Prostate cancer is a complex, multifactorial disease with genetic and environmental factors involved in its etiology. The search for genetic determinants involved in the disease has proven to be challenging, in part because such complex diseases are often not amenable to characterization by linkage analysis and positional cloning as is the case for diseases with simple Mendelian genetic inheritance. Prostate cancer susceptibility loci that have been reported so far include HPC1 (1q24–q25), PCAP (1q42–q43), HPCX (Xq27–q28), CAPB (1p36), HPC20 (20q13), HPC2/ELAC2 (17p11) and 16q23. Prostate cancer aggressiveness loci have also been reported (5q31–q33, 7q32 and 19q12). Further complicating the process is the existence of polymorphisms in several genes associated with prostate cancer including, AR, PSA, SRD5A2, VDR and CYP isoforms. These polymorphisms, however, are not thought to be highly penetrant alleles in families at high risk for prostate cancer. It is clear that prostate cancer etiology involves several genetic loci with no major gene accounting for a large proportion of susceptibility to the disease.

Prostate cancer susceptibility loci: rare with high penetrance

Prostate cancer can be sporadic, familial or hereditary. Familial prostate cancer is defined by clustering of prostate cancer cases within male members of a family; for example, two brothers having the disease. Steinberg et al. (5) reported the results of a case control study to determine the frequency of prostate cancer in male relatives of 691 men with prostate cancer and male relatives of 640 of their spouses. They found that men with either a father or brother diagnosed with prostate cancer were twice as likely to develop the disease compared with men with no affected relatives. More striking was that men with two or three first-degree affected relatives had a 5- and 11-fold increased risk of developing prostate cancer, respectively. Walsh and Partin (6) estimate that 25% of men with prostate cancer have a family history of the disease. Hereditary prostate cancer refers to a subtype of the disease in which Mendelian inheritance of a susceptibility gene is evident (7). Whereas data from Monroe et al. (8) along with Narod et al. (9) support an X-linked or recessive model of inheritance, results from three independent segregation analyses support the autosomal dominant model for Mendelian inheritance of prostate cancer (10–12). This rare allele would account for 9% of all prostate cancer cases at ≤85 years of age, but could account for as much as 43% of prostate cancer cases diagnosed at ≤55 years of age. Although the dominant alleles have low population frequency of 0.36–1.67%, they are highly penetrant such that by 85 years of age, 63–89% of men carrying a mutation are likely to be diagnosed with prostate cancer (10–12). The notion that inherited susceptibilities play a role in the development of prostate cancer is supported by evidence for Mendelian segregation and by strong evidence for a familial effect on risk of the disease.
Smith et al. (13) reported the first putative hereditary prostate cancer locus, HPC1, localized to chromosome 1q24–q25 by a genome-wide scan. They studied 91 families from North America and Sweden with an average number of 4.9 prostate cancer cases in each family with an average age of diagnosis of 65 years for affected individuals. A peak multipoint LOD score of 5.43 was achieved, assuming heterogeneity. HPC1 was originally proposed to account for prostate cancer in 34% of families in this data set based upon heterogeneity testing. A subsequent study of the characteristics of HPC1-linked families suggested that the evidence for linkage was primarily from families with four or more close relatives with the disease, an early mean age at diagnosis <65 years, and proportionately more advanced-stage disease (14). A pooled analysis of 772 families suggested that the actual proportion of familial prostate cancer linked to HPC1 is on the order of 6% (15). A number of replication studies have been published and results are mixed. A number of confirmatory studies provide weak evidence for linkage to HPC1 (16–19). In two of the HPC1 confirmatory studies, P-values reported by Cooney et al. (16) and Hsieh et al. (17) were between 0.03 and 0.045, which do not exceed the threshold recommended by Lander and Kruglyak (20) for declaration of significant linkage initially (P < 0.000049) or for replication of significant linkage (P < 0.01). Interestingly, in the report by Cooney et al. (16), 11 African-American families contributed disproportionately to the observation of linkage. Several other studies reported no evidence of linkage to HPC1 (21–24).

A second prostate cancer susceptibility locus, known as PCAP, maps to 1q42–q43 (22). A two-point LOD score of 2.7 was achieved, and homogeneity analysis suggested an estimated 40–50% of the families linked. All families in the data set were from France and Germany. Families with an average age at onset <65 years contributed significantly to the evidence of linkage. In a subsequent linkage study to determine the contribution of several susceptibility loci including HPC1, PCAP, CAPB and HPCX in the southern and western European population, Cancel-Tassin et al. (25) reported that PCAP was the only region showing evidence of linkage in the 64 families studied. They concluded that PCAP is the major contributing prostate cancer susceptibility locus in southern and western Europe. Three other PCAP confirmatory studies found no or only weak evidence for linkage (19) (26,27).

A third prostate cancer susceptibility locus, known as HPCX, maps to Xq27–q28 (28). Replication of these findings has been reported by independent researchers (29,30). In a study of 186 prostate cancer families, 81 families with no evidence of male-to-male transmission contributed disproportionately to the observation of linkage (30). The results were consistent with a small percentage of the 81 families being linked to the Xq27–q28 but not to the extent of 16% originally reported by Xu et al. (15). HPCX linkage appears to be related to maternal inheritance of prostate cancer with an early age of onset of ≤65 years.

A fourth prostate cancer susceptibility locus, known as CAPB, which maps to 1p36, has been reported in families with a history of both prostate and brain cancers (31). A genome scan of 71 high-risk prostate cancer families revealed that the 12 families with both a history of prostate cancer and a blood relative with primary brain cancer showed evidence of linkage to genetic markers at 1p36 region. One linkage study of all putative prostate cancer loci mapping to chromosome 1 provided no supporting evidence for linkage at the 1p36 locus (19). An independent study of 207 multiple-case prostate cancer families including nine families with prostate and brain cancer found no evidence of linkage to 1p36 in the subset of families with prostate and brain cancer (32). However, they found suggestive evidence of linkage in those families with early onset (<66 years of age), leading them to conclude that linkage to 1p36 may be a feature of early-onset prostate cancer.

Results from a genome-wide scan of 162 North American families with three or more members affected with prostate cancer suggested evidence for yet another locus at 20q13, now known as HPC20 (33). Results suggested that the strongest evidence of linkage was seen in families with less than five affected individuals, a later age at onset, and no male-to-male transmission. Several studies have sought to confirm linkage to HPC20 using independent data sets. An independent replications study of 159 high-risk prostate cancer families reported evidence of linkage to HPC20 in families fitting similar criteria as those reported originally by Berry and colleagues (34). However, two other confirmatory studies were unable to support the notion of an HPC20 prostate cancer susceptibility locus in their data sets (25,35).

In a genome-wide scan using multiplex sibships, Suarez et al. (36) reported the identification of a number of linkage peaks, with the most convincing evidence of linkage at markers surrounding the chromosome 16q23 region. Other regions of interest reported in the study were at 2q, 12p, 15q and 16p, although with less convincing evidence of linkage. Interestingly, these investigators reported a strong linkage signal at chromosome 1p35 in families with prostate cancer sibships along with a family history of breast cancer. These results require further study to determine the true contribution of these loci in prostate cancer susceptibility.

Yet to be confirmed is the existence of yet another susceptibility locus at 17p11 known as HPC2/ELAC2 (37). An expanded set of 127 high-risk prostate cancer families was chosen from the Utah Population Database. The analysis focused on those families in which a common haplotype at chromosome 17p12 was shared by at least four cases, with a LOD score of 1.0 or more, of families in which haplotypes were shared by at least six cases, regardless of the LOD score. Haplotype analysis led to the refinement of the genetic locus, and positional cloning identified a gene known as ELAC for which a frameshift mutation and a number of missense mutations were identified. An association between increased risk of developing prostate cancer and HPC2/ELAC2 missense mutations was reported prior to the publication of HPC2/ELAC2 gene cloning (38). Two subsequent studies were unable to confirm these data (39,40). One recent study found an association of one HPC2/ELAC2 missense mutation with prostate cancer cases from high-risk families (41). However, there was no evidence of the allele segregating in these families and there was little or no evidence of linkage in these families. Therefore, the role of HPC2/ELAC2 in prostate cancer susceptibility is still controversial.

Locus heterogeneity seems to be a major factor in the identification of linkage or confirmation of linkage for many datasets. As methods for statistical modeling improve, geneticists will have better tools to deal with the issue of extreme heterogeneity within their data sets. Goddard et al. (42) were able to identify several significant linkage peaks,
including previously reported regions such as HPC1 and PCAP and novel loci, by modeling locus heterogeneity using Gleason score, age at onset, male-to-male transmission and/or number of affected first-degree family members as covariates in a model-free analysis. An alternative method has also been reported, which used covariates in a regression-based analysis to identify those covariates or sets of covariates that best predict a family being of the linked type to alleviate some of the problems caused by locus heterogeneity within a data set (43). Chromosomal loci of rare but highly penetrant prostate cancer genes identified to date are illustrated in Figure 1.

**ADDITIONAL PROSTATE CANCER LOCI**

The pace at which new candidate genes involved in prostate carcinogenesis in general has increased rapidly since the complete mapping of the human genome. Data from genome-wide scans of families with multiple prostate cancers suggest that multiple prostate cancer susceptibility genes exist. The possible existence of multiple prostate cancer genes may explain why there has been limited confirmatory evidence of linkage for the susceptibility genes that have been identified to date. The multifactorial nature of the disease is demonstrated by the occurrence of both hereditary and sporadic cases in families, which complicates linkage analyses (44). A 10 cM genome-wide scan of 94 families with hereditary prostate cancer, including 432 affected men gave evidence of several putative prostate cancer susceptibility loci (45). Regions of interest were identified on chromosomes 10, 12 and 14, with a dominant model of inheritance, whereas regions on chromosomes 1, 8, 10 and 16 were identified using a recessive model of inheritance. More recently, Xu et al. (46) reported evidence of linkage and marker association to markers mapping at 8p22–p23, a region believed to harbor a prostate cancer tumor suppressor gene (47,48).

One report has focused on the identification of inherited prostate cancer loci associated with tumor aggressiveness (49). Prostate cancer aggressiveness was measured directly as a quantitative trait in a genome-wide scan of 513 brother pairs with prostate cancer. Results obtained point to candidate regions on chromosomes 5q (5q31–q33, between markers D5S1480 and D5S820), 7q (7q32 between markers D7S3061 and D7S1804) and 19q (19q12 at D19S433). They suggest that these loci may contain genes that influence the progression of prostate cancer. Identification of the genes involved would be important in understanding prostate cancer onset, progression and treatment.

Allelic imbalance in tumors is a hallmark feature for the involvement of tumor suppressor genes in cancer etiology. The most common regions of allelic imbalance in prostate cancer include 1p, 6q, 8p, 10q, 13q, 16q and 18q (50). Of these regions, 8p and 16q also have been implicated in prostate cancer linkage studies. Allelic imbalance at 16q23 in both sporadic tumors and tumors from men with a positive family history has been reported (51). These data suggest that 16q23 may harbor a prostate cancer tumor suppressor gene implicated.
in the development of non-familial and possibly familial forms of prostate cancer. A number of studies have sought to determine the extent of allelic imbalance in other regions implicated in harboring prostate cancer susceptibility loci. A number of reports suggest a low frequency of allelic imbalance at the PCAP and HPC1 loci (52–55).

PROSTATE CANCER SUSCEPTIBILITY LOCI: COMMON WITH LOW PENETRANCE

We have discussed how a number of rare highly penetrant loci may contribute to Mendelian inheritance of prostate cancer. However, other genetic alterations have been studied in prostate cancer, which are common low penetrant alleles. There is some understanding of how polymorphisms in a number of genes involved in prostate cancer determine the onset, progression and response to treatment for the disease. A number of polymorphisms have been studied extensively for associations with prostate cancer. We will discuss polymorphisms that exist in the following genes: androgen receptor (AR), prostate-specific antigen (PSA), steroid 5-α-reductase (SRD5A2) and the cytochrome P450 (CYP) isozymes.

The AR is an androgen-activated transcription factor, which belongs to the steroid hormone receptor superfamily (56). It is an intracellular cytosolic receptor that binds androgens to form an AR–ligand complex which translocates to the nucleus thus activating transcription of certain genes containing androgen-responsive elements (AREs) in their promoters (57). Mutations (8%) have been identified in exons 1–8 of the AR gene. However, although AR mutations appear not to play a role in the initial phase of prostate carcinogenesis, a significant number of AR mutations are seen in metastatic disease (58). These mutations may facilitate growth or acquisition of the metastatic phenotype (59). Two trinucleotide repeat polymorphisms have been identified in the AR, including the CAG or polyglutamine polymorphism and the GGC or polyglycine polymorphisms (60). Polyglutamine alleles containing less than 15 CAG repeats appear to be associated with prostate cancer risk, while certain GGC polymorphisms hold promise for the influence of the polymorphism on prostate cancer 5-fold. The allelic variation in the AR gene promoter may be androgen dependent, and the PSA/AR interaction supports a multigenic etiology for prostate cancer.

The PSA gene promoter polymorphisms in combination with AR polymorphisms may be associated with prostate cancer outcome (68). The PSA homozygous (GG) genotype is believed to be associated with prostate cancer risk. However, the combination of the PSA (GG) genotype combined with AR CAG-short genotype increases the risk of prostate cancer 5-fold. The allelic variation in the PSA gene promoter may be androgen dependent, and the PSA/AR interaction supports a multigenic etiology for prostate cancer.

The SRD2A gene located on chromosome 2p23 spans >40 kb in five exons and codes for the membrane-bound protein steroid 5-α-reductase type II, which converts testosterone to the most active intraprostatic androgen, dihydrotestosterone (69). Two polymorphisms have been identified in the gene. The V89L substitution of leucine for valine at codon 89 variant occurs at a frequency of 8.5% in Caucasians, 2.5% in African-Americans and 28% in Taiwanese men. Although this variant may affect serum concentrations of androstenediol glucouronide (AAG), it appears to be relatively benign (70). The A49T variant (missense mutation of alanine to threonine), however, has been linked to pathological characteristics of prostate cancer. It increases the levels of steroid 5-α-reductase activity 5-fold. It appears to increase the risk of prostate cancer in African-American (7.2-fold) and Latino men (3.6-fold) (71,72). In addition to the two variants above, genetic alterations occur in the polymorphic TA-dinucleotide repeat in the SRD2A gene 3′-UTR, but its association with prostate cancer is unclear.

Polymorphisms in the CYP gene family may influence prostate cancer onset and outcomes because of the role of these enzymes in the metabolism of a variety of substrates, including chemotherapeutic drugs. CYP3A4 is involved in the metabolism of testosterone and has an A→G transition in the promoter at position –292 from the ATG start site. It exhibits ethnic variability that may have significant consequence in drug metabolism. It is associated with a higher clinical grade and stage in Caucasian men with prostate cancer. It is associated with clinical characteristics that play a role in the clinical course of prostate cancer in African-American men with prostate cancer (73,74). CYP17 is involved androgen metabolism. Also, a T→G transition in the 5′ promoter region creates an Sp-1-type (CCACC box) promoter site. It occurs at a frequency of 17% in Caucasians, 16% in African-American and 27% in Taiwanese men (75). Other isoforms including CYP2D6 at 22q13 and CYP2C19 at 10q24 contain polymorphisms with variable association with prostate cancer (76).

REMARKS

Complex, multifactorial diseases such as prostate cancer may not be amenable to characterization by linkage analysis and positional cloning as is the case for Mendelian-based diseases such as cystic fibrosis, sickle cell disease, etc. Thus, there is a new emphasis on using genome-wide scans to look for simple nucleotide polymorphisms, including short deletions and insertions, multinucleotide changes and single nucleotide substitutions. In light of the difficulties surrounding the genetics of prostate cancer, the community remains optimistic. With new technologies available, such as microarrays (77), new possibilities exist for the identification of new target genes involved in prostate cancer. Also, the development of large consortia such as the International Consortium on Prostate Cancer Genetics and the African American Hereditary Prostate Cancer Study Network will aid in the identification and confirmation of prostate cancer genetic loci (15,78).
improvements in technology and family collection, novel methodologies for statistical modeling of prostate cancer genetics will be key to the understanding of the multifactorial nature of prostate cancer. Although the incidence rates for prostate cancer are leveling off, it still remains one of the major health problems in the world. The understanding of the genetics of this disease will ultimately lead to better diagnostic and therapeutic strategies.

REFERENCES


