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REVIEW ARTICLE
Genetics of Prostate Cancer: Too Many Loci, Too Few Genes

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Introduction

It is with enormous excitement, last month, that the prostate cancer–mapping community acknowledges the cloning and characterization, by Tavtigian et al. (2000), of a hereditary prostate cancer (HPC) susceptibility gene, HPC2/ELAC2. In the past 5 years, investigators in the field have struggled, with mixed success, to localize genes responsible for this very common, yet complex phenotype. Although a half-dozen loci have been reported after analysis of conventional genomewide scans of "high-risk families," confirmation studies have been few, and, until recently, there have been no public reports of cloned loci. As investigators in the field have wrestled with issues related to the variability in disease phenotype, large numbers of sporadics in the population, and statistical issues related to age-dependent penetrance, it seemed that the prostate cancer field was beginning to follow the tortuous path set by investigators mapping genes for diabetes and schizophrenia. Last month, those issues were temporarily set aside, when Rebbeck et al. (2000), in a clinic-based, follow-up study to the reported cloning of HPC2/ELAC2 (Tavtigian et al. 2000), demonstrated that men who carry both of two common polymorphisms in the HPC2/ELAC2 gene experience a modest increase in risk for prostate cancer. HPC2/ELAC2 seems well established, therefore, as the first prostate cancer–susceptibility gene characterized by positional cloning (Tavtigian et al. 2000). These data, together with several genome-scan reports and a host of follow-up papers, offer intriguing lessons for those in the field, suggesting new ways to approach the difficult problem of understanding prostate cancer susceptibility.

Inherited Prostate Cancer

The familial aggregation of prostate cancer was first recorded by Morganti et al. (1956), who noted that patients with prostate cancer reported a higher frequency of the disease among relatives than did hospitalized controls. Subsequently, Woolf (1960) found that deaths due to prostate cancer were three times as high among the fathers and brothers of men dying from prostate cancer than among deceased relatives of men dying from other causes. The notion that there are prostate cancer–susceptibility genes has since been suggested by case-control, cohort, and twin studies (Steinberg et al. 1990; Grönberg et al. 1994, 1996; Whittemore et al. 1995*b*; Page et al. 1997; Lichtenstein et al. 2000). The effect is strongest among first-degree relatives, where the relative risk estimates are in the range of 1.7–3.7 (Fincham et al. 1990; Steinberg et al. 1990; Hayes et al. 1995; Whittemore et al. 1995*b*). Several of these studies found no significant increase in risk for men reporting second-degree affected relatives (Steinberg et al. 1990; Spitz et al. 1991; Whittemore et al. 1995*b*). However, younger ages at diagnosis and multiple relatives with prostate cancer were both associated with even higher relative risks. For example, compared with men having no family history of prostate cancer, men with three or more first-degree relatives with prostate cancer have an almost 11-fold increased risk of the disease (Steinberg et al. 1990). Although most studies focused on whites, similar two-fold or higher elevations in risk associated with a family history of prostate cancer have been reported for Asians (Whittemore et al. 1995*b*) and for blacks in the U.S. (Hayes et al. 1995; Whittemore et al. 1995*b*) and in Jamaica (Glover et al. 1998). Although most of the data seem to point toward autosomal dominant genes, evidence for an X-linked or recessive mode of inheritance has also been reported, on the basis of observation of a higher relative risk for prostate cancer among men who report an affected brother(s) with prostate cancer than among those reporting an affected father (Monroe et al. 1995; Narod et al. 1995).

The first segregation analysis, completed by Carter et al. (1992), provided insight into the likely features of HPC genes. They examined 691 families affected by prostate cancer ascertained through 740 consecutive probands undergoing radical prostatectomy for primary clinically localized prostate cancer at Johns Hopkins during 1982–1989. The results suggested that familial clustering of disease among those with early onset was

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best explained by the presence of rare autosomal dominant, highly penetrant allele(s) ($q = .0030$), with carriers having an 88% cumulative risk of disease by age 85 years, compared with only 5% for noncarriers (Carter et al. 1992). HPC gene(s) were predicted to account for ~43% of early-onset disease (at age ⩽55 years) and 9% of total prostate cancer in men diagnosed through age 85 years.

In two other segregation analyses, similar conclusions were reached. The results of the study by Grönberg et al. (1997*a*), from a population-based sample of 2,857 Swedish nuclear families, also support an autosomal dominant mode of inheritance but suggest a higher frequency of the susceptibility allele (1.67%) and a lower lifetime penetrance (63%). Schaid et al. (1998), who analyzed 4,288 men undergoing radical prostatectomy for clinically localized disease at the Mayo Clinic, reported that no single-gene model of inheritance clearly explained the observed familial clustering. But the best-fitting model was also that of a rare autosomal dominant susceptibility gene, with the best fit observed in probands diagnosed at <60 years of age. These investigators proposed a gene population frequency of .006, with a risk of 89% by age 85 years, for carriers. In addition, their data suggest that a high proportion of prostate cancer is accounted for by autosomal dominant genes, ~68% at age <60 years (Schaid et al. 1998). These conclusions are supported by other types of studies. For instance, in an analysis of 44,788 pairs of twins from the Swedish, Danish, and Finnish twin registries, Lichtenstein et al. (2000) concluded that 42% (95% confidence interval (CI), 29%–50%) of prostate cancer risk may be accounted for by heritable factors.

A generally agreed upon definition of hereditary or high-risk prostate cancer families now exists. Referred to as the "Hopkins Criteria," hereditary families are those in which there is either (1) prostate cancer in three or more first-degree relatives; (2) prostate cancer in three successive generations of either the maternal or paternal lineages; or (3) a cluster of two relatives affected at age ⩽55 years (Carter et al. 1993). Armed with these criteria, we and others have collected large data sets of likely hereditary families and have undertaken genomewide scans expecting, perhaps naively, that, in this genomic era, the mapping and cloning of prostate cancer–susceptibility genes could be accomplished rapidly. On the basis of experience gathered to date, this has proven to be anything but the case.

Mapping HPC Genes

The first prostate cancer locus, HPC1, was mapped to chromosome 1 in 1996 by a team of investigators from the Johns Hopkins Medical Center, the National Human Genome Research Institute, and Umeå University in Sweden. The study, which generated enormous excitement in the field, used 91 high-risk prostate cancer families from the U.S. and Sweden (Smith et al. 1996) and demonstrated strong evidence of linkage at 1q24-25. A maximum multipoint LOD score of 5.43 was obtained under the assumption of heterogeneity, with 34% of families hypothesized to be linked. These conclusions were supported by nonparametric multipoint linkage (NPL) analysis, using the program GENEHUNTER (Kruglyak et al. 1996), with highly significant nonparametric multipoint Z scores reported (maximum 4.71, $P < .000001$). The NPL statistic is considered most appropriate for analysis of complex traits such as prostate cancer because it is not based on assumed genetic models; rather, it simply compares the observed versus the expected sharing of chromosomal regions identical by descent among affected relatives (Ott 1996). The initial report did not suggest that any subgroup of families was more or less likely to be linked, although a strong age-at-onset effect has since been noted in both North American and Swedish families, with nearly all putatively linked families having an average age at diagnosis of <65 years (Grönberg et al. 1997*c*, 1999).

Given the strength of the initial result, it was surprising that subsequent reports attempting to confirm linkage were inconclusive. The most confirmatory results came from nonparametric multipoint analyses published independently by groups at the University of Michigan and at Stanford University. Cooney et al. (1997) and Hsieh et al. (1997) observed maximum NPL Z scores of 1.58 and 1.71, respectively, and P values of .057 and .046, in their complete data sets of 59 and 92 families. Results were slightly stronger in families diagnosed earlier in life (at age <67 years) or that best fit the definition of HPC. Although these data are certainly indicative of linkage, it was surprising that the results did not reach a P value of ⩽.01, which was needed for formal replication of linkage (Lander and Kruglyak 1995). In addition, several papers, including two from our own group, were published that used seemingly similar data sets to those described by Smith et al. (1996) but nevertheless found no evidence for HPC1 linkage (McIndoe et al. 1997; Berthon et al. 1998; Eeles et al. 1998; Goode et al. 2000). Given the strength of the original result, these reports were surprising and provided the first hints that the mapping and subsequent cloning of prostate cancer genes might prove more complex than originally suspected. This has, indeed, proven to be the case.

Mapping of loci to chromosomes 1q42.2-43, Xq27-28, 1p36, and, very recently, to 20q13 followed quickly, as did an additional series of reports that were unable to provide statistically significant confirmation of linkage (Whittemore et al. 1999; Berry et al. 2000; Peters et al., in press). For instance, linkage to Xq27-28 was

reported by a consortium of four groups after they combined independently collected data sets from Johns Hopkins Medical Institutions, Tampere University Hospital in Finland, Umeå University in Sweden, and the Mayo Clinic. The results were strongly significant, with a maximum two-point LOD score of 4.6 (recombination fraction [θ] 0.26), and both parametric and nonparametric multipoint analyses were consistent. Linkage to Xq27-28 was predicted to account for 16% of prostate cancer in the data set of 360 families. Yet, again, there has been difficulty in confirming these seemingly incontrovertible findings in independent data sets, with <5% of families projected to be linked in other published reports (Peters et al., in press).

Statistical Power Considerations

What possible explanations can account for these disparate results? Overall, the difficulties seem to stem from genetic heterogeneity inherent in prostate cancer and from the accompanying difficulty of developing appropriate transmission models. The solutions may lie in "model-free" methods of analysis and in stratification of data into homogeneous subsets for subsequent analysis. The key piece of supporting data was provided in an analysis of HPC1 (Neuhausen et al. 1999). In an analysis of 41 large Utah families, with a mean number of affected men per family of 10.7, Neuhausen et al. confirmed linkage by reporting two- and three-point LOD scores of 1.73 ($P = .005$) and 2.06 ($P = .002$), respectively, at 1q24-25. The authors hypothesize that the extraordinarily large number of cases per family provided sufficient power to overcome the problem of sporadic cases in families segregating disease mutations. They argued that this would be critical for untangling the genetics of prostate cancer overall. The authors also observed that adjusting the transmission model to better fit the true age at onset observed in the Utah families strengthened the results. This latter fact suggested that model misspecification could easily be a factor contributing to the contradictory results, and that nonparametric or non–model-driven analyses are the most useful approach, as had been suggested by Cooney et al. (1997) and by Hsieh et al. (1997), in their initial confirmatory reports of HPC1.

Suspecting that the real problem might indeed be one of power, the International Consortium for Prostate Cancer Genetics (ICPCG) agreed to a single, very large, joint analysis, thus providing the second piece of the puzzle (Xu and ICPCG 2000*a*). Researchers from North America, Australia, Finland, Norway, Sweden, and the United Kingdom pooled their data and analyzed a set of 772 families for linkage to 1q24-25. The initial analysis provided only weak evidence for linkage at 1q24, with a peak parametric multipoint LOD score, assuming heterogeneity (HLOD), of 1.40 ($P = .01$), and the estimated proportion of linked families was only 6%. The extraordinary size of the data set, however, meant that stratifications to develop homogeneous subsets could be undertaken with confidence. These analyses confirmed linkage in a subset of families and revealed that, overall, a disproportionate amount of linkage was derived from families characterized by male-to-male inheritance patterns. Within such families, the strongest evidence was contributed by those with an early mean age at diagnosis (<65 years) or by those who had strong family histories of disease (five or more affected men). Data from nonparametric analysis supported these findings, as well (Xu and ICPCG 2000*b*). These conclusions are also supported in a report by Berry et al. (2000), who also showed modest evidence for linkage to HPC1 when the analysis was restricted to a data set of 102 families with clear evidence of male-to-male transmission (NPL $= 1.99$, $P = .03$).

Overall, these results suggest three guiding principles. First, the number of genes that contribute to prostate cancer susceptibility is sufficiently large for initial reports of linkage to reflect, in part, the draw of a "lucky hand," where a significant number of families may attribute their disease to a specific locus. If all published reports of linkage are to be believed, there are at least six HPC loci and probably more. As a result, power will always be limited in confirmatory studies that will be done on data sets unlikely to represent such a "lucky hand." If the number of genes is large, as it appears to be for prostate cancer, the more representative a limited-sized data set of families is of the real distribution of prostate cancer loci in the general population, the less likely that data set will be to confirm any single finding of linkage or to generate any reports of linkage to new loci.

Second, model misspecification is a serious problem when diseases that are genetically heterogeneous are mapped. Segregation analyses produce summary data but cannot specify the allele frequency or penetrance of any single locus. In the case of the data presented by Neuhausen (1999), the model-misspecification hypothesis is supported by the fact that LOD scores using the Utah-specific model generally maximized at values of θ closer to 0 than what was observed when using the model presented by Smith et al. (1996). The Utah model includes a higher sporadic disease rate than the model presented by Smith et al.—in particular, for cases diagnosed at older ages. Although this causes some loss of power, it provides more accurate data. The so-called model-free analysis may provide the best approach.

Finally, development of homogeneous subsets for both finding and confirming linkage is an effective strategy. The mapping of the HPCX and CAPB loci provides two examples. The initial mapping of *HPCX* to Xq27-

28 relied on families without evidence of male-to-male transmission. These families accounted for about two-thirds of the final significant LOD score. Given a lack of observed linkage in black families to Xq27-28, stratification by race further strengthened the results (Lange et al. 1999).

The mapping of the CAPB locus also illustrates the power of subset identification. Focusing only on prostate cancer families with a confirmed family history of primary brain cancer, a prostate cancer–susceptibility locus at 1p36 was detected (Gibbs et al. 1999). This region was of particular interest, since an excess of brain and CNS cancers had been reported in high-risk prostate cancer families (Goldgar et al. 1994; Isaacs et al. 1995) and because 1p36 is a region of frequent loss of heterozygosity in brain tumors (Bello et al. 1995*a,* 1995*b;* Kraus et al. 1995; White et al. 1995). The maximum two-point LOD score in these 12 families was 3.22 at $\theta = 0.06$, with most of the result coming from families with a mean age of <66 years at diagnosis of prostate cancer (maximum two-point LOD score of 3.65 at $\theta = 0.0$). The NPL score across the most narrowly defined region of interest, however, was not sufficiently robust to declare a significant finding of linkage (2.24, $P = .02$). This may reflect the fact that GENEHUNTER uses only data from affected individuals. Thus, older unaffected men who did not share the affected haplotype and contributed significantly to the parametric LOD score results do not contribute to the NPL result. The CAPB locus is estimated to be only a small player in prostate cancer susceptibility overall, perhaps not >5%. However, it illustrates nicely how development of homogeneous subsets can greatly enhance power.

One additional strategy for developing homogeneous subsets is by consideration of clinical features of disease. But given that any single family will likely have men presenting with widely different stages of disease and tumor grades at diagnosis, it is not obvious how these issues are best handled statistically. There is no clear way to "average" stage and grade across a family and it is not obvious that it is appropriate, since there is no indication that stage or tumor grade is a good indicator of hereditary disease. One way around this problem is to consider only a subset of disease types, such as advanced stage or high grade.

Clinical Features of Disease

Witte et al. (2000) have used clinical features of disease to try to map genes responsible for high-grade disease, specifically, by stratifying families on the basis of the Gleason score. Because most prostate tumors express more than one histologic glandular pattern, the Gleason system records a grade with a range of 1–5 for the two predominant patterns for a given tumor (e.g., 4 and 5). These two numbers are added, to give a Gleason score in the range of 2–10 (i.e., 9 in the example). Tumors with low Gleason scores tend to be small in volume and have low metastatic potential, whereas tumors with high Gleason scores tend to be larger in volume and have significant metastatic potential. The preoperative Gleason score correlates closely with important indicators of extent of disease, such as pelvic lymph node involvement and distant metastasis (Gleason 1977). Witte et al. (2000), using the Gleason score taken from biopsy or prostatectomy as a quantitative measure of disease aggressiveness, conducted a genomewide linkage analysis of 326 affected sib pairs, reflecting 233 unique families. Their scan highlighted regions on chromosome 5q31-33, 7q32, and 19q12, as containing potential loci important in the development of aggressive disease ($P = .0002$, .0007, and .0004, respectively). None of these loci was strongly suggested in an independent sibpair analysis of the same samples stratified by family history considerations, age at diagnosis, and family history of breast cancer (Suarez et al. 2000*a*).

Genomewide Scans for Prostate Cancer

Given the apparent value of stratifying data sets by features such as age at onset, family history of other cancers, or clinical characteristics, some thought should be given to what results are likely to stand the test of time. Thus far, three complete genome scans for prostate cancer–susceptibility genes have been published. In the scan of Smith et al. (1996), the strongest evidence for linkage was at *HPC1,* although two-point analysis also revealed a LOD score of ⩾1.5 at D4S430 and LOD scores of ⩾1.0 at several loci including markers at Xq27-28. A second scan, from our own group (Gibbs et al. 2000), reported two-point LOD scores of ⩾1.5 for chromosomes 10q, 12q, and 14q, when the entire data set is considered under an autosomal dominant model of inheritance and for chromosomes 1q, 8q, 10q, and 16p, when a recessive model of inheritance is considered. The strongest data for all 94 families were observed at D10S1223 (LOD 2.46, $\theta = 0.04$) and at D8S2324 (LOD 2.17, $\theta = .10$), under the recessive model. Stratification by age at diagnosis revealed several other regions of interest, including two-point LOD scores of 2.35, also at D10S1223, for 50 families with a mean age at diagnosis of <66 years, and of 3.02, at ATA34E08 on chromosome 11, for 44 families with a mean age at diagnosis of ⩾66 years, both analyzed under an autosomal dominant model. None of these results meet the statistical criteria for significance, but they are clearly worth following up in larger data sets. What is less clear, however, is how to balance the statistical penalty for multiple sampling schemes with the desire to develop homogeneous subsets to reduce locus heterogeneity.

The scan published by Suarez et al. (2000*a*) faces

similar issues. In their initial scan, these authors analyzed 504 brothers from 230 multiplex sibships and identified five regions with nominal evidence for linkage on 2q, 12p, 15q, 16q, and 16p. Three preplanned subanalyses were performed, stratifying families by means of the "Hopkins Criteria" of likely "hereditary" versus "nonhereditary," by age at onset, and by a family history of breast cancer. Several additional loci were identified in these specific subsets, with the strongest signals on chromosomes 1p35.1, 4q, and 1q, in a region proximal to the HPC1 locus, and on 21q. When the data were examined in totality, the most consistent evidence for linkage, overall, in several partitions, was on chromosome 16 (Suarez et al. 2000*a*, 2000*b*).

HPC2/ELAC2

Given the strength of the linkages observed, particularly at 1q24-25 and at Xq27-28, and the expertise of the groups involved, it was generally expected that these would be the first prostate cancer genes cloned. Instead, as we learned in last month's issue of the *American Journal of Human Genetics,* and as mentioned above, the HPC2/ELAC2 gene, located on chromosome 17p, claims that distinction (Tavtigian et al. 2000). HPC2/ELAC2 was mapped by taking advantage of the Utah Family Resource, a set of extended pedigrees, each with several affected individuals, that has proven invaluable for mapping and cloning cancer genes in the past (Cannon et al. 1982; Miki et al. 1994; Wooster et al. 1994). HPC2/ELAC2 was originally mapped in a set of 33 pedigrees with a maximum two-point LOD score of 4.5 ($\theta = .07$). To clone the gene, the data set was expanded to 127 families, which, overall, failed to provide a significant LOD score. After excluding branches of the family potentially linked to HPC1, and by focusing on a subset of families who either had individual family LOD scores of $\geqslant 1.0$ or who had six or more cases that shared a haplotype, irrespective of LOD score, the authors quickly zeroed in on a likely candidate. Mutational analysis revealed a subset of carriers in one family with a germline insertion that leads to premature termination of translation after incorporation of 67 miscoded residues. A common missense variant, which changed a serine to a leucine at amino acid 217, was also found. This gene was named "HPC2/ELAC2," since it is the larger of two human genes that were found to be homologues of *Escherichia coli* elaC.

Examination of 45 additional unrelated cases diagnosed at age $\leqslant 55$ years failed to reveal any additional frameshift mutations, suggesting that truncation of the protein, caused by germline changes, is unlikely to be a common cause of prostate cancer among high-risk families. It did, however, reveal a relatively rare Ala to Thr change at amino acid 541. The latter was only observed in the presence of the Ser217Leu variant and seemed to segregate with disease in at least one family (Tavtigian et al. 2000). In a clinic-based study of 359 incident–prostate cancer cases and 266 male controls matched for age and race, Rebbeck et al. (2000) observed that the relative risk of having prostate cancer is increased in men who carry the Leu217/Thr541 variants (OR 2.37; 95% CI 1.06–5.29). The Thr541 missense is present in 2.9% of unaffected controls and the Leu217, in 31.6%. The estimated risks did not differ significantly by family history or race. If the carrier frequency of the Leu217/Thr541 genotype is assumed to be ~4%, and the relative risk associated with the at-risk genotype is 2.4, then the percent of prostate cancer in the population caused by this genotype is ~5.3%. The functional significance of these missense changes is not known, although the Thr541 change is adjacent to a highly conserved histidine motif, suggesting that it lies near a functionally relevant region of the protein. Population-based case-control studies are needed to determine the contribution of this locus to prostate cancer in the general population.

The Leu217/Thr541 change in the HPC2/ELAC2 gene does not represent the first missense change to be associated with prostate cancer susceptibility. Analyses of genes important in steroid metabolism and signaling have identified several others. For instance, several studies show an association between shorter (CAG)n repeats within exon one of the androgen-receptor gene and prostate cancer risk (Giovannucci et al. 1997; Stanford et al. 1997). Also, missense changes within the steroid 5-alpha-reductase type II gene, which are believed to increase the catalytic activity of the enzyme, are associated with an increased risk of advanced prostate cancer (Reichardt et al. 1995; Makridakis et al. 1999; Jaffe et al. 2000). Polymorphisms in several positions in the vitamin D receptor gene are also associated with an increased risk of disease (Taylor et al. 1996; Ingles et al. 1997). What is unique about the reports of Tavtigian and Rebbeck is that this is the first announced prostate cancer–susceptibility gene cloned after a genomewide scan of high-risk families, and the first for which there is evidence that both frameshift changes and missense changes are disease associated. These studies hopefully pave the way for additional, similar reports at other loci.

Lessons Learned

It seems, therefore, that mapping and cloning of prostate cancer genes will be complicated by three issues. First, there are a large number of men with sporadic disease in the population. An estimated one in eight men will get prostate cancer at some point in their lives (Ries et al. 1999), with ~180,400 men diagnosed in the year 2000 (Greenlee et al. 2000). Indeed, in the year 2000, prostate cancer accounted for 29% of all newly diag-

nosed cancers (Greenlee et al. 2000). Certainly, a portion of these men will not carry germline mutations, but will be related to individuals who do. A priori, there seem to be no discernible differences in morbidity or mortality in genetic versus nongenetic cases, with the exception that hereditary cases tend to be diagnosed earlier in life. A caveat to this stems from a report by Grönberg et al. (1997*b*), who argue that high-grade cancers and advanced-stage disease were more common in families whose disease is potentially linked to HPC1. This has, however, been debated by others (Laniado 1998; Walther 1998). Narrowing a putative region of linkage can be very difficult; a single recombinant whose disease is not due to a germline change can incorrectly be used to define the critical region, thus misleading investigators to focus their search for candidate genes in the wrong region of the chromosome.

A second major consideration relates to age at onset, which, in distinguishing individuals with inherited versus sporadic disease, has proven to be less hopeful than hoped for. In the United States, the average age at diagnosis for prostate cancer is 71 years for whites and 69 years for blacks (Stanford et al. 1999). Early age at diagnosis is generally defined as ⩽60 years, with men in this age group accounting for <10% of all prostate cancers (Stanford et al. 1999). However, most of the data sets collected for mapping report a mean age at diagnosis of ~65 years, and the identification of men diagnosed at age <50 years is very rare (Xu and ICPCG 2000*a*). By contrast, the median age at diagnosis for breast cancer is 63 years (Ries et al. 2000), and in families segregating BRCA1 and BRCA2 mutations, it is not uncommon to observe women diagnosed in their twenties. Thus, for breast cancer, the distinction between those diagnosed with early-onset disease and those diagnosed at the mean age is greater than that observed for prostate cancer. Therefore, the use of age at diagnosis to estimate the likelihood that an individual's disease is inherited is probably less accurate for prostate than for breast cancer.

Finally, there is enormous variation in the phenotype of disease at diagnosis as well as disease progression within single families. The introduction of prostate-specific antigen (PSA) testing in the mid to late 1980s has probably contributed to that variability. On the basis of statistical modeling, Etzioni et al. (1998) estimate that 50% of new cases are unlikely to have come to clinical diagnosis in the absence of PSA testing. In addition, men diagnosed by PSA, as opposed to digital rectal examination or physical symptoms, are diagnosed ~3–5.5 years earlier (Gann et al. 1995; Whittemore et al. 1995*a;* Pearson et al. 1996). Stratification by year at diagnosis has recently been proposed as a useful way to develop homogeneous subsets for linkage studies. Support for this proposal was recently provided by Xu et al. (2000), who reported that disease in men diagnosed <1990—i.e., before PSA came into common use in the U.S.—is more likely to be linked to HPC1 than disease in men diagnosed >1990, suggesting that a time-dependent phenocopy rate may be contributing to apparent disease heterogeneity.

Given all the above, how best are we to proceed as a field if we wish to most efficiently clone the major prostate cancer–susceptibility genes? Clearly, we now recognize that HPC is in some ways more complicated and certainly involves more loci than do other common cancers, such as breast. Statistical power is almost always limiting in such situations, and combined analysis will be key for understanding the true contribution of any locus to disease in the overall population, as will be careful consideration of the statistical model. The stratification of data sets by clinical features and other cancers has only barely been tapped as a mechanism for defining homogeneous subsets for analysis. But we need to be wary of the statistical penalty that must be paid for such an approach. Finally, missense changes may be one of the important ways in which prostate cancer–susceptibility genes affect disease. Therefore, we need to become more facile in moving between data sets of high-risk families and population-based case-control studies. One suspects that if we can adequately define ways in which to tackle the genetics of prostate cancer, we may, in the end, develop a clear blueprint for how to tackle the genetics of other complex diseases.

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