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(54) **METHODS AND COMPOSITIONS FOR CORRELATING GENETIC MARKERS WITH RISK OF AGGRESSIVE PROSTATE CANCER**

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(60) Provisional application No. 61/430,352, filed on Jan. 6, 2011.

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CPC ***C12Q 1/6886*** (2013.01); ***G06F 19/28*** (2013.01); ***G06F 19/22*** (2013.01); *C12Q 2600/156* (2013.01)

(57) **ABSTRACT**

The present invention provides a method of identifying a subject as having an increased risk of having or developing aggressive prostate cancer, comprising detecting in the subject the presence of various polymorphisms associated with an increased risk of having or developing aggressive prostate cancer.

Fig. 1

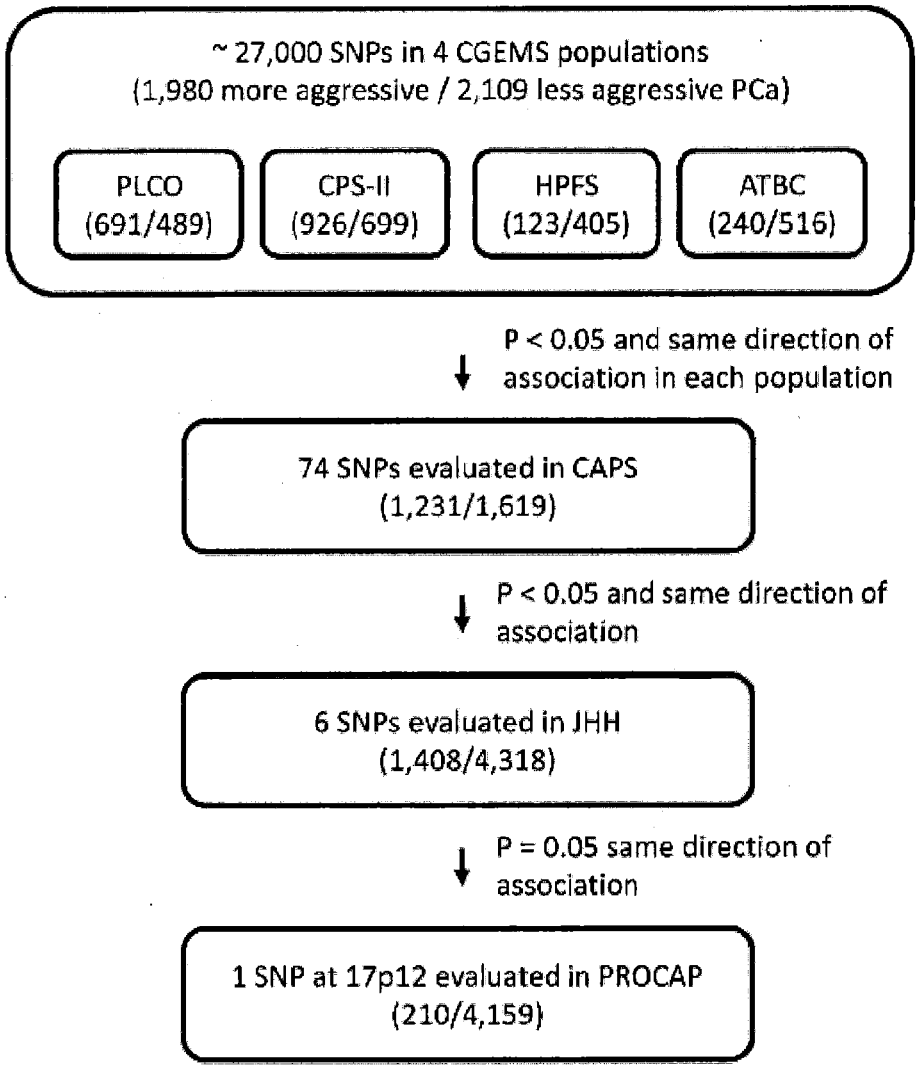
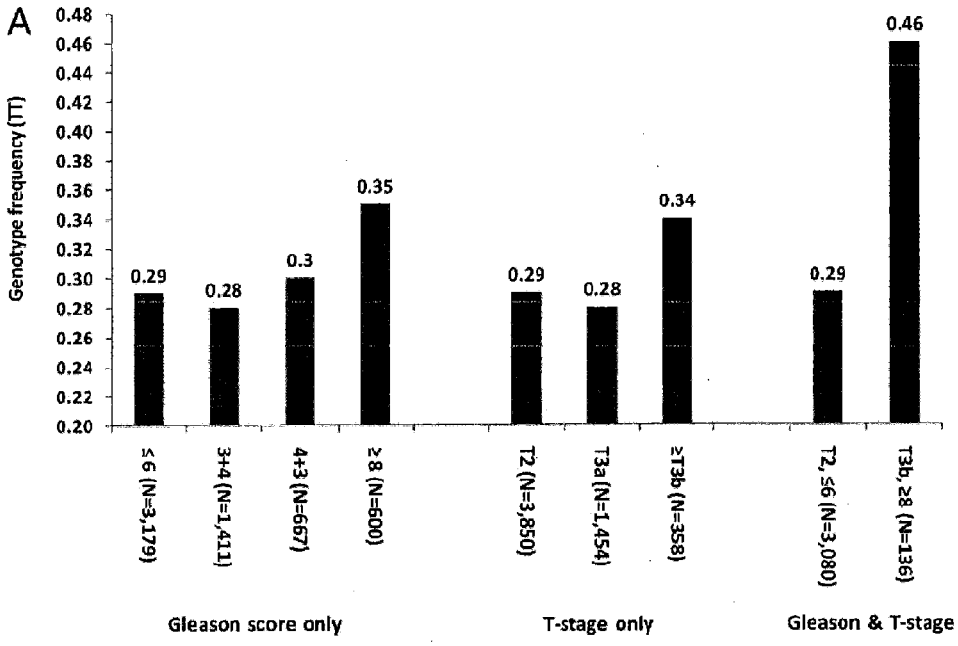
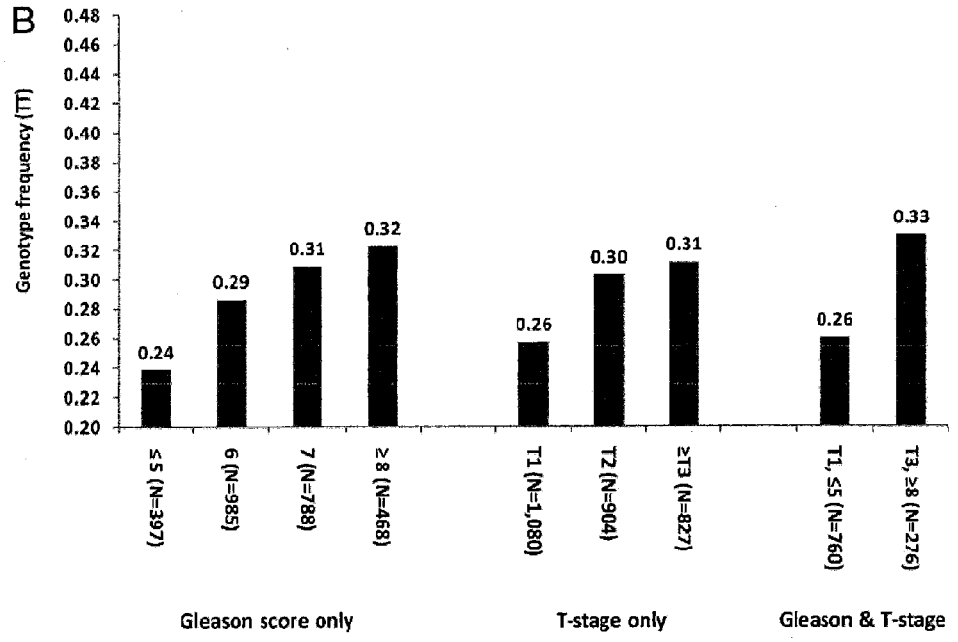

~ 27,000 SNPs in 4 CGEMS populations
(1,980 more aggressive / 2,109 less aggressive PCa)
PLCO (691/489)
CPS-II (926/699)
HPFS (123/405)
ATBC (240/516)
P < 0.05 and same direction of association in each population
74 SNPs evaluated in CAPS (1,231/1,619)
P < 0.05 and same direction of association
6 SNPs evaluated in JHH (1,408/4,318)
P = 0.05 same direction of association
1 SNP at 17p12 evaluated in PROCAP (210/4,159)

Fig. 2


A
Genotype frequency (TT)
0.48
0.46
0.44
0.42
0.40
0.38
0.36
0.34
0.32
0.30
0.28
0.26
0.24
0.22
0.20
0.29
0.28
0.3
0.35
0.29
0.28
0.34
0.29
0.46
≤ 6 (N=3,179)
3+4 (N=1,411)
4+3 (N=667)
≥ 8 (N=600)
T2 (N=3,850)
T3a (N=1,454)
≥T3b (N=358)
T2, ≤6 (N=3,080)
T3b, ≥8 (N=136)
Gleason score only
T-stage only
Gleason & T-stage


B
Genotype frequency (TT)
0.48
0.46
0.44
0.42
0.40
0.38
0.36
0.34
0.32
0.30
0.28
0.26
0.24
0.22
0.20
0.24
0.29
0.31
0.32
0.26
0.30
0.31
0.26
0.33
≤ 5 (N=397)
6 (N=985)
7 (N=788)
≥ 8 (N=493)
T1 (N=1,080)
T2 (N=904)
≥T3 (N=827)
T1, ≤5 (N=760)
T3, ≥8 (N=276)
Gleason score only
T-stage only
Gleason & T-stage

METHODS AND COMPOSITIONS FOR CORRELATING GENETIC MARKERS WITH RISK OF AGGRESSIVE PROSTATE CANCER

STATEMENT OF PRIORITY

[0001] This application is a continuation application of, and claims priority to, U.S. application Ser. No. 13/344,907, filed Jan. 6, 2012, which claims the benefit, under 35 U.S.C. §119(e), of U.S. Provisional Application Ser. No. 61/430,352, filed Jan. 6, 2011, the entire contents of each of which are incorporated by reference herein.

STATEMENT OF GOVERNMENT SUPPORT

[0002] This invention was made with government support under Grant Nos. CA129684, CA106523, CA105055, CA95052, CA1125117, CA133009 and CA131338 awarded by the National Cancer Institute and Grant Nos. PC051264 and W81XWH-09-1-0488 awarded by the Department of Defense. The government has certain rights in the invention.

FIELD OF THE INVENTION

[0003] The present invention provides methods and compositions directed to identification of genetic markers associated with prostate cancer.

BACKGROUND OF THE INVENTION

[0004] Prostate cancer accounts for one-fourth of all cancer diagnoses in men in the United States, with an estimated 192,280 new cases in 2009 (1). Although most men will have an indolent form of the disease, aggressive prostate cancers are currently the second leading cause of cancer deaths in men in the United States. Most cases of prostate cancer are diagnosed as a result of having an elevated serum level of prostate-specific antigen (PSA). PSA-based disease screening leading to early detection and treatment of prostate cancer (PCa) has contributed to the reduction in mortality observed for this disease in the United States over the past several years (1). However, results from two large randomized trials in Europe and the US provide strong evidence that PSA-based screening for PCa is associated with a high risk of overdiagnosis (2,3). In the European trial, PSA screening was associated with decreased PCa related mortalitiy but at a great cost: ~1,410 men needed to be screened, and 48 additional PCa cases would need to be treated to prevent one death from PCa (2). Although interpretation of these findings is still a subject of discussion, the current inability to accurately distinguish risk for life-threatening, aggressive PCa from the overwhelming majority of indolent cases contributes to the dilemma.

[0005] Recent breakthroughs in genome-wide association studies (GWAS) have led to the discovery of more than two dozen reported single nucleotide polymorphisms (SNPs) that are associated with PCa risk by comparing men with and without PCa using case-control study designs (6-25). Unfortunately, none of these PCa risk associated SNPs consistently distinguishes risk for more or less aggressive cancer (26-28), nor are they associated with prostate cancer-specific mortality (29). As a result, there has been much debate regarding the clinical utility of these SNPs as a risk stratification tool (30,31). Clearly, an alternative approach is needed to identify genetic markers that distinguish those men who are at risk for developing more aggressive PCa.

[0006] The present invention overcomes previous shortcomings in the art by identifying significant statistical associations between genetic markers and prostate cancer. Thus, the present invention provides methods and compositions for identifying a subject at increased risk of developing aggressive prostate cancer by detecting the genetic markers of this invention in the subject.

SUMMARY OF THE INVENTION

[0007] The present invention provides a method of identifying a human subject as having an increased risk of developing aggressive prostate cancer, comprising detecting in a nucleic acid sample from the subject a T allele at single nucleotide polymorphism rs4054823 in chromosome region 17p12, wherein the detection of said allele identifies the subject as having an increased risk of developing aggressive prostate cancer.

[0008] Also provided herein is a method of identifying a human subject as having an increased risk of developing aggressive prostate cancer, comprising detecting in a nucleic acid sample from the subject an allele that is in linkage disequilibrium with the T allele at single nucleotide polymorphism rs4054823 in chromosome region 17p12, wherein the detection of said allele identifies the subject as having an increased risk of developing aggressive prostate cancer.

[0009] Furthermore, the present invention provides a kit containing oligonucleotides and other reagents for detecting an allele or combination of alleles of this invention.

[0010] Additionally provide herein is a computer-assisted method of identifying a proposed treatment for aggressive prostate cancer as an effective and/or appropriate treatment for a subject carrying a genetic marker correlated with aggressive prostate cancer, comprising the steps of: (a) storing a database of biological data for a plurality of subjects, the biological data that is being stored including for each of said plurality of subjects: (i) a treatment type, (ii) at least one genetic marker associated with aggressive prostate cancer, and (iii) at least one disease progression measure for prostate cancer from which treatment efficacy can be determined; and then (b) querying the database to determine the dependence on said genetic marker of the effectiveness of a treatment type in treating prostate cancer, thereby identifying a proposed treatment as an effective and/or appropriate treatment for a subject carrying a genetic marker correlated with prostate cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] FIG. **1**. Flow chart of the study design. Numbers of subjects with more or less aggressive prostate cancer in each study population are indicated in parentheses.

[0012] FIG. **2**. Frequency of TT genotype of rs4054823 at 17p12 among PCa patients from the (A) JHH population and (B) CAPS population of Sweden.

DETAILED DESCRIPTION OF THE INVENTION

[0013] The present invention is explained in greater detail below. This description is not intended to be a detailed catalog of all the different ways in which the invention may be implemented, or all the features that may be added to the instant invention. For example, features illustrated with respect to one embodiment may be incorporated into other embodiments, and features illustrated with respect to a

particular embodiment may be deleted from that embodiment. In addition, numerous variations and additions to the various embodiments suggested herein will be apparent to those skilled in the art in light of the instant disclosure, which do not depart from the instant invention. Hence, the following specification is intended to illustrate some particular embodiments of the invention, and not to exhaustively specify all permutations, combinations and variations thereof.

[0014] The present invention is based on the unexpected discovery of particular alleles of single nucleotide polymorphisms (SNPs) that are statistically associated with an increased risk of developing aggressive prostate cancer. There are numerous benefits of carrying out the methods of this invention to identify a subject having an increased risk of developing aggressive prostate cancer, including but not limited to, identifying subjects who are good candidates for prophylactic and/or therapeutic treatment, and screening for cancer at an earlier time or more frequently than might otherwise be indicated, to increase the chances of early detection of an aggressive prostate cancer.

[0015] Thus, in one aspect, the present invention provides a method of identifying a subject (e.g., a human subject) as having an increased risk of developing aggressive prostate cancer, comprising detecting in a nucleic acid sample from the subject a T allele at single nucleotide polymorphism rs4054823 in chromosome region 17p12, wherein the detection of said alleles identifies the subject as having an increased risk of developing aggressive prostate cancer.

[0016] The present invention further provides a method of identifying a subject as having an increased risk of developing aggressive prostate cancer, comprising detecting in a nucleic acid sample from the subject an allele in linkage disequilibrium (LD) with the T allele at single nucleotide polymorphism rs4054823 in chromosome region 17p12. Alleles in LD with the T allele at single nucleotide polymorphism rs4054823 in chromosome region 17p12 are provided herein in Table 1. Such alleles can be detected individually (e.g., detection of a risk allele at a single SNP location) as well as in any combination (e.g., detection of a risk allele at more than one (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, etc.) SNP location). In some embodiments, when analyzed in combination, the combination can comprise detection of the T allele at rs4054823 in addition to detection of one or more of the alleles of Table 1. In some embodiments, the combination can be a (e.g., any) combination of the alleles of Table 1 without the T allele of rs4054823.

[0017] In some embodiments of this invention, the subject can be homozygous for the T allele at single nucleotide polymorphism rs4054823 in chromosome region 17p12. In other embodiments, the subject can be heterozygous for the T allele at single nucleotide polymorphism rs4054823 in chromosome region 17p12. The presence of the T allele, either homozygously or heterozygously, at single nucleotide polymorphism rs4054823 in chromosome region 17p12 identifies the subject as having an increased risk of developing aggressive prostate cancer. In the methods provided herein wherein a combination of alleles is analyzed, the subject can be heterozygous or homozygous for any given allele in any combination relative to the other alleles in the combination.

[0018] In certain embodiments of this invention, the methods described herein can be employed to identify 1) a subject at increased or decreased risk of a more aggressive form of prostate cancer (e.g., having a Gleason score of 7 (4+3) to 10), 2) a subject at increased or decreased risk of a poor prognosis (e.g., increased likelihood the cancer will metastasize, will be poorly responsive to treatment and/or will lead to death) once cancer has been diagnosed in the subject; and/or 3) a subject at increased or decreased risk of an early age of onset of prostate cancer (e.g., aggressive prostate cancer), by identifying in the subject the alleles of this invention.

[0019] It is further contemplated that the methods of this invention can be carried out to diagnose aggressive prostate cancer in a subject, by detecting the T allele of SNP rs4054823 and/or detecting any combination of the alleles of this invention in nucleic acid from the subject.

[0020] In further aspects, the present invention provides a kit for carrying out the methods of this invention, wherein the kit can comprise oligonucleotides (e.g., primers, probes, primer/probe sets, etc.), reagents, buffers, etc., as would be known in the art, for the detection of the alleles of this invention in a nucleic acid sample. For example, a primer or probe can comprise a contiguous nucleotide sequence that is complementary (e.g., fully (100%) complementary or partially (50%, 60%, 70%, 80%, 90%, 95%, etc.) complementary) to a region comprising an allele of this invention. In particular embodiments, a kit of this invention will comprise primers and probes that allow for the specific detection of the alleles of this invention. Such a kit can further comprise blocking probes, labeling reagents, blocking agents, restriction enzymes, antibodies, sampling devices, positive and negative controls, etc., as would be well known to those of ordinary skill in the art. Thus, in some embodiments, the present invention provides a kit comprising oligonucleotides to detect the T allele of single nucleotide polymorphism rs4054823 in chromosome region 17p12 in a nucleic acid sample. In further embodiments, the present invention provides a kit comprising oligonucleotides to detect an allele or combination of alleles in linkage disequilibrium with the T allele of single nucleotide polymorphism rs4054823 in chromosome region 17p12 in a nucleic acid sample, such as the alleles set forth in Table 1 herein. Such oligonucleotides can be identified and prepared and employed in methods according to the teachings and protocols described herein and as are well known in the art.

DEFINITIONS

[0021] As used herein, "a," "an" or "the" can mean one or more than one. For example, "a" cell can mean a single cell or a multiplicity of cells.

[0022] Also as used herein, "and/or" refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative ("or").

[0023] Furthermore, the term "about," as used herein when referring to a measurable value such as an amount of a compound or agent of this invention, dose, time, temperature, and the like, is meant to encompass variations of ±20%, ±10%, ±5%, ±1%, ±0.5%, or even ±0.1% of the specified amount.

[0024] As used herein, the term "prostate cancer" or "PCa" describes an uncontrolled (malignant) growth of cells in the prostate gland, which is located at the base of the urinary bladder and is responsible for helping control urination as well as forming part of the semen. Symptoms of prostate cancer can include, but are not limited to, urinary

problems (e.g., not being able to urinate; having a hard time starting or stopping the urine flow; needing to urinate often, especially at night; weak flow of urine; urine flow that starts and stops; pain or burning during urination), difficulty having an erection, blood in the urine and/or semen, and/or frequent pain in the lower back, hips, and/or upper thighs.

[0025] As used herein, the term "aggressive prostate cancer" means prostate cancer that is poorly differentiated, having a Gleason grade of 7 or above. An "indolent prostate cancer" means prostate cancer having a Gleason grade below 7 (e.g., 6 or less). The Gleason grading system is the most commonly used method for grading PCa and is well known in the art.

[0026] All the SNP positions described herein are based on Build 36.

[0027] The term "chromosome region" as used herein refers to a part of a chromosome defined either by anatomical details, especially by banding, or by its linkage groups. The particular chromosome region of this invention is 17p12.

[0028] Also as used herein, "linked" describes a region of a chromosome that is shared more frequently in family members or members of a population manifesting a particular phenotype and/or affected by a particular disease or disorder, than would be expected or observed by chance, thereby indicating that the gene or genes or other identified marker(s) within the linked chromosome region contain or are associated with an allele that is correlated with the phenotype and/or presence of a disease or disorder (e.g., aggressive PCa), or with an increased or decreased likelihood of the phenotype and/or of the disease or disorder. Once linkage is established, association studies (linkage disequilibrium) can be used to narrow the region of interest or to identify the marker (e.g., allele or haplotype) correlated with the phenotype and/or disease or disorder.

[0029] Furthermore, as used herein, the term "linkage disequilibrium" or "LD" refers to the occurrence in a population of two or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, etc.) linked alleles at a frequency higher or lower than expected on the basis of the gene frequencies of the individual genes. Thus, linkage disequilibrium describes a situation where alleles occur together more often than can be accounted for by chance, which indicates that the two or more alleles are physically close on a DNA strand.

[0030] The term "genetic marker" or "polymorphism" as used herein refers to a characteristic of a nucleotide sequence (e.g., in a chromosome) that is identifiable due to its variability among different subjects (i.e., the genetic marker or polymorphism can be a single nucleotide polymorphism an allele of a single nucleotide polymorphism, a restriction fragment length polymorphism, a microsatellite, a deletion of nucleotides, an addition of nucleotides, a substitution of nucleotides, a repeat or duplication of nucleotides, a translocation of nucleotides, and/or an aberrant or alternate splice site resulting in production of a truncated or extended form of a protein, etc., as would be well known to one of ordinary skill in the art).

[0031] A "single nucleotide polymorphism" (SNP) in a nucleotide sequence is a genetic marker that is polymorphic for two (or in some case three or four) alleles. SNPs can be present within a coding sequence of a gene, within noncoding regions of a gene and/or in an intergenic (e.g., intron) region of a gene. A SNP in a coding region in which both forms lead to the same polypeptide sequence is termed synonymous (i.e., a silent mutation) and if a different polypeptide sequence is produced, the alleles of that SNP are non-synonymous. SNPs that are not in protein coding regions can still have effects on gene splicing, transcription factor binding and/or the sequence of non-coding RNA.

[0032] The SNP nomenclature provided herein refers to the official Reference SNP (rs) identification number as assigned to each unique SNP by the National Center for Biotechnological Information (NCBI), which is available in the GenBank® database.

[0033] In some embodiments, the term genetic marker is also intended to describe a phenotypic effect of an allele or haplotype, including for example, an increased or decreased amount of a messenger RNA, an increased or decreased amount of protein, an increase or decrease in the copy number of a gene, production of a defective protein, tissue or organ, etc., as would be well known to one of ordinary skill in the art.

[0034] An "allele" as used herein refers to one of two or more alternative forms of a nucleotide sequence at a given position (locus) on a chromosome (e.g., at a single nucleotide polymorphism). An allele can be a nucleotide present in a nucleotide sequence that makes up the coding sequence of a gene and/or an allele can be a nucleotide in a non-coding region of a gene (e.g., in a genomic sequence). A subject's genotype for a given gene is the set of alleles the subject happens to possess. As noted herein, an individual can be heterozygous or homozygous for any allele of this invention.

[0035] Also as used herein, a "haplotype" is a set of alleles on a single chromatid that are statistically associated. It is thought that these associations, and the identification of a few alleles of a haplotype block, can unambiguously identify all other alleles in its region. The term "haplotype" is also commonly used to describe the genetic constitution of individuals with respect to one member of a pair of allelic genes; sets of single alleles or closely linked genes that tend to be inherited together.

[0036] The terms "increased risk" and "decreased risk" as used herein define the level of risk that a subject has of developing aggressive prostate cancer, as compared to a control subject that does not have the alleles of this invention in the control subject's nucleic acid.

[0037] A sample of this invention can be any sample containing nucleic acid from a subject, as would be well known to one of ordinary skill in the art. Nonlimiting examples of a sample of this invention include a cell, a body fluid, a tissue, biopsy material, a washing, a swabbing, etc., as would be well known in the art.

[0038] A subject of this invention is any animal that is susceptible to prostate cancer as defined herein and can include, for example, humans, as well as animal models of prostate cancer (e.g., rats, mice, dogs, nonhuman primates, etc.). In some aspects of this invention, the subject can be Caucasian (e.g., white; European-American; Hispanic), as well as of black African ancestry (e.g., black; African, Sub-Saharan African, African American; African-European; African-Caribbean, etc.) or Asian. In further aspects of this invention, the subject can have a family history of prostate cancer or aggressive prostate cancer (e.g., having at least one first degree relative having or diagnosed with prostate cancer or aggressive prostate cancer) and in some embodiments, the subject does not have a family history of prostate cancer or aggressive prostate cancer. Additionally a subject of this invention can have a diagnosis of prostate cancer or aggres-

sive prostate cancer in certain embodiments and in other embodiments, a subject of this invention does not have a diagnosis of prostate cancer or aggressive prostate cancer. In yet further embodiments, the subject of this invention can have an elevated prostate-specific antigen (PSA) level and in other embodiments, the subject of this invention can have a normal or non-elevated PSA level. In some embodiments, the PSA level of the subject may not be known and/or has not been measured.

[0039] As used herein, "nucleic acid" encompasses both RNA and DNA, including cDNA, genomic DNA, mRNA, synthetic (e.g., chemically synthesized) DNA and chimeras, fusions and/or hybrids of RNA and DNA. The nucleic acid can be double-stranded or single-stranded. Where single-stranded, the nucleic acid can be a sense strand or an antisense strand. In some embodiments, the nucleic acid can be synthesized using oligonucleotide analogs or derivatives (e.g., inosine or phosphorothioate nucleotides, etc.). Such oligonucleotides can be used, for example, to prepare nucleic acids that have altered base-pairing abilities or increased resistance to nucleases.

[0040] An "isolated nucleic acid" is a nucleotide sequence that is not immediately contiguous with nucleotide sequences with which it is immediately contiguous (one on the 5' end and one on the 3' end) in the naturally occurring genome of the organism from which it is derived or in which it is detected or identified. Thus, in one embodiment, an isolated nucleic acid includes some or all of the 5' non-coding (e.g., promoter) sequences that are immediately contiguous to a coding sequence. The term therefore includes, for example, a recombinant DNA that is incorporated into a vector, into an autonomously replicating plasmid or virus, or into the genomic DNA of a prokaryote or eukaryote, or which exists as a separate molecule (e.g., a cDNA or a genomic DNA fragment produced by PCR or restriction endonuclease treatment), independent of other sequences. It also includes a recombinant DNA that is part of a hybrid nucleic acid encoding an additional polypeptide or peptide sequence.

[0041] The term "isolated" can refer to a nucleic acid or polypeptide that is substantially free of cellular material, viral material, and/or culture medium (e.g., when produced by recombinant DNA techniques), or chemical precursors or other chemicals (when chemically synthesized). Moreover, an "isolated fragment" is a fragment of a nucleic acid or polypeptide that is not naturally occurring as a fragment and would not be found in the natural state.

[0042] The term "oligonucleotide" refers to a nucleic acid sequence of at least about five nucleotides to about 500 nucleotides (e.g. 5, 6, 7, 8, 9, 10, 12, 15, 18, 20, 21, 22, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 100, 125, 150, 175, 200, 250, 300, 350, 400, 450 or 500 nucleotides). In some embodiments, for example, an oligonucleotide can be from about 15 nucleotides to about 30 nucleotides, or about 20 nucleotides to about 25 nucleotides, which can be used, for example, as a primer in a polymerase chain reaction (PCR) amplification assay and/or as a probe in a hybridization assay or in a microarray. Oligonucleotides of this invention can be natural or synthetic, e.g., DNA, RNA, PNA, LNA, modified backbones, etc., as are well known in the art.

[0043] The present invention further provides fragments of the nucleic acids of this invention, which can be used, for example, as oligonucleotides, primers and/or probes. Such fragments or oligonucleotides can be detectably labeled or modified, for example, to include and/or incorporate a restriction enzyme cleavage site when employed as a primer in an amplification (e.g., PCR) assay.

[0044] The detection of a polymorphism, genetic marker or allele of this invention can be carried out according to various protocols standard in the art and as described herein for analyzing nucleic acid samples and nucleotide sequences, as well as identifying specific nucleotides in a nucleotide sequence.

[0045] For example, nucleic acid can be obtained from any suitable sample from the subject that will contain nucleic acid and the nucleic acid can then be prepared and analyzed according to well-established protocols for the presence of genetic markers according to the methods of this invention. In some embodiments, analysis of the nucleic acid can be carried by amplification of the region of interest according to amplification protocols well known in the art (e.g., polymerase chain reaction, ligase chain reaction, strand displacement amplification, transcription-based amplification, self-sustained sequence replication (3 SR), Qβ replicase protocols, nucleic acid sequence-based amplification (NASBA), repair, chain reaction (RCR) and boomerang DNA amplification (BDA), etc.). The amplification product can then be visualized directly in a gel by staining or the product can be detected by hybridization with a detectable probe. When amplification conditions allow for amplification of all allelic types of a genetic marker, the types can be distinguished by a variety of well-known methods, such as hybridization with an allele-specific probe, secondary amplification with allele-specific primers, by restriction endonuclease digestion, and/or by electrophoresis. Thus, the present invention further provides oligonucleotides for use as primers and/or probes for detecting and/or identifying genetic markers according to the methods of this invention.

[0046] In some embodiments of this invention, detection of an allele or combination of alleles of this invention can be carried out by an amplification reaction and single base extension. In particular embodiments, the product of the amplification reaction and single base extension is spotted on a silicone chip.

[0047] In yet additional embodiments, detection of an allele or combination of alleles of this invention can be carried out by matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF-MS).

[0048] It is further contemplated that the detection of an allele or combination of alleles of this invention can be carried out by various methods that are well known in the art, including, but not limited to nucleic acid sequencing, hybridization assay, restriction endonuclease digestion analysis, electrophoresis, and any combination thereof.

[0049] The genetic markers (e.g., alleles) of this invention are correlated with (i.e., identified to be statistically associated with) aggressive prostate cancer as described herein according to methods well known in the art and as disclosed in the Examples provided herein for statistically correlating genetic markers with various phenotypic traits, including disease states and pathological conditions as well as determining levels of risk associated with developing a particular phenotype, such as a disease or pathological condition. In general, identifying such correlation involves conducting analyses that establish a statistically significant association and/or a statistically significant correlation between the

presence of a genetic marker or a combination of markers and the phenotypic trait in a population of subjects and controls (e.g., a population of subjects in whom the phenotype is not present or has not been detected). The correlation can involve one or more than one genetic marker of this invention (e.g., two, three, four, five, or more) in any combination. An analysis that identifies a statistical association (e.g., a significant association) between the marker or combination of markers and the phenotype establishes a correlation between the presence of the marker or combination of markers in a population of subjects and the particular phenotype being analyzed. A level of risk (e.g., increased or decreased) can then be determined for an individual on the basis of such population-based analyses.

[0050] Thus, in certain embodiments, the present invention provides a method of screening a subject for a genetic marker (e.g., an allele at a SNP site) that is associated with aggressive prostate cancer, comprising: a) performing a population based study to detect polymorphisms (e.g., alleles) in a group of subjects with aggressive prostate cancer and a group of control subjects; b) identifying polymorphisms in the aggressive prostrate cancer group of subjects that are statistically associated with the presence of aggressive prostate cancer; and c) screening a subject for the presence of the polymorphisms identified in step (b).

[0051] The present invention further provides a method of identifying an effective and/or appropriate (i.e., for a given subject's particular condition or status) treatment regimen for a subject with aggressive prostate cancer, comprising detecting one or more of the polymorphisms and genetic markers associated with aggressive prostate cancer of this invention in the subject, wherein the one or more polymorphisms and genetic markers are further statistically correlated with an effective and/or appropriate treatment regimen for aggressive prostate cancer according to protocols as described herein and as are well known in the art.

[0052] Also provided is a method of identifying an effective and/or appropriate treatment regimen for a subject with aggressive prostate cancer, comprising: a) correlating the presence of one or more genetic markers of this invention in a test subject or population of test subjects with aggressive prostate cancer for whom an effective and/or appropriate treatment regimen has been identified; and b) detecting the one or more markers of step (a) in the subject, thereby identifying an effective and/or appropriate treatment regimen for the subject.

[0053] Further provided is a method of correlating a polymorphism or genetic marker of this invention with an effective and/or appropriate treatment regimen for aggressive prostate cancer, comprising: a) detecting in a subject or a population of subjects with aggressive prostate cancer and for whom an effective and/or appropriate treatment regimen has been identified, the presence of one or more genetic markers or polymorphisms of this invention; and b) correlating the presence of the one or more genetic markers of step (a) with an effective treatment regimen for aggressive prostate cancer.

[0054] Examples of treatment regimens for prostate cancer are well known in the art. Subjects who respond well to particular treatment protocols can be analyzed for specific genetic markers and a correlation can be established according to the methods provided herein. Alternatively, subjects who respond poorly to a particular treatment regimen can also be analyzed for particular genetic markers correlated with the poor response. Then, a subject who is a candidate for treatment for aggressive prostate cancer can be assessed for the presence of the appropriate genetic markers and the most effective and/or appropriate treatment regimen can be provided as early as possible.

[0055] In some embodiments, the methods of correlating genetic markers with treatment regimens of this invention can be carried out using a computer database. Thus the present invention provides a computer-assisted method of identifying a proposed treatment for aggressive prostate cancer and/or appropriate treatment for a subject carrying a genetic marker correlated with aggressive prostate cancer. The method involves the steps of (a) storing a database of biological data for a plurality of subjects, the biological data that is being stored including for each of said plurality of subjects, for example, (i) a treatment type, (ii) at least one genetic marker associated with aggressive prostate cancer and (iii) at least one disease progression measure for aggressive prostate cancer from which treatment efficacy can be determined; and then (b) querying the database to determine the correlation between the presence of said genetic marker and the effectiveness of a treatment type in treating aggressive prostate cancer, to thereby identify a proposed treatment as an effective for aggressive prostate cancer and/or an appropriate treatment for a subject carrying a genetic marker correlated with aggressive prostate cancer. In such methods, the genetic marker associated with aggressive prostate cancer can be a T allele in single nucleotide polymorphism rs4054823 in chromosome region 17p12.

[0056] In some embodiments, treatment information for a subject is entered into the database (through any suitable means such as a window or text interface), genetic marker information for that subject is entered into the database, and disease progression information is entered into the database. These steps are then repeated until the desired number of subjects has been entered into the database. The database can then be queried to determine whether a particular treatment is effective for subjects carrying a particular marker or combination of markers, not effective for subjects carrying a particular marker or combination of markers, etc. Such querying can be carried out prospectively or retrospectively on the database by any suitable means, but is generally done by statistical analysis in accordance with known techniques, as described herein.

[0057] The following examples are not intended to limit the scope of the claims to the invention, but are rather intended to be exemplary of certain embodiments. Any variations in the exemplified methods that occur to the skilled artisan are intended to fall within the scope of the present invention. As will be understood by one skilled in the art, there are several embodiments and elements for each aspect of the claimed invention, and all combinations of different elements are hereby anticipated, so the specific combinations exemplified herein are not to be construed as limitations in the scope of the invention as claimed. If specific elements are removed or added to the group of elements available in a combination, then the group of elements is to be construed as having incorporated such a change.

EXAMPLES

[0058] Abstract.

[0059] Autopsy studies suggest that most aging men will develop lesions that, if detected clinically, would be diag-

nosed as prostate cancer (PCa). Most of these cancers are indolent and remain localized; however, a subset of PCa is aggressive and accounts for more than 27,000 deaths in the United States annually. Identification of factors specifically associated with risk for more aggressive PCa is urgently needed to reduce overdiagnosis and overtreatment of this common disease. To search for such factors, the frequencies of SNPs were compared among PCa patients who were defined as having either more aggressive or less aggressive disease in four populations examined in the Genetic Markers of Susceptibility (CGEMS) study performed by the National Cancer Institute. SNPs showing possible associations with disease severity were further evaluated in an additional three independent study populations from the United States and Sweden. In total, 4,829 and 12,205 patients with more and less aggressive disease, respectively, were studied. It was found that the frequency of the TT genotype of SNP rs4054823 at 17p12 was consistently higher among patients with more aggressive compared with less aggressive disease in each of the seven populations studied, with an overall P value of 2.1×10^{-8} under a recessive model, exceeding the conservative genome-wide significance level. The difference in frequency was largest between patients with high-grade, non-organ-confined disease compared with those with low-grade, organ-confined disease. This study demonstrates that inherited variants predisposing to aggressive but not indolent PCa exist in the genome and demonstrates the clinical potential of such variants as potential early markers for risk of aggressive PCa.

[0060] Study Subjects.

[0061] Seven independent populations were included in this study (Table 2). The first four populations were from the publicly available CGEMS study, and include the Prostate, Lung, Colon and Ovarian (PLCO) Cancer Screening Trial, the American Cancer Society Cancer Prevention Study II (CPS-II), the Health Professionals Follow-up Study (HPFS), and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) (9, 11). PCa aggressiveness was defined by the CGEMS study as follows: patients with clinical stage T3/T4 or Gleason score of 7 or higher (stage and grade designations as described herein) based on biopsy specimens were classified as having more aggressive disease, whereas the remaining patients were classified as having less aggressive disease.

[0062] The other three populations were from our collaborative research group, including a hospital-based case series from the Johns Hopkins Hospital (JHH), and two population-based studies based on the National Prostate Cancer Register of Sweden; a case-control study; CAncer Prostate in Sweden (CAPS) (41, 26), and a case series of PCa patients treated for localized PCa (PROCAP) (42, 43).

[0063] PCa patients from the CAPS study were identified and recruited from four regional cancer registries in Sweden, diagnosed between July 2001 and October 2003. Patients were classified as having more aggressive disease if their cancers met any of the following criteria: advanced stage as evidenced by disease spread outside of the prostate; presence of cancer in the lymph nodes or other metastatic sites (clinical stage T3/T4, N+, M+, respectively); presence of poorly differentiated cancer at biopsy as indicated by a high Gleason score (i.e., 4+4=8 or higher; Gleason scores are the sum of the two most prevalent histologic patterns, rated on a scale of 1-5, with 5 being the most poorly differentiated); or a serum PSA level associated with a high likelihood of extensive disease (>50 ng/mL (n=1,231). Otherwise, the patients were classified as having less aggressive disease (n=1,619) (Table 4).

[0064] The PCa patients from the JHH study were men who underwent radical prostatectomy for treatment of PCa at JHH from Jan. 1, 1999, through Dec. 31, 2008. Because of the non-JHH populations analyzed in this study including only individuals of European descent, the JHH population was similarly confined. Tumors were graded and staged after resection; those with Gleason scores of 7, with the most prevalent pattern being 4, or higher, or stage T3b or higher, or N+ or M+ were defined as more aggressive disease (n=1,408). Tumors with Gleason score of 7 with most prevalent pattern 3, or lower and no evidence of disease dissemination (pathologic stage T2/N0/M0) were defined as having less aggressive disease (n=4,318) (Table 5).

[0065] The PROCAP study was a cohort of PCa patients diagnosed predominantly with clinically localized disease between 1997 and 2002 and recruited from the National Prostate Cancer Register of Sweden. Among 4,356 patients, 210 were classified as having more aggressive disease (clinical stage T3/T4, N+, M+, Gleason Score ≥8, or pre-treatment serum PSA ≥50 ng/mL). The remaining 4,159 patients were classified as having less aggressive disease.

[0066] SNPs and Genotyping Methods.

[0067] The genotyping data for ~27,000 SNPs in four CGEMS study populations (PLCO, CPS-II, HPFS, and ATBC) were publically available. These SNPs were genotyped because they were significantly associated with PCa risk in the first-stage GWAS of the CGEMS study (PLCO) using a case-control analysis (11). Individual genotype data from PLCO were obtained through an approved data request application. Summary genotype information from CPS-II, HPFS, and ATBC were downloaded from a publicly accessible CGEMS website (cgems.cancer.gov/data/).

[0068] SNP genotyping in the CAPS, JHH, and PROCAP subjects was performed using the MassARRAY iPLEX genotyping system (Sequenom) at Wake Forest University. Duplicate test samples and two water samples (PCR negative controls) that were blinded to the technician were included in each 96-well plate. The rate of concordant results between 100 duplicate samples was >99%.

[0069] Statistical Analysis.

[0070] Allele frequency differences between two groups of patients were tested for each SNP using a χ^2 test with 1 degree of freedom within each population. The allelic odds ratio (OR) and 95% confidence interval (95% CI) were estimated based on a multiplicative model. Genotype frequency differences between two groups of patients were also tested using both a dominant and a recessive model for SNPs that were confirmed in an allele test from multiple populations. Results from multiple populations were combined using a Mantel-Haenszel model in which the populations were allowed to have different allele frequencies but were assumed to have a common OR. The homogeneity of ORs among different study populations was tested using Breslow-Day χ^2 test.

[0071] For SNPs that were confirmed to be significantly associated with aggressiveness of PCa, a χ^2 test using a 2×K table was performed for Gleason scores and T-stage, in which K is the number of possible categories within each variable. All reported P values were based on a two-sided test.

[0072] To identify inherited genetic markers that are associated with aggressiveness of PCa, publicly available genotype data were analyzed for ~27,000 SNPs across the genome among 1,980 patients with more aggressive disease and 2,109 patients with less aggressive disease from four CGEMS study populations (PLCO, CPS-II, HPFS, and ATBC) using a case-case analysis (FIG. **1**, Table 2). Based on the results of a combined allelic test, a subset of SNPs (n=74) was selected for further evaluation, where $P<0.05$ for the difference between more and less aggressive disease, and the direction of association was consistent among the four studies. These SNPs were subsequently evaluated in an independent cohort of 1,231 patients with more aggressive disease and 1,619 patients with less aggressive disease from the CAPS study (Table 4). Six of these 74 SNPs were confirmed; $P<0.05$ for the allelic test, with the same direction of association (Table 7). These six SNPs were then evaluated in 1,408 patients with more aggressive disease and 4,318 patients with less aggressive disease from the Johns Hopkins Hospital (JHH) study population (Table 5). One SNP (rs4054823 at 17p12) had a marginally different allele frequency between the two types of PCa patients ($P=0.051$), with the same direction of association as in the previous studies (Table 8). This SNP was further evaluated in an additional independent Swedish PCa patient population (PROCAP), comprising 210 patients with more aggressive disease and 4,159 patients with less aggressive disease. The allelic test confirmed the association ($P=0.01$).

[0073] As summarized in Table 3, the frequency of allele T of SNP rs4054823 was consistently higher in patients with more aggressive disease compared with patients with less aggressive disease in each of the four CGEMS populations, and was significant in the combined allelic test ($P=9.8\times10^{-4}$). The T allele of rs4054823 was also more frequent in patients with more aggressive disease in each of the three independent populations in the confirmation stage, with a value of $P=5.0\times10^{-4}$ from a combined allelic test. Combining the data from all seven populations, the allelic test of the SNP and aggressiveness of PCa was highly significant ($P=2.1\times10^{-6}$). When genotype frequencies of this SNP between the two types of PCa were tested using dominant and recessive models, the recessive model (allele T) was most significant ($P=2.1\times10^{-8}$). This P value exceeded a study-wide significance level at a 5% false positive rate using a conservative Bonferroni correction (27,000 SNPs and three genetic models). The TT genotype was found in 32% of 4829 cases with aggressive disease and 28% of 12,205 cases with less aggressive disease. Compared with PCa patients who had CC or CT genotypes, patients who had the TT genotype of this SNP had an odds ratio (OR) of 1.26 (95% confidence interval [CI], 1.16-1.36) for aggressive PCa. No heterogeneity was observed in the OR estimates among different populations ($P=0.56$, Breslow-Day test).

[0074] To overcome potential limitations arising from the heterogeneous definitions of aggressive PCa used among these seven study populations, and to more fully characterize the association, an in-depth analysis was performed of the correlation of SNP rs4054823 with specific clinicopathologic variables of PCa including tumor grade as assessed by Gleason score and TNM stage in populations for which this information was available. This analysis was first performed in patients from JHH for the following reasons: (i) a large number of patients (n=5,955) recruited from the same hospital were available; (ii) all patients were treated with radical prostatectomy and thus, unlike patients receiving either no or nonsurgical treatment, their tumors were available for extensive pathologic evaluation; and (iii) tumors were uniformly graded and staged by pathologists at JHH using the same protocol (32, 33). In this analysis, it was found that the frequency of the TT genotype was lower in patients with well-to moderately differentiated cancers (29%, 28%, and 30% in cancers with Gleason scores ≤6, 3+4, and 4+3, respectively) and increased only in patients with more poorly differentiated tumors, i.e., Gleason scores ≥8 (35%), $P=0.002$ from a χ^2 test comparing patients with Gleason score ≥8 and <8 (FIG. **2**A). Similarly, it was found that the frequency of the TT genotype was lower in patients with low disease stage (pT2, 29% and pT3a, 28%) and was increased in patients with higher disease stage (≥pT3b, 34%; $P=0.03$, from a χ^2 test comparing patients with stage ≥pT3b and <pT3b). The difference in TT genotype frequency was largest between the most extreme groups with regard to likelihood of disease progression and lethality: 29% of patients with the least aggressive disease (Gleason score ≤6 and organ-confined stage, pT2, n=3,080), compared with 46% of patients with the most aggressive PCa (Gleason score ≥8 and non-organ-confined stage, ≥pT3b, n=136; OR=2.11; 95% CI: 1.507-2.99), $P=1.6\times10^{-5}$.

[0075] The association of this SNP with clinicopathologic variables was also examined in the Swedish CAPS population, although this population differed from the JHH population in that the treatments included multiple modalities (none, radiation, surgery, and hormonal), resulting in less uniform tumor staging and grading. In this population, the TT genotype frequency also increased with increasing Gleason score and stage; the largest difference was between the most and least aggressive PCa patients (FIG. **2**B). The pattern of association, however, differed from that of JHH: a threshold increase of TT genotype frequency in patients with Gleason score ≥8 or stage ≥pT3b was observed in the JHH patients, whereas a gradual increase of TT genotype frequency was observed with increasing Gleason score or stage in CAPS patients. This difference may be due to the pathologic evaluation of prostatectomy specimens in the JHH study versus the clinical grading of biopsy specimens and clinical staging of the majority of cases in the CAPS study. Typically, a ~20-30% discrepancy in grading and staging is observed between clinical and pathologic evaluations of the same patient (34).

[0076] This study reflects an important shift in genetic association studies of PCa. Most studies to date have searched for inherited genetic variants that predispose men to overall PCa risk, by comparing men with and without PCa using a case-control design. In contrast, this study was strategically designed to identify inherited genetic markers that distinguish between risk for aggressive versus indolent PCa, by comparing SNPs among PCa patients with these two disease phenotypes using a case-case design. The need for this change in approach is supported by several trends, including a concern over increased rates of diagnosis and treatment of indolent disease and the lack of consistently validated markers of aggressive disease identified using currently used case-control study designs (26).

[0077] In this study, a SNP has been identified with a genotype frequency that is consistently different between patients with more or less aggressive PCa in each of the seven independent populations studied. The difference between the two types of PCa was statistically significant

($P=2.1\times10^{-8}$), exceeding a conservative study-wide and even genome-wide significance level. More importantly, the difference in frequency was largest between patients with high-grade, non-organ-confined disease and thus at high risk for adverse outcomes compared with patients with low-risk, low-grade, organ-confined disease.

[0078] It is of interest to note that the frequency of the TT genotype of SNP rs4054823 in unaffected controls is similar to that observed in less aggressive cases (Table 6), and is significantly higher only among more aggressive cases. This observation implicates such SNPs as not only being informative of risk for aggressive PCa at the time of diagnosis, but also before diagnosis, to possibly target men for more effective PSA screening based on their risk for clinically important PCa.

[0079] Based on this study, it is envisioned that a panel of SNPs with characteristics similar to the one described here could be an important part of a genetic-based, targeted PSA screening strategy that is effective in reducing the number of men requiring disease screening, thereby reducing overdiagnosis while also decreasing mortality by facilitating identification of those men at risk for aggressive PCa at a stage when the disease is potentially curable.

[0080] All publications and patent applications, nucleotide sequences and/or amino acid sequences identified by GenBank® Database Accession numbers are herein incorporated by reference to the same extent as if each individual publication or patent application or sequences was specifically and individually indicated to be incorporated by reference.

[0081] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be apparent that certain changes and modifications may be practiced within the scope of the list of the foregoing embodiments and the appended claims.

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TABLE 1

Risk Allele Distribution of 183 Aggressive Versus 184 Non-Aggressive Prostate Cases in a Johns Hopkins Hospital Population

SNP	CHR	Position	Alleles	Risk allele	Frequency in aggressive prostate cancer	Frequency in non-aggressive prostate cancer	OR
rs17641637	17	12957061	C/T	T	0.67	0.67	1.03
rs11654550	17	13499770	T/C	C	0.59	0.56	1.15
rs2190856	17	13502089	T/G	G	0.58	0.55	1.13
rs7215323	17	13509789	A/G	A	0.43	0.36	1.39
rs7215137	17	13509982	A/G	G	0.59	0.58	1.06
rs12948596	17	13511800	T/C	T	0.30	0.29	1.01
rs62056886	17	13512134	C/T	T	0.53	0.50	1.14
rs62056887	17	13512555	A/G	A	0.23	0.21	1.13
rs9890022	17	13516145	T/C	T	0.26	0.24	1.12
rs9892382	17	13516433	T/C	C	0.60	0.58	1.10
rs58402698	17	13516645	G/A	G	0.26	0.24	1.14
rs9898581	17	13517421	G/C	G	0.26	0.25	1.08
rs8077904	17	13519696	C/G	G	0.60	0.58	1.11
rs9914411	17	13520722	G/C	G	0.22	0.21	1.06
rs9916271	17	13520827	A/T	A	0.26	0.23	1.15
rs9895696	17	13522216	A/C	A	0.26	0.24	1.13
rs9896834	17	13522666	C/T	T	0.60	0.58	1.12
rs2874922	17	13523506	T/C	C	0.61	0.58	1.12
rs13342347	17	13523600	A/C	A	0.26	0.23	1.16
rs13342371	17	13523675	T/G	T	0.26	0.23	1.16
rs8071527	17	13523773	G/A	A	0.60	0.58	1.11
rs9899320	17	13526026	C/G	C	0.26	0.24	1.14
rs55904171	17	13526981	C/G	C	0.26	0.24	1.14
rs9909795	17	13527634	C/T	C	0.25	0.24	1.11
rs62056948	17	13530709	A/G	A	0.25	0.24	1.09
rs55777305	17	13531676	G/A	G	0.30	0.29	1.01
rs12602893	17	13534884	T/G	T	0.25	0.21	1.25
rs11078175	17	13536856	C/T	T	0.61	0.58	1.13
rs62056953	17	13536977	G/A	G	0.26	0.23	1.15
rs4622548	17	13538724	C/T	T	0.57	0.52	1.23
rs28824801	17	13541019	G/A	G	0.26	0.23	1.15
rs12325885	17	13543663	T/C	C	0.60	0.57	1.11
rs9910556	17	13544834	T/C	C	0.60	0.58	1.10

TABLE 1-continued

Risk Allele Distribution of 183 Aggressive Versus 184 Non-Aggressive Prostate Cases in a Johns Hopkins Hospital Population

SNP	CHR	Position	Alleles	Risk allele	Frequency in aggressive prostate cancer	Frequency in non-aggressive prostate cancer	OR
rs17588248	17	13548141	G/C	G	0.26	0.24	1.13
rs11078178	17	13548190	A/T	T	0.60	0.58	1.11
rs17588297	17	13548205	T/C	T	0.25	0.21	1.21
rs2874927	17	13548602	C/T	C	0.25	0.21	1.21
rs8074120	17	13549576	A/G	G	0.60	0.58	1.10
rs9908002	17	13549722	C/T	C	0.26	0.23	1.17
rs59486592	17	13550210	A/G	A	0.25	0.23	1.13
rs4791554	17	13552900	G/A	G	0.25	0.22	1.20
rs11656731	17	13552932	T/A	T	0.25	0.21	1.21
rs56662934	17	13555214	A/G	A	0.26	0.23	1.18
rs12949913	17	13556021	G/T	T	0.59	0.57	1.07
rs12453942	17	13560013	C/G	C	0.25	0.21	1.24
rs13353193	17	13562260	A/G	A	0.25	0.22	1.20
rs9911679	17	13562733	G/A	A	0.78	0.73	1.34
rs11078179	17	13563342	G/T	T	0.79	0.74	1.30
rs12942445	17	13564329	C/T	T	0.87	0.86	1.13
rs12940830	17	13564583	G/A	G	0.19	0.16	1.17
rs17665271	17	13564994	C/T	T	0.81	0.78	1.23
rs56216350	17	13565289	C/T	T	0.81	0.78	1.23
rs16948318	17	13565430	A/G	G	0.78	0.73	1.35
rs4054823	17	13565749	C/T	T	0.61	0.57	1.21
rs12942294	17	13566080	T/G	G	0.78	0.72	1.39
rs12942086	17	13566150	T/C	C	0.78	0.73	1.38

TABLE 2

Number of Patients with More or Less Aggressive Prostate Cancer in Each of Seven Populations

Study Population	No. of Prostate Cancer Patients	
	More Aggressive	Less Aggressive
CGEMS*		
PLCO	691	489
ACS(CPS-II)	926	699
HPFS	123	405
ATBC	240	516
Subtotal	1,980	2,109
CAPS†	1,231	1,619

TABLE 2-continued

Number of Patients with More or Less Aggressive Prostate Cancer in Each of Seven Populations

Study Population	No. of Prostate Cancer Patients	
	More Aggressive	Less Aggressive
JHH‡	1,408	4,318
PROCAP§	210	4,159
Total	4,829	12,205

*In the CGEMS study, more aggressive disease is defined as Gleason ≥ 7 or T-stage ≥ T3.
†n the CAPS study, more aggressive disease is defined as Gleason ≥ 8 or T-stage ≥ T3.
‡In the JHH study, more aggressive disease is defined as Gleason ≥ (4 + 3) or T-stage ≥ T3b or N+.
§In the PROCAP study, more aggressive disease is defined as Gleason ≥ 8 or N+.

TABLE 3

Association of SNP rs4054823 at 17p12 with Aggressiveness of PCa

Study	Genotype Frequency						Allele Test			
	Aggressive			Nonaggressive			Frequency (T)			
Populations	CC	CT	TT	CC	CT	TT	Agg	Nonagg	OR (95% CI)	P
CGEMS study										
ACS	171	467	275	152	349	183	0.56	0.52	1.15 (1.00-1.32)	0.05
ATBC	52	119	67	124	253	132	0.53	0.51	1.10 (0.88-1.37)	0.39
HPFS	29	43	46	75	191	123	0.57	0.56	1.04 (0.78-1.40)	0.78
PLCO	119	332	233	104	253	126	0.58	0.52	1.28 (1.08-1.51)	3.7E−03
Sub Total	371	961	621	455	1046	564	0.56	0.53	1.17 (1.06-1.28)	9.8E−04
Confirmation										
CAPS	247	589	387	331	841	428	0.56	0.52	1.11 (1.00-1.24)	0.04
JHH	289	662	448	912	2152	1217	0.56	0.54	1.09 (1.00-1.19)	0.05

TABLE 3-continued

Association of SNP rs4054823 at 17p12 with Aggressiveness of PCa										
PROCAP	35	93	81	853	2079	1215	0.61	0.54	1.31 (1.07-1.61)	0.01
Sub Total	571	1344	916	2096	5072	2860	0.56	0.54	1.12 (1.05-1.19)	5.0E−04
All Populations	942	2305	1537	2551	6118	3424	0.56	0.54	1.13 (1.08-1.19)	2.1E−06

		Genotype Test			
	Study	Recessive		Dominant	
	Populations	OR (95% CI)	P	OR (95% CI)	P
	CGEMS study				
	ACS	1.18 (0.95-1.47)	0.14	1.24 (0.97-1.58)	0.09
	ATBC	1.12 (0.79-1.58)	0.52	1.15 (0.80-1.66)	0.45
	HPFS	1.38 (0.90-2.12)	0.14	0.73 (0.45-1.20)	0.21
	PLCO	1.46 (1.13-1.89)	3.6E−03	1.30 (0.97-1.75)	0.08
	Sub Total	1.27 (1.10-1.47)	9.1E−04	1.18 (1.00-1.38)	0.04
	Confirmation				
	CAPS	1.27 (1.08-1.49)	4.5E−03	1.03 (0.86-1.24)	0.75
	JHH	1.19 (1.04-1.35)	1.0E−02	1.04 (0.90-1.21)	0.61
	PROCAP	1.53 (1.15-2.03)	3.5E−03	1.29 (0.89-1.87)	0.18
	Sub Total	1.25 (1.13-1.37)	6.2E−06	1.06 (0.95-1.18)	0.32
	All Populations	1.26 (1.16-1.36)	2.1E−08	1.09 (1.00-1.20)	0.05

Recessive and dominant models are defined in terms of risk allele T. For Subtotal and All Populations, the P value or OR (95% CI) were calculated from the CMH test. Breslow-Day P value for all populations/recessive mode is 0.5646.

TABLE 4

Clinical and Demographic Characteristics of Subjects in CAPS

	No. (%) of cases			
Characteristic	Aggressive (n = 1,231)	Localized (n = 1,619)	All cases (n = 2,899)	No. (%) of controls (n = 1,722)
Age at enrollment (y)				
Mean (SD)	68.04 (7.32)	65.14 (6.74)	66.36 (7.13)	67.15 (7.39)
Age, y, at diagnosis				
65	514 (41.75)	926 (57.19)	1469 (50.78)	N/A
>65	717 (58.25)	693 (42.81)	1424 (49.22)	N/A
Family history (first-degree relatives)				
No	1013 (82.29)	1295 (79.99)	2,342 (80.95)	1,565 (90.57)
Yes	218 (17.71)	324 (20.01)	551 (19.05)	163 (9.43)
Missing data	0	0	0	0
PSA levels at diagnosis for cases or at enrollment for controls (ng/mL)				
4	36 (2.95)	185 (11.61)	221 (7.85)	1,438 (83.56)
4.01-9.99	171 (14.00)	755 (47.39)	926 (32.91)	230 (13.36)
10-19.99	216 (17.69)	438 (27.50)	654 (23.24)	37 (2.15)
20-49.99	252 (20.64)	215 (13.50)	467 (16.60)	13 (0.76)
50-99.99	229 (18.76)	0	229 (8.14)	2 (0.12)
100	317 (25.96)	0	317 (11.27)	1 (0.06)
Missing	10	26	85	1
T-stage				
T0	2 (0.16)	7 (0.44)	9 (0.32)	N/A
T1	147 (12.07)	933 (58.24)	1080 (38.30)	N/A
T2	242 (19.87)	662 (41.32)	904 (32.06)	N/A
T3	724 (59.44)	0	724 (25.67)	N/A
T4	103 (8.46)	0	103 (3.65)	N/A
TX	13	17	79	N/A
N-stage				
N0	222 (70.03)	302 (100.00)	524 (84.65)	N/A
N1	95 (29.97)	0	95 (15.35)	N/A
NX	914	1317	2280	N/A

TABLE 4-continued

Clinical and Demographic Characteristics of Subjects in CAPS

Characteristic	No. (%) of cases: Aggressive (n = 1,231)	Localized (n = 1,619)	All cases (n = 2,899)	No. (%) of controls (n = 1,722)
M-stage				
M0	589 (68.25)	655 (100.00)	1244 (81.95)	N/A
M1	274 (31.75)	0	274 (18.05)	N/A
MX	368	964	1381	N/A
Gleason (biopsy)				
4	9 (0.83)	98 (6.32)	107 (4.06)	N/A
5	43 (3.96)	247 (15.93)	290 (10.99)	N/A
6	153 (14.08)	832 (53.64)	985 (37.34)	N/A
7	414 (38.09)	374 (24.11)	788 (29.87)	N/A
8	258 (23.74)	0	258 (9.78)	N/A
9	185 (17.02)	0	185 (7.01)	N/A
10	25 (2.30)	0	25	N/A
Missing	144	68	261	N/A

Forty-nine patients could not be classified as having aggressive or localized disease because of missing phenotypes.

TABLE 5

Clinical and Demographic Characteristics of Study Subjects

Characteristic	No. (%) of cases: Aggressive (n = 1,408)	Indolent (n = 4,318)	All cases (n = 5,955)	Controls (n = 482)
Age at enrollment (y)				
Mean (SD)	59.8 (6.72)	57.7 (6.49)	58.3 (6.69)	59.91 (7.19)
Age at diagnosis (y)				
≤65	1,112 (78.98)	3,833 (88.77)	5,115 (85.89)	
>65	296 (21.02)	485 (11.23)	839 (1409)	
PSA levels at diagnosis for cases or at enrollment for controls (ng/mL)				
≤4	139 (9.87)	1,095 (25.36)	1,262 (21.19)	481 (99.79)
4.01-9.99	611 (43.39)	2,264 (52.43)	2,951 (49.55)	0
10-19.99	182 (12.93)	247 (5.72)	451 (7.57)	0
20-49.99	84 (5.97)	36 (0.83)	131 (2.2)	0
50-99.99	34 (2.41)	4 (0.09)	58 (0.97)	0
≥100	63 (4.47)	3 (0.07)	117 (1.96)	0
Missing	196 (13.92)	669 (15.49)	985 (16.54)	1 (0.21)
T-stage				
T0	NA	NA	NA	NA
T1	NA	NA	NA	NA
T2	368 (26.14)	3,416 (79.11)	3,850 (64.65)	NA
T3a	536 (38.07)	902 (20.89)	1,454 (24.42)	NA
T3b/c	355 (25.21)	0	355 (5.96)	NA
T3/T3X	9 (0.64)	0	15 (0.25)	NA
T4	3 (0.21)	0	3 (0.05)	NA
TX	137 (9.73)	0	278 (4.67)	NA
N-stage				
N0	1,085 (77.06)	4,318 (100)	5,469 (91.84)	NA
N1	140 (9.94)	0 (0)	140 (2.35)	NA
NX	183 (13)	0 (0)	346 (5.81)	NA
M-stage				
M0	NA	NA	NA	NA
M1	NA	NA	NA	NA
MX	1,408	4,318	5,955	NA

TABLE 5-continued

Clinical and Demographic Characteristics of Study Subjects

Characteristic	No. (%) of cases: Aggressive (n = 1,408)	Indolent (n = 4,318)	All cases (n = 5,955)	Controls (n = 482)
Gleason score (biopsy)				
≤4	0	0	2 (0.03)	NA
5	2 (0.14)	67 (1.55)	73 (1.23)	NA
6	23 (1.63)	3,042 (70.45)	3,104 (52.12)	NA
7 (3 + 4)	106 (7.53)	1,254 (29.04)	1,411 (23.69)	NA
7 (4 + 3)	667 (47.37)	0	667 (11.2)	NA
8	317 (22.51)	0	317 (5.32)	NA
9	265 (18.82)	0	265 (4.45)	NA
10	18 (1.28)	0	18 (0.3)	NA
Missing	10 (0.71)	0	98 (1.65)	NA

A total of 229 patients could not be classified as having aggressive or indolent disease because of missing phenotypes.

TABLE 6

Genotype Frequency of SNP rs4054823 at 17p12 in Controls as Well as Case Patients With Aggressive or Indolent Disease

Study	Genotype frequency: Controls			Aggressive			Indolent		
population	CC	CT	TT	CC	CT	TT	CC	CT	TT
CGEMS study									
AC5	339	904	532	171	467	275	152	349	183
ATBC	228	473	219	52	119	67	124	253	132
HPFS	126	304	181	29	43	46	75	191	123
PLCO	226	548	319	119	312	233	104	253	126
Sub total	919	2,229	1,251	371	961	621	455	1,046	564
Confirmation									
CAP5	362	865	484	247	589	387	331	841	428
JHH	106	234	140	289	662	448	912	2,152	1,217
Sub total	468	1,099	624	536	1,251	835	1,243	2,993	1,645
All populations	1,387	3,328	1,875	907	2,212	1,456	1,698	4,039	2,209

Study	Genotype test (recessive model for T): Controls vs. aggressive		Controls vs. indolent	
population	OR (95% CI)	P	OR (95% CI)	P
CGEMS study				
AC5	1.01 (0.85-1.20)	0.937	0.85 (0.70-1.04)	0.116
ATBC	1.25 (0.91-1.73)	0.166	1.12 (0.87-1.44)	0.371
HPFS	1.52 (1.01-2.28)	0.045	1.10 (0.83-1.45)	0.504
PLCO	1.25 (1.02-1.54)	0.031	0.86 (0.67-1.09)	0.208
Sub total	1.15 (1.02-1.29)	0.019	0.95 (0.84-1.08)	0.386
Confirmation				
CAP5	1.17 (1.00-1.37)	0.050	0.93 (0.79-1.08)	0.322
JHH	1.14 (0.91-1.44)	0.244	0.96 (0.78-1.19)	0.734
Sub total	1.16 (1.02-1.33)	0.023	0.94 (0.83-1.06)	0.318
All populations	1.16 (1.06-1.26)	1.1E−03	0.94 (0.87-1.03)	0.188

P value and OR (95% CI) in combined populations are for the CMH test. In Controls vs. Aggressive, the Breslow-Day P value for all populations is 0.4142.

TABLE 7: Confirmation of SNPs Associated With Aggressiveness of Prostate Cancer in CAPS

				CGEMS, 1st stage			CGESM, 2nd stage									CGEMS		CAPS				
dbSNP ID	Chromosome	Physical Position (bp)	Allele	Aggressive-PLCO, n=691	Indolent-PLCO, n=488	P-PLCO	Aggressive-ACS, n=928	Indolent-ACS, n=699	P-ACS	Aggressive-ATBC, n=240	Indolent-ATBC, n=516	P-ATBC	Aggressive-HPFS, n=123	Indolent-HTFS, n=405	P-HPFS	P-CMH	Rank	Allele	Aggressive, n=1,231	Indolent, n=1,619	P	OR
rs9438989	1	39,041,936	G	0.24	0.2	0.0419	0.25	0.24	0.7291	0.24	0.2	0.0949	0.33	0.24	0.0084	0.0041	237	T	0.24	0.24	0.8664	0.99
rs4950142	1	98,253,698	C	0.23	0.27	0.0162	0.23	0.27	0.013	0.16	0.17	0.6353	0.24	0.24	0.9814	0.0014	103	T	0.22	0.23	0.3348	0.94
rs603246	1	166,824,862	G	0.45	0.41	0.0343	0.47	0.44	0.1138	0.51	0.45	0.0371	0.44	0.42	0.8606	0.0013	100	A	0.45	0.45	0.7575	1.02
rs286324	2	183,527,094	A	0.48	0.43	0.0398	0.5	0.44	0.0012	0.51	0.48	0.1575	0.52	0.46	0.144	2E-05	3	C	0.48	0.49	0.1625	0.93
rs2049716	2	184,291,156	A	0.17	0.21	0.0344	0.19	0.22	0.0537	0.16	0.18	0.3384	0.18	0.21	0.4185	0.0021	139	C	0.19	0.19	0.6158	0.97
rs6738940	2	208,868,469	G	0.17	0.21	0.0185	0.15	0.18	0.039	0.14	0.18	0.0914	0.17	0.17	0.8912	0.0007	61	A	0.16	0.16	0.6966	0.97
rs7631088	3	1,054,024	G	0.48	0.52	0.0435	0.49	0.51	0.2277	0.5	0.51	0.6716	0.43	0.53	0.0097	0.0039	226	A	0.49	0.48	0.6587	1.02
rs12490386	3	4,021,849	A	0.15	0.12	0.0175	0.13	0.12	0.2911	0.11	0.08	0.0284	0.15	0.11	0.2046	0.0011	91	G	0.14	0.14	0.3879	0.94
rs12632229	3	72,722,484	G	0.43	0.37	0.007	0.43	0.4	0.0959	0.47	0.41	0.0425	0.41	0.4	0.7841	0.0005	39	A	0.42	0.42	0.7796	0.98
rs7639273	3	108,211,376	G	0.17	0.13	0.0068	0.15	0.13	0.0793	0.1	0.08	0.2189	0.14	0.14	0.7321	0.0011	87	T	0.11	0.12	0.1717	0.89
rs1515577	3	121,611,630	T	0.49	0.45	0.0495	0.51	0.48	0.1016	0.5	0.46	0.1091	0.54	0.47	0.0524	0.0006	53	C	0.48	0.48	0.7694	0.99
rs6772915	3	125,553,929	G	0.4	0.33	0.0019	0.36	0.34	0.1099	0.46	0.45	0.5306	0.37	0.31	0.0586	0.0003	29	T	0.4	0.39	0.3406	1.05
rs9825812	3	127,506,666	T	0.45	0.5	0.0301	0.46	0.47	0.631	0.4	0.46	0.0152	0.45	0.52	0.0746	0.0021	135	C	0.46	0.44	0.2024	1.07
rs12629405	3	169,834,562	A	0.48	0.44	0.0418	0.47	0.44	0.0981	0.65	0.61	0.2214	0.52	0.44	0.0427	0.0008	68	A	0.47	0.49	0.2336	0.94
rs734526	4	7,715,523	C	0.37	0.32	0.0077	0.35	0.31	0.0373	0.41	0.38	0.3496	0.39	0.34	0.1409	0.0002	21	T	0.36	0.35	0.496	1.04
rs17579876	4	114,423,937	A	0.16	0.2	0.0198	0.17	0.2	0.1115	0.17	0.19	0.3694	0.14	0.16	0.2791	0.0024	158	G	0.19	0.18	0.2943	1.08
rs13128882	4	116,569,315	A	0.38	0.34	0.0446	0.38	0.37	0.3915	0.38	0.34	0.218	0.43	0.36	0.0443	0.005	291	G	0.39	0.39	0.8024	1.01
rs4582131	4	153,582,583	T	0.11	0.08	0.0236	0.09	0.08	0.1443	0.09	0.06	0.0991	0.12	0.1	0.3849	0.0016	111	C	0.09	0.09	0.8448	1.02
rs11132055	4	182,697,954	G	0.11	0.15	0.004	0.13	0.14	0.2089	0.09	0.11	0.2157	0.1	0.13	0.2363	0.001	82	T	0.1	0.11	0.394	0.93

TABLE 7 CONTINUED

				CGEMS, 1st stage			CGESM, 2nd stage									CGEMS		CAPS				
dbSNP ID	Chromosome	Physical Position (bp)	Allele	Aggressive-PLCO, n=691	Indolent-PLCO, n=489	P-PLCO	Aggressive-ACS, n=926	Indolent-ACS, n=699	P-ACS	Aggressive-ATBC, n=240	Indolent-ATBC, n=516	P-ATBC	Aggressive-HPFS, n=123	Indolent-HTFS, n=405	P-HPFS	P-CMH	Rank	Allele	Aggressive, n=1,231	Indolent, n=1,619	P	OR
rs16903125	5	34,618,695	C	0.12	0.08	0.0026	0.11	0.08	0.034	0.11	0.09	0.0949	0.12	0.1	0.4187	6E-05	7	A	0.01	0.01	0.9583	0.98
rs6451722	5	43,747,135	G	0.19	0.24	0.0048	0.2	0.24	0.0043	0.15	0.16	0.5206	0.21	0.23	0.6136	0.0001	12	A	0.19	0.19	0.6309	1.03
rs159574	5	55,515,418	T	0.39	0.34	0.0327	0.39	0.37	0.2688	0.36	0.35	0.5547	0.47	0.39	0.0298	0.0046	266	C	0.39	0.39	0.7228	1.02
rs1826592	5	116,652,980	A	0.33	0.37	0.0478	0.35	0.38	0.1222	0.29	0.33	0.0818	0.36	0.38	0.6221	0.003	185	C	0.35	0.34	0.8512	1.01
rs249888	5	155,599,372	C	0.33	0.25	5E-05	0.3	0.28	0.1577	0.34	0.31	0.2177	0.33	0.3	0.3151	7E-05	8	T	0.29	0.28	0.4397	1.05
rs4704998	5	155,613,992	A	0.26	0.21	0.0055	0.24	0.23	0.2442	0.29	0.25	0.0702	0.27	0.23	0.2257	0.0006	51	G	0.24	0.23	0.4429	1.05
rs12194118	6	4,272,255	T	0.44	0.49	0.0143	0.47	0.51	0.0079	0.43	0.46	0.4056	0.5	0.52	0.628	0.0003	30	G	0.45	0.45	0.7227	1.02
rs2806371	6	109,328,539	A	0.4	0.45	0.0209	0.42	0.43	0.3709	0.31	0.38	0.0052	0.39	0.43	0.3759	0.001	83	G	0.42	0.42	0.7459	0.98
[illegible]																						
rs1229655	7	26,206,164	C	0.27	0.23	0.0374	0.28	0.24	0.1598	0.17	0.15	0.3239	0.29	0.22	0.0303	0.0015	108	T	0.24	0.22	0.267	1.07
rs2391671	7	28,325,617	A	0.29	0.24	0.0267	0.27	0.24	0.0924	0.29	0.26	0.2283	0.27	0.25	0.5863	0.0027	171	G	0.27	0.25	0.2224	1.08
rs2726005	7	85,205,173	G	0.16	0.12	0.0084	0.15	0.14	0.5543	0.16	0.13	0.2501	0.22	0.13	0.0005	0.0006	55	A	0.15	0.14	0.5121	1.05
rs1487745	8	18,665,612	G	0.09	0.13	0.0015	0.09	0.11	0.3302	0.12	0.14	0.2257	0.06	0.1	0.0695	0.0005	49	A	0.1	0.11	0.5837	0.95
rs6472429	8	70,000,821	C	0.51	0.46	0.0181	0.51	0.48	0.0805	0.53	0.5	0.3454	0.55	0.48	0.082	0.0007	63	C	0.49	0.5	0.2985	0.95
rs7011777	8	124,036,356	T	0.25	0.2	0.0192	0.26	0.22	0.007	0.21	0.19	0.5165	0.25	0.24	0.9771	0.0008	70	C	0.25	0.24	0.3082	1.07
rs11994203	8	125,672,479	G	0.18	0.13	0.0022	0.17	0.14	0.054	0.29	0.25	0.1431	0.19	0.16	0.2253	9E-05	11	T	0.22	0.21	0.7452	1.02
rs13293901	9	12,897,902	C	0.18	0.22	0.0231	0.17	0.2	0.0322	0.17	0.19	0.5315	0.16	0.18	0.4539	0.0016	115	A	0.18	0.2	0.1581	0.91
[illegible]																						
rs11139934	9	83,009,358	A	0.23	0.19	0.0168	0.24	0.22	0.2442	0.19	0.15	0.0881	0.27	0.2	0.0236	0.0005	48	G	0.2	0.2	0.83	0.99

TABLE 7 CONTINUED

				CGEMS, 1st stage			CGESMI, 2nd stage									CGEMS		CAPS				
dbSNP ID	Chromosome	Physical Position (bp)	Allele	Aggressive-PLCO, n=691	indolent-PLCO, n=489	P-PLCO	Aggressive-ACS, n=926	indolent-ACS, n=699	P-ACS	Aggressive-ATBC, n=240	indolent-ATBC, n=515	P-ATBC	Aggressive-HPFS, n=123	indolent-HTFS, n=405	P-HPFS	P-CMH	Rank	Allele	Aggressive, n=1,231	indolent, n=1,619	P	OR
rs1875411	9	108,824,524	A	0.13	0.1	0.0163	0.13	0.1	0.0349	0.08	0.06	0.1918	0.11	0.11	0.8351	0.0009	76	G	0.1	0.1	0.5589	1.05
rs1871692	9	113,580,831	T	0.27	0.31	0.0317	0.27	0.3	0.0648	0.34	0.36	0.5993	0.25	0.28	0.447	0.0047	271	C	0.29	0.3	0.4047	0.95
rs7909593	10	12,442,472	A	0.08	0.11	0.0228	0.1	0.12	0.0819	0.11	0.12	0.4424	0.09	0.12	0.1472	0.0017	118	C	0.12	0.12	0.5741	0.95
rs2148308	10	21,092,954	A	0.46	0.4	0.0124	0.46	0.44	0.2321	0.4	0.35	0.0635	0.5	0.43	0.0425	0.0004	33	C	0.39	0.42	0.04485	0.9
rs7907981	10	44,051,001	T	0.25	0.2	0.0092	0.25	0.23	0.3796	0.31	0.24	0.0053	0.29	0.21	0.0074	6E-05	6	C	0.25	0.25	0.6056	1.03
rs9416489	10	57,531,487	G	0.46	0.51	0.0088	0.47	0.51	0.037	0.49	0.55	0.0394	0.46	0.48	0.7116	0.0002	17	G	0.49	0.5	0.8346	0.99
rs7917290	10	71,536,167	T	0.17	0.13	0.0117	0.16	0.14	0.1974	0.22	0.19	0.1301	0.19	0.18	0.5209	0.0022	147	G	0.18	0.18	0.8748	0.99
rs10831706	11	2,262,602	A	0.07	0.11	0.0036	0.11	0.13	0.1804	0.1	0.12	0.1424	0.11	0.12	0.4926	0.0013	98	G	0.09	0.09	0.5637	0.95
rs7114018	11	8,046,522	C	0.4	0.46	0.0045	0.44	0.47	0.0871	0.35	0.41	0.0359	0.4	0.43	0.466	0.0002	15	T	0.42	0.42	0.9301	1
rs12576547	11	10,599,800	C	0.38	0.43	0.0204	0.41	0.44	0.1078	0.39	0.42	0.3764	0.39	0.41	0.4594	0.0034	209	A	0.44	0.43	0.8446	1.01
rs4077215	11	11,530,606	T	0.4	0.36	0.0467	0.44	0.4	0.0485	0.3	0.28	0.4531	0.4	0.39	0.5602	0.0043	247	G	0.32	0.33	0.3188	0.94
rs10837311	11	39,936,524	G	0.19	0.23	0.011	0.19	0.23	0.0208	0.11	0.15	0.0811	0.19	0.21	0.6019	0.0002	16	A	0.18	0.17	0.924	1.01
rs6589849	11	98,391,541	C	0.25	0.3	0.0119	0.26	0.29	0.0463	0.25	0.32	0.0059	0.25	0.26	0.8373	9E-05	10	A	0.26	0.27	0.373	0.95
rs1105721	11	130,573,660	C	0.37	0.32	0.0228	0.34	0.31	0.0919	0.41	0.37	0.1946	0.34	0.33	0.7764	0.0028	176	A	0.35	0.33	0.2058	1.07
rs16919663	12	32,345,199	A	0.16	0.13	0.0472	0.15	0.13	0.0471	0.21	0.19	0.3358	0.14	0.13	0.6937	0.0037	219	C	0.16	0.15	0.5395	1.05
rs10861272	12	103,613,005	A	0.08	0.11	0.0118	0.11	0.13	0.053	0.09	0.12	0.0973	0.08	0.12	0.0847	0.0001	13	G	0.01	0.01	0.7437	0.92
rs9513353	13	97,548,317	A	0.18	0.13	0.002	0.18	0.15	0.0271	0.21	0.2	0.442	0.17	0.15	0.4432	0.0002	22	G	0.14	0.15	0.6093	0.96
rs9300549	13	98,901,735	A	0.41	0.36	0.0122	0.39	0.35	0.0358	0.44	0.41	0.2989	0.42	0.38	0.2705	0.0004	37	G	0.38	0.37	0.2793	1.06
rs4773194	13	109,930,491	G	0.21	0.18	0.0279	0.2	0.17	0.0203	0.16	0.15	0.6374	0.18	0.17	0.8332	0.0025	161	A	0.17	0.18	0.3968	0.94

TABLE 7 CONTINUED

				CGEMS, 1st stage			CGESM, 2nd stage									CGEMS		CAPS				
dbSNP ID	Chromosome	Physical Position (bp)	Allele	Aggressive-PLCO, n=691	Indolent-PLCO, n=489	P-PLCO	Aggressive-ACS, n=926	Indolent-ACS, n=699	P-ACS	Aggressive-ATBC, n=240	Indolent-ATBC, n=516	P-ATBC	Aggressive-HPFS, n=123	Indolent-HTFS, n=405	P-HPFS	P-CMH	Rank	Allele	Aggressive, n=1,231	Indolent, n=1,619	P	OR
rs7999702	13	110,180,265	T	0.18	0.22	0.0227	0.18	0.2	0.1121	0.27	0.29	0.4378	0.17	0.2	0.2647	0.0033	200	G	0.21	0.21	0.9617	1
rs914009	14	55,876,856	G	0.37	0.32	0.0078	0.35	0.32	0.0276	0.35	0.32	0.1759	0.33	0.31	0.6322	0.0003	24	T	0.35	0.35	0.7209	0.98
rs2921452	14	76,010,170	G	0.51	0.47	0.0288	0.47	0.45	0.1194	0.51	0.46	0.1153	0.46	0.45	0.7772	0.003	184	G	0.49	0.49	0.9825	1
rs12438353	15	85,116,084	C	0.3	0.35	0.0196	0.3	0.33	0.1494	0.4	0.44	0.2058	0.29	0.33	0.2103	0.0017	116	T	0.35	0.34	0.3369	1.06
rs11247363	15	96,441,465	C	0.43	0.49	0.007	0.45	0.48	0.1617	0.47	0.54	0.0143	0.41	0.45	0.3095	0.0002	19	T	0.48	0.48	0.778	1.02
rs972317	17	31,395,772	A	0.12	0.09	0.0329	0.13	0.1	0.0336	0.16	0.16	0.9916	0.15	0.11	0.1038	0.0028	175	G	0.11	0.11	0.8008	1.02
rs12150382	17	65,734,367	G	0.24	0.29	0.0112	0.22	0.26	0.0175	0.19	0.23	0.0957	0.21	0.26	0.1093	3E-05	4	A	0.24	0.24	0.8583	0.99
rs1790588	18	65,886,164	T	0.47	0.42	0.0341	0.49	0.45	0.0223	0.49	0.44	0.1178	0.54	0.51	0.447	0.0004	35	G	0.47	0.48	0.2156	0.94
rs2306199	19	8,226,890	T	0.38	0.45	0.0009	0.38	0.41	0.0847	0.22	0.24	0.4226	0.38	0.41	0.4524	0.0004	32	G	0.35	0.36	0.3041	0.94
rs2288888	19	43,636,022	A	0.33	0.28	0.0147	0.35	0.3	0.0083	0.36	0.3	0.0227	0.35	0.31	0.2413	1E-05	2	G	0.31	0.31	0.806	0.99
rs5992590	22	15,787,360	T	0.25	0.3	0.0099	0.27	0.3	0.043	0.32	0.33	0.7308	0.24	0.31	0.0433	0.0005	42	C	0.26	0.26	0.9281	1.01
rs2091051	22	47,933,870	C	0.41	0.45	0.023	0.42	0.44	0.1981	0.51	0.57	0.0498	0.38	0.4	0.5567	0.0019	130	A	0.46	0.47	0.3694	0.95
rs6010061	22	49,441,868	C	0.43	0.36	0.0022	0.4	0.38	0.1209	0.6	0.57	0.3278	0.43	0.39	0.2309	0.0005	44	T	0.47	0.46	0.5013	1.04

TABLE 8: Confirmation of SNPs Associated With Aggressiveness of Prostate Cancer in CAPS

				CGEMS, 1st stage			CGESM, 2nd stage									CGEMS		CAPS				JHH*		
dbSNP ID	Chromosome	Physical Position (bp)	Allele	Aggressive-PLCO, n=691	indolent-PLCO, n=489	P-PLCO	Aggressive-ACS, n=926	indolent-ACS, n=699	P-ACS	Aggressive-ATBC, n=240	indolent-ATBC, n=516	P-ATBC	Aggressive-HPFS, n=123	indolent-HPFS, n=405	P-HPFS	P-CMH	Rank	Allele	Aggressive, n=1,231	indolent, n=1,619	P	Aggressive, n=1,258	indolent, n=4,258	P
rs9996597	4	111,652	T	0.49	0.45	0.05	0.46	0.41	0.00	0.56	0.54	0.57	0.46	0.42	0.28	0.0005	41	T	0.47	0.51	0.02	0.58	0.54	0.04
rs886505	7	8,559,297	A	0.43	0.5	4.5E-04	0.46	0.49	0.08	0.56	0.61	0.12	0.48	0.48	0.96	1.6E-04	18	G	0.44	0.48	1.7E-03	0.48	0.49	0.63
rs2713328	7	9,260,649	A	0.18	0.13	6.3E-04	0.17	0.14	0.01	0.22	0.2	0.39	0.15	0.14	0.84	9E-05	9	C	0.2	0.16	2.1E-03	0.17	0.17	0.99
rs10217763	9	22,588,914	A	0.19	0.22	0.03	0.19	0.23	0.03	0.17	0.2	0.17	0.21	0.21	0.82	1.1E-03	90	G	0.2	0.22	0.04	0.2	0.21	0.42
rs1320722	11	79,156,374	T	0.36	0.41	0.01	0.35	0.39	0.03	0.44	0.44	0.95	0.35	0.37	0.46	2.4E-03	156	C	0.41	0.44	0.03	0.36	0.38	0.24
rs4054823	17	13,565,749	T	0.42	0.48	3.7E-03	0.44	0.48	0.05	0.47	0.49	0.39	0.43	0.44	0.78	9.8E-04	81	C	0.44	0.47	0.04	0.44	0.46	0.05

*For rs4054823, the numbers of aggressive and indolent subjects are 1408 and 4318, respectively.

That which is claimed is:

1. A method of identifying a human subject as having an increased risk of developing aggressive prostate cancer, comprising detecting in a nucleic acid sample from the subject a T allele at single nucleotide polymorphism rs4054823 in chromosome region 17p12, wherein the detection of said allele identifies the subject as having an increased risk of developing aggressive prostate cancer.

2. A method of identifying a human subject as having an increased risk of developing aggressive prostate cancer, comprising detecting in a nucleic acid sample from the subject an allele that is in linkage disequilibrium with the T allele at single nucleotide polymorphism rs4054823 in chromosome region 17p12, wherein the detection of said allele identifies the subject as having an increased risk of developing aggressive prostate cancer.

3. The method of claim **1**, wherein the subject is homozygous for the T allele at single nucleotide polymorphism rs4054823.

4. The method of claim **1**, wherein detecting is carried out by an amplification reaction.

5. The method of claim **1**, wherein detecting is carried out by an amplification reaction and single base extension.

6. The method of claim **5**, wherein the product of the amplification reaction and single base extension is spotted on a silicone chip.

7. The method of claim **1**, wherein detecting is carried out by matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF-MS).

8. The method of claim **4**, wherein the amplification reaction is a polymerase chain reaction.

9. The method of claim **1**, wherein detecting is carried out by sequencing, hybridization, restriction endonuclease digestion analysis, electrophoresis, or any combination thereof.

10. A computer-assisted method of identifying a proposed treatment for aggressive prostate cancer as an effective and/or appropriate treatment for a subject carrying a genetic marker correlated with aggressive prostate cancer, comprising the steps of:

(a) storing a database of biological data for a plurality of subjects, the biological data that is being stored including for each of said plurality of subjects:
  (i) a treatment type,
  (ii) at least one genetic marker associated with aggressive prostate cancer, and
  (iii) at least one disease progression measure for prostate cancer from which treatment efficacy can be determined; and then

(b) querying the database to determine the dependence on said genetic marker of the effectiveness of a treatment type in treating prostate cancer, thereby identifying a proposed treatment as an effective and/or appropriate treatment for a subject carrying a genetic marker correlated with prostate cancer.

11. The method of claim **10**, wherein the genetic marker associated with aggressive prostate cancer is a T allele in single nucleotide polymorphism rs4054823 in chromosome region 17p12.

12. The method of claim **1**, wherein the subject has an elevated prostate serum antigen level.

13. The method of claim **1**, wherein the subject has a family history of prostate cancer.

14. A kit comprising oligonucleotides to detect the T allele of single nucleotide polymorphism rs4054823 in chromosome region 17p12 and/or a risk allele of a single nucleotide polymorphism in linkage disequilibrium with single nucleotide polymorphism rs4054823 in chromosome region 17p12 in a nucleic acid sample.

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