Genetic Determinants of Familial and Hereditary Prostate Cancer

8

Jesse K. McKenney, Christopher G. Przybycin and Cristina Magi-Galluzzi

Introduction

Prostate carcinoma (PCa) is a multifactorial disease influenced by both environmental and genetic factors. After advancing age and ethnic background, the strongest epidemiological risk factor for PCa is a positive family history. Although genetic factors implicated in the development of PCa are as yet ill defined, over the past 20 years the body of evidence that gene abnormalities may be specifically associated with prostate cancer risk has grown immensely, ranging from familial aggregation and twin studies, to family-based linkage studies, to detection of likely functional genes via mutation screening, to molecular epidemiological studies of both rare and common polymorphisms of candidate genes [1]. Gene–environment interactions play a crucial role in cancer development, particularly when low penetrance genes such as genetic polymorphisms are the major contributor. Strengthening the genetic evidence is a high frequency of prostate cancer in monozygotic as compared to dizygotic twins. Two different analyses have revealed a concordance for prostate cancer diagnosis of 21.1 and 27.1 % for monozygotic versus 6.4 and 7.1 % for dizygotic twins, respectively [2, 3]. Using a model developed to determine the effects of heritable versus environmental factors, heritable factors have been estimated to account for 42 % of prostate cancer risk in one study [2].

For practical purposes, PCa can be divided into three groups: hereditary, familial, and sporadic. Up to 85 % of all prostate cancers are sporadic and only 10–15 % are genetically determined [4]. Hereditary PCa, compatible with Mendelian inheritance criteria, is demonstrated only in 5 % of cases with PCa family history, whereas familial PCa accounts for about 13–25 % of cases. Hereditary prostate cancer has been defined as families that meet at least one of the following three criteria: 1—three or more first-degree relatives (e.g., father, son, brother) affected with PCa in any nuclear family; 2—occurrence of PCa in each of three successive generations in either of the proband's paternal or maternal lineages; or 3—at least two relatives, both affected with PCa diagnosed before age 55 [5]. Familial aggregations of PCa that do not fulfill the previously reported criteria but have at least two affected first-degree relatives are defined as familial forms. Sporadic PCa are likely due to nonhereditary causes. Even if there is more than one case in the family, there is no particular pattern of inheritance.

C. Magi-Galluzzi (✉)
Department of Pathology, Cleveland Clinic, Robert J. Tomsich Pathology and Laboratory Medicine Institute, Cleveland, OH, USA
e-mail: magic@ccf.org

J. K. McKenney
Department of Pathology, Cleveland Clinic, Robert J. Tomsich Pathology and Laboratory Medicine Institute, Cleveland, OH, USA
e-mail: mckennj@ccf.org

C. G. Przybycin
Department of Pathology, Cleveland Clinic, Robert J. Tomsich Pathology and Laboratory Medicine Institute, Cleveland, OH, USA
e-mail: przybyc@ccf.org

C. Magi-Galluzzi, C. G. Przybycin (eds.), *Genitourinary Pathology,* DOI 10.1007/978-1-4939-2044-0_8,

The relative risk of PCa in a man with a brother or father with PCa is 3.4 and 2.2, respectively [6, 7], and increases proportionally to the number of diseased relatives and their decrease in age at diagnosis, so that the risk of developing PCa is assessed 8.5 for men with both first-and second-degree affected relatives [1]. Family history is associated with 2.2-fold risk of PCa before age 65 years and 1.7-fold risk for onset after age 65; in the presence of a family history that includes both PCa and either breast or ovarian cancer, the risk is approximately 5.8, but results differ between studies [8, 9].

No distinct clinicopathologic characteristics or tumor progression attributes have been generally identified for hereditary versus sporadic PCa, except an earlier age at diagnosis (hereditary PCa occurs on average 6 years earlier than the sporadic form) [10, 11].

Apart from *RNaseL*-, *ElaC2*-, *MSR1*-, *HOXB13*- as well as low number of CAG repeats in the androgen receptor (AR) gene, there are no other identified high-risk genetic variants which might be considered responsible for hereditary PCa. These findings suggest that even familial PCa is a genetically heterogeneous disease, related to changes in many gene loci rather than a specific major susceptibility gene. These genetic changes likely interact not only reciprocally, but also with environmental conditions that are generally more strongly associated with sporadic PCa initiation [1].

Strong Candidates for Susceptibility Genes

Recent studies suggest that hereditary prostate cancer is a complex disease, involving multiple susceptibility genes with variable phenotypic expression. Family-based studies have identified three strong candidate susceptibility genes involved in the hereditary form of prostate cancer: the endoribonuclease *RNaseL* gene (*RNaseL*/*hereditary prostate cancer 1* (*HPC1*)), the 3′ processing endoribonuclease *ELaC2*/*HPC2* gene, the macrophage scavenger receptor 1 gene (*MSR1*), and *HOXB13* (Table 8.1).

RNaseL/HPC1 (1q24–25)

The identification of genetic susceptibility loci for prostate cancer has been extremely difficult. It was only in 1996 that the first prostate cancer susceptibility locus, *HPC1*, was mapped to chromosome 1q24–25, which was subsequently identified as the RNaseL gene. RNaseL is a uniquely regulated endoribonuclease requiring 5′-triphosphorylated, 2′,5′-linked oligoadenylates (2–5A) for its activity. This enzyme is important in immune response to viral infection, induction of apoptosis, and cell cycle and cell differentiation regulation. The presence of germ-line mutations in RNaseL that segregate with disease within hereditary-prostate-cancer-affected families and the loss of heterozygosity (LOH) in tumor tissues suggest a relationship between innate immunity and tumor suppression.

RNaseL mutations have an autosomal dominant type of inheritance with high penetrance; consequently, carriers of this mutant variant have a high risk of prostate cancer development [4]. The *HPC1* locus is associated with disease that affects younger men (age <66 years) and multiple family members [12]. Men with this predisposition typically have more aggressive cancer (higher Gleason score), often locally advanced or even metastatic. Germ-line mutations in the tumor-suppressor gene *RNaseL* have been reported to track in PCa families, and have been implicated in up to 13 % of all prostate cancer cases [13].

ElaC2/HPC2 (17p11.2)

The *ElaC2*/*HPC2* gene at 17p11.2 is the first candidate gene identified for human prostate cancer based on linkage analysis and positional cloning [14]. *HPC2* gene encodes ElaC protein 2, a zinc phosphodiesterase located in the nucleus. *ElaC2* displays transfer ribonucleic acid (tRNA) 3′-processing endonuclease activity, inducing tRNA maturation. The *ELaC2*/*HPC2* gene displayed several sequence variants: missense mutations Ser217Leu, Ala541Thr, and Arg781His and a frame-shift mutation 1641 insG [14]. Two previous studies found an association between

Table 8.1 Genes involved in prostate cancer development

Gene localization	Candidate gene/locus	Gene function	Key features
Strong candidates for susceptibility genes			
1q25.3	*RNaseL/HPC1*	Antiviral and pro-apoptotic role	<65 year old, high GS, advanced disease at diagnosis, strong relationship with PCa in families with >5 affected men
17p11	*ELaC2/HPC2*	Induces tRNA maturation	
8p22–23	*MSR1*	Involved in arterial wall deposition of cholesterol and in endocytosis of low density lipoproteins	Meta analysis failed to reveal correlation between locus for *MSR1* and hereditary risk for PCa
17q21–22	*HOXB13*		5% of families, predominantly of European descent, more frequent in males diagnosed with PCa with early-onset disease and family history
Weak candidates for susceptibility genes (*low-risk alleles*)			
Xq27–28	*HPCX*		Gonosomal inheritance, higher risk of PCa in men with affected brother than with affected father; early-onset prostate cancer, responsible for 16% of hereditary PCa
20q13	*HPC20*		PCa diagnosed at older age
17q21	*BRCA1*	Regulation of cell cycle progression and DNA repair	Germ-line mutations observed in 0.44% of PCa cases; 9.5% lifetime risk of PCa by age 65 years
13q12–13	*BRCA2*	DNA recombination and repair	Relative risks estimated as high as fivefold to sevenfold at young age (≤65 years); 20% lifetime risk of PCa
1q42–43	*PCAP*		Male-to-male transmission, average age at diagnosis <66 years, and ≥5 affected individuals

GS Gleason score, *PCa* prostate cancer, *tRNA* transfer ribonucleic acid

Ser217Leu and Ala541Thr and their combination with PCa [14, 15].

The finding of a nonsense mutation in the *HPC2/ELaC2* gene confirms its potential role in genetic susceptibility to prostate cancer. However, *HPC2/ELaC2* germ-line mutations are rare in hereditary prostate cancer and variants Leu217 and Thr541 do not appear to influence the risk for hereditary prostate cancer, suggesting that alterations within the *HPC2/ELaC2* gene play a limited role in genetic susceptibility to hereditary prostate cancer [16].

MSR1 (8p22–23)

The *MSR1* gene at 8p22–23 has been implicated as a candidate gene for hereditary prostate cancer. *MSR1* encodes membrane glycoproteins, MSR type-I and type-II, involved in the modulation of interaction between foreign cells and macrophages, cell adhesion and phagocytosis, arterial wall deposition of cholesterol during atherogenesis, and endocytosis of low density lipoproteins. The frequencies of deleterious alleles is low, and the penetrance is apparently moderate, suggesting that *MSR1* is not a major susceptibility gene in prostate cancer families [17]. Meta analysis of existing data has failed to show any clear correlation between the *MSR1* locus and the hereditary risk of prostate cancer [18].

HOXB13 (17q21–22)

HOXB13 is a transcription factor gene important in prostate development. *HOXB13* is suppressed in AR negative prostate cancer cells and

its overexpression results in significant inhibition of cell growth. In addition, *HOXB13* has been shown to suppress androgen-stimulated AR activity by interacting with the receptor [19].

A recurrent germ-line mutation (G84E) in the *HOXB13* has been recently identified by Ewing et al. in a previously recognized region of linkage at 17q21–22 as harboring an increased risk for familial prostate cancer [20]. Xu et al. have utilized a large sample of prostate cancer-prone families recruited by the International Consortium for Prostate Cancer Genetics (ICPCG) to confirm that the *HOXB13* G84E mutation is rare, but significantly associated with predisposition to PCa. G84E mutation was present in ~5% of prostate cancer families, predominantly of European descent, and was encountered more frequently in males diagnosed with PCa (51%) than in unaffected male family members (30%) [21]. The frequency of the mutation was higher in PCa patients with early-onset disease (age at diagnosis ≤55 years, 2.2%) or with positive family history (2.2%), and most common in patients with both features (3.1%). In a family-based analysis, the proportion of G84E mutation-associated PCa was highest in families from the Nordic countries of Finland (22.4%) and Sweden (8.2%), particularly for early-onset PCa and cases with substantially elevated prostate-specific antigen (PSA) [22]. *HOXB13* G84E variant poses a statistically significant risk of hereditary PCa, while accounting for only a small fraction of all prostate cancers.

Weak Candidates for Susceptibility Genes

An indeterminate number of weak candidate susceptibility loci have been suggested to be involved in hereditary PCa (Table 8.1). However, high-risk PCa alleles, associated with a lifetime penetrance of at least 66%, have a frequency unlikely above 2–3% of the cases, whereas low-risk PCa alleles may have a more frequent impact on sporadic PCa.

HPCX (Xq27–28)

A linkage analysis of 360 families at high risk for PCa identified the q27–28 region on chromosome X as the potential location of a gene, hereditary prostate cancer X-linked (*HPCX*), involved in prostate cancer susceptibility [23]. Results supporting this localization were obtained in another analysis of 153 American families. The most significant evidence of linkage to this locus was found in pedigrees without male-to-male transmission and with early-onset prostate cancer [24]. Studies have revealed a higher relative risk of prostate cancer for men with a brother affected by PCa than for men with an affected father. It is presumed that *HPCX* is responsible for 16% of hereditary PCas [25]. *HPCX* variants seem to be associated with prostate tumor aggressiveness [12].

HPC20 (20q13)

A recent study of hereditary prostate cancer has provided evidence for a prostate cancer-susceptibility locus, *HPC20*, which maps to 20q13. It is speculated that *HPC20* may potentially play a role in men with PCa diagnosed at older age [26].

PCAP (1q42–43)

PCAP (predisposing for cancer prostate) was identified on 1q42.2–43 on a combined analysis of French and German families [27]. PCa tumor antigen-1 (*PCTA-1*), located within the PCa susceptibility locus 1q42.2–43, is not a high-risk PCa gene, but data suggest that it might make a low-risk contribution [28]. *PCTA-1* belongs to the family of galectins. Galectins expression correlates with tumor growth and differentiation, modulates tumor cell adhesion, and mediates cell proliferation, survival, and apoptosis. Linkage studies using microsatellite markers on 144 prostate cancer families found suggestive evidence for linkage to *PCAP* in 21 families that met the

criteria of male-to-male transmission, average age at diagnosis < 66 years, and ≥ 5 affected individuals [29]. The role of *PCAP* in prostate cancer warrants further investigation.

8q24

Two independent genome-wide association studies of prostate cancer, using different methodologies, converged on the same chromosomal locus, 8q24 [30, 31]. A 3.8-megabase region of 8q24 has been identified as significantly associated with prostate cancer risk. The region contains nine known genes, including the oncogene *MYC*, commonly gained in PCa. Single nucleotide polymorphisms (SNPs) within three adjacent regions at 8q24 have been recently identified to be connected with familiar PCa risk [32, 33]. In 2009, two additional risk regions were discovered at 8q24 [34]. At least nine SNPs, all independently associated with PCa risk, reside within these five loci. Notably, all 8q24 risk polymorphisms reside in intergenic, noncoding regions of the genome [35]. Chung et al. have recently shown that a critical region at 8q24 is transcribed as a ~13 kb intron-less non-coding RNA (ncRNA), termed *PRNCR1* (prostate cancer ncRNA 1). *PRNCR1* expression was found to be upregulated in some prostate cancer cells as well as the precursor lesion prostatic intraepithelial neoplasia [36].

Variability at 8q24 seems to be associated with high risk of aggressive PCa patterns at diagnosis.

16q23

Prostate cancer linkage to the region of 16q23 has been observed in a SNP-based genome-wide linkage scan on 131 Caucasian prostate cancer families participating in the University of Michigan Prostate Cancer Genetics Project. Linkage to this same region, which contains several strong candidate genes including the known prostate cancer tumor-suppressor genes *ATBF1* and *WWOX*, has also been observed [37].

Prostate Cancer Associated with Other Tumors

Several epidemiological studies have shown a possible, either synchronous or metachronous association of different tumors (e.g., breast, brain, gastrointestinal tumors, and lymphomas) with PCa, thus suggesting common genetic risk factors.

BRCA1 (17q21), *BRCA2* (13q12)

The breast cancer susceptibility genes 1 (*BRCA1*) and 2 (*BRCA2*) are tumor-suppressor genes that are inherited in an autosomal dominant fashion with incomplete penetrance. They are normally expressed in breast, ovary, prostate, and other tissues. Their germ-line mutation is the cause of hereditary breast-ovarian cancer syndromes. Both genders have the same probability of inheriting the trait; however, the phenotype is different in males and females, and the risk of cancer is significantly lower in males. Although the results of some studies are conflicting, it has been clearly shown that male *BRCA* mutation carriers are predisposed to an increased risk of breast, prostate, pancreas, gastric, and hematologic cancers when compared to non-carriers.

Deleterious mutations in both genes have been associated with more aggressive prostate cancer and poor clinical outcome [38].

BRCA1 is on chromosome 17q21 and encodes a protein that has been implicated in the regulation of cell cycle progression, DNA damage response and repair, transcriptional regulation and chromatin modeling. BRCA1 has been associated with an increased risk of sporadic PCa (3.5-fold), even though germ-line mutations in this gene have only been observed in 0.44% of PCa cases [39] (Table 8.1).

BRCA2 is on chromosome 13q12 and its function seems to be limited to DNA recombination and repair processes. There is consistent evidence that germ-line mutations in BRCA2 lead to an increased risk of prostate cancer, with relative risks estimated as high as fivefold to sevenfold,

and some evidence suggesting a more important role in prostate cancer presenting at a young age (≤65 years) [38] (Table 8.1).

The lifetime risk of PCa in *BRCA2* mutation carriers has been estimated to be 20%, while for BRCA1 the risk is 9.5% by age 65 years [39], similar to that in non-carriers.

Currently, the IMPACT study is evaluating the utility of PSA-based PCa screening in asymptomatic *BRCA1* and *BRCA2* mutation carriers [40].

CAPB (1p35–36)

The *CAPB* (prostate and brain cancer) gene, localized to 1p36 is reportedly linked to a predisposition to both brain and prostate cancer. Strong evidence of linkage to this locus was reported with 12 families showing both hereditary prostate cancer and a history of brain tumors [41]. However, other investigations have reported data that do not support linkage to this locus based on an independent analysis of 13 pedigrees representing the same clinical profile [29].

E-cadherin (16q)

Somatic mutations in the E-cadherin (*CDH1*) gene have frequently been reported in cases with diffuse gastric and lobular breast cancers. Germ-line mutations of the CDH1 gene at 16q have recently been associated with familial gastric cancer. Specifically, diffuse-type gastric cancers (such as signet-ring adenocarcinoma), while relatively uncommon, have a strong genetic association with mutation of the *CDH1* gene. Prostate-specific cancer antigen (PSCA) was demonstrated to be associated with an increased risk of diffuse gastric cancer, but not with intestinal-type gastric cancer [42].

Individual rare mutations and polymorphisms in the *CDH1* gene, such as S270A, may contribute to the onset of PCa. A significant rise in gastric cancer has been shown in pedigrees of PCa patients diagnosed before the age of 55 years; however, no association between PCa and *CDH1* germ-line mutation has been found so far [43].

2q, 16q, 17q

Some hereditary PCa families have a co-occurrence of pancreatic adenocarcinoma. Three chromosomal regions (2q, 16q, 17q) have been noted as harboring potential susceptibility loci, suggesting a linkage between prostate and pancreatic cancer [44].

NBN (8q21)

Nibrin (*NBN*), located on chromosome 8q21, is a gene involved in DNA double-strand break repair that has been implicated in the rare autosomal recessive chromosomal instability syndrome known as Nijmegen Breakage Syndrome (NBS). NBS is characterized by specific physical characteristics (microcephaly and dysmorphic facies), immunodeficiency, and increased risk of malignancy. Individuals who are heterozygous for NBN mutations are clinically asymptomatic, but may display an elevated risk for certain cancers including, but not limited to, ovarian and prostate cancer and various lymphoid malignancies [45].

Androgen Receptor and Steroid Hormone Metabolism-Related Genes' Involvement in Prostate Cancer

Conversion of testosterone to dihydrotestosterone (DHT), its active metabolite on prostatic target cells, is catalyzed in prostatic tissue by the enzyme 5-α-steroid-reductase (srd5α). The two genes *srd5α1* and *srd5α2*, encoding for srd5α isoforms type I and type II, are located on chromosomes 5p15 and 2p23, respectively. It is believed that isoform type II predominates in the prostate. A larger number of dinucleotide thymine-adenine (TA) repeats (≥18) on the last exon of the *srd5α2* gene (locus 2p22–23) is common in African-American men, and seems to confer an increased PCa predisposition [46].

AR is encoded by a gene located on the short arm of chromosome X (Xq11–12). This locus is one of the most conserved regions of the human genome, with only very rare mutations occurring

at this site [47]. One of the critical functions of the product of the AR gene is to activate the expression of target genes. This activity resides in the transcriptional N-terminal domain of the protein, which is encoded in exon 1 and contains polymorphic guanine-guanine-cytosine (GGC) and cytosine-adenine-guanine (CAG) repeats. The variability in the *AR* gene length is determined by polymorphisms in the N-terminal region. A smaller number of either GGC (<16) or CAG (<18) repeats appears to be associated with a higher level of AR activity, resulting in an increased PCa risk [48]. The number of CAG and GGC base triplet repetition in the first exon of the AR gene is substantially lower in African-American than in Caucasian men [4, 49].

Loss of chromosomal Y segment is the most common chromosomal alteration that may be identified in prostate cancer tissue. Sex-related gene on chromosome Y (*SRY*) is downregulated in PCa. Since *SRY* acts as negative regulator of AR, the loss of chromosome Y results in an increase in prostate cancer growth [50].

Immunohistochemical studies have shown that the percentage of AR-positive cancer cells is higher in hereditary PCa than in sporadic forms, whereas the mean number of estrogen-α-receptor-positive stromal cells is higher in sporadic PCa than in the hereditary form [51].

Gene Mutations Possibly Associated with Prostate Cancer Development and Progression

PTEN (10q23.3)

Phosphatase and tensin homologue deleted on chromosome 10 (*PTEN*), also referred to as mutated in multiple advanced cancers (*MMAC1*) and transforming growth factor-beta (TGF-β) regulated and epithelial cell enriched phosphatase (*TEP1*), was first discovered in 1997 [52, 53]. *PTEN*, mapped to 10q23.3, is frequently inactivated in somatic cancers and is the second most common mutated tumor-suppressor gene after *p53* [54]. It plays a role in various cell processes including apoptosis, cell cycle progression, cell proliferation, angiogenesis, aging, and DNA damage response [55]. *PTEN* encodes a dual specificity phosphatase with the ability to dephosphorylate both lipid and protein substrates. By dephosphorylating PIP3 thereby opposing PI3K activity and resulting in subsequent downregulation of Akt, *PTEN* is the main negative regulator of the PI3K/Akt pathway [55].

PTEN functions may be impaired by mutations and other genetic alterations. *PTEN* inactivation may be due to inappropriate subcellular compartmentalization, altered proteasome degradation, somatic intragenic mutations, and epigenetic inactivation in sporadic tumors [55]. *PTEN* alterations include a variety of possible posttranslational modifications which may alter the phosphatase activity, direct subcellular localization, affect PTEN complexes and influence protein stability. PTEN function can be impaired not only by heterozygous mutations and homozygous losses, but also by other molecular mechanisms, such as transcriptional regression, epigenetic silencing, and microRNAs regulation [56].

Normal cells usually show strong nuclear *PTEN* expression which is lost during transformation to neoplasia. Germ-line mutations of *PTEN* cause the *PTEN* hamartoma tumor syndrome (PHTS), which includes those previously called Cowden, Bannayan-Riley-Ruvalcaba, Proteus, Proteus-like, and Lhermitte-Duclos syndromes [57]. Somatic mutations of *PTEN* have been observed in glioblastoma, prostate cancer, and breast cancer cell lines, to mention only few tissues where the involvement has been proven [52]. A common feature of *PTEN* somatic mutations is the association with advanced stage tumors (mainly glial and prostate cancers) [57].

Monoallelic [58, 59] and biallelic *PTEN* loss has been reported in approximately 42 and 10% of prostate cancers, respectively [52, 53].

In mice, heterozygous loss (mutations in one allele) of PTEN has been shown to lead to cancers in various organs or systems, such as prostate, thyroid, colon, lymphatic system, breast, and endometrium [60]. There is compelling evidence in mice confirming *PTEN* as a haploinsufficient tumor-suppressor gene [56]: loss of one allele leads to the progression of a lethal polyclonal

autoimmune disorder [61]; epithelial cancers, such as prostate cancer, are driven by *PTEN* heterozygosity [62]; cellular levels of *PTEN* protein inversely correlate with the occurrence of invasive prostate cancer [56]. Consequently, functional loss of one *PTEN* allele is critical for the onset of cancer in mice.

KLF 6 (10p15)

The loss-of-function mutation of Krüppel-like factor 6 (*KLF 6*) at chromosome 10p15 is a genetic change that can lead to deregulation of cell proliferation. *KLF 6* is a tumor-suppressor gene inactivated in a significant percentage (up to 55%) of sporadic prostate cancers [63], however, its role in hereditary PCa has not been confirmed [64, 65]. KLF 6 is a ubiquitously expressed zinc finger transcription factor, which is part of a growing family of KLFs. The KLF family is broadly involved in differentiation and development, growth-related signal transduction, cell proliferation, apoptosis, and angiogenesis [65].

References

1. Alberti C. Hereditary/familial versus sporadic prostate cancer: few indisputable genetic differences and many similar clinicopathological features. Eur Rev Med Pharmacol Sci. 2010;14(1):31–41.
2. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, et al. Environmental and heritable factors in the causation of cancer—analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med. 2000;343(2):78–85.
3. Page WF, Braun MM, Partin AW, Caporaso N, Walsh P. Heredity and prostate cancer: a study of World War II veteran twins. Prostate. 1997;33(4):240–5.
4. Kral M, Rosinska V, Student V, Grepl M, Hrabec M, Bouchal J. Genetic determinants of prostate cancer: a review. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2011;155(1):3–9.
5. Carter BS, Bova GS, Beaty TH, Steinberg GD, Childs B, Isaacs WB, et al. Hereditary prostate cancer: epidemiologic and clinical features. J Urol. 1993;150(3):797–802.
6. Bruner DW, Moore D, Parlanti A, Dorgan J, Engstrom P. Relative risk of prostate cancer for men with affected relatives: systematic review and meta-analysis. Int J Cancer. 2003;107(5):797–803.
7. Zeegers MP, Jellema A, Ostrer H. Empiric risk of prostate carcinoma for relatives of patients with prostate carcinoma: a meta-analysis. Cancer. 2003;97(8):1894–903.
8. Chen YC, Page JH, Chen R, Giovannucci E. Family history of prostate and breast cancer and the risk of prostate cancer in the PSA era. Prostate. 2008;68(14):1582–91.
9. Mastalski K, Coups EJ, Ruth K, Raysor S, Giri VN. Substantial family history of prostate cancer in black men recruited for prostate cancer screening: results from the prostate cancer risk assessment program. Cancer. 2008;113(9):2559–64.
10. Gronberg H, Damber L, Tavelin B, Damber JE. No difference in survival between sporadic, familial and hereditary prostate cancer. Br J Urol. 1998;82(4):564–7.
11. Roupret M, Fromont G, Bitker MO, Gattegno B, Vallancien G, Cussenot O. Outcome after radical prostatectomy in young men with or without a family history of prostate cancer. Urology. 2006;67(5):1028–32.
12. Agalliu I, Leanza SM, Smith L, Trent JM, Carpten JD, Bailey-Wilson JE, et al. Contribution of HPC1 (RNASEL) and HPCX variants to prostate cancer in a founder population. Prostate. 2010;70(15):1716–27.
13. Casey G, Neville PJ, Plummer SJ, Xiang Y, Krumroy LM, Klein EA, et al. RNASEL Arg462Gln variant is implicated in up to 13% of prostate cancer cases. Nat Genet. 2002;32(4):581–3.
14. Tavtigian SV, Simard J, Teng DH, Abtin V, Baumgard M, Beck A, et al. A candidate prostate cancer susceptibility gene at chromosome 17p. Nat Genet. 2001;27(2):172–80.
15. Rebbeck TR, Walker AH, Zeigler-Johnson C, Weisburg S, Martin AM, Nathanson KL, et al. Association of HPC2/ELAC2 genotypes and prostate cancer. Am J Hum Genet. 2000;67(4):1014–9.
16. Wang L, McDonnell SK, Elkins DA, Slager SL, Christensen E, Marks AF, et al. Role of HPC2/ELAC2 in hereditary prostate cancer. Cancer Res. 2001;61(17):6494–9.
17. Maier C, Vesovic Z, Bachmann N, Herkommer K, Braun AK, Surowy HM, et al. Germline mutations of the MSR1 gene in prostate cancer families from Germany. Hum Mutat. 2006;27(1):98–102.
18. Sun J, Hsu FC, Turner AR, Zheng SL, Chang BL, Liu W, et al. Meta-analysis of association of rare mutations and common sequence variants in the MSR1 gene and prostate cancer risk. Prostate. 2006;66(7):728–37.
19. Kim SD, Park RY, Kim YR, Kim IJ, Kang TW, Nam KI, et al. HOXB13 is co-localized with androgen receptor to suppress androgen-stimulated prostate-specific antigen expression. Anat Cell Biol. 2010;43(4):284–93.
20. Ewing CM, Ray AM, Lange EM, Zuhlke KA, Robbins CM, Tembe WD, et al. Germline mutations in HOXB13 and prostate-cancer risk. N Engl J Med. 2012;366(2):141–9.

21. Xu J, Lange EM, Lu L, Zheng SL, Wang Z, Thibodeau SN, et al. HOXB13 is a susceptibility gene for prostate cancer: results from the International Consortium for Prostate Cancer Genetics (ICPCG). Hum Genet. 2013;132(1):5–14.
22. Laitinen VH, Wahlfors T, Saaristo L, Rantapero T, Pelttari LM, Kilpivaara O, et al. HOXB13 G84E mutation in Finland; population-based analysis of prostate, breast and colorectal cancer risk. Cancer Epidemiol Biomarkers Prev. 2013;22(3):452–60.
23. Xu J, Meyers D, Freije D, Isaacs S, Wiley K, Nusskern D, et al. Evidence for a prostate cancer susceptibility locus on the X chromosome. Nat Genet. 1998;20(2):175–9.
24. Lange EM, Chen H, Brierley K, Perrone EE, Bock CH, Gillanders E, et al. Linkage analysis of 153 prostate cancer families over a 30-cM region containing the putative susceptibility locus HPCX. Clin Cancer Res. 1999;5(12):4013–20.
25. Baffoe-Bonnie AB, Smith JR, Stephan DA, Schleutker J, Carpten JD, Kainu T, et al. A major locus for hereditary prostate cancer in Finland: localization by linkage disequilibrium of a haplotype in the HPCX region. Hum Genet. 2005;117(4):307–16.
26. Berry R, Schroeder JJ, French AJ, McDonnell SK, Peterson BJ, Cunningham JM, et al. Evidence for a prostate cancer-susceptibility locus on chromosome 20. Am J Hum Genet. 2000;67(1):82–91.
27. Berthon P, Valeri A, Cohen-Akenine A, Drelon E, Paiss T, Wohr G, et al. Predisposing gene for early-onset prostate cancer, localized on chromosome 1q42.2–43. Am J Hum Genet. 1998;62(6):1416–24.
28. Maier C, Rosch K, Herkommer K, Bochum S, Cancel-Tassin G, Cussenot O, et al. A candidate gene approach within the susceptibility region PCaP on 1q42.2–43 excludes deleterious mutations of the PCTA-1 gene to be responsible for hereditary prostate cancer. Eur Urol. 2002;42(3):301–7.
29. Berry R, Schaid DJ, Smith JR, French AJ, Schroeder JJ, McDonnell SK, et al. Linkage analyses at the chromosome 1 loci 1q24–25 (HPC1), 1q42.2–43 (PCAP), and 1p36 (CAPB) in families with hereditary prostate cancer. Am J Hum Genet. 2000;66(2):539–46.
30. Amundadottir LT, Sulem P, Gudmundsson J, Helgason A, Baker A, Agnarsson BA, et al. A common variant associated with prostate cancer in European and African populations. Nat Genet. 2006;38(6):652–8.
31. Freedman ML, Haiman CA, Patterson N, McDonald GJ, Tandon A, Waliszewska A, et al. Admixture mapping identifies 8q24 as a prostate cancer risk locus in African-American men. Proc Natl Acad Sci U S A. 2006;103(38):14068–73.
32. Cussenot O, Azzouzi AR, Bantsimba-Malanda G, Gaffory C, Mangin P, Cormier L, et al. Effect of genetic variability within 8q24 on aggressiveness patterns at diagnosis and familial status of prostate cancer. Clin Cancer Res. 2008;14(17):5635–9.
33. Sun J, Lange EM, Isaacs SD, Liu W, Wiley KE, Lange L, et al. Chromosome 8q24 risk variants in hereditary and non-hereditary prostate cancer patients. Prostate. 2008;68(5):489–97.
34. Al Olama AA, Kote-Jarai Z, Giles GG, Guy M, Morrison J, Severi G, et al. Multiple loci on 8q24 associated with prostate cancer susceptibility. Nat Genet. 2009;41(10):1058–60.
35. Pomerantz MM, Freedman ML. Genetics of prostate cancer risk. Mt Sinai J Med. 2010;77(6):643–54.
36. Chung S, Nakagawa H, Uemura M, Piao L, Ashikawa K, Hosono N, et al. Association of a novel long non-coding RNA in 8q24 with prostate cancer susceptibility. Cancer Sci. 2011;102(1):245–52.
37. Lange EM, Beebe-Dimmer JL, Ray AM, Zuhlke KA, Ellis J, Wang Y, et al. Genome-wide linkage scan for prostate cancer susceptibility from the University of Michigan prostate cancer genetics project: suggestive evidence for linkage at 16q23. Prostate. 2009;69(4):385–91.
38. Castro E, Eeles R. The role of BRCA1 and BRCA2 in prostate cancer. Asian J Androl. 2012;14(3):409–14.
39. Leongamornlert D, Mahmud N, Tymrakiewicz M, Saunders E, Dadaev T, Castro E, et al. Germline BRCA1 mutations increase prostate cancer risk. Br J Cancer. 2012;106(10):1697–701.
40. Mitra AV, Bancroft EK, Barbachano Y, Page EC, Foster CS, Jameson C, et al. Targeted prostate cancer screening in men with mutations in BRCA1 and BRCA2 detects aggressive prostate cancer: preliminary analysis of the results of the IMPACT study. BJU Int. 2011;107(1):28–39.
41. Gibbs M, Stanford JL, McIndoe RA, Jarvik GP, Kolb S, Goode EL, et al. Evidence for a rare prostate cancer-susceptibility locus at chromosome 1p36. Am J Hum Genet. 1999;64(3):776–87.
42. Lao-Sirieix P, Caldas C, Fitzgerald RC. Genetic predisposition to gastro-oesophageal cancer. Curr Opin Genet Dev. 2010;20(3):210–7.
43. Ikonen T, Matikainen M, Mononen N, Hyytinen ER, Helin HJ, Tommola S, et al. Association of E-cadherin germ-line alterations with prostate cancer. Clin Cancer Res. 2001;7(11):3465–71.
44. Pierce BL, Friedrichsen-Karyadi DM, McIntosh L, Deutsch K, Hood L, Ostrander EA, et al. Genomic scan of 12 hereditary prostate cancer families having an occurrence of pancreas cancer. Prostate. 2007;67(4):410–5.
45. Zuhlke KA, Johnson AM, Okoth LA, Stoffel EM, Robbins CM, Tembe WA, et al. Identification of a novel NBN truncating mutation in a family with hereditary prostate cancer. Fam Cancer. 2012;11(4):595–600.
46. Ntais C, Polycarpou A, Ioannidis JP. SRD5A2 gene polymorphisms and the risk of prostate cancer: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2003;12(7):618–24.
47. Brooke GN, Bevan CL. The role of androgen receptor mutations in prostate cancer progression. Curr Genomics. 2009;10(1):18–25.
48. Cancel-Tassin G, Cussenot O. Prostate cancer genetics. Minerva Urol Nefrol. 2005;57(4):289–300.

49. Silva Neto B, Koff WJ, Biolchi V, Brenner C, Biolo KD, Spritzer PM, et al. Polymorphic CAG and GGC repeat lengths in the androgen receptor gene and prostate cancer risk: analysis of a Brazilian population. Cancer Invest. 2008;26(1):74–80.
50. Yuan X, Lu ML, Li T, Balk SP. SRY interacts with and negatively regulates androgen receptor transcriptional activity. J Biol Chem. 2001;276(49):46647–54.
51. Fromont G, Yacoub M, Valeri A, Mangin P, Vallancien G, Cancel-Tassin G, et al. Differential expression of genes related to androgen and estrogen metabolism in hereditary versus sporadic prostate cancer. Cancer Epidemiol Biomarkers Prev. 2008;17(6):1505–9.
52. Li J, Yen C, Liaw D, Podsypanina K, Bose S, Wang SI, et al. PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. Science. 1997;275(5308):1943–7.
53. Steck PA, Pershouse MA, Jasser SA, Yung WK, Lin H, Ligon AH, et al. Identification of a candidate tumour suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers. Nat Genet. 1997;15(4):356–62.
54. Georgescu MM. PTEN tumor suppressor network in PI3K-Akt pathway control. Genes Cancer. 2010;1(12):1170–7.
55. Govender D, Chetty R. Gene of the month: PTEN. J Clin Pathol. 2012;65(7):601–3.
56. Salmena L, Carracedo A, Pandolfi PP. Tenets of PTEN tumor suppression. Cell. 2008;133(3):403–14.
57. Romano C, Schepis C. PTEN gene: a model for genetic diseases in dermatology. ScientificWorldJournal. 2012;2012:252457.
58. Feilotter HE, Nagai MA, Boag AH, Eng C, Mulligan LM. Analysis of PTEN and the 10q23 region in primary prostate carcinomas. Oncogene. 1998;16(13):1743–8.
59. Rubin MA, Gerstein A, Reid K, Bostwick DG, Cheng L, Parsons R, et al. 10q23.3 loss of heterozygosity is higher in lymph node-positive (pT2–3,N+) versus lymph node-negative (pT2–3,N0) prostate cancer. Hum Pathol. 2000;31(4):504–8.
60. Podsypanina K, Ellenson LH, Nemes A, Gu J, Tamura M, Yamada KM, et al. Mutation of Pten/Mmac1 in mice causes neoplasia in multiple organ systems. Proc Natl Acad Sci U S A. 1999;96(4):1563–8.
61. Di Cristofano A, Kotsi P, Peng YF, Cordon-Cardo C, Elkon KB, Pandolfi PP. Impaired Fas response and autoimmunity in Pten+/- mice. Science. 1999;285(5436):2122–5.
62. Di Cristofano A, De Acetis M, Koff A, Cordon-Cardo C, Pandolfi PP. Pten and p27KIP1 cooperate in prostate cancer tumor suppression in the mouse. Nat Genet. 2001;27(2):222–4.
63. Narla G, Heath KE, Reeves HL, Li D, Giono LE, Kimmelman AC, et al. KLF6, a candidate tumor suppressor gene mutated in prostate cancer. Science. 2001; 294(5551):2563–6.
64. Koivisto PA, Hyytinen ER, Matikainen M, Tammela TL, Ikonen T, Schleutker J. Kruppel-like factor 6 germ-line mutations are infrequent in Finnish hereditary prostate cancer. J Urol. 2004;172(2):506–7.
65. Narla G, Friedman SL, Martignetti JA. Kruppel cripples prostate cancer: KLF6 progress and prospects. Am J Pathol. 2003;162(4):1047–52.