Genetic changes observed in prostate cancer

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KEY WORDS

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ABSTRACT

The cause of prostate cancer remains unknown. However, it is clear that prostate cancer is a heterogeneous disease with multiple genetic and environmental factors involved in its etiology. This review focuses on the main changes in the human genome, which may be important for the development of hereditary prostate cancer: HPC1 (1q24-25), CAPB (1p36), PCAP (1q42-43), HPC2 (17p12), HPC20 (20q13), HPCX (Xq27-28). Furthermore, in this article we present other acquired molecular defects that may increase the risk of developing this cancer when accumulating in cells (e.g. deletions at 6q, 8p, 10q, 13q, 16q, amplifications or profit chromosome of 7p, 7q, 8q, and Xq). On the other hand, the text underlines that scientific reports do not indicate any single major, specific gene that would be responsible for a large percentage of HPC cases, and therefore be of clinical significance.

The analysis of genetic condition of prostate cancer encounters numerous serious obstacles. These problems result from the phenomenon of phenocopy (random, non-hereditary changes caused for example by environmental factors). Developing the disease in old age and lack of clinical features that would make possible grouping patients in a way that would reflect and explain genetic heterogeneity [1].

Mutations of classic oncogenes and suppressor genes are infrequently found in primary prostate cancer. No specific mutations have been identified for this type of neoplasm. Although certain molecular and genetic changes were observed in prostate cancer (Table 1), none of them were unambiguously associated with its initiation or progression [2].

Currently 6 loci have been isolated in the human genome that would be responsible for hereditary type of prostate cancer: HPC1 (1q24-25), CAPB (1p36), PCAP (1q42-43), HPC2 (17p12), HPC20 (20q13), and HPCX (Xq27-28) [1, 3, 4].

HPC1 (PCS1) – HEREDITARY PROSTATE CANCER 1 (PROSTATE CANCER SUSCEPTIBILITY 1)

In 1996 Smith et al., on the basis of linkage analysis of the whole genome, suggested a region localized at the long arm of chromosome 1 (1q 24-25) as the susceptible locus in the hereditary prostate cancer. Mutations of this region were observed in 34% of studied families with high risk of prostate cancer [5].

The association of HPC1 with hereditary or sporadic prostate cancer was confirmed in several later studies [6, 7]. However, some researchers did not observe any statistically significant associations [8, 9].

RNASEL (ribonuclease L) gene, mapped in region 1q25, was suggested as a suppressor gene, correlating with hereditary prostate cancer. In normal cells it is expressed constitutively and codes for an endoribonuclease. This enzyme mediates the antiviral and antiproliferative action of interferons (INFs) [10]. It was demonstrated that RNase L (interferon-induced ribonuclease) has an effect on viral activation of JNK (c-Jun NH_2-terminal kinase) (family of MAP kinases) and viral induction of apoptosis [11].

In patients from families with high risk of prostate cancer, certain mutations with the sequence of RNASEL gene were found. For example, E265X mutation, which results in the synthesis of a shorter peptide, was significantly more frequent in patients with prostate cancer (4.3%) comparing to the control group (1.8%) [12]. Other studies refuted the association between the influence of the mutation mentioned above and the etiology of prostate cancer to be false [13]. Another mutation – R462Q (Arg462Gln) – is associated with both increased [12, 14, 15], as well as with decreased risk of HPC [16]. It was found that the Arg462Gln variant has a threefold shorter period of enzymatic activity comparing to the normal variant. Moreover, it was estimated that the risk of falling ill with prostate cancer in heterozygotic carriers of this variant is increased by 50% compared to non-carriers, while susceptibility in homozygotes is increased two-fold [14]. Other studies did not confirm any significant effect of Gly/Gly genotype at codon 462 on the predisposition towards prostate cancer [15, 17].

A significant increase of prostate cancer prevalence was found in the Japanese population in the case of D541E (Glu541Asp) mutation. As this correlation was not found in any other study, it may be a specific trait of families with prostate cancer in Japan [15].

In the population of German and Central European Jews (Ashkenazi Jews) another variant of the RNASEL gene was identified, known as 471delAAAG. This variant was present in 7% of Ashkenazi men with prostate cancer, while only in three percent of older but healthy men [18]. However, this mutation does not seem to be crucial for the development of prostate cancer [19].

CAPB – CARCINOMA PROSTATE AND BRAIN

CAPB, situated within 1p36, is a region of frequent loss of heterozygosity in the pathological process of brain formation tumors. Epidemiological studies found an association between brain cancer (BC) and prostate cancer (PC) [1]. It was suggested that a common oncogene for both cancers may exist. Recently, a potential candidate for region 1p36 has been identified. It is the HSPG2 (heparan sulfate proteoglycan) gene. Perlecan (HSPG2) is a proteoglycan – heparan sulfate, which is secreted into the extracellular matrix, where it may combine with growth factors and modulate their functions. It participates, among others, in the Hedgehog signal pathway, which plays an important role in the formation of metastases in numerous types of neoplasms [20].

PCAP – PREDISPOSING FOR PROSTATE CANCER

On the basis of analysis of 47 French and German families, Smith et al. found another gene responsible for hereditary prostate cancer. The primary location of this gene (1q42,2-43) was confirmed using different markers, on 3 genetic models [5]. Certain studies suggested that PCAP

Table 1. Genes the are connected with HPC and/or may increase the risk of prostate cancer.

GENE	NAME	LOCUS	
HPC1 (PCS1) RNASEL	Hereditary Prostate Cancer 1 Ribonuclease L	1q24-q25 1q25	Genes connected with hereditary prostate cancer (HPC)
CAPB HSPG2	Carcinoma Prostate Brain Heparan Sulfate Proteoglycan	1p36	
PCAP	Predisposing for Prostate Cancer	1q42.2-1q43	
HPC2	Hereditary Prostate Cancer 2	17p12	
HPC20 MYBL2 (BMYB, B-MYB) STK15	Hereditary Prostate Cancer 20-linked V-Myb Avian Myeloblastosis Viral Oncogene Homolog-Like 2 Serine/Threonine Kinases	20q13 20q13.1 20q13	
HPCX LDOC1 SPANX	Hereditary Prostate Cancer, X-linked Leucine Zipper, Down-Regulated in Cancer 1 Sperm Protein Associated with The Nucleus on The X Chromosome	Xq27-q28	
CHROMOSOME 8			Genes connected with higher susceptibility to prostate cancer (PC)
NKX3-1	NK-3 Transcription Factor, Locus 1	8p21	
MSR1	Macrophage Scavenger Receptor 1	8p22	
MYC	V-Myc Myelocytomatosis Viral Oncogene Homolog	8q24,12-24,13	
PSCA	Prostate Stem Cell Antigen	8q24,2	
EIF3S3	Eukaryotic Translation Initiation Factor 3, Subunit 3	8q22-23	
CHROMOSOME 10			
ANX7	Annexin 7	10q21	
PTEN (MMAC1,MHAM)	Phosphatase and Tensin Homolog	10q23,3	
CHROMOSOME 13			
KLF5	Kruppel-Like Factor 5	13	
RB1	Retinoblastoma 1	13q14.2	
BRCA2	Breast Cancer 2	13q12.3	
EDNRB	Endothelin Receptor Type B	13q22	
CHROMOSOME 16			
ATBF1	AT-Binding Transcription Factor 1	16q22.3-q23.1	
CHROMOSOME X			
AR	Androgen Receptor	Xq11.2-q12	
GSTP1	Glutathione S-Transferase pi	11q13	Genes hypermethylating in prostate cancer
EDNRB	Endothelin Receptor Type B	13q22	
ESR1 ESR2	Estrogen Receptor	6q25.1 14q23	
KAI1	Kangai 1	11p11.2-13	Metastasis suppressor genes in prostate cancer
NME1	Non-Metastatic Cells 1	17q21.3	
KISS1	KiSS-1 Metastasis-Suppressor	1q32	
MAP2K4	Mitogen-Activated Protein Kinase 4	17p11.2	

is the most frequent locus predisposing to hereditary prostate cancer in Southern and Western Europe [21].

HPC2 – HEREDITARY PROSTATE CANCER 2

In 2001 gene HPC2/ELAC2 (named with reference to the homology with gene elaC of *Escherichia coli*) was mapped and characterized. This gene is located on chromosome 17p12. In the study based on the analysis of 33 HPC gene lineages from the state of Utah, gene ELAC2 was identified as a prostate tumor susceptibility gene. Sequence analysis indicates that the gene codes an evolutionary constitutive metallo-dependent hydrolase. Additional gene products of gene ELAC2 turned out to be similar to a family of proteins associated with DNA repair mechanisms. Therefore, it seems probable that this gene may play a role in the origin of prostate cancer [1, 22].

Relations between prostate cancer and the presence of certain polymorphisms of gene ELAC2; Ser217Leu, Ala541Thr have been found. Ser217Leu variant is located in the hydrophilic part of the protein, while substitution with a hydrophobic leucine may cause changes in its tridimensional structure. The second variant, Ala541Thr, adjoins a histidine motif and may reduce the functions of this protein [22, 23]. Suarez et al. [24] and the results of study by Yokomizo et al. [25] supported this discovery, but not all researches indicate a significant effect of gene ELAC2 on the risk of developing prostate cancer [26].

HPC20 – HEREDITARY PROSTATE CANCER 20-LINKED

While studying 162 North America families with three or more relatives with prostate cancer, scientists observed linkage with chromosome 20q13 [27]. Within chromosome 20q13, overexpression of four genes was found: CSE1L, 2NF217, MYBL2 and STK15. Additionally, genes MYBL2 (v-myb myeoloblastosis viral oncogene homolog -like 2) and STK15 (serine/threonine kinases) were found to be associated with the process of metastases and can be used as markers of prostate cancer development [28]. Not all studies demonstrated statistical support for the existence of prostate cancer susceptibility in HPC20 [29].

HPCX – HEREDITARY PROSTATE CANCER, X-LINKED

Approximate calculations suggest that 16% of hereditary prostate cancer is linked with region Xq27-28. It was additionally demonstrated that a gene located in that region shows low penetration, relatively high frequency and causes the occurrence of prostate cancer in older age (over the age of 65) [30].

There are speculations on 2 transcription units, mapped within HPCX, that are genes LDOC1 (leucine zipper down-regulated in cancer 1) and SPANX (sperm protein associated with the nucleus on the X chromosome) [31].

Apart from the genes associated with hereditary prostate cancer that have been mentioned above, other genetic changes at chromosomal and sub-chromosomal level are often observed in prostate cancer. The most common anomalies include deletions at 6q, 8p, 10q, 13q, 16q and amplification and chromosome gain of 7p, 7q, 8q, and Xq [2, 32].

Deletions at 8p are among the most common genetic changes observed in prostate cancer. Deletion at 8p was found in 25% of early cases of the disease, which may to prove that this is a relatively early event in the genesis of prostate cancer [32]. One of the potential suppressor candidates is gene NKX3-1 (NK-3 transcription factor, locus 1), participating in cell proliferation and mechanisms of apoptosis [33]. It belongs to region 8p21, where loss of heterozygosity is observed in 60-80% of prostate tumors [34].

This region of frequent allelic deletion also includes gene MSR1 (macrophage scavenger receptor 1), mapped at 8p22. This gene codes a macrophage receptor protein, which binds various ligands, including bacterial lipopolysacharides and lipoteichoic acids. As a component of the immune response, MSR1 is associated with various normal and pathological processes, such as inflammatory state, oxidative stress and apoptosis. Detailed information on the role of MSR1 in the genesis of prostate cancer is not known, it is assumed that the mutations of this gene disturb the function of macrophages and cause a chronic or recurring inflammatory state of the prostate, which may result in the development of prostate cancer [4, 35, 36].

Analysis of the MSR1 gene in patients with hereditary prostate cancer revealed six infrequent sense mutations (Pro36Ala, Ser41Tyr, Val113Ala, Asp174Tyr, Gly369Ser and His441Arg) and one non-sense mutation (Arg293X) [37]. The influence of this gene on the development of prostate cancer was confirmed in numerous studies [37, 38], although other researchers did not find correlations between the mutations of gene MSR1 and prostate cancer risk [39, 40].

Loss of heterozygosity in region 10q21, where gene ANX7 (annexin 7) is located, was found in 35% of cases of primary prostate cancer. It is interesting that gene ANX7 seems to be as powerful and effective as p53, for which deactivation of only one allele is sufficient for cancerogenesis. Protein ANX7 is a substrate for C kinase and other kinases associated with proliferation. *In vitro* studies revealed that this gene has an inhibitory effect on proliferation of different cell lines in human prostate cancer (LNCaP, DU-145, PC-3) [4, 41].

Mutations of PTEN (phosphatase and tensin homolog) at 10q23,3 are found in different types of cancers, including prostate cancer, breast cancer or ovarian cancer. PTEN is responsible for the inhibition of signals mediated by PIP3 and AKT, which are responsible for increasing cellular proliferation. Studies show that inactivation of PTEN in prostate cancer plays an important role in of achieving its androgen independence [42].

Chromosome losses at 6q (33-73%) and 13q (22-91%) have been observed in initial stages of prostate cancer, as well as in stages associated with the presence of distant metastases [32]. The regions of chromosome 13 that are most frequently deleted are associated with genes: KLF5 (kruppel-like factor 5), RB1 (retinoblastoma 1), BRCA2 (breast cancer 2) and EDNRB (endothelin receptor type B) [43, 44]. It was noted that 2.3% of 263 men studied with prostate cancer (below the age of 55) had mutations of the coding sequence of BRCA2. Carriers of mutations of this gene have 23-times higher relative risk of developing prostate cancer before the age of 56 [45]. Numerous modern studies confirm increased risk of prostate cancer in men with mutations of BRCA1 and BRCA2, as well as worse clinical prognosis in these patients [46, 47].

In human cancers, including prostate cancer, deletions at the long arm of chromosome 16 are also frequent. Changes at 16q24,3 were observed in 68% of primary and 90% of recurrent cases of prostate cancer [48]. Recent studies suggest that ATBF1 (AT-binding transcription factor 1), which codes a transcription factor that negatively regulates AFP (alpha-fetoprotein) and MYB (v-myb avian myeloblastosis viral oncogene homolog) and transactivates CDKN1A (cyclin-dependent kinase inhibitor 1A), may be the suppressor gene of region 16q22 [49].

Matsuyama et al., using *in situ* hybridization, studied the association of deletions at 8p (8p22, 8p23), 10q (10q24), and 16q (16q24) with different clinical parameters of prostate cancer. The frequency of deletions at 8p, 10q, and 16q in prostate cancer was 74, 55 and 55%, respectively. It was also observed that when the advancement of prostate cancer increases, the frequency of deletions at 8p and 16q also increases, but not at 10q [48].

The majority of chromosomal deletions, as well as deactivation of classic suppressor genes (for example P53 – tumor protein p53; RB1 – retinoblastoma 1; CDKN2A – cyclindependent kinase inhibitor 2A) applies to late stages of prostate cancer and most probably is associated with the process of forming metastases and gaining hormonal independence. Suppressor genes of the metastasis are defined as genes that do not affect the growth of primary tumor, but may inhibit the growth at distant metastases. Identified candidates for prostate cancer are: CD44 (CD44 antigen), KAI1 (Kangai 1), NME1 (non-metastatic cells 1), KISS1 (KiSS-1 metastasis-suppressor) and MAP2K4 (mitogen-activated protein kinase 4) [2, 50].

Amplifications within chromosome 8 are also observed in prostate cancer. Genes that are their targets include among others MYC (v-myc avian myelocytomatosis viral oncogene homolog) (8q24,12-24,13), PSCA (8q24,2), and EIF3S3 (eukaryotic translation initiation factor 3, subunit 6) (8q22-23). Gain chromosomes of 8p and/or 7pq have been reported as potential biomarkers for assessing tumor aggressiveness [32, 51]. Other regions, often duplicated in prostate cancer, are the regions for androgen receptors (Xq11.2-q12). Amplification of androgen receptor (AR) genes may lead to androgen independence of prostate cancer by changing their sensitivity to circulating androgens. Secondly, mutations of AR genes cause these receptors to lose their specificity allowing them to be activated by non-specific ligands, for example other steroid hormones [2].

Beside mutations of proto-oncogenes and suppressor genes, one of the most frequent causes of neoplasms is the epigenetic change of gene expression, associated with inappropriate methylation of CpG isles in DNA sequences. Silencing of gene GSTP1 (glutathione s-transferase pi) (11q13) by hypermethylation of its promoter region is a frequent event in prostate cancer and is present in more than 90% of cases of the disease. Gene GSTP1, known as genome „caretaker", codes for an enzyme, which plays a crucial role in preventing oxidative and electrophilic damage to DNA. Cells that lack GSTP1 have an impaired DNA repair system, which leads to the accumulation of genomic changes. Other examples of genes silenced by hypermethylation in prostate cancer include: EDNRB (endothelin receptor type B), ER-α, and ER-β (estrogen receptor) [2, 52].

In spite of numerous studies, there is no unambiguous answer to the question of genetic predisposition to prostate cancer. Lack of consistency in the studies indicates that prostate cancer is a disease of diverse genetic backgrounds (cooperation of „weak" mutations of numerous genes) and is also correlated with environmental factors (for example diet, environmental pollution), which influence its etiology [1]. Scientists are still trying to „track down" a highly selective allel in genes associated with hereditary prostate cancer. Currently the diagnosis of hereditary prostate cancer at the level of DNA is practically impossible, as it requires diagnosing mutations specific for prostate cancer. Although we may currently perform DNA tests for genes such as BRCA 1, and BRCA 2, P53, PTEN, and CDKN2A, the increase of risk of prostate cancer for known mutations of the majority in these genes is minute. Therefore, family history still remains the most fundamental factor in determining the risk of prostate cancer.

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