Hereditary prostate cancer

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Identity

Alias: Familial prostate cancer

Note: Form of prostate cancer with a familial background, OMIM: 176807, 601518.

Inheritance: The inherited form is predicted to account for 5-9% of prostate cancers. Multiple forms of inheritance have been suggested based on segregation analyses: autosomal dominant (rare, high-penetrant gene, mostly linked to disease onset at a younger age), autosomal recessive, X-linked (mostly linked to late-onset cases), multi-factorial and co-dominant.

Clinics

Note: Hereditary/familial prostate cancer is a heterogeneous disease entity with complex genetics.

Phenotype and clinics

The definition of hereditary prostate cancer (HPC) is based on the family history (pedigree). The suggested criteria include 1) nuclear family with three (or more) cases of prostate cancer, 2) prostate cancer in three successive generations, or 3) at least two men diagnosed with the disease before the age of 55 years. Familial aggregation of cases that don't fulfill the HPC criteria are defined as familial prostate cancer. The onset of HPC is on average 6 years earlier than of sporadic prostate cancer but the clinical course is otherwise no different.

Neoplastic risk

There is a greater risk of prostate cancer for brothers and sons of men with the disease. The relative risk of prostate cancer is about two-fold in first-degree relatives of affected men and the risk increases with increasing number of affected relatives and their decreasing age at diagnosis. The incidence and absolute risk of prostate cancer varies among different ethnic backgrounds. However, increase in relative risk for males with a positive family history of the disease is essentially the same in all studied populations. In epidemiological studies increased risk of breast cancer, ovarian cancer, gastric cancer and liver cancer, Hodgkin's disease, leukaemia and melanoma have been detected in relatives of prostate cancer patients.

Treatment

Curative treatment is possible for localized prostate cancer. Men with strong positive family history should be offered risk assessment and regular follow-ups. Early detection is possible through PSA (prostate specific antigen) testing and DRE (digital rectal examination). In rare families where known mutations are segregating, genetic testing may be possible.

Prognosis

Prognosis is more dependent on extent of the disease at diagnosis than on the genetic susceptibility. PSA testing is as efficient in HPC families as in the general population.

Genes involved and proteins

Note: There is strong evidence from epidemiological and family studies in support of genetic predisposition to prostate cancer. Despite this, no major susceptibility gene has been identified. It is commonly accepted that predisposition may be mediated through multiple common low-to-moderate-penetrance risk alleles. Only few rare (high-risk) mutations in candidate genes have
been found in families fulfilling the HPC definition. Familial prostate cancer is likely a mixture of cases caused by dominant high-risk genes, risk-modulating genes, environmental risk factors and ageing.

**RNASEL**

**Location**
1q25

**Note**
Ribonuclease L (2',5'-oligoisoadenylate synthetase-dependent), encodes an antiviral, proapoptotic and interferon-activated RNase.

**DNA/RNA**
Description: 6 coding exons spanning 13,337 bases of genomic DNA, mRNA has a size of 4,166 kb.

**Protein**
Description: 741 amino acids, 83,533 Da.
Expression: Highly expressed in spleen and thymus followed by prostate, testis, uterus, small intestine, colon and peripheral blood leukocytes.
Localisation: Cytoplasm and mitochondrion.
Function: Endoribonuclease, mediator of interferon action, which play a role in mediating resistance to virus infection and apoptosis. Possibly play a central role in the regulation of mRNA turnover.
Homology: Mouse, rat.

**Mutations**
Germinal: About 20 mutations/variants described. Met1Ile, Glu265>Stop and Arg462Gln were the first identified risk alleles for HPC. Arg462Gln has three times reduced enzymatic activity. A founder 471delAAAG has been found in Ashkenazi Jews. Glu265>Stop and Asp/Asp genotype of codon 541 have been associated with familial prostate cancer risk in Finnish and Japanese populations, respectively. These mutations are often associated with early age of onset.

**ELAC2**

**Location**
17p11.2

**DNA/RNA**
Description: 24 coding exons spanning 25,658 bases of genomic DNA, mRNA has a size of 3,026.

**Protein**
Description: Zinc phosphodiesterase ELAC protein 2.
Localisation: Membrane; Single-pass type II membrane protein.
Function: Membrane glycoproteins implicated in the pathologic deposition of cholesterol in arterial walls during atherogenesis. Two types of receptor subunits exist. These receptors mediate the endocytosis of a diverse group of macromolecules, including modified low density lipoproteins (LDLs).
Homology: Mouse, rat.

**Mutations**
Germinal: Truncating mutations originally found in African-American and European-American men. Arg293X truncating mutation results in a dominant negative mutant of the gene.
To be noted

Note
In addition to the three strong candidate susceptibility genes (RNASEL, ELAC2, and MSR1), a number of other loci have been identified in genome-wide genetic linkage studies using HPC families. These include for example 1p35-36 (CAPB), 1q42-43 (PCAP), 16q23, 17q22, 20q13 (HPC20) and Xq27-28 (HPCX). However, many of the reported loci have been hard to validate in other populations and therefore the results of the linkage analyses have remained disparate. More recently, using genome-wide SNP analyses, even more susceptibility loci have been localized, including repeatedly detected 3p, 8q24, 10q11, 11q13, 17q and Xp11. In addition, association with familial prostate cancer has been detected with mutations of CHEK2 (22q12.1), BRCA2 (13q12), CDKN1B (12p13.1-p12), PON1 (7q21.3), SRD5A2 (2p23) and PALB2 (16p12.1) although the results are not fully consistent in all populations and ethnic groups studied.

References


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Schleutker J


with Breast and prostate cancer. Genet Epidemiol. 2002


Bratt O. What should a urologist know about hereditary predisposition to prostate cancer? BJU Int. 2007 Apr;99(4):743-7; discussion 747-8


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