Caucasian men (4–8.1.%) (79–81). Studies among Caucasian and Indian men showed a tendency for this polymorphism to increase risk of PCa (78, 81), but large scale population studies failed to confirmed the results in Caucasian men (75, 79, 80).

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4.6. *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 (82) (see details in Table 1).

4.7. *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 is encoded by *HSD17B1* gene located on 17q21 and involved in estrogen and testosterone biosynthesis. The polymorphism of *HSD17B1* (Ser313Gly, rs605059) is detected in Caucasian men (40%), and associated with either familial or sporadic cases of PCa (83). In studies from multi-ethnic groups (The Breast and Prostate Cancer Cohort Consortium, BPC3), four common SNPs (rs676387, rs605059, rs598126, rs2010750) were detected, although none were found to be associated with PCa risk, however, only varying frequencies of haplotypes between different races. The haplotype CAAC is commonly found in AA men and CAGC is more prevalent in white and black than Asian men, whereas inverse association with PCa risk in Latino and Japanese American but not in AA, Native Hawaiian, or white men (83).

17β-HSD2 is encoded by *HSD17B2* and located on 16q24. 17β-HSD2 is involved in the conversion of active androgens into their less active forms. SNPs in HSD17B2 (rs1424151) are significantly associated with plasma testosterone level in Caucasian men (84), but no association with PCa was detected (84, 85).

17β-HSD3 is encoded by *HSD17B3* and located 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 (86), but studies in Finnish and Swedish men found no positive associations (87).

HSD17B4 gene is located on 5q21 and encodes androgen/estrogen inactivating enzyme 17β-HSD4. It was reported to be associated with the outcome of PCa patients (88, 89). 17β-HSD5 belongs to the aldo-keto reductase (AKR) superfamily and is formally known as AKR1C3 encoded by the *AKR1C3* gene located 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, and 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 (90). Moreover, promoter polymorphism (A to G, rs3763676) of *AKR1C3* is more prevalent in Caucasian than Asian men (90), whereas men with the A allele have significantly lower risk of PCa (91).

4.8. *UGT2B15*

UGT2B15 is a member of UDP glucuronosyltransferases (UGTs) family, which glucuronidate steroids and other endogenous molecules, encoded by the *UGT2B15* gene and located on 14q13–q21.1. It has a high capacity to glucuronidate 3α- and rostenediol and a

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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 have higher 85D allele frequency than Caucasians (92), however, other studies are inconclusive (93, 94).

5. OTHER FACTORS INVOLVE IN PROSTATE CANCER DEVELOPMENT

5.1. Sex hormone binding globulin

Sex hormone-binding globulin (*SHBG*) gene is located on 17p12-p13 and encodes a steroid binding protein, and act as regulator of free plasma androgens. It also mediates androgen and estrogen signaling at the cell membrane via cyclic adenosine monophosphate. Most of the studies are reported that black men have higher PCa risk with higher plasma SHBG levels in prostate tissue than white and Asian men (95). Interestingly, 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 (96). A common polymorphism in the *SHBG*, and *D356N* gene encodes for an additional N-glycosylation consensus site, which may reduce its clearance from circulation and alter its binding to membrane receptors (97). In the multicenter study the *SHBG-D356N* heterozygotic polymorphism had a higher frequency in white men (17%) than black men (7.8.%) (129). 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 found between PCa and *SHB*G polymorphisms (98).

5.2. Growth factors and receptors

In most studies growth factor receptors concerning the racial disparity of PCa are EGFR and EPHB2 (Table 2). In addition, AA men have been found to have higher IGF-1 and lower IGFB-3 levels, which may cause higher tumor growth with lower anti-tumor activity (99).

5.3. Differences in apoptotic genes in relation to prostate cancer racial disparity

5.3.1. Anti-apoptotic *BCL-2*—Studies show that altered expression of the *BCL-2* gene may be an important factor underlying the greater aggressiveness of PCa in AA men (100). *BCL-2* has a central role in preventing cancer cells from death, via its anti-apoptotic effect, and its up-regulation in AA men may be responsible for PCa cell survival and resistance to therapies. Thus, a positive connection between over-expression of *BCL-2* and increased in prostate tumors proliferation in AA but not in CA men, and suggest *BCL-2* dependent aggressive behavior of PCa in AA men (100).

5.3.2. *MDM2*—In response to stress, cells activate a complex pathway involving tumor suppressor gene p53that is responsible for cell cycle arrest, DNA repair, and apoptosis as protection from the deleterious effects of mutation (101). *MDM2* is a key negative regulator of tumor suppressor p53, by targeting p53 for proteasomal degradation (102–104). Several reports suggested that *MDM2* overexpression was significantly associated with advanced stage PCa (105–107). Another studies have also shown that inhibiting *MDM2* expression enhances the effects of radiation and chemotherapy on PCa cells (108–110). A single

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nucleotide polymorphism in the MDM2 promoter, SNP309, enhances transcriptional activation of *MDM2* and has been associated with early onset of several types of cancer (111–115). Interestingly, *MDM2*, protein expression was significantly higher in CA(78%) than AA(45%) patients (116), and also *MDM2* and AA ethnicity have both been associated with poor prognosis. However, the relationship between these two variables was neither causative nor correlative.

5.4. Genetics variations between AA and CA prostate cancer

PCa is also caused by multiple genes through complex interaction including environmental factors (85, 117–119). There may be ethnic variation in the frequency of alleles that may be associated with PCa risk and/or progression. Although the incidence and mortality for PCa may differ among different racial groups, the increased risk for PCa attributed to family history of this disease is consistent across different racial backgrounds, supporting the possibility of a common genetic basis of disease (120). The analysis of genetic alterations in PCa is challenging because PCa often has genetic and morphological heterogeneity, multifocality and the presence of more than one lesion of independent origin (121–124). Linkage studies, determine the susceptibility loci for PCa on several chromosomes and several candidate genes if the tumors in AA men are different from those in CA men (125).

5.4.1. Chromosome 8—The short arm of chromosome 8 (8p22–23) has been proposed as a potential location for one or more genes important in the development of PCa (126, 127). The short arm of chromosome 8 is frequently deleted in both adenocarcinomas and PINs (128, 129), which has lead to the assumption that the inactivation of an unidentified tumor suppressor gene on 8p is involved in prostate tumor initiation (130–132). Other studies on the loss of chromosome 8p in AA and CA men have generated conflict findings (133), however, the racial differences in the association between PCa recurrence and several prognostic factors of cancer progression, including Gleason score, surgical margin, and TNM stage are positively correlated.

5.4.2. miRNA—MicroRNAs (miRNAs) are a class of small, endogenous, non-coding RNAs that regulate gene expression at the levels of transcription and post-transcription (134, 135). miRNA inhibits translation of target genes involved in a variety of fundamental cellular processes including organ development, differentiation, and cancer formation (136–139). Functional studies of individual miRNAs have shown that miRNAs can act as oncogenes or tumor suppressor genes (140). miRNAs are differently dysregulated in uterine leiomyomas in both AA and CA women, indicating that miRNAs expression are associated with the racial disparity in cancer (145). In the prostate, the expression of 5 miRNAs, miR-30c, miR-301, miR-219, miR-261, and miR- 1b1, were reported racially different in benign prostate tissue (146). Expression of commonly dysregulated miRNAs in PCa revealed racial differences in the expression of let-7c and miR30c in AA prostate tissue (147). Thus, distinct gene expression and genome-wide copy number variation between AA and CA prostate cancer might play a role in the racial disparity of PCa.

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5.5. PSA levels in AA and CA prostate cancer patients

FDA approved the PSA test in the year 1986 for monitoring the status of disease and diagnosis (1992)., The test is performed on symptomatic and asymptomatic men in an effort to diagnosed PCa early and to monitor disease recurrence and progression (148). Past surveys of urologists revealed significant variation in the use of the PSA test (149), including racial disparities in PSA surveillance, with AA men half as likely as CA men to receive annual monitoring (150). A recent study concluded that PSA testing is probably not able to explain current racial differences in PCa mortality rates (151). Interestingly, recently a relationship was reported between serum PSA levels and polymorphisms in the PSA and AR genes (152). Specifically, serum PSA levels increased by 7% with each decreasing AR CAG repeats allele size among individuals homozygous for a single nucleotide polymorphism in the PSA gene promoter. A recent study of the ERDA1 locus revealed that large CAG repeats are more common among Asian populations, less common in populations of European ancestry, and least common in African populations (153). This pattern showed similarity with the AR trinucleotide repeats studies.

5.6. Familial prostate cancer susceptibility genes

Variation in genetic susceptibility also play a key role in the incidence of, and mortality from, prostate cancer in AA and CA men (154). Although the etiology of PCa is complex, the study on family and twin cases suggested that the inherited genetic susceptibility is a critical risk factor in PCa. PCa susceptibility genes have been mapped to 1q24–25 (155), Xq27–28 (156), and 8p22–23 (126), and other loci including PCaP and CaPB (157), HPC20 (158), and HPC2/ELAC (159), have been examined. The frequency of these genes and an understanding of their importance in hereditary prostate cancer cases, sporadic white American cases, and unaffected controls continues to evolve, but almost all reported studies contain few AA. Recently, more groups have begun to examine affected AA families. Familial aggregation rates were similar in AA and white Americans men (85). Race-specific penetrance estimates for the carriers of deleterious genotypes, which were similar in AA and white Americans, but low in Asian Americans (160). The higher incidences of prostate cancer in AA may not be caused by a higher prevalence of germline mutations predisposing to the disease in AA. Men with more than six family members with prostate cancer had a higher chance of presenting with lymph node metastatic or widely metastatic prostate cancer than men with only four to six family members affected (161). Linkage analysis of 33 AA prostate cancer families from two independent research groups provided some evidence for clustering at HPC1. Increased evidence of linkage was found in families with prostate cancer diagnosis younger than age 65 years, and male-to-male transmission (162). These studies, though very preliminary, suggest that genetics could contribute to the increased aggressiveness of prostate cancer in AA.

5.7. Other genes in prostate cancer

5.7.1. *MSR1*—Recently, the macrophage scavenger receptor 1 (*MSR1*) gene has been proposed as a link between germline alterations in 8p and PCa (163, 164). Both common sequence variants and rare germline mutations have been suggested as potential PCa susceptibility factors. Several rare germline mutations of the *MSR1* gene were found to co-

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segregate with PCa, and one of the germline mutations was associated with an increased risk of PCa among AA men (163). In a subsequent study of CA men, the same authors examined five common sequence variants of *MSR1* and reported significantly different allele frequencies for each of the variants among men with PCa compared with unaffected men (164), with each, except INDEL7, associated with an elevated risk for PCa. An ensuing study examined each of these five common *MSR1* sequence variants in AA men (118). They found that the Asp174Tyr mutation is nearly twice as common among PCa patients compared with controls; however, after adjusting for age, none of the sequence variants were associated with a significantly increased risk of PCa, providing limited support for an association in AA men.

5.7.2. *Caveolin-1*—Caveolin-1 is a structural protein found in caveolae that support cholesterol transport and signal transduction. Caveolin-1 suppresses c-myc-mediated apoptosis, and is overexpressed in murine and human PCa. Caveolin-1 is expressed higher levels in PCa in AA than CA (165), and PCa grows more rapidly in AA due to reduced rates of apoptosis (165). Therefore, radiation and androgen-deprivation therapy are less effective for AA PCa patients (166).

6. CONCLUSIONS

Due to the complex nature of the AR signaling pathway, there are different ways that genetic polymorphisms contribute to the deregulation of this pathway and increase PCa risk. Future detailed 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 the development of PCa. Analysis of these complex polymorphisms in androgen synthesis and AR signaling pathway with racial disparities are causing difficult situation at clinical front to achieve functional confirmation to establish their contribution to PCa development. Recent molecular and biotechnological approaches in the field of proteomics and genomics will greatly aid the advancement of translational research on racial disparity in PCa, which may help, in finding new prognostic markers and novel therapeutic approaches for the treatment of PCa in AA.

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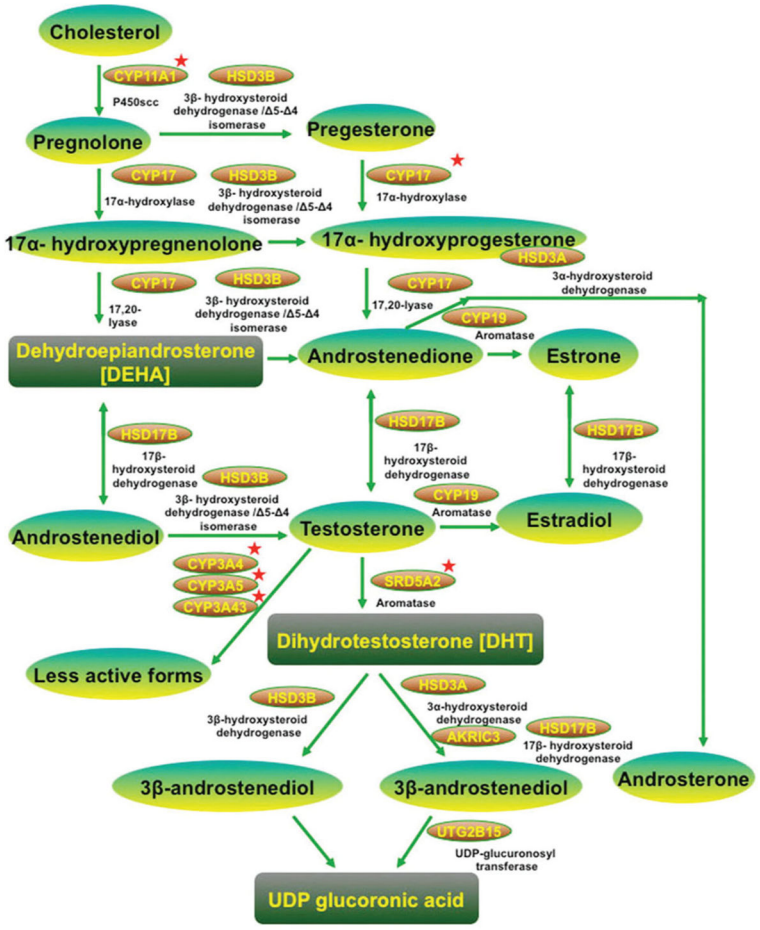

Figure 1.

Gene involved in Androgen biosynthesis and metabolism in prostate cancer. Genetic polymorphisms in genes associated with androgen biosynthesis/metabolism and AR, which show differential racial frequencies and potential association with prostate cancer. Red star indicates the genes, which has racial frequency difference.

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Table 1

CYP3A family genes and their allelic functions

Gene	Characteristic	Reference
CYP3A4	• Cytochrome P4503A4 (*CYP3A4*) protein facilitates the oxidative deactivation of testosterone to biologically less active metabolites, and the inhibition of *CYP3A4* causes increased levels of testosterone. • *CYP3A4* supports oxidative metabolism of finasteride and may be a effective molecule in PCa treatment. • Germline genetic variation in the 5′ regulatory region of the *CYP3A4* gene (A to G transition) on chromosome 7 has been reported. This variant G allele (referred to as *CYP3A4* G variant) is more common among AA men (gene frequency>50%) than CA (<10%), Hispanic, or Asian men. • The G variant is inversely associated with less aggressive PCa. ., and the CYP3A4 variant is strongly associated with AA population.	(167–169) (170, 171) (172)
CYP3A5	• *CYP3A5* expressed at high levels in the non-tumoral prostate tissue, specifically in the basolateral cells and catalyzes 6β-hydroxylation of testosterone. An A to G transition (A6986G) within intron 3 leads to a variant in the *CYP3A5* mRNA expression in human prostatic tissue. Allele *CYP3A5*1* (A allele) produces a correctly spliced transcript leading to high levels of full-length CYP3A5 mRNA and protein, however 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. • *CYP3A5**1 has a higher frequency in AA individuals than Caucasian or Asian men. • *CYP3A5*3/*3* decreases *CYP3A5* mRNA content 13-fold compared to *CYP3A5*1/*3. CYP3A5*1* and show linkage disequilibrium with *CYP3A4*1B* in Caucasian and African men, • *CYP3A4*1B/CYP3A5*1* haplotype is inversely associated with risk among Caucasian men with less aggressive disease. • In Japanese population, *CYP3A5*1/*1* men have lower risk of developing a low-grade localized PCa than CYP3A5*3/*3 carried men. *CYP3A5*3* is not associate with PCa in either white or African men, the *CYP3A4*1B/CYP3A5*3* haplotype is significantly associated with increasing PCa risk in European American but not in AA men. • *CYP3A5* interacts with *SRD5A2* or *KLK3*, which influenced the development of PCa.	(173) (170, 174) (175, 176)
CYP3A43	• *CYP3A43* is predominantly expressed in the prostate. The allelic frequency of *CYP3A43*3* (rs680055) is higher in AA than CA men. • There is a 2.6.-fold increase in PCa risk among individuals with the *CYP3A43*3* homozygous genotype compared with those with the *CYP3A43*1* homozygous genotype in AA, but not in CA men.	(177, 178) (179)

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Table 2

Growth receptors and their characteristics in the prostate cancer heath disparities

Growth receptors	Characteristics	References
EGFR (Epidermal growth factor receptor)	• EGFR helps in cellular proliferation, progression, tumor cell invasion and also a target of anticancer agents for androgen-independent PCa,. • Over-expresses of EGFR in PCa is more common in African American (AA) than Caucasian American (CA). • EGFR inhibitors hinder the growth of both androgen dependent and independent PCa xenografts. • Androgen independent, metastatic PCa and androgen ablation increases the expression of EGFR Intronic dinucleotide repeats (CA) n (range from 14 to 21 correlated with transcriptional activity) polymorphism. • Longer allele of EGFR is associated with 80% reduction in EGFR protein expression than shorter allele. • Three out of four missense mutations in EGFR TK domain identified as oncogenic in nature. These mutations are reported in 3 Koreans, 1 in CA but none in AA.	(180–186)
EPHB2 (Ephrin type-B receptor 2)	• Located on 1p36, and link with hereditary PCa with racially diverse family. • Studies in DU145 PCa cell line suggested that it may be tumor suppressor gene. • Screening of the EphB2 gene for germline polymorphisms in AA PCa identified ten sequence variants in the gene, including a common nonsense mutation and K1019X. • The risk for PCa increased 3-fold among AA men who carried at least one copy of the K1019X allele and had a family history of PCa.	(187–189)
VDR (Vitamin D receptor)	• European American men have high plasma levels of the active form of vitamin D, 25-hydroxyvitamin D, which is associated with decreased risk of lethal PCa. • SNP sets linked to 7 vitamin D pathway-related genes, including VDR, which are associated with PCa risk. • A single VDR polymorphism, the *BsmI B* allele, is protective against recurrence of PCa in European American men but not in AA men. • The decrease VDR signaling contributes to the greater risk of advanced or lethal PCa in AA population.	(190–192)