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Review

Polymorphisms in androgen signaling pathway predisposing to prostate cancer

Johanna Schleutker *

Institute of Biomedical Technology, University of Tampere, and Centre for Laboratory Medicine, Tampere University Hospital, Biokatu 8, 33520 Tampere, Finland

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ABSTRACT

Prostate cancer is the most frequent male malignancy diagnosed in western countries and androgens are known to mediate key physiological processes in prostate tissue. Since endogenous androgens have long been considered to be risk factors for prostate cancer, genes involved in androgen biosynthesis and metabolism have been extensively studied. In this review, association of androgen pathway genes, their polymorphic sites and risk of prostate cancer in different ethnic backgrounds is addressed together with their use to predict susceptibility and clinical outcomes of prostate cancer patients. The effect of the polymorphisms seems vary in different patients, populations and ethnic backgrounds. To date it is evident that the association between androgen pathway gene polymorphisms and prostate cancer risk is complex and many of the results are characterized by irreproducibility, which can be attributed to a variety of biological, statistical and technical reasons. In the future, with increasing knowledge, developing technologies and new genomic biomarkers it likely becomes possible to better estimate the risk of prostate cancer, and distinguish indolent disease from aggressive based on molecular profiling, and the analysis of gene–gene and gene–environment interactions.

Contents

Abbreviations: AKR1C3, 3α-hydroxysteroid dehydrogenase; AR, androgen receptor; CNV, copy number variation; CYP, cytochrome P450; DHEA, dehydroepiandrosterone; DHT, dehydrotestosterone; HSD17B, 17β-hydroxysteroid dehydrogenase; HSD3B, hydroxy-δ-5-steroid dehydrogenase type 3; LH, luteinizing hormone; MIM, Mendelian Inheritance in Man; NGS, next generation sequencing; PCa, prostate cancer; PSA, prostate specific antigen; SHBG, sex hormone binding globulin; SNP, single nucleotide polymorphism; SRD5A2, steroid 5α-reductase type II; SULT, sulfotransferase; UGT, uridine diphosphate-glucuronosyltransferase enzyme; UTR, untranslated region.

* Tel.: +358 50 4437237; fax: +358 33 1174168.
E-mail address: Johanna.Schleutker@uta.fi

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1. Introduction

Prostate cancer (PCa) (MIM 176807) is the most common malignancy among men in most western populations. PCa screening with prostate specific antigen (PSA) test has become increasingly common during the last two decades, so that today, majority of PCa patients are diagnosed with organ-confined disease (Wirth et al., 2004). However, current clinical parameters have limited performance to accurately distinguish risk for life-threatening, aggressive PCa from the overwhelming majority of indolent cases in early stages of the disease.

Despite the substantial public health impact of PCa, the underlying etiology is still relatively poorly understood, with both genetic predisposition and environmental factors likely contributing to risk. Prostate cancer has proven to be a heterogeneous disease, where definitive risk factors include age, ethnic origin and family history (Carter et al., 1992). In recent years, the role of genetic factors has become increasingly clear. Although environmental factors may play a role in the development of prostate cancer, results from various types of molecular epidemiologic studies including twin studies, segregation analyses, genome-wide linkage and association analyses have been constant in suggesting a significant role for genetic components in PCa epidemiology (Schaid, 2004). In fact, the ~40% heritability component in prostate cancer risk is the highest ever reported for a common malignancy (Lichtenstein et al., 2000).

Androgens are essential for the development, growth and secretory activities of the prostate. Since androgen signaling and metabolism are regulated by a number of androgen-related genes they are among the most natural candidates for conferring genetic susceptibility for PCa. Evidence exists that genes involved in the signaling and metabolism of androgens affect PCa risk. In this review, a background is given to the reported polymorphisms in the androgen pathway genes and their relation to PCa risk. A PubMed search was done using the key words prostate cancer, and 20 select gene names combined with variant and polymorphism. Relevant articles during 1998 and 2011 were reviewed for data on the association between polymorphisms and prostate cancer risk.

2. Testosterone biosynthesis genes

The androgen pathway is presented in Fig. 1. Genes included in the present review are shown in respective sites of the biosynthesis and metabolic steps. Genes and relevant SNPs in the testosterone biosynthesis pathway are presented in Table 1.

2.1. LHB

Luteinizing hormone (LH) is an α:β heterodimer, in which the α-unit is common to glycoprotein hormones, and the unique β-subunit, coded by the gene *LHB* (MIM 152780) on 19q13, determines biological specificity. A weak positive association between the *LHB*-V genotype that carries two linked substitution mutations with higher bioactivity, and risk of familial PCa has been reported but has not been confirmed (Elkins et al., 2003; see Table 1).

2.2. CYP11A1

Cytochrome P450scc (the P450 side chain cleavage enzyme) coded by *CYP11A1* (MIM 118485) on 15q23–q24 catalyzes the first step in the androgen synthesis pathway. The most studied polymorphism is a $(tttta)_n$ repeat located in the 5′UTR of the gene. Japanese PCa patients without the $(tttta)_4$ allele were originally detected to have an increased risk of high-grade PCa (Gleason score 8 or more, or poorly differentiated cancer) compared to those with the $(tttta)_4$ allele. Further, absence of the shortest allele, $(tttta)_4$, was associated with an increased risk of metastatic disease (stage D) compared to those with the $(tttta)_4$ allele (Kumazawa et al., 2004). More recent studies performed in US population have, however, failed to confirm these results (see Table 1).

2.3. HSD3B family

The *HSD3B1* (MIM 109715) and *HSD3B2* (MIM 201810) genes on 1p13.1, express hydroxy-δ-5-steroid dehydrogenase, 3β- and steroid δ-isomerase (3β-HSD) types 1 and 2 that are required for the biosynthesis of androgens. The protein encoded by these genes is a bifunctional enzyme that catalyzes the oxidative conversion of δ(5)-ene-3β-hydroxy steroid, and the oxidative conversion of ketosteroids. They catalyze the conversion of active DHT into inactive metabolites in steroid target tissues such as prostate. These genes are predominantly expressed in the adrenals and the gonads and play a crucial role in the biosynthesis of all classes of hormonal steroids.

The rs1047303 in *HSD3B1* has been reported to increase PCa risk among Caucasians especially with another variant rs1819698 found on 3′UTR of *HSD3B2* (Chang et al., 2002a). Men with the variant

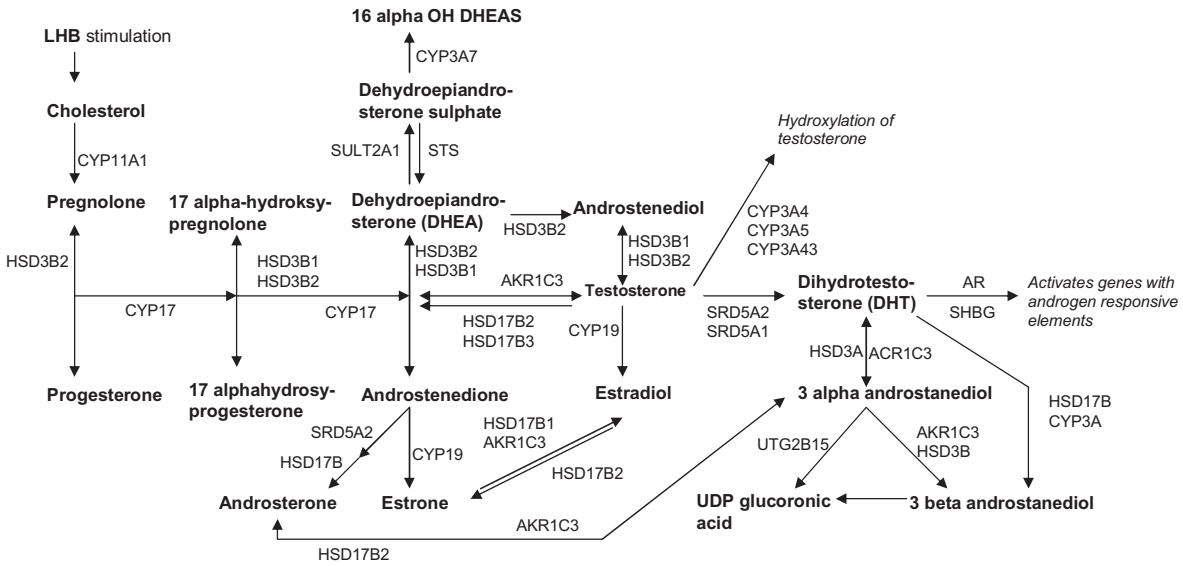

Fig. 1. The androgen pathway with genes involved in successive steps of biosynthesis and metabolism.