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Hereditary prostate cancer

Dziedziczny rak prostaty

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Summary

Epidemiologic research conducted over the last two decades has led us to believe that inherited factors play an important role in the etiology of prostate cancer, but the genes, which underlie the inherited susceptibility are elusive. In Poland, we have initiated a program to identify DNA variants, which confer an increased risk of prostate cancer. We found that germline mutations in *CHEK2*, *NBS1*, *HOXB13* and the rs188140481 variant in the 8q24 region confer an increased prostate cancer risk in Polish men. Our studies provide evidence that the list of known genetic markers of high risk of prostate cancer can be extended by these specific variants in men with a positive family history of prostate cancer in at least one first or second degree relative (the risk increased about 3-8 fold). Based on our findings, we recommend that genetic testing for prostate cancer susceptibility in Poland be based on the seven founder alleles (IVS2 + 1G > A, 1100delC, del5395, I157T in CHEK2; 657del5 in NBS1; G84E in HOXB13; allele A of rs188140481). Identification of genetic markers of prostate cancer susceptibility will improve prevention, diagnosis and management of prostate cancer in Poland.

Streszczenie

Badania epidemiologiczne ostatniego dwudziestolecia dowodzą, że czynniki genetyczne mają ogromne znaczenie w etiologii raka gruczołu krokowego, jednakże geny związane z dziedziczną predyspozycją do tego nowotworu pozostają w dużej mierze niepoznane. W Polsce prowadzimy badania, których celem jest wyjaśnienie podłoża genetycznego raka prostaty. Dotychczas wykryliśmy jednoznaczny związek pomiędzy nosicielstwem zmian konstytucyjnych genów *CHEK2*, *NBS1*, *HOXB13* oraz zmiany polimorficznej w regionie 8q24 (rs188140481) a zwiększonym ryzykiem zachorowania na raka prostaty w polskiej populacji. Nasze badania dowodzą, że do poznanych genetycznych markerów wysokiego ryzyka raka prostaty również można zaliczyć nosicielstwo tych specyficznych zmian DNA, u których w rodzinie stwierdzono co najmniej jedno zachorowanie na raka prostaty u krewnego I lub II stopnia (ryzyko zachorowania zwiększone około 3-8-krotnie). W oparciu o wyniki naszych badań uważamy, że badanie genetycznej predyspozycji do raka prostaty w polskiej populacji może być oparte o wykrywanie siedmiu konstytucyjnych zmian DNA (IVS2+1G>A, 1100delC, del5395, I157T in CHEK2; 657del5 in NBS1; G84E in HOXB13; allele A of rs188140481). Identyfikacja genetycznych markerów podatności na raka prostaty ma na celu usprawnienie profilaktyki, diagnostyki i postępowania z rakiem stercza w Polsce.

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Familial clustering of prostate cancer was first described in 1955, and a term hereditary prostate cancer (HPC) was first used in 1992 by Carter who reported the results of linkage analysis in a series of 691 men with prostate cancer (PC) (1). This analysis revealed that 9% cases of familial clustering of prostate cancer

is associated with a single rare allele. Penetrance of this allele was 88% to age of 85. The allele conferring high risk for prostate cancer was found on long arm of chromosome 1 (1q24-25), and this loci was named *HPC1* (2).

Since that time, a number of prostate susceptibility chromosomal loci have been identified, but no particular genes at these loci were found to be associated with a significant proportion of HPC and clinical importance of these loci is still very limited. Although the molecular basic of HPC largely remains unknown, epidemiologic research clearly shows that inherited factors play an important role in the etiology of prostate cancer. Genes of high penetrance may be responsible for 5-10% of prostate cancer cases and for as many as 30-40% of early onset prostate cancer (3). Scandinavian study of twins suggested that the heritability of prostate cancer may be as high as 42% (4).

FAMILY HISTORY AND PROSTATE CANCER RISK

Familial clustering of prostate cancer is the most important risk factor for prostate cancer (3, 5). Many studies show an elevated risk of PC in brothers and sons of affected individuals. It is important to note that the risk of PC (especially early onset) is higher in relatives of individuals affected by prostate cancer in early age. Some of the studies show that the risk is higher in brother than in sons of PC patients (it is possible that inheritance is X-linked or HPC could be an autosomal recessive trait in some families). The risk of prostate cancer by the presence of prostate cancer in first and second degree relatives is shown in table 1.

Table 1. Family history and prostate cancer risk.

Family history	Relative Risk
Negative	1
Father with PC at age of 60 or above	1.5
1 brother with PC at age of 60 or above	2
Father with PC before age of 60	2.5
1 brother with PC before age of 60	3
2 first degree relatives with PC	4
3 or more relatives with PC	5

CLINICAL CRITERIA FOR HPC

Clinical criteria for HPC (fig. 1a and 1b) (6):

1. Definitive diagnosis of HPC:
a) PC in 3 or more first degree relatives; or
b) PC in 3 generations; or
c) PC at age below 56, in two or more relatives.
2. Diagnosis of cases suspected for HPC:
a) PC in 3 or more relatives but does not fulfil criterion a) or b) for definitive diagnosis; or
b) PC in 2 relatives, including at least one diagnosed below age of 60 and/or vertical transmission but without fulfilling criterion c) for definitive diagnosis; or
c) at least one PC below age of 50, not matching criteria for definitive diagnosis.

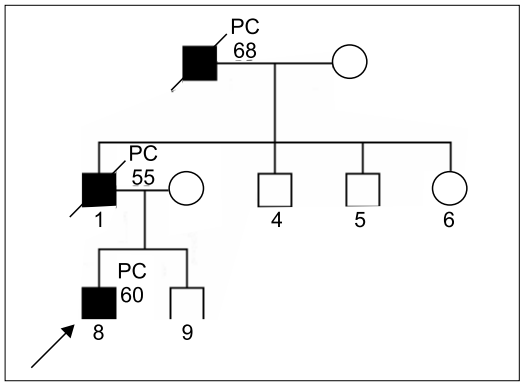

Fig. 1a. Pedigree of family with diagnosis of HPC.

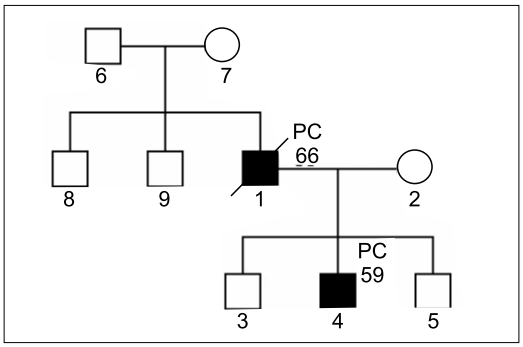

Fig. 1b. Pedigree of a family suspected for HPC, which does not fulfil clinical criteria.

CLINICAL CHARACTERISTICS OF HPC

The most important features of HPC include: autosomal dominant inheritance of prostate cancer (rarely autosomal recessive or X-linked dominant inheritance) and early age of diagnosis – the mean age below 56, so 6-7 years younger than that seen in sporadic cases (2). Because of the early onset of disease, a bigger proportion of HPC patients die (75%), than in sporadic cases (50%) (7, 8).

OTHER CANCERS IN FAMILIES WITH HPC

Epidemiological studies provide evidence that in families with prostate cancer the risk of this cancer is increased, but the data are controversial regarding increased risk of other cancers. Some studies suggest that risk for brain tumours, stomach cancer or breast cancer is increased in HPC, but in most studies HPC is characterized as susceptibility to prostate cancer in isolation (site specific syndrome). The controversy will remain questioned until the majority of HPC susceptibility genes are identified (9).

HEREDITARY CANCER SYNDROMES AND PC RISK

Mutations in *BRCA1* or *BRCA2* gene confer high risk of breast and ovarian cancer. Several studies suggested two-fold increased risk of prostate cancer in Ashkenazi Jewish men with a *BRCA1* mutation (185delAG or 5382insC) (10-12). While studies in other non-Jewish populations have found little or no evidence of an increased risk for prostate cancer in *BRCA1* mutation carriers (13-16). The reason

of this difference may be a different spectrum of mutations in *BRCA1* gene and/or other modifying factors in particular populations.

Association of *BRCA2* mutations with increased prostate cancer risk is well documented. It was reported that, carriers of germ-line mutations in *BRCA2* are at 5 fold increased risk of PC, the risk higher (increased by 7 fold) to age of 65, and even 20-fold to age of 56 (9). Recent studies suggest that *BRCA2* carriers are more likely to develop aggressive prostate cancer (high grading G3 and G4) in early age (on an average 5 years younger than non-carriers). Prognosis was reported to be much worse for men with a *BRCA2* mutation, i.a. one study showed that the mean survival was approximatelly 2 years in *BRCA2* carriers versus 12 years in non-carriers. However, mutations in *BRCA2* or *BRCA1* are rare and the contribution of these two genes to HPC is relatively small, which is largely a site specific syndrome.

In addition increased prevalence of prostate cancer was observed in families with Cowden syndrome, Li-Fraumeni syndrome, and hereditary stomach cancer caused by mutations of *E-cadherin* (3, 9).

PROSTATE CANCER SUSCEPTIBILITY GENES (HPC CANDIDATE GENES)

Through linkage analysis, numerous prostate cancer susceptibility chromosomal loci have been identified (i.e. *HPC1* (1q24-25), *PCaP* (1q42-43), *HPCX* (Xq27-28), *CAPB* (1p36), *HPC2* (17p12) and *HPC20* (20q13)). From these regions three candidate susceptibility genes (i.a. *RNASEL* and *MSR1*) have been positionally cloned. Germ-line mutations in *RNASEL* and *MSR1* genes have been reported in several families affected with hereditary prostate cancer in USA, and frequent polymorphisms of these genes were reported as variants of low penetrance for prostate cancer (17-19). Unfortunately further studies provided evidence that none of these genes found for HPC is a high-risk susceptibility gene for prostate cancer, including studies in Polish population (20).

HOXB13 GENE

Through linkage analyses in HPC families a number of chromosomal loci was found to be associated with PC. The first gene conferring high risk of PC identified in one of these loci was only discovered in 2012. Ewing et al. performed next generation sequencing of chromosomal region 17q21-22 (above 200 genes) in 94 families with PC and found a recurrent mutation G84E in *HOXB13* gene (21). The mutation was confirmed in familial segregation analysis and association analysis showed high risk of prostate cancer linked to this mutation (OR = 20; $p < 0.0001$). High risk of prostate cancer in carriers of mutation G84E in *HOXB13* gene conferred in different studies and in different populations, including Polish population (22).

CHEK2 GENE

CHEK2 (a.k.a. “CHK2”) is a checkpoint kinase gene which is activated in response to DNA damage and prevents entry of cells into mitosis. Mutations in the *CHEK2* were first found to be associated with prostate cancer risk in the United States. 18 different *CHEK2* mutations were found, mostly in single patients (23). In Finland two recurrent mutations of *CHEK2* gene (1100delC and I157T) were reported to be associated with prostate cancer risk (24). Truncating mutations of *CHEK2* increase prostate cancer risk by 2-3 fold. However, the risk of prostate cancer for man with a *CHEK2* mutation is not determined solely by the presence of the mutation; penetrance is also dependent on the family history of cancer. That is, the risk for man with a mutation and a positive family history of prostate cancer is greater than that of a carrier of the same mutation who has no family history of prostate cancer. For example the risk for prostate cancer associated with *CHEK2* 1100delC in Finnish population in familial cases was increased 8-fold (24).

NBS1 (*NBN*) GENE

NBS1, also known as Nibrin (*NBN*), is a gene involved in DNA damage repair pathway and it is responsible for Nijmegen breakage syndrome (NBS), a rare autosomal recessive disorder. Frequency of Nijmegen breakage syndrome is significantly higher in Slavic population than anywhere else in the world. The 657del5 mutation is responsible for 90% of all reported cases of NBS to date. The distribution of 657del5 allele of *NBS1* is not worldwide, and this allele is most common in Slavic populations of Eastern Europe (25). In Polish population, carriers of *NBS1* mutation have 2.5 times higher risk of having PC. Additionally the 657del5 mutation also confers poor prognosis of PC in these men, half of the men die within 5 years after diagnosis of PC (HR = 1.9; $p = 0.008$) (26). *NBS1* is a DNA repair gene and mutation carriers lack properly functioning Nibrin protein in their prostate tumours, so the DNA damage repair is retarded in these tumours. This gives us reason to believe that these tumours could benefit from DNA damaging chemo-drugs like cisplatin and PARP inhibitors and it can well be a subject for future clinical trials.

A number of mutations in different genes have been reported to be linked with PC risk, however these were published in single studies and did not show any confirmatory evidence in other studies (27-29). Most of these mutations were located in DNA repair and cell cycle regulatory genes (e.g. *CDKN1B*, *CDKN1A*, *ATM*, *XRCC1*, *ERCC2*).

It is possible that most of the PC with hereditary background are caused by multiple variants of low penetrance and environmental factors can significantly modify the risk. In the past years numerous genome-wide association studies (GWAS) have identified over 70 prostate cancer susceptibility loci (30) which can explain around 30% of the familial risk for PC. First

PC susceptibility region identified in GWAS was 8q24 which has also shown the strongest correlation with PC risk until now. These numerous variants are currently not in use in clinical practice.

SUSCEPTIBILITY TO PROSTATE CANCER IN THE POLISH POPULATION

Identification of markers for genetic predisposition to cancer is effective in populations which are genetically homogenous and exhibit founder effect, such as Polish population. In these populations, generally a small spectrum of different germ-line mutations is often associated with large proportion of genetic disorders, which allows us to develop inexpensive and effective genetic testing. In Poland we have initiated a programme to identify DNA variants which confer an increased risk of prostate cancer and other cancers.

There are four CHEK2 founder mutations identified in Polish populations, three truncating mutations and one missense variant I157T. Carriers of truncating mutations of *CHEK2* (1100delC, IVS2+1G>A, del5395), which are present with a frequency 1% in the Polish population are at 2.5 fold increased PC risk. Carriers of a missense mutation I157T, which is present in frequeny of 5% in Polish population, are at 1.7-fold increased risk for PC (26, 31, 32). The risk is almost twice higher if there are more cases of PC in the family of *CHEK2* mutation carrier. One of our latest study on 2907 Polish men showed that PSA screening is more effective in diagnosing PC at earlier age in *CHEK2*-I157T mutation carriers, risk of PC is particularly higher in individuals between 40-60 years (OR = 5.5; p = 0.001) and individuals with a family history of PC (OR = 3.2; p = 0.0004) (33). Prostate cancer risk at 85 years of age was 16% for any *CHEK2* mutation carriers, for individuals with *CHEK2* mutation and one first degree relative with PC the risk was 24% and the risk was even higher (32%) if the mutation was truncating.

A single founder mutation of *NBS1* gene, 657del5, which is present with a frequency of 0.5% in the Polish population, increase prostate cancer risk by 2.5 times and it can be as high as 4.3-fold if the mutation carrier has one family member with PC. Additionally the 657del5 mutation confers poor prognosis of PC in these men, half of the men die within 5 years of diagnosis of PC (HR = 1.9; p = 0.008) (26). Prostate cancer risk at the age of 85 years is approximately 20% for carriers of *NBS1* mutation and if the mutation carrier has one family member with PC the risk can be as high as 34%. Frequency of 657del5 mutation in Polish population is around 0.6% while it is 1.4% in men with PC, additionally the frequency of this mutation is as high as 2.5% in familial PC cases.

Presence of G84E mutation of *HOXB13* gene results in 5-fold increase of the risk of PC in Polish men. If the mutation carrier had at least one I or II degree relative with PC, the risk increase up to 8.4 times. *HOXB13* mutation carriers have 40% probablity of having PC by the age of 85 and presence of one first degree relative with PC increase the risk up to 67% in these individuals. Population frequency of G84E mutation is 0.12% in Poland, while the frequency of this mutation in men with PC and in familial aggregation of PC is 0.6% and 1% respectively (22).

Recently, a single SNP (rs188140481) in the 8q24 chromosomal region was associated with a threefold increased risk of prostate cancer in Europe and North America (36). In Poland, the A allele of rs188140481 was detected in 44 of 3467 (1.3%) men with prostate cancer and in 7 of 1958 (0.4%) controls (OR = 3.6; p = 0.0006). The allele was present in 8 of 390 (2.1%) men with familial prostate cancer (OR = 5.8; p = 0.001) (37).

Based on these findings, we recommend that genetic testing for prostate cancer susceptibility in Poland be based on the seven founder alleles (IVS2+1G>A, 1100delC, del5395, I157T in *CHEK2*; 657del5 in *NBS1*; G84E in *HOXB13*; allele A of rs188140481). One of these seven alleles is present in 14% of men with unselected prostate cancer and 21% of men with familial prostate cancer in Poland.

DNA TESTING IN DIAGNOSIS OF HPC

Groups of individuals with an increased risk of prostate cancer in the Polish population can be identified by testing of specific variants in the *NBS1*, *CHEK2* and *HOXB13* genes. The list of known genetic markers of high risk of prostate cancer (in addition to strong family history of prostate cancer) may be extended by specific mutations in the *NBS1*, *CHEK2* and *HOXB13* genes in men with a positive family history of prostate cancer in at least one 1st or 2nd degree relative (the risk increased about 5-15 fold), in the Polish population.

DNA testing of *BRCA2*, *p53* (Li-Fraumeni syndrome), *PTEN* (Cowden syndrome) and *E-cadherin* genes may be performed. However mutations of these mutations are rare, and such testing is justified only in the cases of prostate cancer occurring in the course of hereditary syndromes caused by these mutations.

DIAGNOSTIC METHODS FOR PROSTATE CANCER

Prostate cancer in its early course is asymptomatic. Major diagnostic methods for prostate cancer diagnosis include measurement of serum PSA level (prostate specific antigen), DRE (digital rectal examination) and TRUS (trans-rectal ultrasonography). An abnormal PSA test result has been defined as a value of more than 4.0 ng/ml. Sensitivity of PSA test based upon cut-off value 4 ng/ml varies from 29% to 80% in different studies (i.e. in some prostate cancers (e.g. poorly differentiated) PSA level is not increased). Some cases of prostate cancer cases can be diagnosed by digital rectal examination of the prostate however DRE is less

effective in detecting prostate cancer than PSA testing. Major role of TRUS in diagnosis of prostate cancer is to perform guided biopsy. Prostate cancer is diagnosed based on histopathological examination of biopsied tissue. TRUS guided prostate core biopsy is a standard procedure for PC diagnosis. A sextant lateral biopsy is generally performed (6-10 cores). Saturation biopsy (> 20 sections) can be recommended in the cases highly suspected for prostate cancer, if the results of sextant lateral biopsy are negative.

SCREENING OF PC IN MEN WITH INCREASED RISK OF PROSTATE CANCER

Systematic PSA testing of asymptomatic men in middle age definitely allows early diagnosis of PC and decrease the number of PC diagnosed at advanced stage. Screening examinations of high risk individuals has better economic justification than the screening of whole male population. Therefore screening should primarily be provided to the individuals with positive family history and higher PSA level. Screening includes PSA testing, DRE and prostate biopsy in case of suspicion. According to the American Cancer Society, screening tests should start at the age of 45 years in high risk individuals. In members of HPC families screening should start at an age at least 5 years earlier than the age of earliest diagnosed PC case in family and at least 10 years earlier than the age of earliest diagnosed PC with metastasis.

Screening is recommended up to an age of 70 years, as the risk of PC related death is low after 70 years (33). Recommended level of PSA for high risk individuals (from HPC families) is 3 ng/ml. In case of negative screening results, PSA and DRE should be repeated more often than in low risk men (3, 34, 35).

Moderate (and high) risk variants might be used to define a group of men at higher than average risk of prostate cancer. Genetic testing might enable personalized approach to prostate cancer prevention and screening. For example, a panel of moderate risk genetic variants (with average odds ratio of 3) which are present in 20% of the population would enable targeted PSA screening of 20% the population that would detect 60% of all prostate cancers in the population. Currently PSA screening has not been shown to decrease overall mortality from prostate cancer in the general population, but it might perform better in the high risk setting (38). **To date we identified six founder alleles in three genes (*CHEK2*, *HOXB13* and *NBN*) and a single allele of rs188140481 which predispose to prostate cancer in Poland, and in combination, these have a combined prevalence of 7.0% in the population. One of these seven alleles is present in 14% of men with unselected prostate cancer and 21% of men with familial prostate cancer. No founder alleles of BRCA2 in Poland are sufficiently common to be included in the panel. Based on these findings, we recommend that genetic testing for prostate cancer susceptibility in Poland be based on the seven founder alleles (IVS2+1G>A, 1100delC, del5395, I157T in CHEK2; 657del5 in NBS1; G84E in *HOXB13*; allele A of rs188140481). The American Cancer Society currently recommends a discussion about PSA screening with men aged ≥ 50 years, or aged ≥ 45 years for men at increased prostate cancer risk (African-American men or those with a family history of prostate cancer) (39). Therefore, in the event of a positive test we suggest annual PSA screening proceed from age 45 years** (fig. 2).

Family history (FH) of prostate cancer in I or II degree relatives

FH of prostate cancer negative*

Consider as low risk → Discuss option of PSA from age 50

FH of prostate cancer positive

HPC clinical criteria matched → Consider as increased risk → Offer annual PSA from age 45 or from age 5 years lower than youngest age of PC diagnosis in relatives

HPC clinical criteria not fulfilled → Offer genetic testing for the 7 variant panel**
Genetic test positive → Consider as increased risk → Offer annual PSA from age 45
Genetic test negative → Consider as low risk → Discuss option of PSA from age 50

Fig. 2. Recommendations for genetic testing for prostate cancer susceptibility in Poland.

Footnote to fig. 2:
HPC (hereditary prostate cancer) clinical criteria by Carter et al. (6)
*If FH is negative may consider genetic testing for the panel on patients' request
**The panel includes 7 variants (IVS2+1G>A, 1100delC, del5395, I157T in CHEK2; 657del5 in NBS1; G84E in HOXB13; allele A of rs188140481)

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